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Original Paper

Protocol

Mindfulness-Based Smoking Cessation Delivered Through Telehealth and Text Messaging for Low-Income Smokers: Protocol for a Randomized Controlled Trial

Claire A Spears[1], PhD; Josephine Mhende[1], MPH; China Hawkins[1], BA; Vuong Van Do[1], MPH; Matthew J Hayat[2], PhD; Michael P Eriksen[1], ScD; Donald Hedeker[3], PhD; Lorien C Abroms[4], ScD; David W Wetter[5], PhD

[1]Department of Health Policy & Behavioral Sciences, School of Public Health, Georgia State University, Atlanta, GA, United States

[2]Department of Population Health Sciences, School of Public Health, Georgia State University, Atlanta, GA, United States

[3]Department of Public Health Sciences, University of Chicago, Chicago, IL, United States

[4]Department of Prevention and Community Health, Milken Institute School of Public Health, George Washington University, Washington, DC, United States

[5]Department of Population Health Sciences, University of Utah and Huntsman Cancer Institute, Salt Lake City, UT, United States

Corresponding Author:
Claire A Spears, PhD
Department of Health Policy & Behavioral Sciences
School of Public Health
Georgia State University
140 Decatur Street SE
Atlanta, GA, 30303
United States
Phone: 1 404 413 9335
Email: cspears@gsu.edu

Abstract

Background: Tobacco use is the leading cause of preventable morbidity and mortality. Adults with low income and members of certain racial and ethnic minority groups are less likely to quit, and therefore, they experience profound tobacco-related health disparities. Mindfulness training can increase the rates of smoking cessation and lapse recovery, and telehealth and SMS text messaging have the potential to provide more accessible treatment.

Objective: This study aims to test the efficacy of delivering mindfulness-based smoking cessation treatment through text messaging (iQuit Mindfully) and telehealth (group videoconferencing), both as stand-alone interventions and in combination. In addition, it aims to examine the underlying mechanisms of mindfulness treatment.

Methods: In this 2×2 randomized controlled trial, participants are randomized into 1 of 4 groups based on assignment to iQuit Mindfully text messages (yes or no) and mindfulness videoconference groups (yes or no). The primary outcomes are biochemically verified smoking abstinence at 8, 12, and 24 weeks after the start of treatment. Secondary outcomes include the frequency of home mindfulness practice and self-reported levels of mindfulness, emotions, craving, withdrawal, dependence, self-efficacy, and social support.

Results: Recruitment, treatment, and assessment began in spring and summer 2021, and data collection is expected to continue through spring 2024.

Conclusions: This project aims to improve smoking cessation outcomes for low-income, racially and ethnically diverse smokers through mindfulness-based telehealth group counseling and text messaging support. We also aim to advance the scientific study of the mechanisms of action of mindfulness treatment, which could inform the development of more efficacious and efficient treatments to reduce tobacco disparities.

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KEYWORDS

mobile health; mHealth; telehealth; SMS text messaging; mindfulness; smoking cessation; tobacco; health disparities; mobile phone

Introduction

Background

Tobacco use, the leading cause of preventable morbidity and mortality [1], disproportionately affects low-income and African American populations [2]. Both low-income and African American smokers have higher incidence and mortality rates of tobacco-related cancers [3-5]. Furthermore, cigarette smoking is more prevalent among adults living below the federal poverty line (25.3%) compared with those at or above the poverty level (14.3%) [6]. Smoking cessation greatly reduces the risk of cancer and related death [7,8], and most smokers in the United States (regardless of income, race, or ethnicity) want to quit smoking. However, only 7% quit each year [9], and the rates of successful smoking cessation are even lower among low-income and African American adults [2,9]. There is an urgent need to improve evidence-based smoking cessation interventions to better serve these populations.

Mindfulness training can increase the rates of smoking cessation and lapse recovery [10-12]. These programs teach individuals to observe present-moment sensations without judging or reacting to them. For example, mindfulness involves moment-to-moment awareness of stress, unpleasant emotions, and craving (all of which can be potent triggers for smoking) so that people can purposefully choose how to respond, rather than automatically react to the triggers by smoking [13]. Most research on mindfulness-based interventions (MBIs) has focused on higher-income and non-Latino White populations. However, MBIs have shown benefits for smoking cessation in low-income [14] and racially and ethnically diverse adults [10,11]. In addition, mindfulness-based relapse prevention has been reported to be more efficacious than traditional relapse prevention in reducing drug use among racial and ethnic minority women [15]. In a sample of racially and ethnically diverse adult smokers, higher mindfulness was indirectly associated with a lower likelihood of smoking lapse through its association with reduced stress [16]. Moreover, among low-income African American adults, the ability to practice mindfulness on one's own, without having to rely on external resources, has been described as helpful for managing stress and improving health [17].

Although mindfulness practice does not require substantial resources, the mindfulness interventions that have undergone the most empirical testing involve considerable time and resources. Mindfulness-based stress reduction (MBSR) [18] and mindfulness-based cognitive therapy (MBCT) [19] are typically provided by highly trained instructors in 8 weekly, in-person 2- to 2.5-hour sessions, plus a day-long retreat. Although these programs are beneficial for those with the requisite time, transportation, and financial and other resources, there is a need for more cost-effective and scalable MBIs for a broader reach. For example, offering MBIs through telehealth (eg, group videoconferencing) could improve treatment access. A 2020 systematic review supported the feasibility and acceptability of delivering MBSR and MBCT via group videoconferencing, with moderate positive effects on mental health outcomes compared with inactive controls and no significant differences compared with in-person delivery [20]. A broader 2021 systematic review of web-based MBIs (including MBIs other than MBSR and MBCT as well as various forms of guided and unguided web-based delivery) found pre-post intervention benefits for well-being, depression, anxiety, stress, and mindfulness [21]. Therapist-guided web-based MBIs were superior for reducing stress compared with unguided web-based MBIs [21]. To our knowledge, mindfulness-based smoking cessation treatment has not been delivered through group videoconferencing, although MBIs for smoking cessation have been provided through web-based prerecorded video instructions with telephone counseling support [22] and smartphone apps [23,24]. Given the safety concerns with in-person groups during the COVID-19 pandemic and our goal of developing more scalable interventions, we recently transitioned mindfulness-based addiction treatment (MBAT), an 8-week group-based smoking cessation intervention, from in-person to web-based delivery [25]. The first 5 weekly sessions were conducted in person, with the last 3 successfully delivered through group videoconferencing. Providing all 8 MBAT sessions on the web could further improve access to treatment.

In addition, innovative methods are needed to increase MBI engagement and promote adherence to mindfulness practice in daily life; that is, MBIs encourage participants to practice mindfulness between sessions, and consistent home practice is hypothesized to be a key factor in producing therapeutic outcomes [26]. However, mastering a new skill in treatment does not necessarily mean that it will translate to real-life situations, and a consistent barrier to treatment success occurs when individuals fail to practice mindfulness in daily life. MBI participants often do not practice mindfulness as frequently as directed [11,26]. Relatedly, the lack of support between weekly MBI sessions could limit the effectiveness of the intervention. Additional support may be needed for low-income smokers who experience significantly more stress and smoking-conducive contexts on a day-to-day basis [16,27] and have lower health care access [2]. Mobile health (mHealth) technology (eg, delivering interventions through text messaging) offers promise to (1) deliver more cost-effective and scalable treatment, (2) increase engagement with mindfulness home practice, and (3) provide vital 24/7 support to improve smoking cessation outcomes for low-income smokers. For example, text messages could encourage people to use mindfulness coping strategies amid day-to-day stress, cravings, and other challenges. As text messaging does not require a smartphone, internet access, or advanced technical skills, this intervention modality could be appropriate for individuals with lower socioeconomic resources. Indeed, there is strong empirical support for text messaging interventions for smoking cessation [28].

On the basis of iterative feedback from low-income smokers, we developed a text messaging program (*iQuit Mindfully*) as an adjunct to in-person, mindfulness-based smoking cessation treatment [29,30]. In a pilot study (N=71), participants were highly engaged and benefited from tailored, in-the-moment strategies and social support from text messages [29]. Notably, although poverty status predicted worse cessation outcomes among participants receiving only in-person treatment, poverty status was unrelated to cessation among those receiving iQuit Mindfully. In fact, 23.1% of participants living in poverty who received iQuit Mindfully achieved biochemically confirmed abstinence at the end of treatment and at the 1-month follow-up, whereas none of those living in poverty quit in the in-person-only treatment. Building on this initial work, we incorporated participant feedback to further increase interactivity and personalization so that iQuit Mindfully can more flexibly adapt to the changing needs of the participants. We also developed a version of iQuit Mindfully that can be implemented as a stand-alone program (ie, without weekly mindfulness-based group sessions) [25].

In addition to delivering MBIs via telehealth (eg, group videoconferencing) and mHealth (eg, text messaging), mHealth methods could further our scientific understanding of how treatments work. Researchers have highlighted the need to clarify the mechanisms of action of MBIs [31-33]. Intensive longitudinal assessment on mobile phones could elucidate how mindfulness impacts smoking behavior on a day-to-day basis, which could inform the development of more efficacious and efficient treatments. Our conceptual framework, rooted in social cognitive theory [34], relapse prevention theory [35], and past work on MBI mechanisms [13,32,36], describes the hypothesized mechanisms by which MBIs enhance smoking cessation outcomes. First, MBIs are thought to increase dispositional mindfulness (ie, present-focused, nonjudgmental attention in everyday life), which predicts better smoking cessation outcomes [37,38]. Second, mindfulness appears to impact emotions and emotion regulation, which are critical to quit smoking. Escaping, avoiding, or reducing negative affect are key drivers of substance use [39]. In the "addictive loop" [13], unpleasant cues elicit negative affect, which triggers craving and smoking. MBIs have been shown to reduce negative affect [40] and its volatility (ie, lability or instability) [36]. Although more mindfulness research has studied the effects of negative than positive emotions, mindfulness might also increase positive affect [41], which could be protective in the process of quitting [42]. Third, mindfulness may reduce craving and withdrawal [36]. That is, nonjudgmental observation of craving could diminish the intensity of unpleasant sensations associated with craving and withdrawal.

Fourth, mindfulness might weaken associations of both negative affect and craving with smoking, thus targeting key aspects of the addictive loop [13]. Even when smokers inevitably experience craving and negative affect, mindfulness moderates their responses to these experiences. For example, "urge surfing" encourages smokers to nonjudgmentally observe cravings as ocean waves that rise and eventually pass [43]. People learn that cravings are transient sensations that they can "ride out" without smoking. Previous research suggests that mindfulness "decouples" the links among negative affect, craving, and substance use [13,44,45]. Fifth, mindfulness may increase self-efficacy for abstaining from smoking in high-risk situations [36]. Low self-efficacy often predicts the lapse and relapse of smoking [46]. By teaching nonreactive observation of smoking triggers, MBIs might increase confidence in one's ability to encounter triggers without smoking. Finally, providing mindfulness treatment through videoconferencing groups and text messaging could enhance the perceived social support of the participants, which predicts better cessation [47]. Participants in our pilot study with iQuit Mindfully indicated feeling a sense of social support and accountability from the text messages [29,30].

Objectives

This randomized controlled trial aims to (1) test the efficacy of delivering mindfulness-based smoking cessation treatment through text messaging (iQuit Mindfully) and telehealth (MBAT through group videoconferencing), both as stand-alone interventions and in combination, and (2) examine the underlying mechanisms of mindfulness treatment. On the basis of clinical trial results, iQuit Mindfully and videoconference-delivered mindfulness treatment for smoking cessation could be highly scalable and cost-effective.

Methods

Study Design, Aims, and Hypotheses

This study is a 2×2 randomized controlled trial to investigate the effects of the iQuit Mindfully text messaging program and telehealth-delivered MBAT, both as stand-alone interventions and in combination. Approximately 485 participants will be randomized into 1 of 4 groups based on assignment to iQuit Mindfully text messages (yes or no) and MBAT videoconference groups (yes or no). The four conditions are Usual Care (self-help materials and nicotine replacement therapy [NRT]), MBAT (8 weekly videoconference group MBAT sessions, self-help materials, and NRT), iQuit Mindfully (iQuit Mindfully text messages, self-help materials, and NRT), and MBAT+iQuit Mindfully (8 weekly videoconference group MBAT sessions, iQuit Mindfully text messages, self-help materials, and NRT). Assessments are performed at baseline and weeks 1, 3, 5, 8, 12, and 24.

The primary outcomes are smoking abstinence at 8 weeks after the start of treatment (7-day abstinence, biochemically verified by expired carbon monoxide [CO] <6 ppm), 12 weeks after the start of treatment (3-month follow-up; 7-day abstinence, verified by CO <6 ppm), and 24 weeks after the start of treatment (6-month follow-up; 7-day abstinence, biochemically verified by saliva cotinine <20 ng/mL). Secondary outcomes include the frequency of home mindfulness practice and self-reported levels of mindfulness, emotions, craving, withdrawal, dependence, self-efficacy, and social support.

The aims and hypotheses are subsequently outlined.

The first aim is to test the efficacy of a mindfulness-based text messaging program for smoking cessation (iQuit Mindfully) and telehealth-delivered MBAT, both as stand-alone interventions and in combination.

We hypothesize the following:

- MBAT+iQuit Mindfully will result in higher rates of smoking cessation and lapse recovery than MBAT or iQuit Mindfully alone. MBAT and iQuit Mindfully, as stand-alone interventions, will also produce higher cessation and lapse recovery than usual care.
- As an exploratory aim, we will examine whether poverty status moderates treatment efficacy (ie, poverty status will predict worse cessation outcomes in MBAT but not in MBAT+iQuit Mindfully, which provides 24/7 mHealth support).

The second aim is to investigate the mechanisms through which mindfulness training impacts smoking cessation. Participants will complete questionnaires from baseline to 24 weeks after the start of treatment, in addition to intensive diary assessments for 6 contiguous weeks during treatment. We hypothesize the following:

- Compared with usual care, the mindfulness treatment arms (MBAT, iQuit Mindfully, and MBAT+iQuit Mindfully) will increase mindfulness, reduce negative affect and volatility of negative affect (ie, greater affective stability), increase positive affect, reduce craving and withdrawal, and increase self-efficacy and social support, all of which will mediate the effects of mindfulness-based treatment arms versus usual care on abstinence.
- Compared with usual care, MBAT, iQuit Mindfully, and MBAT+iQuit Mindfully will all attenuate the links between links between negative affect and craving with smoking. That is, in addition to reducing negative affect and craving, mindfulness training is hypothesized to weaken the relationships between negative affect and craving with smoking.
- Compared with MBAT, MBAT+iQuit Mindfully will produce stronger effects on the mechanisms mentioned above. The mechanisms outlined in the mindfulness treatment arms will mediate the effects of MBAT+iQuit Mindfully versus MBAT on abstinence.

Ethics Approval and Registration

This study was approved by the Georgia State University (GSU) institutional review board (protocol H20479) and was registered on clinicaltrials.gov (NCT04965181).

Participants and Recruitment

The following are the inclusion criteria: a minimum age of 18 years; current smoker with a history of >3 cigarettes/day (and expired CO >6 ppm); motivation to quit smoking within the next 30 days; a valid home address in the greater Atlanta, Georgia, area; a functioning telephone number; and the ability to speak, read, and write in English. The following are the exclusion criteria: contraindication for nicotine patch or nicotine lozenge; current problematic substance use or clinically significant depressive symptoms; current use of tobacco cessation medications; pregnancy, planning to become pregnant in the next 5 months, or lactation; household member enrolled in the study; or those enrolled in previous studies on iQuit Mindfully at GSU.

Recruitment focuses on flyers; print, radio, and social media; community outreach; and partnerships with local health care systems, with targeted recruitment of low-income and racially and ethnically diverse smokers in Atlanta, Georgia. Flyers are posted at and near local clinics and community health centers, community organizations, and shelters; on and near GSU campuses; and near local train and bus stops. The research team also attends meetings sponsored by county and state health departments to communicate with stakeholders and hand out recruitment flyers. Web-based recruitment strategies include advertising posted on the Craigslist and Nextdoor websites.

Study Interventions

Nicotine Replacement Therapy (All Conditions)

Participants are provided with 8 weeks of nicotine patches and nicotine lozenges, with dosages depending on the number of cigarettes per day and time to first cigarette upon waking. Participants receive 4 weeks of nicotine patches and lozenges at baseline, and they are mailed the additional 4 weeks of NRT when needed.

Self-help Materials (All Conditions)

All participants are given evidence-based self-help materials for smoking cessation (based on the Treating Tobacco Use and Dependence Clinical Practice Guideline) [48]. Materials include the “Clearing the Air” booklet published by the National Cancer Institute and a referral to the Tobacco Cessation Quitline (1-800-QUIT-NOW).

MBAT (MBAT and MBAT+iQuit Mindfully Conditions)

Participants in the MBAT and MBAT+iQuit Mindfully conditions receive videoconference group counseling (using the Zoom platform) based on the MBAT manual (D Wetter, unpublished data, June 2009). Instructors are certified MBSR teachers and licensed clinicians who received additional training on tobacco cessation. MBAT consists of 8 weekly 2-hour sessions. Participants are encouraged to choose their own quit date between day 7 and day 30 of the program. MBAT sessions teach participants to notice the tendency for mindlessness (“automatic pilot”) and focus attention on the present moment, including observing sensations of craving and difficult emotions, so that they can choose to cope in adaptive ways other than smoking. MBAT emphasizes daily mindfulness practice in several forms including sitting meditation, body scan meditation, walking meditation, eating meditation, and gentle yoga. The program also teaches cognitive behavioral strategies for smoking cessation, including clearing the environment of smoking cues, recognizing and coping with high-risk situations, and managing stress [11].

Several strategies are being implemented to promote engagement with telehealth-delivered MBAT among adults of low-income populations. For example, participants in the MBAT and MBAT+iQuit conditions can borrow a study tablet for the 8 weeks of the program. Participants are also given the option to join videoconference groups in an individual room at our research office, in cases in which they do not have a private place to join groups. Finally, the research team provides guidance and technical support for using Zoom through an

in-person baseline session, Zoom group orientation session, and ongoing troubleshooting as needed.

iQuit Mindfully Text Messages (iQuit Mindfully and MBAT+iQuit Mindfully Conditions)

Participants receive text messages throughout the 8-week treatment period as well as less frequent messages during the follow-up period, depending on their preferences. All messages are automated using the Upland Mobile Commons platform. Participants are asked to set a quit date at baseline, which is integrated into text messages and can be changed by the participant. Text messages encourage participants to practice mindfulness and other strategies for smoking cessation (for more details, refer to the study by Spears et al [29]). The messages are designed to be interactive. That is, participants are asked questions through a series of flow logic (eg, "Would you like to practice mindfulness right now?" If participants replies "yes," they are provided a mindfulness technique, later asked about how it went, and are encouraged to continue practice). Participants can also text CRAVE, STRESS, SLIP, or FACT at any point to receive additional text message support for coping with cravings, stress, smoking lapses, or to receive facts about the effects of smoking, respectively. Participants can answer "group poll" questions so that they later receive a text with the most common (deidentified) responses. Text messages include quotes sharing the anonymous experiences of former smokers in our program. Participants can also text keywords (MIND, BODY, or 3MIN) to receive a phone call with a short recording of a mindfulness practice. Participants are given small pocket cards with basic information on the text messaging program and reminders about the text keywords.

Text messages are personalized based on first names, personal reasons for quitting, and the amount of money to be saved based on individual smoking habits and price paid per pack. Picture messages are included based on our initial qualitative work [30]. On the basis of the feedback from our previous message testing [29], message timing and frequency are flexible and personalized. Participants choose the frequency of their choice (ie, very low to very high, ranging from 1 to 2 to 5 to 6/day) as well as a 12-hour time slot of their choice (7 AM to 7 PM or 10 AM to 10 PM). Text messages periodically ask participants about their preferred text message frequency and timing so that participants can change their message schedule as needed.

Study Procedures

Overview

Individuals who are interested in the study either call the research office to complete telephone screening or click on a link to take a web-based screener survey. Eligible individuals are then scheduled for an in-person session to finalize eligibility, engage in further discussion about the study, and provide written informed consent. To confirm eligibility, the participants provide a breath sample for the assessment of expired CO. Individuals who decline or are ineligible are given self-help materials and referred to other cessation programs. In addition, potential participants complete the Patient Health Questionnaire-2 [49] and Severity of Dependence Scale [50] to screen for clinically significant depressive symptoms and substance dependence, respectively. Individuals who are ineligible for these reasons are provided with appropriate mental health referrals in addition to smoking cessation referrals.

Eligible individuals who provide written informed consent are then asked to complete baseline questionnaires, followed by randomization. Permutated block randomization is implemented, with stratification by race and poverty status. Participants are provided with information and materials specific to their intervention condition and scheduled for their next study visits. Web-based surveys are administered at weeks 1, 3, and 5. In addition, electronic diary assessments (brief surveys sent via text message or email depending on participant preference) are administered in the evening on every other day from week 2 to week 8, thus capturing key processes surrounding quitting smoking. Diary assessments assess smoking behavior ("How many cigarettes did you smoke today?") and each of the hypothesized mechanisms (mindfulness, emotions, craving and withdrawal, weakened associations of negative affect and craving with smoking, self-efficacy, and social support). In-person assessments take place at weeks 8, 12, and 24, including assessment of expired CO (all in-person visits) and salivary cotinine (week 24) for biochemical confirmation of smoking behavior. The descriptions of the questionnaires are provided below.

Smoking Behavior

Tobacco History assesses the onset of regular smoking, previous quit attempts, abstinence history, smoking rate, and partner smoking status. This includes the Heaviness of Smoking Index (HSI), which comprises two items from the Fagerström Test for Nicotine Dependence [51]: self-reported average number of cigarettes smoked per day and time to first cigarette upon waking ("time to first cigarette"). The HSI is a strong indicator of nicotine dependence [52]. Smoking status surveys tobacco use, use of other tobacco products, and nicotine replacement medications. Smoking abstinence is assessed according to the Society for Research on Nicotine and Tobacco guidelines [53]. The use of novel tobacco products (eg, e-cigarettes) is also assessed, and participants indicate which forms of NRT and/or pharmacotherapy (if any) they used in the past week. Additional resources used for smoking cessation assesses the use of various strategies for quitting smoking (eg, acupuncture, hypnosis, other text messaging programs, or mobile apps) outside of the treatment provided by the study.

The Brief Wisconsin Dependence Motives Questionnaire [54] is a 37-item measure that yields an overall dependence score and subscale scores for other dimensions (ie, cognitive enhancement, affective enhancement, automaticity, affiliative attachment, loss of control, craving, cue exposure or associative processes, social or environmental goals, taste or sensory processes, weight control, and tolerance). The Wisconsin Smoking Withdrawal Scale [55] includes subscales for anger, anxiety, sadness, concentration difficulty, craving, hunger, and sleep. The Self-Efficacy Scale assesses confidence in resisting smoking urges in specific situations (eg, when feeling stressed or when with friends) [56]. Subscales include negative affect, pleasure, social image, social influence, and diet.

Mindfulness

The Mindful Attention Awareness Scale [57] is a 15-item self-report measure of dispositional mindfulness [57]. The Five-Facet Mindfulness Questionnaire-Short Form [58] is a 24-item self-report questionnaire on facets of dispositional mindfulness (nonreactivity, observing, acting with awareness, describing or labeling with words, and nonjudging of experience). Participants also complete a Mindfulness Practice Log [11] to indicate how frequently they practice each mindfulness technique taught in treatment. The Self-Compassion Scale-Short Form [59] is a 12-item self-report measure of self-compassion. Subscales include self-kindness, self-judgment, common humanity, isolation, mindfulness, and overidentification.

Stress and Emotions

The Perceived Stress Scale [60] is a 10-item self-report measure of the extent to which individuals view their lives as stressful. The Positive and Negative Affect Schedule [61] is a 20-item self-report measure of affective experience, yielding two factors (positive and negative affect).

Social Support

The Multidimensional Scale of Perceived Social Support [62] is a 12-item scale, with subscales assessing perceived social support from family, friends, and significant others. The Group Climate Questionnaire [63] is a 12-item self-report scale that measures the climate and cohesion of the group (only applicable for MBAT participants).

Program Evaluation

Participants provide feedback about their experiences receiving the text messages (text message feedback). They also complete 4 items to indicate perceived benefits of the smoking cessation program. As described by Hoeppner et al [64], participants rate the extent to which the program gave them confidence to quit smoking, made them think it was worthwhile to quit, made them feel that someone cared if they quit, and made them feel that they knew the right steps to take to quit. Items are rated from 1 (completely disagree) to 5 (completely agree). Participants also complete program evaluations to provide feedback and suggestions for improving MBAT and iQuit Mindfully. Usual care participants answer one program evaluation question: “On the scale below, please circle the number that best represents whether you would recommend this quit smoking program (or something similar) for others who are interested in quitting smoking” (rated on a 1 to 10 scale).

Financial Compensation and Retention Procedures

Participants receive financial compensation for the time and inconvenience associated with participation as well as parking validation or train or bus vouchers to defray the cost of travel. Participants are compensated up to US $30 for web-based surveys at weeks 1, 3, and 5 (US $25 for each survey plus US $5 bonus if completed within 24 hours). They are also compensated US $40 for week 8, US $60 for week 12, and US $70 for week 24 (all in-person visits). In addition, participants are compensated US $5 per each of the every-other-day surveys (maximum US $120 for all 6 weeks). The maximum compensation per person for completing all aspects of the study is US $380.

Other procedures to increase adherence include the following: (1) reminder phone calls, e-mails, and text messages; (2) requiring a phone number and valid home address so that participants can be contacted; (3) loaning participants a mobile phone for the study duration if they do not have one; and (4) obtaining names, addresses, and phone numbers of up to 3 collaterals who can provide information on participants’ whereabouts if necessary. In addition to traditional procedures for the informed consent process, research staff members engage eligible individuals in a discussion of the pros and cons of participating as well as participants’ ambivalence about behavior change and research participation. These methods have been suggested to improve retention [65].

Analytic Plan

Overview

We will conduct both intent-to-treat (ITT) and per-protocol analyses. ITT includes all randomized participants, regardless of compliance, withdrawal, and other events after randomization. A strength of ITT is that it is based on the original randomization. However, effect estimation using ITT may be conservative and misleading with increasing attrition. Per-protocol analysis considers only participants who fully complied and completed the study. Per-protocol analysis is less conservative and may reflect true treatment differences for patients with full compliance. Including both approaches will provide a more complete understanding of the treatment effects.

Analyses will be performed using the SAS software. All analyses will control for demographics (age, gender, race, education level, and partner status) and baseline nicotine dependence (cigarettes per day and time to first cigarette).

Aim 1: Intervention Efficacy

The relationship between the treatment condition and each dichotomous study outcome (smoking cessation and lapse recovery) will be assessed using a generalized linear mixed model with a binomial distribution and logit link function. This is an appropriate statistical model with repeated measures data collected over time [66]. A 2-level multilevel generalized linear mixed model will be specified, with time nested within the subject. This approach will properly account for the multilevel data structure. The fixed effects considered in each model will include demographics, baseline nicotine dependence, treatment condition and time as main effects, and a treatment condition by time interaction. Testing of the covariance structure will be conducted, and information criteria will be used to assess model fit and selection. Linear contrasts will be built into the analysis to estimate the specific comparative effects of all treatment conditions. To test treatment effects on primary smoking cessation outcomes, repeated measures outcomes will be biochemically confirmed at 7-day point prevalence abstinence at weeks 8, 12, and 24. To test the effects of treatment on lapse recovery, this analysis will also be conducted among participants classified as smoking at the last treatment session [11]. In addition, gender, race and ethnicity will be assessed as potential moderators of the treatment effects.

The moderating effect of poverty status will be examined with the addition of a poverty status by treatment condition interaction into the models described above. This will be tested using both dichotomous (ie, below vs at or above the federal poverty threshold) and continuous poverty status variables (ie, depth of poverty as indicated by the ratio of income to poverty and income deficit or surplus) according to the United States Census Guidelines [67,68].

Aim 2: Underlying Mechanisms

Hypotheses regarding the mechanisms will be tested separately using both traditional questionnaire data (collected from baseline to 24 weeks after the start of treatment) and electronic diary data (collected for 6 continuous weeks during treatment). Mediation testing will be conducted regardless of the statistical significance of the intervention effects because of statistical, conceptual, and practical reasons for testing mediation in such cases [69]. Volatility will be calculated using the mean square successive difference approach [70] to capture both within-person variability and temporal instability. Mediation will be examined using multilevel mediation analyses for binary outcomes in the developed generalized linear mixed model. Bootstrapping with 5000 replications will be used to estimate the standard errors and *P* values for indirect effects. In addition to the mediators of associations between treatment and abstinence outcomes, we will test more fine-grained day-to-day associations using electronic diary assessments. We will test moderated mediation (ie, the hypothesis that mindfulness not only reduces stress, negative affect, and craving but also weakens the associations between these variables and smoking) using a model proposed by Preacher et al [71], as the independent variable (mindfulness training) also functions as a moderator. Kline [72] termed this "second-stage moderation," as the second path of the indirect effect of the predictor on the dependent variable depends on the moderator. Conditional mediation and moderation effects will be tested using bootstrapping methods [71].

Missing Data

Although there is no complete, comprehensive method for handling missing data for generalized linear mixed models, several different approaches can be used to address this issue [66]. We will use multiple imputations of missing data whereby missing observations for individuals are estimated based on baseline responses and other study covariates, and we will perform additional sensitivity analyses regarding various missing data assumptions for smoking outcomes [73].

Power and Sample Size Determination

The sample size was estimated based on the number of participants required to detect meaningful treatment effects of the iQuit Mindfully and MBAT interventions. We obtained effect sizes (converted to Cohen *d* for comparability across measures) from relevant meta-analyses and used the Optimal Design program to estimate the sample size for the generalized linear mixed models [74]. Smoking abstinence in MBIs versus usual care was quantified as Cohen *d*=0.35 in a meta-analysis [12], and a Cochrane review [75] of primarily text messaging–based interventions for smoking cessation concluded an effect size of Cohen *d*=0.33. Assuming 80% power, a level of significance of .05, 2-tailed statistical tests, an error variance of 1, a coefficient variance of 2, and oversampling to account for 20% attrition, this results in 145 participants in each treatment group. An unequal allocation ratio was used to allocate fewer participants to usual care (n=50) [76,77] for an overall sample size of 485 participants (145 per treatment group and 50 in usual care). We expect this sample size to adequately allow for mediational testing (aim 2) at the 80% power level. Fritz and MacKinnon [78] offer a guide regarding the sample size required to detect mediated effects and report that 79.9% of studies in their literature review applied mediational testing with <400 participants, suggesting that our study plan with 485 participants will be ample to achieve all study aims.

Results

Recruitment, treatment, and assessment began in spring and summer 2021, and data collection is expected to continue through spring 2024. Participants are enrolled into sequential cohorts to allow participants in a given cohort to start the 8-week videoconference MBAT groups together. The final cohort is expected to complete treatment by the end of 2023 and the final 24-week assessments in the first quarter of 2024.

Discussion

Overview and Purpose of Study

This paper describes the design of a randomized controlled trial of telehealth and text messaging delivery for mindfulness-based smoking cessation treatment. This project aims to improve smoking cessation outcomes for low-income, racially and ethnically diverse smokers through mindfulness-based telehealth group counseling and text messaging support, both separately and in combination. An overarching goal is to increase the reach and accessibility of mindfulness for more diverse populations, given that most mindfulness research has focused on higher-income and non-Latino White participants. We hypothesize that in this racially and ethnically diverse and predominantly low-income sample, the combination of mindfulness-based treatment through telehealth plus text messaging (MBAT+iQuit Mindfully) will result in higher rates of smoking cessation and lapse recovery than either program alone and that MBAT and iQuit Mindfully as stand-alone interventions will be superior to usual care. Furthermore, we aim to advance the scientific study of the mechanisms underlying mindfulness-based smoking cessation, which could inform the development of more efficacious and efficient treatments to reduce tobacco-related health disparities.

Strengths, Limitations, and Future Directions

This study is strengthened by a rigorous experimental design to test the effects of mindfulness-based telehealth group counseling and text messaging, both as stand-alone interventions and in combination. The usual care control condition, including 8 weeks of combination NRT, self-help materials, and referral to the Tobacco Quitline, is a more robust comparison treatment than what participants would likely receive within standard health care. Intensive longitudinal data will be used to evaluate

the underlying treatment mechanisms, which could inform the optimization of future treatments. The study is limited by the lack of follow-up after 6 months. Depending on the results of this trial, future trials might evaluate longer-term intervention effects (eg, 12- and 24-month follow-ups) and best practices for dissemination and implementation. It will be critical to ensure that effective treatments are accessible to low-income populations, for example, through partnerships with federally qualified health centers, community centers, the Tobacco Quitline, and/or other accessible resources. Future work might also investigate whether individual differences moderate treatment effects. For example, it is possible that participants with different sociodemographic or clinical profiles may benefit more from mindfulness, mHealth, or other treatment modalities. This information would be useful for practitioners to guide patients to treatment approaches best suited to their needs.

Dissemination Plan

Findings will be presented at scientific meetings and published in a timely fashion, and the published manuscripts will be submitted to the digital archive PubMed Central. The research team will also work with our community collaborators to identify appropriate avenues to communicate project findings to community members in a way that is familiar, comprehensible, and relevant. The research team has formed connections with health care providers and facilities that serve underserved communities and will work to communicate findings through these organizations.

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Conflicts of Interest

LCA receives royalties from the sale of Text2Quit, a text messaging smoking cessation program.

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Abbreviations

CO: carbon monoxide
GSU: Georgia State University
HSI: Heaviness of Smoking Index
ITT: intent-to-treat
MBAT: mindfulness-based addiction treatment
MBCT: mindfulness-based cognitive therapy
MBI: mindfulness-based intervention
MBSR: mindfulness-based stress reduction
mHealth: mobile health
NRT: nicotine replacement therapy

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Protocol

Effects of a Mindfulness Intervention Comprising an App, Web-Based Workshops, and a Workbook on Perceived Stress Among Nurses and Nursing Trainees: Protocol for a Randomized Controlled Trial

Simone Schönfeld[1], MPH; Ines Rathmer[1], MA; Maren M Michaelsen[1], Dr rer oec; Cosima Hoetger[1], PhD; Miriam Onescheit[1], BSc; Silke Lange[2], Dr rer medic; Lena Werdecker[1], DrPH; Tobias Esch[1], MD

[1]Institute for Integrative Health Care and Health Promotion (IGVF), Faculty of Health/School of Medicine, Witten/Herdecke University, Witten, Germany

[2]Interprofessional Graduate College in Integrative Medicine and Health, Witten/Herdecke University, Witten, Germany

Corresponding Author:
Tobias Esch, MD
Institute for Integrative Health Care and Health Promotion (IGVF)
Faculty of Health/School of Medicine
Witten/Herdecke University
Alfred-Herrhausen-Straße 50
Witten, 58448
Germany
Phone: 49 2302926 ext 838
Email: IGVF@uni-wh.de

Abstract

Background: Previous research has found digitally supported mindfulness interventions to be effective when used for stress management among workers in high-stress occupations. Findings on digitally supported mindfulness interventions among nurses working in acute inpatient care settings are heterogeneous, lack long-term follow-up, and do not assess adherence and acceptability.

Objective: This study aimed to investigate the effectiveness and efficacy of a digitally supported mindfulness intervention designed to improve health- and work-related outcomes among nurses and nursing trainees working in acute inpatient care settings.

Methods: We will conduct a multicenter randomized controlled trial using a wait-list control group design. Randomization will be stratified by hospital and job status (nurse or nursing trainee). Recruitment will take place on the web and offline during the working hours of nurses and nursing trainees. The intervention group will receive a digitally supported mindfulness intervention, which will comprise an app, 2 web-based workshops, and a workbook, whereas the wait-list control group will be scheduled to receive the same intervention 14 weeks later. The 2 web-based workshops will be led by a certified mindfulness-based stress reduction trainer. Nurses will use the app and the workbook independently. Self-report web-based surveys will be conducted on the web at baseline, at 10 weeks after allocation, at 24 weeks after allocation, and at 38 weeks after allocation. Outcomes of interest will include perceived stress (primary outcome), health- and work-related variables, and variables related to adherence and acceptability of the digitally supported mindfulness intervention. We will perform intention-to-treat and per-protocol analyses.

Results: Data collection will be completed by the beginning of August 2022. Data analyses will be completed by December 2022.

Conclusions: Our study design, including long-term follow-up and the investigation of variables related to adherence and acceptability, will ensure rigorous evaluation of effectiveness and efficacy. Relative to costly in-person intervention efforts, this program may present a cost-effective and potentially highly scalable alternative. Findings regarding effectiveness, efficacy, adherence, and acceptability will inform stakeholders' decisions regarding the implementation of similar interventions to promote the well-being of nurses and nursing trainees, which may, in turn, alleviate detrimental stress-related outcomes (eg, burnout) because of work-related demands.

Trial Registration: German Clinical Trials Register DRKS00025997; https://tinyurl.com/433cas7u

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KEYWORDS

nurses; nursing trainee; nursing student; acute care; inpatient; health promotion; mindfulness; mobile; web-based; stress; mobile phone

Introduction

Need for Effective Stress Management Interventions for Nurses

The increasing psychological and physical burdens and high workloads of nurses and nursing trainees worldwide have been raising concerns for some time [1,2]. Nurses and nursing trainees in acute inpatient care settings are disproportionately affected by burnout and mental illnesses. Nursing trainees also experience high stress levels, with 34% reporting depressive symptoms before the COVID-19 pandemic [3]. Working in acute inpatient care settings has grown to be increasingly demanding throughout the pandemic; findings from a meta-analysis revealed that 30% [2] to 43% [1] of nurses experience work-related stress. The stress of health care professionals may diminish the quality of care provided to patients and can negatively affect other system-relevant factors [4-7]. Stressful work conditions may also decrease the willingness of nurses to continue working within their profession, which in turn facilitates nursing staff shortages in several countries [8], including Germany [2].

Currently, knowledge about effective stress management interventions to reduce these global challenges is limited. The available research on the effectiveness of stress management interventions for nurses has limitations, including small sample sizes limiting the validity and generalizability of the results and a lack of long-term follow-up [9-11]. More research is needed to examine which interventions result in positive outcomes and, more importantly, the conditions on which intervention effectiveness depends (eg, care setting and acceptability). Therefore, this study distinguishes between efficacy and effectiveness. Efficacy refers to the observed intervention effect when the protocol is followed, whereas effectiveness refers to the effect observed for the entire sample, regardless of protocol adherence.

Requirements for Interventions in Acute Inpatient Care Settings

Stress management interventions should be designed to meet the needs of the target population to effectively decrease stress. A current review showed that stressors and work demands vary across care settings (eg, geriatric care and emergency hospitals) [12]; thus, the integrability of stress management interventions differs across settings and, consequently, so does the added value for all health care professionals to whom the intervention is offered.

Acute inpatient care settings are characterized by the treatment of sudden, urgent, and often life-threatening injuries and illnesses requiring rapid treatment; for example, such treatments include emergency medicine, trauma care, acute care, and critical care [13]. Acute inpatient care settings are marked by an increased risk of immediate involvement in traumatic events, such as experiencing the inability to save a patient's life or feeling overextended because of an inadequate nurse-to-patient ratio [14].

Implementing stress management interventions for nurses working in acute inpatient care settings is difficult because of nurses' demanding work schedules such as changing shifts and difficulties in scheduling breaks in advance [8]. In addition, COVID-19–related safety precautions limit the options of implementing in-person interventions.

In conclusion, appropriate stress management interventions for this target group should help in coping with challenging emotions, be effective in decreasing stress in the long term, and take into account nurses' working conditions when it comes to integrability in the daily working routine.

Digitally Supported Mindfulness Interventions

Digitally supported interventions offer a variety of user-modifiable content. They present a flexible, user-friendly, and cost-effective stress management option as users can engage in stress management practices at a time and place of their convenience.

An effective tool for stress management is mindfulness, especially for individuals with psychological distress [15,16]. Mindfulness has been operationalized as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment" [17]. The most thoroughly researched mindfulness intervention is mindfulness-based stress reduction (MBSR), which is a standardized 8-week course aimed at reducing stress [17]. Mindfulness interventions have been found to be effective for stress reduction and coping with challenging emotions in a variety of populations [15], even if the intervention was digitally supported [18,19]. Findings from systematic reviews and meta-analyses of randomized controlled trials (RCTs) focusing on nonclinical adult populations suggest that digitally supported mindfulness interventions could effectively improve perceived stress [18,19].

The results from the few available RCTs on digitally supported mindfulness interventions among nurses working in acute inpatient care settings are heterogeneous, do not include long-term follow-up (maximum 4 months), and have rarely been conducted in Europe (except for the study by Fiol-DeRoque et al [16]) [20-23]. Two studies showed significant reductions in anxiety and stress, as well as an increase in work satisfaction, following participation in digitally supported mindfulness interventions after 3 months [20-22]. However, 3 studies found no significant between-group differences in their outcomes [16,22,23]. They had an observation time of 1 month and 1 to 4 months [22].

As regular (preferably daily) practice is considered a prerequisite for efficacy [18], heterogeneous results may stem from a lack of acceptance of digitally supported mindfulness interventions, which leads to insufficient or infrequent meditation practice. High dropout rates present a prevalent problem in digitally supported mindfulness intervention research, with dropout rates ranging from approximately 25% [21] to approximately 48% [20]. Nonadherence in intervention instructions or dropout may occur when demanding work schedules and time constraints prevent participants from engaging in meditation practice to a degree that is necessary to achieve desirable outcomes. International differences in health care systems and cultural norms may also influence interest and participation in specific interventions on a regular basis [15].

To decrease dropouts and increase meditation practice, variables related to adherence and acceptability should be investigated [22]. This study distinguishes between adherence and acceptability. Adherence refers to the degree to which participants follow a treatment protocol [24], such as instructions regarding the frequency of meditation practice. Acceptability refers to the factors influencing digitally supported mindfulness intervention use.

In addition, steps should be taken to provide participants with engaging interventions to further treatment adherence and limit dropout risk, which could be achieved by adding user-engaging elements such as web-based workshops and workbooks. Mindfulness workbooks with writing exercises can be effective in stress reduction [25,26] and can be easily used by individuals with limited technological affinity. Previous research suggests that social interactions may enhance the efficacy of digitally supported interventions [15]; for example, studies on individuals with depression found digital interventions to be significantly more effective in reducing depressive symptoms when the intervention was guided by a mental health professional [26,27]. In addition, providing participants with the opportunity to share their experience with the intervention app in a web-based workshop setting could limit dropout risk [20].

Overall, the results on the effectiveness and efficacy of digitally supported mindfulness interventions in nurses working in acute inpatient care settings are rare, which limits the generalizability to different cultural and health care system contexts. Furthermore, the results of these studies are mixed. An intervention period of 3 months has been deemed effective in reducing stress [20,21]. However, the long-term effects (access to intervention for >4 months) of digitally supported mindfulness interventions have not yet been investigated. Importantly, to understand the mixed results in effectiveness, factors associated with adherence and acceptability in nurses deserve further investigation [9].

Aims and Research Questions

Short-term (10-week after intervention start) and long-term efficacy and effectiveness (24-week and 38-week after intervention start) of a digitally supported mindfulness intervention for nurses and nursing trainees will be investigated. As the efficacy and effectiveness of an intervention are likely influenced by participants' degree of adherence to the instructions and acceptability, we will investigate variables that may increase or decrease the likelihood of participant adherence and acceptability. The research questions are as follows:

1. Relative to a wait-list control group (WCG), does access to a digitally supported mindfulness intervention improve subjective health- and work-related outcomes among nurses and nursing trainees in acute inpatient care settings randomized to the intervention group (IG) at 10 weeks after allocation?
2. Relative to scores observed at baseline, does access to a digitally supported mindfulness intervention improve subjective health- and work-related outcomes among nurses and nursing trainees in acute inpatient care settings at 10, 24, and 38 weeks after intervention start? To what degree do app-based minutes of meditation predict each of our outcomes?
3. Which variables are associated with adherence to a digitally supported mindfulness intervention at 10, 24, and 38 weeks after the intervention starts among nurses and nursing trainees in acute inpatient care settings?
4. Which variables are associated with the acceptability of a digitally supported mindfulness intervention at 10, 24, and 38 weeks after the intervention starts among nurses and nursing trainees in acute inpatient care settings?

Methods

Design

We will conduct a multicenter RCT with a WCG design using individual-level randomization, stratified by the hospital or nursing school. The WCG will receive the digitally supported mindfulness intervention 14 weeks after allocation.

Study Setting

This study will be conducted at 4 hospitals and hospital-associated nursing schools in North Rhine-Westphalia, Germany. The number of nurses employed at each institution ranges from 40 to 1400. Two of the hospitals are acute care hospitals with emergency departments, whereas the other 2 hospitals specialize in pneumonology and cardiac surgery. The 2 nursing schools currently have a total of 280 and 380 enrolled nursing trainees.

Eligibility Criteria

Eligible participants were aged ≥18 years, self-identified as nurses or nursing trainees, and reported being employed full-time or part-time at one of the participating hospitals at the time of data collection. Finally, the participants were required to have access to a smartphone. Individuals who did not report employment at one of the participating hospitals or did not self-identify as nurses or nursing trainees were not eligible to participate.

Recruitment

Recruitment took place between August and October 2021 during hospital staff meetings, as well as during web-based meetings among project partners, which were attended by nurses. In addition, participants were recruited via weekly newsletters, handbills, and flyers handed out at participating hospitals and nursing schools.

Eligible nurses and nursing trainees interested in participating in the study were able to register via a website and were emailed the link to the time point 0 (T0) survey (baseline survey). Upon obtaining informed consent, participants were prompted to fill out the web-based survey. Information regarding the study design was not disclosed to the participants.

Informed consent was obtained from all participants before the start of each web-based survey. Informed consent materials are currently available only in German (Multimedia Appendix 1). To prevent individuals from participating more than once, we checked for duplicates in the first and last names and email addresses during registration. Each registered person received personalized invitation letters via email with an individual access key to the survey (token).

Incentives for study registration and survey participation were available at the discretion of each hospital's management, thus varying across locations. A raffle was initiated by the intervention provider at one of the hospitals to incentivize staff participation in the surveys. Incentives included 15 gift cards €15 (US $15.8) each for various shopping websites for the first 2 surveys, whereas the last survey was incentivized by the opportunity to win 1 of the 10 gift cards €30 (US $31.6) each. At some participating hospitals, participants were allowed to participate during work hours, whereas others required their staff to partake during their personal time.

Participant Timeline

The study will be conducted over a 10-month period (Table 1). A total of 4 surveys will be conducted 3 months apart from one another. Participants will be allowed 2.5 weeks to complete each survey. All participants randomized to the IG will receive access to the digitally supported mindfulness intervention 2 weeks after T0 data collection. All participants randomized to the WCG will receive access to the digitally supported mindfulness intervention 2 weeks after time point 1 [T1] data collection (14 weeks after the IG has been given access). Data collection for both groups will take place at 10, 24, and 38 weeks after allocation. In other words, data collection for each group will take place at 10 weeks (T1 for the IG and time point 2 [T2] for the WCG) and 24 weeks (T2 for the IG and time point 3 [T3] for the WCG) after intervention start. For individuals randomized to the IG, data will be collected at 38 weeks after the intervention starts (T3).

Table 1. Schedule of enrollment, interventions, and assessments for the intervention group (IG) and the wait-list control group (WCG).

	Enrollment	Baseline T0[a]	Random allocation Intervention start IG	After allocation T1[b]	Intervention Start WCG[c]	T2[d]	T3[e]
Enrollment							
Eligibility screen	✓						
Informed consent	✓	✓		✓		✓	✓
Allocation			✓				
Intervention[f]							
For IG			✓	✓	✓	✓	✓
For WCG[c]					✓	✓	✓
Assessments							
Participant characteristics[g]		✓		✓[h]		✓[h]	✓[h]
Primary outcome		✓		✓		✓	✓
Secondary outcomes		✓		✓		✓	✓
Adherence		✓		✓ (only IG)		✓	✓
Acceptability		✓		✓ (only IG)		✓	✓

[a]T0: time point 0.

[b]T1: time point 1.

[c]14 weeks after IG.

[d]T2: time point 2.

[e]T3: time point 3.

[f]Digitally supported mindfulness intervention.

[g]Sociodemographic and job-related variables.

[h]Participant information will be updated when applicable.

Assignment of Interventions: Sequence Generation

Only individuals completing the baseline survey T0 were randomized to one of the study conditions. Randomization and allocation were performed by a third blinded research team member not involved in data analyses. Randomization was stratified by hospital and nursing school and job status (nurse or nursing trainee; 8 strata). Randomization was conducted

using the website [28] (computer-generated random numbers), which generates a string of numbers comprising 1 (IG) and 2 (WCG) in random order. The length of the list was predefined and dependent on the number of participants per strata. The third blinded researcher combined each list of random numbers with the strata list of participants, thus randomizing each individual to either the intervention or control group. After the allocation, a research team member sent participants an email containing an access code for the app, links for web-based workshops, and a pickup location for workbooks.

Intervention

The intervention will be initiated by email. The email will contain the app access code, workbook pickup location at each hospital, and a list of proposed dates for web-based workshops. Participants will be given instructions on how to download the app from the app store and activate the code. The access code will allow access to the full app version, including meditations and education courses tailored to nurses for a 12-month period (Figure 1 [29]). The intervention will be free of charge for the participants.

The standardized multimodal stress management intervention comprises 3 components (an app, 2 web-based workshops, and a workbook). The web-based workshops and the workbooks are supplemental to daily app-based meditation. In-person interaction will occur only during the web-based workshops when participants will interact with the MBSR trainer and other group members. In case technical difficulties are encountered, information technology support will be available to the participants.

The app contains >900 meditation exercises and educational content on mindfulness and meditation. The app is available in German, French, Dutch, and English. In addition, the app features 3 content areas tailored specifically to nurses, which were developed by researchers in the nursing field (Table 2).

Figure 1. Timeline of access to the intervention in the multicenter study along four time points: time point 0 (T0), time point 1 (T1), time point 2 (T2), time point 3 (T3; icons: Flaticon [29]).

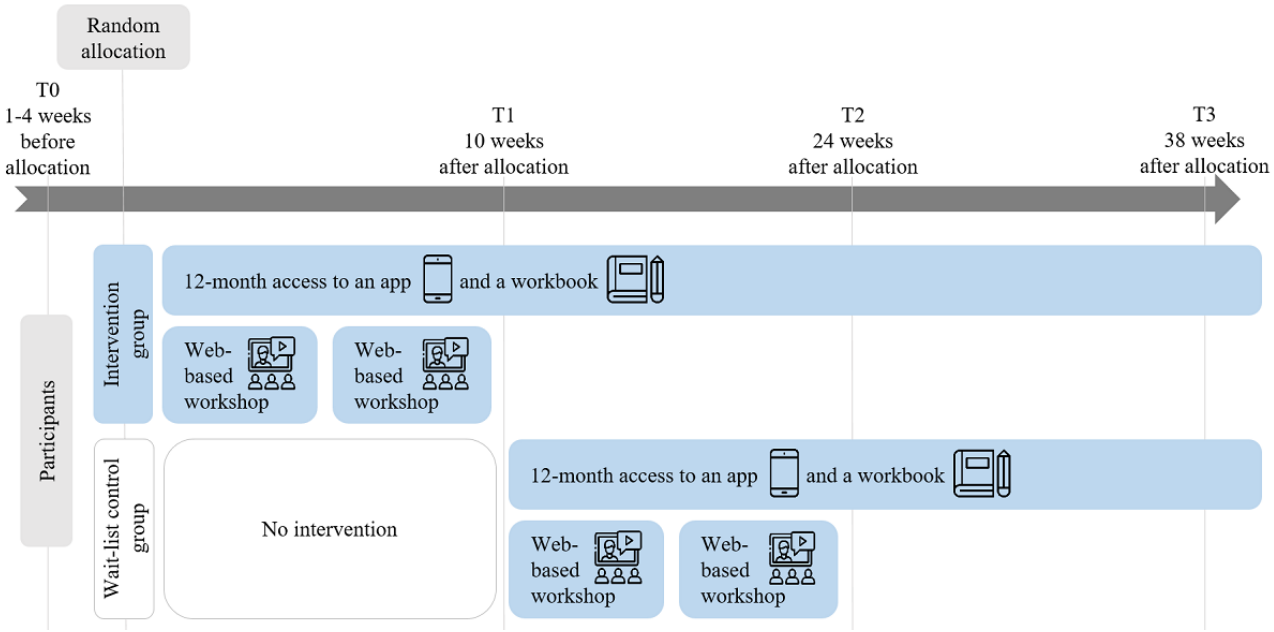

Table 2. App-based nurse-specific care content.

Name	Number of meditations per course[a]	Duration per meditation (minutes)[a]	Content
Specific courses for nurses			
Mindfulness in Everyday Care	7	7-10	Introduction to mindfulness meditation and other relaxation techniques; the course content is derived from scientifically based courses such as the Kabat-Zinn [17] mindfulness-based stress reduction, mindful self-compassion, and reflection and relaxation techniques such as autogenic training and progressive muscle relaxation, which can be used daily.
Resilience in Care 1	7	7-9	During the first week, participants' personal resources (eg, ability to respond mindfully, self-acceptance, self-efficacy) will be strengthened using mindfulness and self-compassion exercises.
Resilience in Care 2	7	7-9	During the second week, participants will learn to use visualization and gratitude and reflection exercises to identify external resources and will learn strategies on how to access these resources in their daily life.
Resilience in Care 3	7	7-10	During the third week, participants will learn how to cope with stressful situations in which one's resources prove to be insufficient; in addition, participants will be taught stress management exercises specifically designed to decrease rumination and promote relaxation.
Resilience in Care 4	7	7-10	The fourth and final week of the course will teach participants coping skills to navigate job-related challenges frequently encountered by nurses working in hospital settings; coping skills include setting boundaries and practicing effective communication and compassion toward others and oneself.
Short situation-specific meditations in everyday care			
Everyday Care	14	3-9	Designed to help nurses integrate mindfulness into their daily work activities; for example, meditations can be used when arriving at the hospital while walking down the hallway, or at the end of the workday; these short meditations are designed to decrease rumination, encourage nurses to take a break to focus on self-compassion, increase well-being, and help nurses cope with negative emotions.

[a]Meditation=one audio file.

Nurses and nursing trainees will be invited to participate in 2 web-based workshops led by a certified MBSR trainer. The web-based workshops (approximately 60 minutes) will take place 1-2 weeks after app access has been granted. Up to 50 participants can take part in each web-based workshop. Per workshop, there will be 4 appointment options. The dates will be scheduled to accommodate individuals' work schedules, and appointments will be offered before and after shifts. Course content on mindfulness and resilience, as well as app-based and non–app-based meditation exercises, will be presented along with advice on how to implement stress management techniques at work. The second workshop will take place approximately 6 weeks after the first workshop. The learning objectives of the second course will be to engage participants with one another, facilitate the exchange of ideas, clarify questions, reflect on relaxation behavior, and discuss motivation and strategies to increase the likelihood of daily meditation.

To supplement the daily content of the 2 app-based courses (*Mindfulness in Everyday Care* and *Resilience in Care*), each participant will be given a paper copy of a mindfulness workbook containing information specifically tailored to nurses. Within the workbook, information regarding the concept of mindfulness and instructions on the use of the app-based courses will be provided. Course content will include self-compassion, resilience, interpersonal relationships, conflict resolution, and boundary setting. In addition, participants will be prompted to provide answers daily to questions including their most enjoyable moment of the day, stressful experience, perceived stress level, mood, quality of sleep, level of relaxation, and quality of social support received.

Participants will be instructed to meditate daily via the app, web-based workshops, and workbook. No standardized prompts or reminders to meditate will be provided, and participants will be able to choose the frequency and duration of their meditation freely. Participants will have the option to choose whether to receive a weekly email newsletter from the intervention provider.

App development started in 2014. Since then, the app has been one of the most frequently downloaded meditation applications in Germany; health insurance companies cover the costs associated with gaining access to specific app-based prevention courses that are otherwise only available via the premium version of the app. There is only one previous peer-reviewed evaluation among office workers indicating significant improvements in mindfulness, work engagement, job satisfaction, emotional exhaustion, emotional intelligence, innovation and creativity, and self-efficacy after using the app for 14 days [30].

No substantial revisions to the app are planned, and the anticipated app updates are limited to minor bug fixes. The present intervention will use the app versions available in the Apple App Store and Google Play Store. No quality assurance

methods have been planned to ensure the accuracy and quality of the information provided by the intervention provider.

Data Collection, Management, and Monitoring

Data will be collected via a web-based data collection tool (*LimeSurvey*; LimeSurvey GmbH [31]), provided by the study sponsor's affiliated university. Participants will be allowed to skip questions if they experience discomfort. At the end of each survey, the participants may enter feedback or additional comments into a text box. Participants will receive reminder emails prompting them to complete the surveys. Data from randomized noncompleters will be used to calculate the loss to follow-up rates.

Data management will take place at the site of the study sponsor. The research team members will be responsible for data entry, coding, security, and storage. Range checks for data values will be conducted, and additional steps will be taken to ensure data quality; data checks will be performed by 2 research team members who will also double check whether the coding has been performed correctly. Data will be stored on a safe university-based network location that will only be accessed by authorized research staff.

The data monitoring committee will comprise the team members of the study sponsor. There will be a regular correspondence between the data collection site and the principal investigator to ensure adherence to the protocol, which has been approved by the university-based institutional review board (IRB). The study funder will reserve the right to terminate the study at any point. Adverse events will be reported to the IRB. Documentation of such events will be stored on the university's safe network location. No interim analyses are planned.

Outcomes

The German version of each questionnaire has been previously validated. All outcomes of interest consist of continuous variables based on self-report data. Our primary outcome will be perceived stress measured using the 10-item Perceived Stress Scale (PSS-10) [32]. Secondary outcomes will include sense of happiness (Likert scale) [33], life satisfaction (L-1) [34], mindfulness (Five Facet Mindfulness Questionnaire) [35], well-being (World Health Organization-Five Well-Being Index) [36], self-care (Hamburg Self-Care Questionnaire; only pacing scale) [37], pain intensity (numerical rating scale 0-10) [38], work-related sense of coherence questionnaire [39], burnout (Copenhagen Burnout Inventory; work-related burnout scale and client-related burnout scale) [40], job satisfaction (Warr-Cook-Wall Scale [41], modified by Cooper et al [42]), and work engagement (Utrecht Work Engagement Scale) [43].

Other Variables

Participants' Characteristics

Sociodemographic variables will include age (in years), gender (male, female, or diverse), relationship status (categorical variable), children (yes or no), previous meditation experience (yes or no), and participation in other studies to promote health (yes or no).

We will assess for job-related variables. We will assess participants' job status (nurse or nursing trainee) and work status (part-time or full-time); if part-time, we will assess the number of work hours per week (per employment contract), number of hours worked per week during the past 4 weeks (including overtime), patient contact during the past 4 weeks (scale 0%-100%), current area of care (eg, internal medicine, surgery, multiple possible answers), duration of employment at the current workplace (in years), job-related tasks that involve caring for patients with COVID-19 more than half of the time (yes or no), working in a hospital with incentives for study participation at T0 (yes or no), and employer permission to participate in study activities during work hours (yes or no). We will assess the following job-related variables for only nurses: qualifications beyond training (eg, additional qualifications, bachelor's degree, or master's degree) and years of work experience. We will assess the following job-related variables for nursing trainees only: focus of training (general nursing, pediatric nursing, or care of older adults) and year of training.

Adherence

Adherence to the instructions for using the digitally supported mindfulness intervention will be operationalized as daily meditation. The frequency of meditation practice (app-based and non–app-based meditation) will be recorded based on the following answer options: several times per day, daily, 4 to 6 times per week, 1 to 3 times per week, less than 1 time per week, or never.

Acceptability

The acceptability of the digitally supported mindfulness intervention will be operationalized as perceived usefulness through 4 separate questions such as "How useful do you rate the [app/online workshop/workbook/all in all]?" We will use a 5-point Likert scale (1=not at all applicable to 5=very applicable). We will assess which of the nursing-specific courses were helpful (listing of the names of the nursing-specific courses; multiple answers possible).

Intensity of Intervention Use

App use will be measured through previous experience with the app ("yes, I have tried out the app"; "yes, I use the app regularly"; or "no, I have never used the app"), previous experience with the app before code activation ("yes, I have tried out the app"; "yes, I use the app regularly"; or "no, I have never used the app"), date of access code activation (yes [date of activation] or no), total amount of app-based meditation (in minutes), total number of app-based meditation exercises, subjective assessment of app use frequency (several times a day, daily, 4-6 times per week, 1-3 times per week, less than once a week, or never), time of use (in my free time, before my shift, during my shift, during my breaks on shift, or after my shift), and use of the app-based nursing-specific courses (list of nursing-specific courses; selection of multiple answers).

Participation in the 2 user-engaging components (web-based workshop and workbook) will be assessed using a binary variable (yes or no). Frequency of workbook use will be assessed using the following answer options: several times a day, daily, 4 to 6 times per week, 1 to 3 times per week, less than once per

week, or never. Finally, we will assess for non–app-based meditation (yes or no).

Sample Size

On the basis of the available literature on interventions similar to ours, we assumed a medium effect size (Cohen d=−0.67) in reducing stress measured by PSS-10 [44]. The sample size calculation was conducted for a 2-tailed t test with a significance level of α=.05 and a power of β=.80 (comparison between the IG and the WCG). Sample size calculations using the G*Power tool (Düsseldorf University) suggested that 72 participants (36 in the IG and 36 in the WCG) are needed to detect an effect size of 0.67. Assuming a dropout rate of 20%, 18 additional participants were required (45 per group).

Statistical Methods

Overview

Analyses will be conducted using *SPSS Statistics* (IBM). For tests involving our primary outcome variable, we will set an α level of .05. For all other analyses, to reduce α-error inflation, we will interpret the obtained P values descriptively, meaning all other analyses will be exploratory and are designed to observe trends and not to identify significance.

Patterns of missing data will be assessed, and adequate data imputation techniques such as multiple imputation with *SPSS Statistics* (IBM) will be applied. Before doing so, we will assess the percentage of missing data. We will also use Little's Missing Completely At Random test to determine patterns of missing data (ie, missing completely at random vs not missing at random).

We will reverse code 3 outcomes [32,38,40] so that a higher score indicates health improvement. For example, the scale assessing burnout [40] is designed to indicate that a score of 1 indicates a rather minuscule risk of burnout, whereas a score of 100 indicates the highest risk of burnout, meaning that greater scores indicate a worsening of symptoms. After recoding this variable, greater scores will reflect a lower risk of burnout (ie, an improvement in symptoms).

Effectiveness will be evaluated using an intention-to-treat (ITT) approach; all randomized participants will be included in our analyses [45].

Efficacy will be evaluated using a per-protocol (PP) approach; only study completers who report adherence will be included in our analyses.

Several analyses will be used to address the research questions. To ensure that our randomization has worked as intended, we will assess for between-group differences for relevant participant characteristics and, if needed, adjust the following analyses. For research questions 2, 3, and 4, we will create a pooled data set merging the data of the IG and the WCG. We will merge the data of the 2 groups so that IG T0 data will be combined with WCG T1 data, and IG T1 data will be combined with WCG T2 data, as described in Textbox 1. For research questions 3 and 4, relationships between variables will be examined using correlation analyses (Pearson correlation coefficient, eta quotient, and chi-square tests). If violations of the assumptions associated with any of the analyses are detected, alternative tests will be used.

Textbox 1. Data pooling procedure.

Newly pooled data set and data included

- Participant data baseline
  - Cases of the intervention group at time point 0
  - Cases of the wait-list control group at time point 1
- Participant data 10 weeks after intervention start
  - Cases of the intervention group at time point 1
  - Cases of the wait-list control group at time point 2
- Participant data 24 weeks after intervention start
  - Cases of the intervention group at time point 2
  - Cases of the wait-list control group at time point 3

Research Question 1

We will present the ITT sample's baseline characteristics and test for detectable between-group differences. For continuous variables, mean, SD, median, minimum, and maximum values will be calculated. For categorical variables, frequencies (absolute and percentages) will be calculated.

To evaluate the effectiveness and efficacy of the 10-week access, we will create one difference score per group for each of our outcomes assessed at T0 and T1. Using a 2-sample t test, we will test whether significant differences exist between the 2 difference scores in the IG and WCG. We will perform this for the ITT and PP sample. If P<.05, Cohen d will be calculated.

Research Question 2

To evaluate long-term effectiveness and efficacy, we will use the pooled data set. To analyze the effect of time on our variables of interest, a repeated-measures ANOVA will be conducted for each of our outcomes. As only participants randomized to the IG will be assessed at 38 weeks after

allocation, long-term efficacy within this group will be examined using an additional repeated-measures ANOVA.

Using a PP approach, we will examine the relationship between *app-based minutes of meditation* and each previously calculated difference score using the pooled data set. Linear regression will be performed to examine the relationship between the minutes of meditation and each outcome. The baseline scores of primary and secondary outcomes will be entered into the model as additional explanatory variables to control for individual differences before the start of the intervention.

Research Question 3

Using the pooled data set, to determine which variables are associated with adherence at 10 weeks and 24 weeks after intervention start, we will examine the correlations between the variable *frequency of meditation practice* and participants' baseline characteristics, acceptability, and intensity of intervention use using the ITT sample. To assess adherence at 38 weeks after the intervention, analyses will be conducted using the ITT data set of the IG.

Research Question 4

Using the pooled data set, to determine which variables are associated with acceptability at 10 weeks after the intervention start and 24 weeks after the intervention start, we will examine the correlations between the variable of *perceived usefulness* (acceptability) and participants' baseline characteristics and intensity of intervention use using ITT sample. To assess acceptability at 38 weeks after the intervention, analyses will be conducted using the ITT data set of the IG.

Sensitivity Analyses

To determine the reliability of the analyses for research questions 1 and 2, we will conduct sensitivity analyses for our primary and secondary outcomes. We will include only complete cases (complete data for T0, T1, T2, and T3).

Ethical Considerations

Research Ethics Approval and Amendments

The IRB approved this study in July 2021 (S-53/2021). If and when applicable, amendments will be submitted to the IRB. After the study is completed, all nurses employed at the study sites will be given free 12-month access to the intervention.

Confidentiality and Access to Data

Personal information about potential and enrolled participants will be collected only by members of the research team and cannot be accessed by other individuals. Personal information and survey data will be pseudonymized using an identification number (token). Only authorized study personnel will have access to any of the data associated with this study. The study funder reserves the right to share the anonymized data with other parties.

Results

Data collection at T0 was conducted from the end of September 2021 until October 2021. At the end of October 2021, a total of 79 individuals were randomized to either the IG (40/79, 51%) or WCG (39/79, 49%). All data collection will be completed by the beginning of August 2022. Data analyses will begin after data collection and will be completed by December 2022.

Discussion

Mixed results have been found for digitally supported mindfulness interventions for nurses working in acute inpatient care settings [16,20-23], highlighting the need for planned research involving long-term follow-ups and analyses of factors of adherence and acceptability-related variables.

Expected Results

Our study design, involving long-term follow-up, a standardized intervention, and our planned investigation variables related to adherence and acceptability, will allow us to rigorously evaluate the effectiveness and efficacy of a digitally supported mindfulness intervention among nurses and nursing trainees working in acute inpatient care settings. The findings of our study will provide valuable information regarding the design and implementation of future stress management interventions for nurses and nursing trainees in acute inpatient care settings.

On the one hand, the digital nature of this intervention allows for the accommodation of nurses' busy work schedules, thus increasing the likelihood of ongoing meditation practice and resulting in higher effectiveness. Given their user-engaging design, the workbook and web-based workshop components may further contribute to the participants' maintained interest in digitally supported mindfulness intervention use. On the other hand, previous research has revealed that implementing health promotion efforts into a demanding daily work routine presents a challenge for nurses worldwide [46], and the unpredictable nature of COVID-19–related conditions likely exacerbates the challenge to implement new stress management habits.

Comparison With Prior Work

For comparison with other studies, we will consider the method and context of the study. These include COVID-19–related working conditions, country, definition of ITT and PP, duration of the intervention, and previously identified variables related to adherence and acceptability.

Generalizability

Results regarding effectiveness, efficacy, adherence, and acceptability may be generalizable to other health care professionals working in similar settings and nurses working in different care settings, as the app contains not only contents specifically tailored to nurses working in German inpatient care settings but also a variety of meditations and courses on various mindfulness topics (>900) independent of any specific context. By conducting a multicenter study, the generalizability may be further improved.

The generalizability of our results may be limited as COVID-19–related health care burden and hospitalization rates vary widely across countries and continents; stressors experienced by nurses and nursing trainees working in Germany may differ from stressors experienced by nurses working in other countries. In addition, nursing training requirements may differ across countries; for example, nursing trainees in Germany

are required to gain hands-on work experience from the start of their training [47]. By receiving reminders to participate in the web-based surveys, participants are likely inadvertently reminded to interact with the app. As these reminders do not occur in real-world settings, the applicability of the findings from our RCT and others should be interpreted with caution.

Strengths and Limitations

The study results will be reported in accordance with international documentation guidelines, including CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) statements [48,49] (Multimedia Appendix 2). We anticipate that our study will have high validity and reliability. In addition, an RCT allows for the identification of the causal effects of our intervention.

Our study will not include an active control group, which is a common limitation in similar studies. The study design was chosen as the primary aim of the study is to evaluate the intervention relative to no intervention, and WCGs are an ethical option to provide the intervention quickly to all participants [50]. A third experimental condition was discussed; however, we ultimately decided against this, given our small sample size.

Our WCG study design is associated with several limitations. This study design may overestimate intervention effects [50], as beneficial effects may occur among participants randomized to the IG simply because of the time spent away from work when participating in web-based workshops. These effects can be identified by including an active control group [10,51]. Furthermore, placebo effects and effects occurring because of participants' expectations may occur with our study design. On the one hand, participants may experience some beneficial effects because of their anticipation of the upcoming intervention [52], which may be further increased by digitalization-specific expectations and participants' trust in the study funder (a large health insurance company) [53]. On the other hand, previous research suggests that participants in WCGs do not improve until they receive the intervention [54].

Our study aims to investigate the effects of this intervention in its entirety. Our study design and analyses do not allow for conclusions regarding the intervention components that drive the identified effect or the proportion of the observed variance that is explained by each component. Some content commonly found in mindfulness interventions may lead to reduced stress [55]. However, several components could influence stress reduction among the participants in our study, irrespective of the mindfulness construct embedded in our intervention. First, the app contains educational content about stress management in general and features relaxation techniques such as the Jacobson progressive muscle relaxation. Second, the app prompts users to engage in self-reflection and mood monitoring and to read the educational content, which in itself can motivate the individual to engage in behavior change that may, in turn, facilitate stress reduction. Third, listening to nature sounds [56] or viewing visually appealing content may improve mood and enhance relaxation. Finally, the web-based workshops take place in group settings, and include social interaction with the trainer [15,55] and one's peers may lead to stress reduction. However, we consider the variety of content provided to the users as a strength of the intervention, as users can choose the content most suitable and effective for them.

Selection bias because of the uneven distribution of confounders is usually not a cause for concern in large RCTs, as one can assume that latent and manifest variables are balanced equally across conditions. For smaller RCTs such as ours, there are steps that can be taken to reduce the risk of uneven distribution of latent or manifest variables across groups. To minimize the risk of confounding variables, we have used stratification for our randomization processes. Furthermore, single-blind randomization and allocation will be used to reduce selection bias. To ensure that our randomization has worked as intended, we will assess for between-group differences for relevant participant characteristics.

Detection bias may occur as blinding of participants is not possible, given the nature of the study. Although the study design is not communicated to the participants, the participants are to be likely aware of which group they have been randomized to. There may be a risk of social desirability as the effects will be evaluated based on subjective reports, including the frequency and intensity of digitally supported mindfulness intervention use, and no biological parameters will be collected. To reduce detection bias, all questions were tested among members of the target group before the start of the study, and all outcome measures were validated in previous studies. Evaluations of the psychometric properties of our primary outcome, the PSS-10, in different countries report a Cronbach α of .78 to .91, with good test-retest reliability [57]. PSS-10 scores correlate significantly with cortisol levels and constitute an objective measure of cumulative stress [58]. We will also seek to reduce the risk of social desirability by informing participants of the pseudonymization and anonymous publication of the data and by conducting data collection without in-person contact. In addition, we will not use participant data collected via the app but will allow participants to report data collected by the app. We refrained from tracking app use and the duration of use for privacy reasons. Not tracking app use may increase rapport, as participants will not feel monitored while using the app. Finally, the item with which we assessed gender may present a limitation as the German language uses the same term for sex assigned at birth and gender identity; thus, we cannot be certain whether participants reported their sex or their gender.

Performance bias will be reduced by using a standardized intervention; however, COVID-19–related differences may occur, as the WCG will receive the intervention at a later time.

Attrition bias may occur in individuals with little technical experience. By conducting a web-based survey, individuals with an affinity for technology are more likely to participate in the surveys on an ongoing basis. This restriction cannot be avoided because of pandemic-related regulations. To reduce bias through loss to follow-up (attrition bias), we will send reminder emails of survey participation, and participation in the survey will be incentivized by the intervention provider at one hospital. We will conduct ITT and PP analyses to reduce the risk of misinterpretation of results because of loss to follow-up.

Conclusions

If effectiveness can be proven, the intervention outlined here may represent a standardized and cost-effective tool to reduce stress among a group of health care professionals experiencing increased stress. Given the strains that the COVID-19 pandemic has placed on health care workers, it is of utmost importance to provide this integral group of professionals with access to effective stress management interventions. Such interventions should be scalable to make them accessible to more individuals. Our results will inform stakeholders' decisions regarding the design and implementation of future intervention efforts to enhance well-being among nurses and nursing trainees.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Used informed consent form in the German language.
[PDF File (Adobe PDF File), 405 KB - resprot_v11i8e37195_app1.pdf]

Multimedia Appendix 2
CONSORT eHEALTH Checklist (V 1.6.1).
[DOCX File , 23 KB - resprot_v11i8e37195_app2.docx]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
IG: intervention group
IRB: institutional review board
ITT: intention-to-treat
MBSR: mindfulness-based stress reduction
PP: per-protocol
PSS-10: Perceived Stress Scale
RCT: randomized controlled trial
T0: time point 0
T1: time point 1
T2: time point 2
T3: time point 3
WCG: wait-list control group

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Protocol

Resilience Enhancement Online Training for Nurses (REsOluTioN): Protocol for a Pilot Randomized Controlled Trial

Cynthia Srikesavan[1], PhD; Zoe Davey[1], PhD; Andrea Cipriani[2], MD, PhD; Catherine Henshall[1], PhD

[1]Oxford School of Nursing and Midwifery, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, United Kingdom

[2]Department of Psychiatry, University of Oxford, Oxford, United Kingdom

Corresponding Author:
Catherine Henshall, PhD
Oxford School of Nursing and Midwifery
Faculty of Health and Life Sciences
Oxford Brookes University
Gipsy Lane
Headington
Oxford, OX3 0BP
United Kingdom
Phone: 44 07768 918298
Email: chenshall@brookes.ac.uk

Abstract

Background: Globally, nurses are facing increased pressure to provide high-quality complex patient care within environments with scarce resources in terms of staffing, infrastructure, or financial reward. The strain and demand on the psychological health and well-being of nurses during COVID-19 has been substantial, with many experiencing burnout; as such, interventions to enhance resilience within the workplace are required. A face-to-face resilience enhancement training program for nurses that was effective in improving resilience levels was translated into a 4-week online training program, Resilience Enhancement Online Training for Nurses (REsOluTioN), to enable greater accessibility for nurses.

Objective: This study aims to compare levels of resilience, psychological health, and well-being in nurses before and after the online resilience training compared to a wait list control group. It will also explore participants' engagement with the trial and their acceptability of the online training.

Methods: This is a two-arm, parallel, randomized controlled trial with a 6-week follow-up period. Up to 100 registered nonagency nurses working at a National Health Service hospital trust in South England will be recruited. Four cohorts will run, and participants will be randomized into a wait list control group or to REsOluTioN. Pre- and postonline surveys will collect study outcome measure data. In the REsOluTioN arm, data will be collected on the perceived usefulness of the online training via an online survey. Institutional and health research authority approvals have been obtained.

Results: REsOluTioN will aim to empower nurses to maintain and enhance their resilience while working under challenging clinical conditions. The online training will be interactive with input from mentors, health care leaders, and peers to promote engagement and enhanced communication, and will create a forum where nurses can express their views and concerns, without hierarchical infrastructures inhibiting them. This can increase self-knowledge and learning around workplace resilience coping strategies and provide a safe space to validate feelings through mentorship and peer support. Findings will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The trial is now finished and was conducted between August 2021 and May 2022.

Conclusions: The REsOluTioN trial will enable preliminary data to be gathered to indicate the online training's effectiveness in enhancing nurses' resilience in the workplace, with the potential for larger scale follow-up studies to identify its value to nurses working across a range of health care settings.

Trial Registration: ClinicalTrials.gov NCT05074563; https://clinicaltrials.gov/ct2/show/NCT05074563

International Registered Report Identifier (IRRID): DERR1-10.2196/37015

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KEYWORDS

online training; nurses; resilience; mental well-being; pilot trial; COVID-19; nursing; mental health; health care staff; psychological health; online health; resilience training; health care setting

Introduction

Worldwide, nurses are facing increased pressure to provide high-quality complex patient care to patients within environments with scarce resources in terms of staffing, infrastructure, or financial reward [1,2]. The constant strain and demand placed on nurses working in highly pressurized and often unsafe conditions, and a lack of career structure or progression means many registered nurses' resilience levels are tested due to stress and burnout [2-4]. This stress has intensified over the last couple of years due to the COVID-19 pandemic with nurses supporting the delivery of expert patient care and rapidly responding to substantial health care challenges [1]. While nurses' contribution to keeping the public safe and protecting the National Health Service (NHS) in the United Kingdom during COVID-19 has been widely recognized, the resulting psychological impact on health and well-being has been substantial; resilience enhancement interventions are one way to tackle this growing problem within health care services [5-8].

The NHS has been facing increased pressure due to the pandemic conditions it is being subjected to [9]. This, in addition to the chronic pressures in terms of staffing, sickness, infrastructure, and financial problems, means that nurses are facing increased pressure [2] and are experiencing burnout, as they struggle to cope with the never ceasing demands of their job roles, which are in continuous high demand [4]. The NHS Health and Wellbeing Framework [10] sets the standards for how NHS organizations should support staff to feel well, healthy, and happy at work, and advocates for the delivery of evidence-based staff health and well-being plans [10]. Resilience-building programs [11-14] are recognized as important in contributing to increased psychological health and well-being in nurses as well as aiding recruitment and retention within international health care organizations [15,16].

Recent literature has recommended that resilience-building initiatives, including mentorship programs outside of nurses' immediate workplace settings, are incorporated into nursing education, as well as specific self-development strategies to help enhance personal resilience [15]. Resilience programs have been found to build and enhance nurses' resilience and can also support recruitment and retention for health care workers [16]. This has been evidenced in a number of recent workplace resilience enhancement interventions within nursing [17-22].

As a result of the need for targeted resilience enhancement interventions within the nursing setting, a UK-based resilience enhancement program was developed [22,23]. A detailed description of the theoretical background of the program is available elsewhere [22]. This face-to-face program targets four core components to improve the ability of the nurses to bounce back from day-to-day problems and to remain resilient in the workplace: workplace hardiness, emotional intelligence, critical thinking, and achieving life balance and enabling spirituality. These components were informed by a 2014 integrative review [15] that reported difficult workplace situations, feelings of emptiness, and a diminishing sense of inner balance as main contributing factors for resilience in nurses. Various strategies such as reflecting on emotions, interactions and guidance from peers and mentors, and skills to develop work-life balance and toughening up are shown to be helpful in building resilience.

The program consisted of six sessions with nurses that covered topics including building hardiness, maintaining a positive outlook, achieving work-life balance, reflective and critical thinking, and enabling spirituality [22,23]. In addition, one-to-one mentor sessions were provided over a 12-week period; senior nurse leaders within the participating trust took on these mentorship roles [23]. The face-to-face program was evaluated using pre- and postsurveys and interviews with nurses. Findings showed that nurses' resilience levels were significantly higher after the training, with reported positive impacts on personal resilience, self-awareness, confidence, well-being, and professional and team-working relationships [22]. As a result, a wider rollout of the training was proposed. However, this planned rollout was disrupted by the onset of the COVID-19 pandemic due to social-distancing measures, making the face-to-face training untenable.

Due to the restrictions imposed by COVID-19, the face-to-face training program [22,23] was adapted and transformed to online training as a means of increasing accessibility for all nurses who were no longer able to attend face-to-face training. The online training was also informed by a recent systematic review examining the effectiveness of online interventions to enhance resilience in health care professionals (C Henshall, unpublished data, 2022) and focus groups with nurses to gather information on what they felt should be key features of an online resilience training program. An online format was felt necessary due to its potential to be rolled out widely to all nurses working in health care settings due to ease of accessibility, flexible access, and a decreased need for other resources such as physical space and in-person facilitation. The online resilience training, entitled Resilience Enhancement Online Training for Nurses (REsOluTioN), is relevant in the COVID-19 climate, where consideration about how to optimize the experiences of the nursing workforce and the resulting impacts on patient care are urgently needed.

In light of the above, the randomized controlled trial described in this paper aims to pilot REsOluTioN, an online resilience training for nurses working during COVID-19. Specific study objectives are:

- To compare levels of resilience, psychological health, and well-being in nurses who complete REsOluTioN with nurses who do not (control arm)
- To explore participant engagement with the trial and acceptability of REsOluTioN
- To collect feedback on various components of REsOluTioN

Methods

Study Design

The study is a two-arm, parallel-group, individually randomized pilot trial comparing REsOluTioN versus a wait list control group. The study flowchart describing the study process is presented in Figure 1. The study schedule of events and assessments are presented in Figure 2.

Figure 1. Study flowchart. NHS: National Health Service. REsOluTioN: Resilience Enhancement Online Training for Nurses. CPD: continuing professional development.

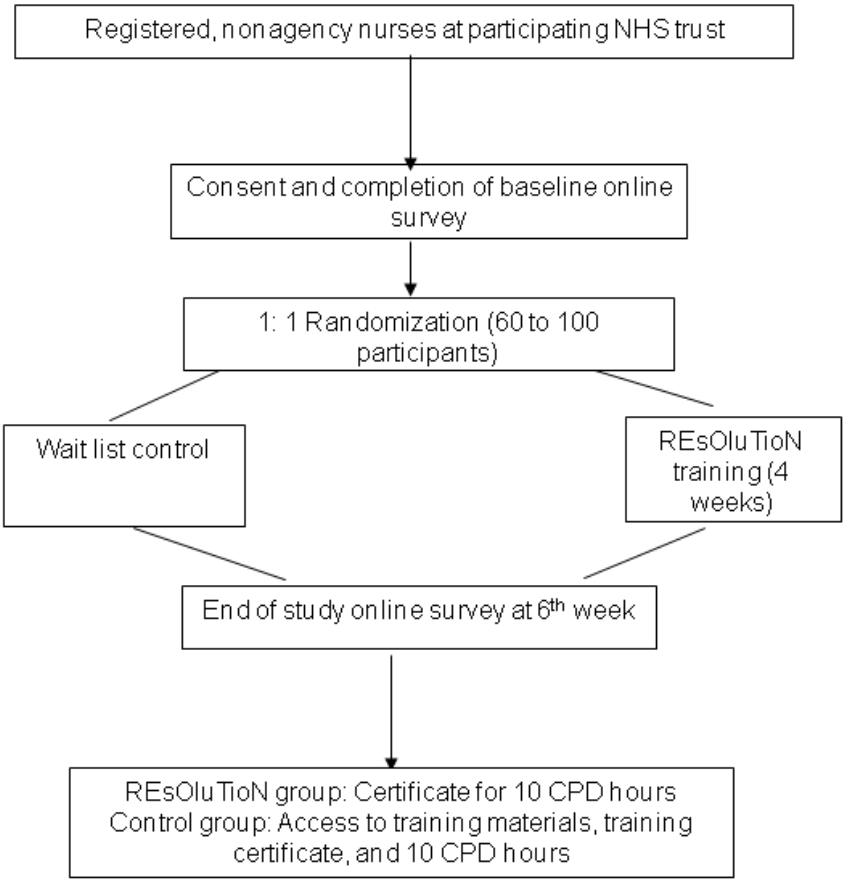

Figure 2. Schedule of study events and assessments. REsOluTioN: Resilience Enhancement Online Training for Nurses.

	Study period		
	Enrollment	Allocation	Postallocation
Time points	$-T_1$	T_0	T_1 = 6 weeks
ENROLLMENT			
Informed consent	X		
Allocation		X	
INTERVENTIONS			
Waiting list		X	
REsOluTioN training for 4 weeks		●———	———●
ASSESSMENTS			
Demographic information	X		
Proportion of nurses consented, randomized, completed training, discontinued, or lost to follow-up	X	X	X
Resilience	X		X
Psychological well-being	X		X
Expectations, perceived usefulness, and further feedback on REsOluTioN training (completed by only those randomized to REsOluTioN)	X		X

Eligibility Criteria

Any registered nonagency nurses working at any level of seniority and across any clinical setting at the participating trust will be eligible to participate. All participants must be able and willing to provide online informed consent.

Recruitment

Nurses will be recruited through study advertisement posters and promotional videos hosted on the trust website, social media platforms, and trust premises. The researchers will attend nurse-led meetings across the trust to promote the study and will contact managers from different specialties including children, adult, and older people's services. The researchers will also work with the hospital communications team who will include information about the study in their weekly news bulletins. The study has been endorsed by the NHS trust's chief nurse who will be asked to share information about the trial to all nurses working in the trust, using email communications and online meeting forums. The trust's research delivery teams will also promote the study to the clinical teams they work with. These multiple recruitment methods are deemed necessary due to the ongoing pressures facing nurses due to the pandemic, making recruitment likely to be challenging. A web link with study information included within it will be shared with people who express an interest in taking part. They will then be directed

to a web page containing the online study information sheet and consent form, prior to any data collection or study procedures being undertaken. Once online consent has been confirmed, participants will be asked to complete a prestudy survey (Figure 2).

Sample Size

Given the study objective to afford a preliminary comparison of training outcomes, as well as funding constraints and the pressures imposed by COVID-19, we propose to recruit a minimum of 60 and up to 100 participants. We aim to recruit participants over four cohorts with approximately 25 participants per cohort.

Allocation

After providing online consent, participants will be randomized to receive either the wait list control or REsOluTioN on a 1:1 ratio. An independent research staff not involved in the design and conduct of the trial will generate a computer-generated random number sequence. Allocation concealment will be upheld using sequentially numbered opaque-sealed envelopes that will be opened sequentially only after entering the name of each participant on the envelope. A research team member who is not involved in the delivery of REsOluTioN or data analysis will implement the group allocation and contact participants to inform them of their group allocation.

Blinding

Participants will not be blinded to their group allocation and will complete self-reported online surveys at the start of the study and after 6 weeks. It is not possible to blind the team member who undertakes the allocation assignment; however, other research team members who analyze the pre-post survey responses will be blinded to treatment allocation.

Patient and Public Engagement

This trial evaluates an online resilience training developed for nurses and was informed by the feedback provided by nurses in the previous face-to-face training and a systematic review [22,23] (C Henshall, unpublished data, 2022).

Interventions

Online Training

REsOluTioN was hosted on the Totara learning management system (version 12) by the Learning and Development (LD) information technology team of the participating NHS trust. A simple layout with clear instructions and prominent widgets to navigate the training pages will be used (Multimedia Appendices 1-3). More details about this are provided below.

Structure

REsOluTioN adopts a blended learning approach of asynchronous learning and synchronous sessions delivered in real time. The landing page includes a brief description about the training, module topics, library of learning materials, and a short welcome and introduction video by the study's chief investigator.

Over a 4-week period, participants will be required to attend four facilitated online large group sessions on four module topics lasting up to 120 minutes in duration. Prior to each session, there will be 30 minutes of independent asynchronous preparatory activities. Additionally, they will attend online mentorship meetings in small groups; the mentors will all hold senior nursing positions at the participating trust. Mentor meetings will be conducted for 30 and 60 minutes twice weekly, at flexible times, over the 4-week training period.

Preparatory Activities

Prior to each large-group facilitated session, participants will be expected to complete some recommended readings on the module topic such as journal articles and reports, and tasks for further discussion during the sessions such as preparing responses to questions (related to module topics) such as "What does emotional intelligence mean to you and why it is important in your role?" and "What are your three main qualities of self-confidence?" The list of prereadings and tasks to be completed will be made available to participants in advance on the REsOluTioN online training page.

Large Group-Facilitated Sessions

Facilitated sessions will be scheduled in advance, and session dates and timings will be shared with those enrolled in each cohort. The facilitated session topics cover building hardiness and maintaining a positive outlook, intellectual flexibility and emotional intelligence, reflective and critical thinking, and achieving life balance and enabling spirituality. Experienced nurses and other multidisciplinary health care staff in senior clinical and academic positions within the local region will deliver the sessions. An outline of the content and objectives for each module is presented in Table 1.

Table 1. Outline of REsOluTioN training.

Components of REsOluTioN[a]	Content	Objectives
Mentorship sessions: establishing positive nurturing relationships and network	• Nurturing personal relationships • Relationships that encourage and motivate • Crucial conversations for health care work	• Focus on protective aspects of positive relationships and networks on the effects of workplace adversity
Module 1: building hardiness and maintaining a positive outlook	• Defining positive outlook and personal hardiness • What is known about workplace hardiness? • Strategies for success: prioritizing activities in time-pressured environments, learned optimism, assertive communication • An authentic life • Self-esteem • Self-awareness: past, present, future	• Identify the elements of a positive outlook and personality hardiness related to nursing • Demonstrate benefits of a positive outlook and developing hardiness for job satisfaction, health, and well-being • Formulate individual strategies for improving and maintaining a positive outlook and hardiness
Module 2: IF[b] and EI[c]	• IF: definitions and characteristics • Links to nursing research and resilience • Dimensions of EI • Emotional labor • Strategies for success: expand your thinking, creative thinking, self-monitoring, expressing emotion creatively	• Define principles of IF and EI • Define significant existing research findings regarding IF and EI as they relate to nursing • Evaluate advantages of applying elements of IF and EI to nursing practice • Reflect on strategies to assist creative/critical thinking
Module 3: reflective and critical thinking	• What is reflection? • Making meaning of experience • Moving from description to reflection • Understanding reflection • Therapeutic use of self • Reflective awareness • Reflective action	• Identify importance of therapeutic use of self and reflection in expert practice • Demonstrate understanding of the benefits of the reflective process to nursing practice and its underlying knowledge, influences, and motivations • Define a model of reflection shown to increase critical thinking skills and develop reflexive practice • Analyze individual strategies to creatively access and explore the reflection process
Module 4: achieving life balance and enabling spirituality	• Work/life balance: What is balance? • Why is it so hard? • Envisioning work/life balance • Historical, gender, and power contexts • Assumptions about “juggling” • Strategies for success: being comfortable doing less; adding new things to life • Enabling spirituality: definition • Spirituality and nursing care, health • Women, spirituality, and communities	• Define the importance of an awareness of work/life balance for health and well-being • Demonstrate strategies for improving work/life balance • Formulate historical/political background of women’s roles in caring and other work • Explore some aspects of spiritually responsive nursing care available to them • Explore personal perspectives on individual spirituality and its relationship to contemporary lifestyles
All modules (cross-cutting): moving forward and planning for the future	• The reflective process • Reflection and expert practice • Strategies for success: thinking critically, reflection circuit, exhibition and participant presentations, planning for the future (goal setting)	• Identify features of a resilient person and relate them to individual experiences • Formulate strategies for continuation and permanency of resilient beliefs and behaviors • Demonstrate an understanding of the ongoing process of resilience and the protective benefits of committing to the long-term maintenance of personal well-being

[a]REsOluTioN: Resilience Enhancement Online Training for Nurses.

[b]IF: intellectual flexibility.

[c]EI: emotional intelligence.

Mentor Meetings

Mentor meetings will be designed to be rewarding and valuable components of the REsOluTioN package. A mentor pool will be established by inviting around 15 experienced registered nurses from the participating trust to contribute to the study as mentors. Mentors will be registered nurses working at a Band 7 level or above. Generally, nurses working at these levels require appropriate leadership or management skills and have widespread experience of the pressures and challenges of working within the NHS. Mentors will be expected to commit to two weekly meetings with mentees for 4 weeks per cohort (mentors will be able to sign up for one or more cohorts). The mentor meetings will aim to support the mentees while they are training and to facilitate discussion relating to a wide range of topics, including but not limited to the topics covered during the facilitated sessions; the course of the discussion will be led by the mentees. The roles and expectations, issues of

accountability, and key goals of the mentoring partnership will also be covered. However, this will not be a formal mentorship relationship and as such no predefined structure or mentoring plans are required.

Two separate documents with frequently asked questions to inform mentors and mentees about the structure and conduct of mentor meetings will be developed. Mentors and mentees will not be expected to maintain additional contact between the weekly meetings though they can choose to do so if they feel it would add benefit.

Delivery of Content

All facilitated sessions and mentor meetings will be delivered online within the parameters of confidentiality via Teams (Microsoft Corporation). Meeting links and reminders will be sent to the participants through the LD platform. Content delivery and user engagement of REsOluTioN will be in the form of text materials, illustrations, PowerPoint (Microsoft Corporation) presentations, explanatory videos, case examples, and additional reference documents such as peer-reviewed journal articles and published guidance. The facilitated sessions will also include discussions, small group work, and breakout activities. A separate YouTube account will be created for the trial, and all REsOluTioN-related videos will be made accessible only to the trial participants.

Time Commitment

At the end of 4 weeks, participants randomized to REsOluTioN will have completed 10 hours of structured content (2 hours of self-learning activities and 8 hours of scheduled facilitated sessions) in addition to 4-8 hours of flexible mentor meetings.

Control Arm

Nurses randomized to the control arm will be allocated to a wait list for 6 weeks. When they have completed the online poststudy surveys at the end of the sixth week, they will be provided access to REsOluTioN study materials.

Outcomes

Participant Engagement With the Trial

Data will be collected on the number of registered nurses who expressed an interest, enrolled, were randomized, or withdrew from the study to estimate the recruitment rate and nurses' engagement with the trial.

Training Outcomes

Acceptability of REsOluTioN

Data will be collected on the number of registered nurses who complete REsOluTioN, discontinued in between, and did not complete the posttraining survey to estimate the acceptability of REsOluTioN.

Resilience and Psychological Well-being

The validated Brief Resilience Scale (BRS) [24] and Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [25] will be used to measure changes in resilience, psychological health, and well-being over time. The BRS is a brief measure of an individual's ability to "bounce back" and has been found to have good psychometric properties compared to measures of resilience [24]. The WEMWBS has been widely used in clinical settings to measure the effects of interventions to improve well-being and can provide an indicator of resilience [25].

Perceived Usefulness of REsOluTioN

At baseline, the following survey data will be collected from those randomized to REsOluTioN: understanding of resilience, what they hope to gain from it, levels of perceived resilience, confidence, workplace satisfaction, and peer support.

At 6 weeks (2 weeks post training), participants' perceived usefulness of REsOluTioN and their perceived levels of personal resilience, self-confidence, belief in own ability to provide quality patient care, relationship with work colleagues, communication skills with colleagues, outlook toward clinical practice, understanding of resilience, and feedback on REsOluTioN will be determined via an online survey.

Data Collection Methods

Participants who expressed interest to participate in the trial will be provided a prestudy survey to provide online consent and demographic information (type of work clinical setting, banding, ethnicity, age, years of experience) before the start of each cohort and 2 weeks post cohort completion (sixth week). Surveys will be hosted on the Qualtrics online survey platform.

The surveys will contain both closed- and open-ended questions and the validated BRS [24] and WEMWBS [25]. Resilience and mental well-being scales will be completed by participants in the control and REsOluTioN arms. The closed survey questions will be completed by all participants and will take a 1 to 5 Likert-style format, with responses ranging from "not important at all" to "extremely important" or "not useful at all" and "extremely useful." The open-ended survey questions will only be completed by REsOluTioN arm participants and will seek feedback relating to what they enjoyed the most about the training and whether any specific modules were particularly helpful.

Following completion of the postsurveys, those randomized to REsOluTioN will receive a training certificate for 10 continuing professional development (CPD) hours and those in the wait list control group will be given access to REsOluTioN materials and the 10 hours CPD training certificate.

Data Management

Online informed consent will be obtained from all participants. All data will be stored securely in line with the university's (study sponsor) policies for data management and storage, and in line with General Data Protection Regulation requirements.

Direct access to source data will be made only to the designated members of the study team as authorized by the chief investigator. All participant-identifiable information will be removed and anonymized using study identification codes. Electronic deidentified data will be stored and backed-up in password-protected Excel (Microsoft Corporation) spreadsheets in a secured drive accessible by the study team only. Data will be retained for 5 years after the completion of the trial.

Statistical Methods

Demographic characteristics of the study participants will be descriptively summarized. The proportion of participants who enrolled, completed the study, provided follow-up data, or discontinued the study, and those responding to each category on the Likert-type closed questions in the survey will be reported. Pre- and postsurveys on resilience and psychological well-being will be presented as means (SDs) or medians (IQRs) depending on the normality as per Shapiro-Wilk test. The differences in resilience and psychological well-being within each arm and between arms at 6 weeks will be assessed using analysis of variance. A significance level of 0.05 will be considered. All analysis will be undertaken in SPSS statistics software, version 22.0 (IBM Corp) [26].

Data Monitoring

The day-to-day management of the trial will be undertaken by the chief investigator and coinvestigator supported by two research associates and members of the LD team. Weekly research team meetings will be held to monitor trial conduct and progress made.

Ethics Approval

The Faculty Research Ethics Committee at the local university approved the protocol (F.20.01.12.1, dated August 22, 2021). NHS ethical approvals were not required as patients are not being recruited to the study; however, health research authority approvals were obtained (21/HRA/1418) as well as the necessary local research and development office approvals from the participating NHS trusts. The trial protocol is registered on ClinicalTrials.gov (NCT05074563).

Results

The trial is now completed and was conducted online via the participating NHS trust's LD e-learning platform in England between August 2021 and May 2022.

The trial findings will be presented in accordance with the CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines [27].

Discussion

The nurse-led REsOluTioN study will aim to empower nurses to maintain and enhance their resilience while working under challenging clinical conditions. The online training delivered will be interactive, with input from mentors, health care leaders, and peers, to promote engagement and enhanced communication between nurses, their teams, and wider health care organizations (C Henshall, unpublished data, 2022). We hypothesize that the online sessions will serve as a forum where nurses can express their views and concerns, without hierarchical infrastructures inhibiting them, while increasing self-knowledge and learning around workplace resilience coping strategies and providing a safe space to validate feelings through mentorship and peer support [23]. With increasing health care pressures and a shortage of health care staff, the need to promote and support nurses' well-being through these evidence-based interventions is vital. This is even more apparent in the current COVID-19 health care climate, where rapid and innovative approaches to patient care are constantly required; this can have a deleterious impact on health care staff due to the pressures it entails. Strategies and training programs such as REsOluTioN that promote mechanisms that enable nurses to feel better equipped to manage the daily work stressors they encounter can have short- and long-term benefits, with positive impacts on well-being, recruitment, retention, and the quality and safety of patient care [16-23].

The mentor meetings incorporated into REsOluTioN have the potential to provide nurses with a platform to vocalize any challenges, worries, and concerns they are facing in a constructive supportive environment. Effective mentee/mentor relationships and interactions with senior leaders have been found to increase resilience and to help resolve workplace challenges through empowering mentees and increasing their self-confidence, developing personal and professional growth, and supporting career progression opportunities [28-31]. Mentoring relationships can also reinforce more junior nurses' sense of value in the workplace when they are being mentored by senior colleagues who make time to listen and respond to their problems or concerns [30]. The integration of the regular mentorship support in the REsOluTioN trial will aim to build nurses' resilience through the promotion of professional development, self-confidence, self-worth, and problem-solving capabilities.

This study is limited to one NHS trust in England, and as a result, demographic and contextual factors may influence the value of the resource to nurses working in a range of settings and environments. As such, if the findings show that the program is effective in improving nurses' levels of resilience, REsOluTioN will be rolled out at a national level in a larger scale randomized controlled trial design. This will enable the generalizability of the findings across a range of health care settings and contexts. In the long term, it is hoped that REsOluTioN will be a valuable resource for nurses caring for patients in challenging clinical care environments during the global pandemic and beyond.

We will publish peer-reviewed journal reports on the trial process and outcomes. Presentations will be made at national and international conferences, including the Royal College of Nursing research conference (COVID-19 permitting). We will update the Burdett Trust for Nursing (funder) with regular updates for use in newsletters and web pages. We will also collaborate and network with local research infrastructure across the region to strengthen the research profile of the project and widen the reach of our research outputs.

Trialing REsOluTioN will enable preliminary data to be gathered to indicate its effectiveness in enhancing nurses' resilience in the workplace, with the potential for larger scale follow-up studies to identify its value to nurses working across a range of health care settings. This may lead to REsOluTioN's widespread implementation as it is embedded within health care organizations' overarching health and well-being strategies, with resulting improvements in the resilience of the nursing workforce and subsequent improvements in patient safety and care quality outcomes.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshot from REsOluTioN online training: overview of training.
[PNG File , 145 KB - resprot_v11i8e37015_app1.png]

Multimedia Appendix 2
Screenshot from REsOluTioN online training: tabs to work through.
[PNG File , 145 KB - resprot_v11i8e37015_app2.png]

Multimedia Appendix 3
Screenshot from REsOluTioN online training: module 1 tasks.
[PNG File , 29 KB - resprot_v11i8e37015_app3.png]

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Abbreviations

BRS: Brief Resilience Scale
CONSORT: Consolidated Standards of Reporting Trials
CPD: continuing professional development
LD: Learning and Development
NHS: National Health Service
REsOluTioN: Resilience Enhancement Online Training for Nurses
WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

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Protocol

Web-Based Delivery of a Family-Based Dating Violence Prevention Program for Youth Who Have Been Exposed to Intimate Partner Violence: Protocol for an Acceptability and Feasibility Study

H Luz McNaughton Reyes[1], MPH, PhD; Eliana Gabriela Armora Langoni[1], BS; Laurel Sharpless[1], MPH; Natalie Blackburn[2], MPH, PhD; Agnieszka McCort[2], MA; Rebecca J Macy[3], MSW, PhD; Kathryn E Moracco[1], PhD; Vangie A Foshee[1], PhD

[1]Department of Health Behavior, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States
[2]Injury Prevention Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States
[3]School of Social Work, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Corresponding Author:
H Luz McNaughton Reyes, MPH, PhD
Department of Health Behavior
Gillings School of Global Public Health
University of North Carolina at Chapel Hill
135 Dauer Drive
302 Rosenau Hall CB 7440
Chapel Hill, NC, 27599-7440
United States
Phone: 1 919 593 4081
Email: mcnaught@email.unc.edu

Abstract

Background: Children exposed to intimate partner violence (IPV) between caregivers are at an increased risk of becoming involved in dating violence during adolescence. However, to date, few adolescent dating violence (ADV) prevention programs have been developed for and evaluated with youth exposed to IPV. An exception is Moms and Teens for Safe Dates (MTSD), an evidence-based ADV prevention program for mothers or maternal caregivers (mothers) exposed to IPV and their teenagers. The MTSD program comprises a series of booklets that families complete together in a home that includes activities to promote positive family communication and healthy teenager relationships. We developed a web-adapted version of the MTSD program—entitled *eMoms and Teens for Safe Dates* (eMTSD)—to provide a delivery format that may increase program appeal for digitally oriented teenagers, lower dissemination costs, lower reading burden for low-literacy participants, and incorporate built-in cues and reminders to boost program adherence.

Objective: This protocol is for a research study that has the following three main objectives: to assess the acceptability of eMTSD; to identify the feasibility of the research process, including program adherence and participant recruitment and assessment; and to explore the acceptability, feasibility, and preliminary efficacy of 2 features—text reminders and the creation of an *action plan* for engaging with the program—that may increase program uptake and completion.

Methods: Approximately 100 mothers and their teenagers will be invited to complete eMTSD, which includes six 30-minute web-based modules over a 6-week period. Mothers will be recruited through community organizations and social media advertising and will be eligible to participate if they have at least 1 teenager aged 12 to 16 years living with them, have experienced IPV after the teenager was born, are not currently living with an abusive partner, and have access to an internet-enabled device. Using a factorial design, enrolled dyads will be randomized to the following four *adherence support* groups (n=25 dyads per group): text reminders and action planning, text reminders only, action planning only, and no adherence supports. All participants will complete brief web-based assessments at enrollment after each module is completed, after the full program is completed, and 90 days after enrollment. Program adherence will be tracked using website use metrics.

Results: The data collected will be synthesized to assess the acceptability of the program and the feasibility of the study procedures. An exploratory analysis will examine the impact of adherence support on program completion levels. In November 2021, ethical approval was received and recruitment was initiated. Data collection is expected to continue until December 2022.

Conclusions: The web-based delivery of a family-based healthy relationship program for teenagers exposed to IPV may offer a convenient, low-cost, and engaging approach to preventing ADV. The findings from this study are expected to guide future research.

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KEYWORDS

dating violence; adolescents; family-based prevention; web-based delivery; feasibility and acceptability; mobile phone

Introduction

Background

Each year, approximately 15 million children in the United States are exposed to intimate partner violence (IPV) between their parents or other caregivers [1], with >25% of children being exposed to IPV in their lifetime [2]. Research suggests that IPV exposure, broadly defined as direct witnessing, hearing, or seeing the aftermath of any form (eg, physical or psychological) of violence between caregivers [3], is a multifaceted traumatic experience that can have adverse impacts on children's cognitive (eg, biases in information processing), emotional (eg, anger dysregulation), and social development (eg, deviant peer affiliation) [4]. Children who experience these adverse impacts, in turn, are at increased risk of involvement in abusive dating and intimate partnerships during adolescence and adulthood [5,6], a pattern referred to as the *intergenerational* transmission of IPV [7].

The intergenerational transmission of IPV may be disrupted by programs that effectively work to interrupt the processes leading to adolescent dating violence (ADV) among youths exposed to IPV. However, although numerous studies have identified programs that prevent dating violence among general samples of youth, relatively little research has been conducted to develop or evaluate dating abuse prevention programs among high-risk youth, such as those who have been exposed to interparental IPV [8]. Furthermore, despite research suggesting that parents and other caregivers play a key role in adolescent relationship development, scant research has been conducted to develop and evaluate family-based approaches to ADV prevention [9]. An exception is Moms and Teens for Safe Dates (MTSD), a family-based dating abuse prevention program developed for youth who have been exposed to IPV and their mothers or maternal caregivers (hereto forth referred to as *mothers* and inclusive of nonbinary people and gender expansive and transgender women who identify as mothers or maternal caregivers) who experienced the abuse [10]. The MTSD program is designed to promote a family environment that is protective against dating abuse and comprises a set of 6 printed booklets with interactive activities that mothers and teenagers complete together (self-administer) in the home. In a randomized controlled trial, the program was found to be effective in increasing family cohesion and preventing dating abuse among youth with higher but not lower levels of IPV exposure [11].

Given that the MTSD program was found to have positive impacts, the next step in the continuum of research on the program is to optimize the program for dissemination (ie, distribution of the program by the community and other agencies to mothers exposed to IPV and their teenagers) and implementation (ie, use of the program by mothers and their teenagers within the real-world family setting). Notably, the MTSD program was structured to avoid 2 main obstacles in the implementation of family-based interventions. First, it avoids logistical barriers that prevent families from attending programs offered at out-of-home locations as the program can be conducted at home (or at any location the family chooses). Second, there are no costs associated with training or paying the delivery staff as the program is self-administered. However, the drawbacks of the program from a dissemination and implementation (D&I) standpoint include the costs of printing and mailing (eg, through the postal service) the booklets, which may be prohibitive to organizations serving mothers exposed to IPV, which are typically low-resourced community-based organizations [12]; insufficient reach to low-literacy members of the target population, given the relatively high reading burden of the program; and a lack of built-in prompts or cues to engage with the program, which may result in poor user engagement in real-world settings. For example, in the MTSD randomized controlled trial, which provided small financial incentives for booklet completion, 62% of families reported completing the final booklet [11].

The research team proposed that each of these D&I barriers could be addressed by adapting the program for web-based delivery. In particular, web-based delivery has the potential to reduce dissemination costs; allow for the audiovisual presentation of information and activities, thus potentially reducing the reading burden and improving understanding among audiences with lower health literacy [13,14]; and allow for automated delivery of reminders, tailored based on website use, to maximize program uptake and completion. Furthermore, the research team postulated that a digital platform for MTSD may increase program appeal among teenager participants, given research suggesting that there has been a pronounced shift among US teenagers away from the use of *legacy* media (eg, books) and toward digital media [15].

Adapting the MTSD Program for Web-Based Delivery

To develop a web-adapted version of the MTSD program, the research team followed a step-by-step process guided by the

Integrate, Design, Assess, and Share framework for developing effective digital interventions [16]. Briefly, stages of the adaptation process included revision of the conceptual model, ideation of potential web-based representations of booklet material, iterative prototype development conducted in collaboration with a mother-teenager advisory board, 3 cycles of prototype user testing and refinement conducted with 6 mothers exposed to IPV and their teenagers, and a *soft launch* of the complete program and study procedures with a different set mother-teenager dyads (n=8) exposed to IPV. For the soft launch, mothers were provided with a link to the web-based program and asked to complete it with their teenagers over a 3-week implementation period. Feedback on design and functionality was obtained through surveys embedded in the website, a follow-up web-based survey, and a brief telephone exit interview. Informed by usability research with low-literacy parents, we prioritized the simplicity of design, content, and technical features during the first phases of prototype development [17]. As part of this process, several text-based program activities were converted to multimedia instructions—communications that use words in combination with graphics, animated videos, and other audiovisual experiences, which have been shown to improve understanding among low-literacy parents compared with the presentation of text alone [18]. Mother and teenager feedback on the program was incorporated across all development phases, consistent with user-centered design principles [19]. Specifically, feedback from mothers and teenagers was used to make decisions about the look and feel of the website; update the program to reflect current adolescent dating language and practices; represent a diverse set of mothers, teenagers, and relationships; and ensure that activities presenting teenager dating and family communication scenarios were realistic. The finalized program, which is titled *eMoms and Teens for Safe Dates* (eMTSD), comprises 6 30-minute modules that can be completed on any device with access to the internet (eg, smartphones, tablets, and computers).

Objectives

Here, we present a protocol for a feasibility and acceptability study of eMTSD, which is a necessary step in the continuum of research on this program. This study has the following three main objectives: (1) to assess the acceptability of the eMTSD program; (2) to identify the feasibility of the research process, including program adherence and participant recruitment and assessment; and (3) to explore the acceptability, feasibility, and preliminary efficacy of 2 *adherence support* factors—SMS text message reminders and action planning—that may increase eMTSD program uptake and completion.

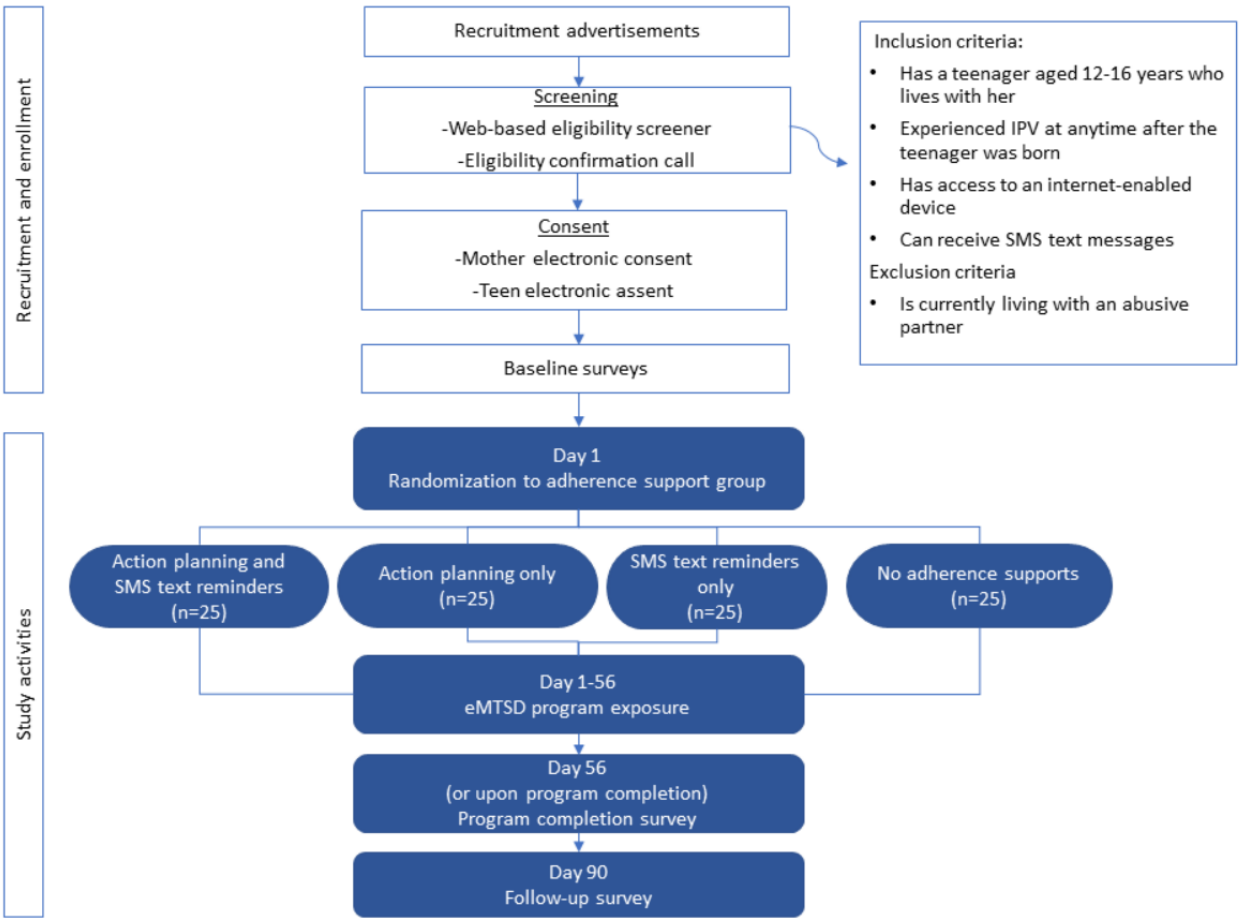
Methods

Study Design Overview

The flow of this study is summarized in Figure 1. Approximately 100 mother-teenager dyads, who may reside anywhere in the United States, will be enrolled in the study. Eligible mothers will have a teenager aged 12 to 16 years living in the home, have experienced IPV at some point after their teenager was born, and not be currently living with an abusive partner. Mother-teenager dyads who enroll will be randomized to 1 of 4 *adherence support* groups: text reminders only, action planning only, text reminders plus action planning, or no adherence support. Mothers in the text reminder groups will receive weekly SMS text messages tailored to their program completion level, which will cue them to engage with the program. Mothers in the action planning groups will complete a form before initiating the program, which will ask them to think about when and where they will work on the program with their teenagers. SMS text message reminders and action planning are referred to as *adherence support factors* as they are posited to increase the uptake and completion of program activities by mothers.

All enrolled mother-teenager dyads, regardless of adherence support group assignment, will be asked to complete the eMTSD program together over a 6-week period with a 2-week grace period allowed for families who are unable to comply with this program completion schedule (ie, up to a maximum of 8 weeks will be allowed to complete the program). Feasibility and acceptability outcomes, described in more detail in the following sections, will be assessed in several ways. First, a study tracking database will allow us to calculate recruitment, enrollment, and retention rates. Second, website use data will allow us to assess program uptake, engagement, and adherence. Third, web-based surveys will be administered to mothers and teenagers at baseline (enrollment), after program completion (maximum of 8 weeks after baseline), and 90 days after baseline (follow-up). These surveys will assess program acceptability and provide information on the feasibility of using web-based surveys to collect data on healthy relationship cognition, skills, and behaviors. Finally, program acceptability will be assessed using brief (1-2 minutes) module acceptability surveys that appear in the web-based program at the end of each module. For each participant, the study is expected to last for approximately 90 days from enrollment to the follow-up assessment.

Figure 1. Study flow. eMTSD: eMoms and Teens for Safe Dates; IPV: intimate partner violence.



Participants

Eligible participants are mothers residing in the United States who (1) have at least 1 child aged 12 to 16 years (hereafter referred to as their *teenager*) who lives with them at least part of the time, (2) have experienced IPV at some point in their lives after at least 1 of their teenagers aged 12 to 16 years was born, (3) are not currently living with an abusive partner, (4) are able to read and speak English, (5) have access to an internet-enabled device, and (6) are able to receive SMS text messages. The age range of 12 to 16 years age range was selected based on evidence indicating that this is an appropriate developmental period for programs focused on the primary prevention of ADV [20].

Recruitment

We aim to recruit approximately 120 eligible mother-teenager dyads and enroll 100 dyads (80% of which will be eligible) over an 8-month period (approximately 13 dyads enrolled per month). Recruitment, which will target potential mother participants, will occur through study advertising via Facebook or Instagram, Craigslist, and Reddit posts and via information dissemination through community agencies (eg, social services organizations) and educational institutions (eg, community colleges) that work with or provide services to mothers, survivors of IPV, and youth exposed to IPV. Study advertisements will direct individuals who are interested in participating to an initial web-based eligibility screener. If the participants want more information, the study telephone number and email address will be provided. Advertisements will also list the study website, which includes detailed information about the study for potential participants and the link to the initial eligibility screener.

Enrollment and Randomization

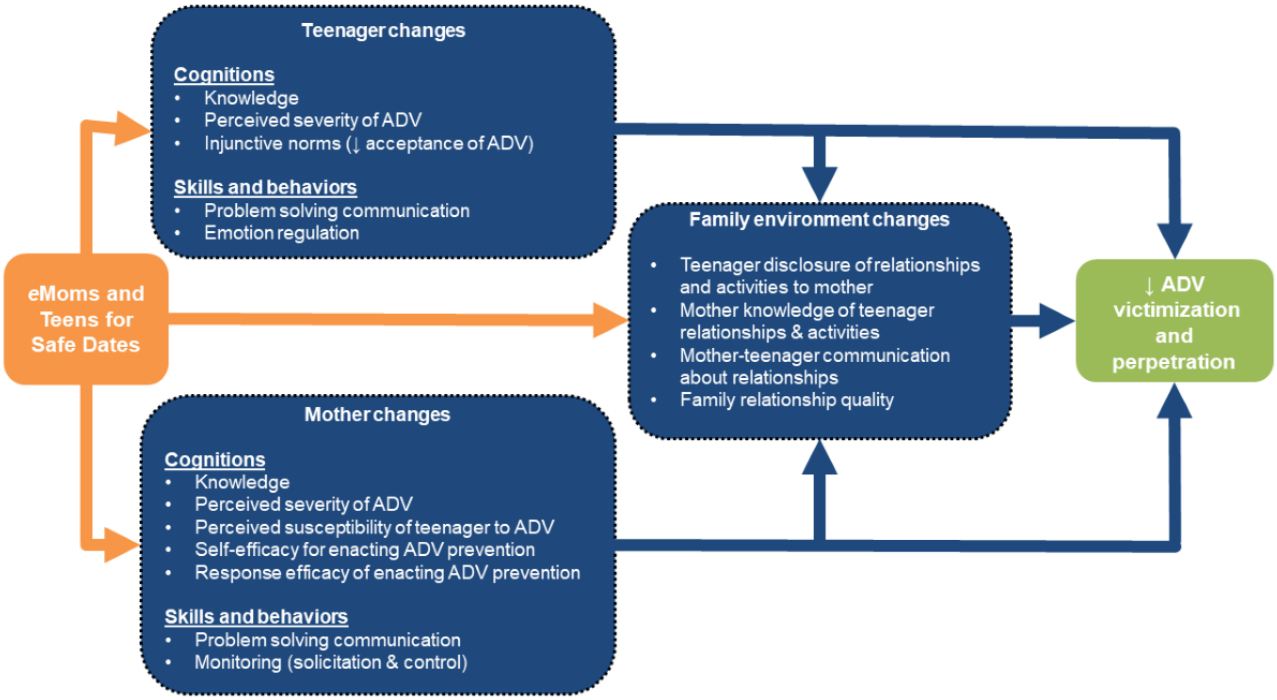
Potentially eligible participants who contact the study, either by completing the web-based screener or by calling the study phone number, will complete a full eligibility screener with staff on the telephone. During this call, the study will be described in detail, and staff will gauge their interest in participating. Mothers with >1 age-eligible teenager will be further asked to select one teenager to participate in the study or, if they prefer, to allow study staff to randomly select the teenager who will participate. Mothers who indicate that they are interested in enrolling will be emailed links to a web-based consent form and parental permission form for them to complete, as well as an assent form for their teenager to complete. Once the consent and assent forms are completed, the study team will send the mother participant links to the baseline surveys via 2 emails (one email with the link for the mother baseline survey and another with the link to the teenager baseline survey). Mother-teenager dyads who complete the consent, assent forms and baseline surveys, all of which will be completed on the web, will be considered enrolled in the study and randomized to 1 of the following 4 *adherence support* groups: (1) action planning

only, (2) SMS text message reminders only, (3) action planning and SMS text message reminders, or (4) no support. A computer random number generator will be used to select random permuted blocks with a block size of 8 and an equal allocation ratio. The random assignment table will be generated by the study principal investigator before the initiation of study enrollment. As participants are enrolled and records are added to the system by the study staff, dyads will be assigned a study ID, and the random assignment table will be consulted to assign the dyad to 1 of the 4 adherence support factor groups.

The eMTSD Program: Program Structure and Conceptual Model

The eMTSD program includes 6 modules, each designed to take approximately 30 minutes to complete, which delivers content adapted from the original MTSD program via text, videos, and interactive activities with questions for discussion between the mother and the teenager. Consistent with the original program, the modules aim to increase parent-teenager communication about healthy and unhealthy relationships and reduce teenagers' risk of experiencing and perpetrating dating abuse. Figure 2 provides a conceptual model, elaborated from the original MTSD conceptual model, which details the specific constructs that the program targets for changes within mothers, teenagers, and at the level of the family dyad, which, in turn, are posited to affect the teenager's risk of becoming involved in dating violence. As noted by Foshee et al [10], protection motivation theory, cognitive developmental theories, and empirical research have been used to select and specify constructs that MTSD aims to change at the family and individual levels.

Figure 2. eMoms and Teens for Safe Dates conceptual model. ADV: adolescent dating violence.



Consistent with the format of the original program, the web-adapted program is designed such that the mothers and teenagers must complete the modules in order. Flow through the program, summarized in Figure 3, begins with a *mother-only* phase, during which the mother prepares to engage in the program with their teenager, and then moves into a *mother-teenager* phase, during which the mother and the teenager engage in the program together. Mothers who log into the program are directed to watch a short animated *onboarding* explainer video that describes how the web-based program is organized. Once the onboarding video has been viewed mothers proceed to complete the *Getting Started* module, which is designed to prepare the mothers to engage in the program with their teenagers. At the end of the *Getting Started* module, mothers will be instructed to create a personal identification number for accessing any content in this module in the future and to start the program with their teenagers. To ensure that mothers are given the choice to discuss their IPV history with their teenagers, the *Getting Started* module, which is the only module that includes content addressing the mothers' IPV history, becomes locked and not viewable to the teenagers after the mothers have completed it. Mothers will then proceed to the program home page, which includes a short video for mothers and teenagers to watch together and then complete 5 modules designed to be completed by mothers and their teenagers together. The five modules for mothers and teenagers to complete together include information and activities focused on (1) positive communication, (2) conflict resolution skills, (3) different forms of dating abuse and the harms they cause, (4) awareness of sexual dating abuse and the importance of consent, and (5) creating family rules and norms around dating relationships. Table 1 summarizes the module goals and sample activities, and Multimedia Appendix 1 provides screenshots of the activities selected from each module.

Figure 3. eMTSD program flow. eMTSD: eMoms and Teens for Safe Dates.

Table 1. Overview of eMoms and Teens for Safe Dates program module goals and sample activities.

Module and goals	Sample activities
Getting Started (mothers only)	
Inform mothers about the program structure	Mothers watch an explainer animated video about the program goals and structure
Motivate mothers' engagement with the program	Mothers identify challenges they face in talking to their teenagers about dating and listen to narrated clips about how to overcome them
Module 1: Talking About Dating	
Identify healthy dating goals	Mothers and teenagers identify qualities they would like in a dating partner
Improve mother-teenager problem-solving communication	Mothers and teenagers identify positive and negative communication skills used in animated microvideos of everyday family conversations
Module 2: Skills for Handling Conflict	
Increase emotion regulation skills	Mothers and teenagers identify events and cues that indicate when they are experiencing an escalation of anger and select strategies they can use for self-calming
Increase positive conflict resolution skills	Mothers and teenagers watch an animated video of a disagreement between dating partners and practice using problem-solving communication to resolve the conflict
Module 3: Recognizing Dating Abuse	
Increase awareness of different forms of dating abuse and their negative consequences	Mothers and teenagers learn about tactics that can be used to control and manipulate dating partners and identify the tactics being used in different abuse scenarios
Foster discussion of healthy relationship characteristics	Mothers and teenagers identify characteristics of "healthy" relationships among their friends and families and in the media and discuss what makes a relationship "healthy"
Module 4: Sexual Dating Abuse	
Increase understanding of the meaning of consent in a dating relationship	Mothers and teenagers watch an animated explainer video that highlights the elements of and importance of consent in a dating relationship
Identify and counter rape myths	Mothers and teenagers read about and discuss false beliefs about sexual dating abuse that shift blame to the victim
Identify strategies to reduce the risk of experiencing sexual dating abuse	Mothers and teenagers brainstorm strategies they can use to reduce the risk of experiencing sexual dating abuse
Module 5: Ready, Set, Prepare!	
Identify healthy relationship goals	Teenagers identify ways they want to treat dating partners and ways that they want to be treated
Increase awareness of signs of dating abuse	Mothers and teenagers identify "red flags" that indicate that someone might be experiencing or perpetrating abusive behavior
Develop safety plans and dating rules	Mothers and teenagers collaboratively develop a set of family guidelines for dating

Adherence Support Factors

Text Message Reminders

A growing body of research suggests the potential of digital *triggers*, such as SMS text messages for fostering engagement in health interventions [21]. Drawing from this research, we developed a set of SMS text message reminders that are personalized by mother and teenager names and tailored based on the completion level. All mother participants will receive SMS text messages welcoming them to the program on the day they are enrolled in the study. Mother participants assigned to the control and action-planning–only conditions who do not log into the program and complete the *Getting Started* module will receive log-in reminders via text 3 and 7 days after enrollment and a text and email reminder 10 days after enrollment (up to 3 reminders).

Mother participants assigned to receive automated SMS text messages will receive up to 8 tailored SMS text message reminders at fixed intervals. Messages 1, 2, and 3 will be sent 3, 7, and 10 days, respectively, after the initial program log-in email and welcome text are sent. Messages 4 through 8 will be sent every 7 days thereafter until they complete all the program modules or the 6-week recommended program completion period is complete. All dyads will be informed that they should complete a minimum of 1 module per week during the study period. Reminders are thus tailored based on whether the dyad is *on trac*k with respect to this recommended completion rate. Mothers who complete the program on time or ahead of schedule or who have already completed the program will receive a *congratulatory message* about their progress. Mothers who have not logged in or are behind schedule receive messages designed to motivate engagement and emphasize the availability of technical support. Examples of reminders are shown in Textbox 1.

Textbox 1. Example SMS text message reminders.

Congratulatory reminder for a mother who is on track

- "Congratulations on completing the Getting Started module of the Moms and Teens program [mom's name]. You are a superstar! To stay on track, make a plan to complete Module 1 with [teen's name] by [goal day]! Module 1 will help you and your teen talk about healthy relationships. Need technical support? We want to help! Text back 'Y' or call XXX-XXX-XXXX"

Motivation reminder for a mother that has not logged in

- "Dear [mom's name], we re-sent the login information for the Moms & Teens program to your email. This fun, convenient, and free research-based program has been shown to benefit moms and teens. Make a plan now to login this week to complete the Getting Started module and begin the program with [teen's name] so that you can get back on track to finish the program by [goal day]. If you need technical support to login to the program text back 'Y' or call XXX-XXX-XXXX!"

Once the recommended six week program completion period is complete, all participants who have not finished the program will be notified via email and text and asked to complete the program before the two week grace period ends.

Action Planning

Gollwitzer [22] proposed a model of action phases for goal attainment, which suggests that people will be more likely to achieve a goal (such as completing the eMTSD program) if they create an *action* plan in the form of implementation intentions that "spell out the where, when, and how of goal striving in advance." Research supports this strategy, with a meta-analysis finding that implementation intentions have a moderate to large positive effect on goal attainment [23]. Drawing from this research, mother participants assigned to receive action planning groups will receive a modified version of the email communication with the program log-in information, including additional instructions directing them to complete a brief *action planning* form administered through the REDCap (Research Electronic Data Capture; Vanderbilt University) web application. The action planning form asks participants to (1) make an individual goal for when they would like to finish the program, (2) create a plan for where and when they will complete the program modules with their teenagers, and (3) complete 3 if-then statements to identify the potential barriers to completion that may arise and how they will overcome them. Mothers will be instructed that they can print or save the form to refer to if they desire.

Definitions and Assessment of Feasibility and Acceptability

Feasibility

In this study, *feasibility* will be assessed both in reference to the research processes and to the eMTSD program; that is, feasibility outcomes provide information that enables us to assess the questions of *can this study be done* and *can this program be done*. Specifically, we define feasibility as the extent to which (1) the study is successfully conducted with respect to recruitment, randomization, delivery of adherence support, retention, and assessment, and (2) the eMTSD program can be successfully conducted by mothers and teenagers [24,25]. Textbox 2 summarizes the key feasibility outcomes and their indicators.

Textbox 2. Feasibility outcomes.

Recruitment rate

- Number of dyads recruited per month

Enrollment rate

- Percentage of eligible dyads who enroll in the study

Randomization

- Percentage of enrolled dyads correctly randomized

Retention rate

- Percentage of enrolled dyads who complete the follow-up survey

Adherence supports

- Percentage of SMS text messages eligible to be delivered and which are sent
- Percentage of mothers eligible for action planning who complete a plan

Data collection

- Percentage of missing data within surveys
- Time taken to complete surveys

Program uptake and adherence

- Percentage of participants who log in at least once
- Percentage of participants who start the program with their teenager
- Percentage of modules completed or pages viewed
- Percentage of enrolled participants who complete the program
- Adherence index, comprising the sum of the number of completed modules, number of unique visits to the site, and maximum time between visits [26]
- Time taken to complete program modules
- Participant report of facilitators of and barriers to engaging with the program, including technical problems accessing or using the website

Acceptability

In this study, acceptability will be assessed in reference to the eMTSD program, as well as with respect to adherence support factors (SMS text message reminders and action planning). Drawing from the Theoretical Framework of Acceptability (TFA), we define acceptability as the extent to which mothers and teenagers consider eMTSD to be appropriate based on their cognitive and emotional responses to the intervention [27,28]. The TFA was applied to develop quantitative indicators assessing the acceptability of the eMTSD across each of the 7 component domains proposed by the TFA (affective attitude, burden, ethicality, coherence, opportunity costs, perceived effectiveness, and self-efficacy). Table 2 lists the acceptability outcomes, including their linkages to each TFA domain.

Table 2. Acceptability outcomes.

Outcome and domain	Indicator or indicators
Program acceptability	
Affective attitude	• I enjoyed doing the module or program[a] • The module or program kept my attention[a]
Burden	• The module or program was easy to do[a] • The module or program was too long[a]
Effectiveness	• I learned useful information from the module or program[a] • The program will reduce my teen's chances of experiencing dating abuse[a]
Ethicality	• The program covered topics that are important to me[a]
Cohesiveness	• I understood what the program is trying to do[a]
Self-efficacy	• I understood how to complete the program[a]
Opportunity cost	• Doing the program was time well spent[a]
Overall[b]	• Percentage of participants who report agreement with all acceptability indicators
Adherence support acceptability	
Effectiveness	• Percentage of participants who report it was helpful to receive text reminders • Percentage of participants who report it was helpful to complete an action plan
Burden	• Percentage of participants who report they received too many SMS text messages

[a]Program acceptability indicators will be operationalized as the percentage of participants who completed the module or program and agreed or strongly agreed with the indicator statement. Some indicators will be asked both in reference to specific modules and in reference to the program as a whole.

[b]We will also create a continuous program acceptability index score for each mother and teenager by summing across acceptability indicators (range 0-9).

Data Collection

Overview

Data sources for assessing feasibility and acceptability outcomes described further in the following sections include (1) web analytics (eg, participant log-ins, page views, and visit times), which capture data needed to assess program adherence; (2) module completion surveys, which are embedded in the web-based program and assess program acceptability; (3) program completion surveys, administered through REDCap, which assess program acceptability and barriers to completion among all participants enrolled in the study; (4) baseline and 90-day follow-up surveys, also administered through REDCap, which access constructs in the program conceptual model (Figure 2); and (5) the web-based screener and study participant contact tracking database, which will be populated by program staff and will capture data on recruitment, eligibility, enrollment, and retention.

Website Use Data

Website use data will include the number of program log-ins, pages viewed, visit times, and modules completed. In addition, the participants will be offered the opportunity to rate the selected videos and activities from 1 to 5 stars. Altogether, ratings and website use data will inform our understanding of the acceptability of videos and activities and allow for the assessment of program engagement and adherence.

Module Completion Surveys

Brief (1- to 2-minute) module completion surveys will be embedded in the web-based program. These surveys will appear at the end of each module and solicit mother and teenager feedback on module acceptability and any technical problems encountered. Mothers and teenagers will be asked to complete separate surveys before proceeding to the next module.

Program Completion Surveys

Both mothers and teenagers will be asked to complete the program completion surveys, which will be administered through REDCap. The links to the surveys will be emailed to the mothers after completion of the final module. Surveys will assess program acceptability indicators (Textbox 2), as well as barriers to completion and suggestions for program improvement. Mothers and teenagers who do not complete the program within the 8-week implementation period, including those who never log into the program or those who log in but do not complete any modules, will be sent a program completion survey tailored to their completion level.

Baseline and Follow-up Surveys

Baseline and follow-up surveys, administered to mothers and teenagers through REDCap at enrollment and 90 days following enrollment, will assess the demographic characteristics of participants, including both the mother's and teenager's past exposure to IPV (baseline only), as well as cognitions, skills, and behaviors targeted by the eMTSD program. The collection of these data will allow us to describe study participants; gauge survey length and completion rates; assess psychometric properties of key measures; and explore pre-post changes in the cognition, skills, and behaviors targeted by the program (Figure 2, program conceptual model).

Web-Based Screener and Recruitment Tracking Data

The web-based screener will capture data on recruitment sources and participant demographics (eg, race, ethnicity, and sex). A study tracking database will capture data on staff contacts with potential participants, telephone eligibility screens, participant enrollment, program log-in, survey completion reminders, and incentive disbursements. These data will be used to explore the effectiveness of different recruitment strategies for identifying individuals who meet the study inclusion criteria by recruitment source and participant characteristics.

Statistical Analysis

Overview

Descriptive statistics will be used to summarize the demographic characteristics of the study population and feasibility and acceptability indicators for the sample. Bivariate statistical procedures (eg, 2-tailed *t* tests and chi-square tests) will be used to examine associations between demographic and background characteristics of mother and teenager participants (age of the mother; sex, gender identity, and race and ethnicity of the teenager; family financial stress; mother and teenager psychological distress; and mother and teenager IPV exposure) and (1) recruitment source (eg, Facebook advertisement, domestic violence agency), (2) program adherence, (3) program acceptability, and (4) study retention. These analyses will help identify potential sources of bias and characterize program feasibility and acceptability as a function of participants' demographic characteristics.

Descriptive statistics will be used to summarize adherence rates by *adherence support* group, and bivariate statistics will be used to examine differences between groups in adherence indicators (program log-in and initiation rates and program adherence). Paired *t* tests and McNemar test will be used to examine trends in pre-post changes in cognition, skills, and behaviors targeted for change by the program (Figure 2) among program completers. These analyses are considered exploratory, given that the study is not powered to assess changes in these constructs.

Power

We used the approach described by Lewis et al [29] to determine the sample size for this feasibility and acceptability trial. This approach uses a *traffic light* system to evaluate the progression to the main trial based on a set of a priori criteria. Hypothesis testing for binary feasibility outcomes tests against being in the red zone (unacceptable outcome) based on the expectation of being in the green zone (acceptable outcome). Using this approach, an adequate sample size is that which gives high power (≥80%) to reject being in the *red zone* if the *green zone* holds true.

Three focal feasibility and acceptability outcomes were selected to determine the sample size: (1) enrollment rate, (2) overall program acceptability, (3) teenager program initiations, and (4) program completion rates. The point estimates that will be considered the red zone upper limit (R_{ul}) and green zone lower limit (G_{ll}) for these outcomes are (1) the proportion of those eligible from those who enroll (R_{ul}=0.60 and G_{ll}=0.75), (2) the proportion of those who agree or strongly agree that the program is acceptable across all indicators >0.60 (R_{ul}=0.55 and G_{ll}=0.75), (3) the proportion of those enrolled who initiated the use of the program with their teenager >0.50 (R_{ul}=0.50 and G_{ll}=0.65), and (4) the proportion of those enrolled who completed the program >0.30 (R_{ul}=0.30 and G_{ll}=0.50). The null hypothesis test, for which the sample size is calculated, is that the true outcome is not greater than R_{ul}.

Table 3 shows that a sample size of 100 provides >80% power to reject the null hypothesis across each of the focal feasibility and acceptability outcomes, with an α of .05 and a 1-tailed, 1-sample binomial test based on normal approximation (with continuity correction).

Table 3. Power for focal binary feasibility and acceptability outcomes.

Outcome	Red zone upper limit, %	Green zone lower limit, %	Power[a], %	N[b]
Enrollment rate (percentage of those eligible who enroll)	60	75	80	68
Program acceptability (percentage of those completing the program who agree or strongly that the program is acceptable across all domains)	55	75	80	40
Teenager program initiation rate (percentage of those enrolled who start the program with their teenager)	50	65	80	73
Program completion rate (within group; percentage of those assigned to the group who complete all 6 program modules)	25	50	80	25 (per group; 100 overall)

[a]Power (1-B) to reject being in the *red zone* if the *green zone* holds true.

[b]Needed sample size for the hypothesis test.

Incentives

Mother and teenager participants will each receive US $30 for completing the baseline, program completion, and follow-up surveys to a total of up to US $180 per dyad for completing all study activities.

Ethics Approval

This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board on November 17, 2021 (reference number: 21-2380). Mothers who screen as eligible will be provided with information about the study and will provide electronic consent for their and their teenager's participation. Teenagers will also complete the electronic assent form. Surveys will include referral information for support in addressing mental health and violence prevention and treatment for all participants. All project data will be deidentified before analysis and securely stored in encrypted files on servers that adhere to the University of North Carolina at Chapel Hill policy on the storage and transmission of sensitive data.

Results

This feasibility and acceptability study began recruitment in November 2021, and the study results will be available in 2023.

Discussion

Anticipated Findings

We anticipate that this feasibility and acceptability study will determine whether the eMTSD program merits rigorous testing in future hybrid effectiveness-implementation trials. Such a trial may be designed to examine program effects on ADV outcomes and the impacts of delivery mode (web-based vs booklet) and implementation support (eg, reminders and action planning) on D&I outcomes. Furthermore, we expect that the results of this study will inform our understanding of optimal recruitment strategies and identify potential changes to the delivery and content of the program and implementation support that would improve acceptability and feasibility.

Comparison With Prior Work

MTSD is one of the few violence prevention programs that has been developed and tested with youth exposed to IPV, and to the best of our knowledge, is the only program that targets risk and protective factors at both the family and individual levels [8]. The feasibility and acceptability study of the web-based version of this program will contribute to a small but growing body of research examining the use of technology and digital delivery methods for prevention programs that aim to make changes to the family environment and, in turn, prevent negative health outcomes among youth [26,30-32].

Strengths and Limitations

The limitations of this study include the use of a convenience sample, which may preclude our ability to generalize findings to the population as a whole and explore differences in findings across subgroups (eg, youth of different gender identities and youth who have been exposed to different types of caregiver IPV). In addition, survey data rely on self-reporting and are, thus, potentially susceptible to social desirability response bias. The strengths of the study include the use of a multipronged recruitment strategy, which will allow us to explore the effectiveness of different recruitment sources and the testing of different implementation strategies (action planning and text reminders) that may increase program adherence.

Conclusions

If eMTSD is acceptable and effective in preventing ADV, it is hoped that the program may be promoted by organizations serving survivors of IPV and their families. Given the dearth of programs designed specifically for youth exposed to IPV, eMTSD may address a critical gap in ADV prevention efforts and decrease the likelihood of abusive dating and intimate partnerships during adolescence and adulthood, as well as the adverse health and social impacts of ADV and IPV.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Program activity screenshots.
[DOCX File , 1353 KB - resprot_v11i8e35487_app1.docx]

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Abbreviations

ADV: adolescent dating violence
D&I: dissemination and implementation
eMTSD: eMoms and Teens for Safe Dates
IPV: intimate partner violence
MTSD: Moms and Teens for Safe Dates
REDCap: Research Electronic Data Capture
TFA: Theoretical Framework of Acceptability

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Protocol

A 2.5-Year Weight Management Program Using Noom Health: Protocol for a Randomized Controlled Trial

Robyn Sysko[1], PhD; Jessica Bibeau[1], MA; Allison Boyar[1], BS; Kayla Costello[1], MS; Andreas Michaelides[2], PhD; Ellen Siobhan Mitchell[2], PhD; Annabel Susanin[1], BA; Tom Hildebrandt[1], PsyD

[1]Eating and Weight Disorders Program, Icahn School of Medicine at Mount Sinai, New York, NY, United States

[2]Noom Inc, New York, NY, United States

Corresponding Author:
Robyn Sysko, PhD
Eating and Weight Disorders Program
Icahn School of Medicine at Mount Sinai
1 Gustave L Levy Place, Box 1230
New York, NY, 10029
United States
Phone: 1 212 659 8724
Fax: 1 212 659 1538
Email: robyn.sysko@mssm.edu

Abstract

Background: Overweight and obesity are serious public health concerns. As the prevalence of excess weight among individuals continues to increase, there is a parallel need for inexpensive, highly accessible, and evidence-based weight loss programs.

Objective: This weight loss trial will aim to examine the efficacy of the Noom weight loss program in comparison to a digital control after a 6-month intervention phase and a 24-month maintenance phase, with assessments continuing for 2 years beyond the intervention (to 30 months—after the baseline). The secondary outcomes include quality of life, psychosocial functioning, sleep quality, physical activity, diet, and health status. This trial will also examine the severity of obesity-related functional impairment, weight loss history, and demographic moderators, along with adherence and self-efficacy as mediators of the outcome.

Methods: A total of 600 participants were randomized in a parallel-group, controlled trial to either Noom Healthy Weight Program (intervention) or Noom Healthy Weight Control (control) for a 6-month intervention. Both intervention and control groups include diet and exercise recommendations, educational content, daily logging capabilities, and daily weigh-in entries. The Noom Healthy Weight Program also includes a coach support for weight loss. Remote follow-up assessments of eating, physical activity, psychosocial factors, app use data, and weight will be conducted at 1, 4, 6, 12, 18, 24, and 30 months after baseline. Weight is measured at each follow-up point during a Zoom call using the participants' scales.

Results: Enrollment began in March 2021 and the 6-month intervention phase ended in March 2022. Data collection for the final assessment will be completed in March 2024.

Conclusions: This study tests commercially available digital lifestyle interventions for individuals with overweight and obesity seeking weight loss support. Data obtained from the study will evaluate whether the Noom Healthy Weight Control Program can help individuals overcome weight loss, achieve long-term maintenance, adhere to lifestyle changes, and feature use barriers that are present in other traditional weight loss treatments.

Trial Registration: ClinicalTrials.gov NCT04797169; https://clinicaltrials.gov/ct2/show/NCT04797169

International Registered Report Identifier (IRRID): DERR1-10.2196/37541

(JMIR Res Protoc 2022;11(8):e37541) doi:10.2196/37541

KEYWORDS

weight loss; weight loss maintenance; digital health; Noom; Diabetes Prevention Program; DPP; mobile phone

Introduction

Overweight and obesity have reached epidemic proportions in the United States [1], with prevalence rates reaching 42% between 2017 and 2018 [2]. Excess weight represents a serious public health concern because of the increased risk of medical sequelae (eg, high blood pressure, sleep apnea, or COVID-19) [3] that require lasting and expensive interventions. In-person behavioral treatments, such as the Diabetes Prevention Program (DPP) [4], are generally effective, producing 4% to 8.3% weight loss after 6 months [5,6], 3.9% to 8.6% after 12 months [6,7], and similar or worse outcomes compared with web-based deliveries [6]. However, weight loss with these interventions is not always sustained over time, weight regain after treatment is common [8,9], and in-person services can be prohibitive with regard to cost and accessibility [6,10,11], as DPP treatment costs more than medication treatment alone (>US $1300 more per participant) in the first year of treatment [10]. Therefore, web-based delivery may improve accessibility and provide a more cost-effective option for in-person weight loss treatment without compromising success [6]. Thus, a major challenge in using behavioral weight loss interventions more broadly is scaling extant empirically based strategies while simultaneously optimizing personalized elements that may help maintain weight loss and lifestyle changes over time. Programs adapted to deliver behavioral weight loss via a mobile app could help overcome these limitations [12].

With approximately 97% of Americans owning a smartphone [13], digital health resources are becoming increasingly accessible [14], and ≥37,000 health or weight apps were available as of 2019 [15]. However, many apps lack evidence-based strategies used in face-to-face behavioral treatments, such as coaching and personalized feedback [16], and provide only self-monitoring and goal-setting [17]. When strategies such as problem solving [18], coaching [19], or increased social support [20,21] are included as features, the observed weight loss results prove significant [22]. Specifically, a pilot project found significant weight loss (1.6% and 2.3%) using problem-solving strategies in a weight loss app over 8 weeks [18]. A program that included social support reported significant group differences in weight (−5.3 kg) compared with a control (−2.2 kg) [21]. Finally, when coaching was added to a weight loss maintenance program, the coaching groups did not show weight regain, whereas there was significant regain in the noncoaching group [19]. Weight loss maintenance is limited; however, only 20.6% of people sustain decreases for a year [23], and approximately 70% of weight loss is regained within the first 2 years [24]. While digital weight loss programs can be successful [11,22,25-28], improvements are needed [16], including a platform that provides comprehensive intervention focusing on both short-term weight loss and long-term maintenance.

In 2008, Noom Inc created a mobile intervention modeled on strategies from the DPP with a goal of improving the accessibility of personalized expert guidance [29,30]. Noom Inc focuses on healthy behavior changes through manageable goal setting, daily monitoring, coach feedback, and a social support group [29,30]. In comparison to other apps for weight loss, the Noom program includes a large proportion of behavioral strategies derived from an evidence-based weight loss program (ie, DPP), including a physical activity goal, exercise safety (both compared with 20% of other apps), benefits of a healthy lifestyle (13.3% of other apps), food substitutions (10% of other apps), stimulus control, portion control, lifestyle activity (6.7% of other apps), problem solving (3.3% of other apps), stress reduction, relapse prevention, negative thinking, social cues, regular eating patterns, and time management (0% of other apps) [31]. Furthermore, only Noom and another app were observed to incorporate all assessed core and motivational interviewing constructs [32]. Over 6 months, 77.9% of Noom users in the general population reported weight loss [33], and those demonstrating greater adherence reported better outcomes [34]. The study described below will extend prior studies of Noom Inc weight loss products using a randomized controlled design with a large sample to test the efficacy of the Noom Healthy Weight Program (intervention) versus Noom Healthy Weight Control (control), during a 6-month intervention and 2-year maintenance phase. In addition, the primary difference between the intervention, which is a commercially available Noom product, and the control, a version created specifically for this research study, is the inclusion of coaching. Thus, this project will help evaluate whether coaching is an essential element in the effectiveness of the intervention. Furthermore, prior studies examining the efficacy of a Noom Inc product were either uncontrolled, did not include long-term follow-up, or failed to include an active digital control group [33,34]. This project will therefore improve extant research by incorporating coaching, problem solving, social support, and a digital control group, and extending the assessments over 30 months, allowing a 24-month follow-up assessment period.

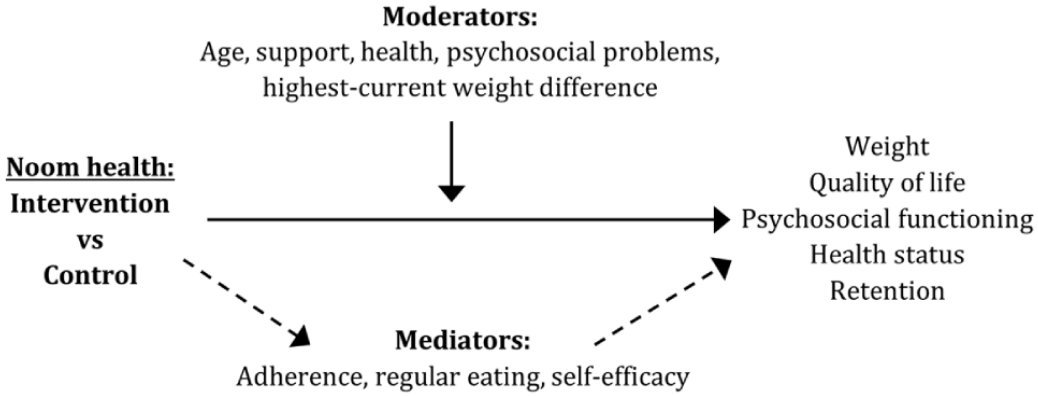
Moderators (or variables that potentially alter the effect of treatment on outcome) are often difficult to replicate in behavioral interventions and a host of demographic, sociocultural, and comorbid health conditions that offer a proxy for obstacles to acceptance, engagement, and outcome [35]. We will use a composite moderator approach to capitalize on the aggregation of potentially small but clinically meaningful effects [36]. Our proposed moderators will include age, comorbid health conditions, demographics (sex, marital status, race or ethnicity, education, and socioeconomic status), and psychosocial functioning. There are well-documented moderating effects of age (favoring younger individuals) on the acceptance and use of mobile health platforms [37] and evidence that social determinants, including sexual identity, socioeconomics, and education, are theoretically robust contributors to digital health engagement, but understudied in the published literature. These individual aspects of identity, health, and status are likely to affect expectations regarding the value of digital interventions, their applicability to individual circumstances, and the acceptance of specific tools used within the program.

Weight suppression, or the difference between current and highest weight, has demonstrated predictive effects for obesity-related prevention [38] and evidence of attenuated weight loss in behavioral weight loss interventions [39,40]. These moderating effects are thought to occur because of the psychological impact of deprivation and physiological

adaptations related to weight suppression. We predicted, in line with others, that those with greater weight suppression at baseline would lose less weight and be more likely to regain weight during the follow-up period. This hypothesis is based on the finding by Wing et al [41] that weight suppression leads to larger time-dependent weight regain in the context of obesity prevention.

Little is known about how digital program features account for efficacy or long-term outcomes [12]; however, there is evidence that personal communication [2,18,19] and self-monitoring mediate weight loss and long-term outcomes [27,30,33,42,43]. These mediator effects largely depend on the evidence of treatment engagement (adherence to recommendations, use of digital tools, and participation in digitally delivered interactions). Consequently, we tested a time-series model that examined the lagged effects of these engagement elements on attrition, weight, and psychosocial outcomes. In addition, we tested whether self-efficacy and regular eating mediate these outcomes. Self-efficacy, which is directly targeted by the Noom intervention, has demonstrated mediation effects in weight loss and sustained weight—after the intervention [44], and regular eating, when experimentally manipulated, is associated with greater reductions in energy intake and associated weight loss [45]. Consequently, we hypothesized that both self-efficacy and regular eating would mediate weight loss at the end of the treatment and follow-up. Figure 1 displays the hypothesized moderator and mediator effects tested in this study.

Figure 1. Hypothesized moderator and mediator effects.



Methods

Study Overview

A total of 600 participants were randomized to receive either the Noom Healthy Weight Program (intervention) or Noom Healthy Weight Control (control), delivered in a smartphone app format. The Noom Healthy Weight Program includes diet and exercise recommendations, communication from a coach to help with goal setting and barriers, dietary logging, daily weigh-ins, articles, and access to the social community on Noom. Noom Healthy Weight Control includes daily logging and the same recommendations, but communication with the coach and social interactions are not available. The primary intervention period occurred during months 1 to 6 and the maintenance phase during months 7 to 30. Follow-up assessments will be conducted at 1, 4, 6, 12, 18, 24, and 30 months after the baseline. Additional details regarding these elements are provided in the following sections.

The project was funded by Noom Inc with participants recruited across the United States who contacted the company expressing interest in their research, which should allow for greater generalizability of app users seeking digital weight loss advice. All study procedures were remote and were conducted by the Icahn School of Medicine at Mount Sinai Eating and Weight Disorders Program.

Ethics Approval

The protocol for this trial was reviewed and approved by the Mount Sinai Institutional Review Board (STUDY-20-01299M).

Study Aims

The primary aim of this study is to test the comparative efficacy of the Noom Healthy Weight Program (intervention) and Noom Healthy Weight Control (control) for weight loss at 6 and 30 months after baseline. The secondary aims are to test caloric intake, dietary behavior, physical activity, sleep impairment, quality of life, psychosocial functioning, and self-reported health status 30 months after baseline. It is hypothesized that greater improvement will be observed after the intervention in Noom Healthy Weight Program users.

Another secondary aim is to test the moderation of the treatment response. We hypothesize that a clinical profile determined via data reduction of relevant demographic and clinical features into a composite variable [35] will show a significant interaction by treatment condition, such that individuals with an increased risk profile (older age, less support, more health conditions, and psychosocial problems) will derive greater benefit from Noom Healthy Weight Program than Noom Healthy Weight Control. These indicators of the latent moderator potentially contribute small but meaningful moderation effects to the treatment. To increase power, they are combined into a latent variable, so the source variability associated with sociodemographic profiles and psychosocial symptoms (typically correlated in samples of individuals with obesity) will allow us to determine if the composite profile suggests a greater effect of the experimental intervention. Second, on the basis of the large extant literature on eating and weight disorders, we hypothesized that the difference between the highest weight and current weight will moderate the efficacy of the intervention compared with the

control because it predicts outcomes for treatments that attempt to change eating behavior by imposing a restrictive structure (eg, traditional behavioral weight loss, regular eating in cognitive behavioral therapy for eating disorders, etc).

Exploratory aims include developing a dynamic model of adherence using a Bayesian belief network [46] that predicts individual changes in the primary outcomes with the intention of identifying within-treatment mechanisms of change in the Noom Healthy Weight Program. This model uses directed acyclic graphs to determine conditional relationships between global and local adherence. Global adherence markers must be present for local markers to occur (eg, app login is global adherence and enter weekly weight is local adherence). This initial model was then extended to a repeated-measures time-series model, resulting in dependent sequential adherence markers. A time-series model of adherence will be used to predict study dropout, successful weight loss, and quality of life. Adherence to intervention features and follow-up completion will be assessed at 12 months. In a separate model, we tested whether regular eating mediates the treatment effects of weight loss over time. We also expect that self-efficacy in weight loss will mediate the effects of the intervention versus control at and 12 months after baseline.

Study Participants, Inclusion and Exclusion Criteria, and Recruitment Procedures

Eligible participants were between the ages of 18 and 60 years, expressed an interest in losing weight, were interested in using the Noom platform, had a BMI >27 kg/m^2, and spoke English. Exclusion criteria included contraindications to smartphone use (eg, seizures from prior smartphone use), not owning a smartphone, acute suicide risk, current use of the Noom commercial program, and current or planned pregnancy over the next 12 months. Prior use of Noom products was not an exclusion criterion. Individuals who are pregnant should not participate in a medically unsupervised weight loss program.

Participants were recruited via links or advertisements on the Noom platform and website. Interested participants were directed to a link to complete an initial eligibility assessment on REDCap [47] and provided availability for a Health Insurance Portability and Accountability Act–compliant videoconference (Zoom) call with trained study staff, including the project manager, research coordinators, and students. During the Zoom call, participants completed the informed consent process, received a comprehensive description of the study, had the opportunity to ask questions, and provided their baseline weight. This discussion included an explanation of the importance of retaining participants in a research study, regardless of success with weight loss. In addition, participants were asked questions during the intervention and follow-up descriptions and study timeline to encourage discussion about possible barriers to participation and directly address any issues regarding time commitment. These procedures were conducted to help with retention, as outlined and discussed in a motivational interviewing approach geared toward enhanced retention [48]. A copy of the consent form was emailed to the participants before the call, and a signed copy was provided upon completion of the call. The participants then received instructions to complete the baseline measures (as described in subsequent sections) on REDCap. Participants received US $35 compensation to complete the baseline measures (approximately 60 minutes).

Enrollment and Randomization Procedures

At this time, recruitment is complete, intervention and data collection are ongoing, and the analysis has not yet begun. After screening, eligible participants were randomized into intervention (n=300) and control (n=300) groups. Randomization was stratified by BMI and gender using R software (R: A Language and Environment for Statistical Computing; R Core Team) [49]. Randomization groups include 4 groups of BMI (27.0-29.9 kg/m^2, 30.0-34.9 kg/m^2, 35.0-39.9 kg/m^2, and ≥40.0 kg/m^2). Each BMI group was split into 3 sex categories (male, female, and other), creating 12 blocks. The randomization sequence created in R was programmed into the REDCap randomization module implemented by the project manager. This module allows for computer-automated randomization based on the defined parameters and concealment of the allocation order from all study staff and participants until after the intervention assignment. Only the project manager had access (concealed) to the randomization module to randomize the participants. After randomization, participants were notified of their assigned condition and information was sent to activate Noom.

Noom Healthy Weight Program and Noom Healthy Weight Control

These interventions are provided at no cost to participants during this trial.

General Features of the Noom App

The Noom app interface includes (1) logging meals, weight, and physical activity, (2) reading curriculum material, (3) a recipe section to provide healthy meal suggestions, (4) talking to a coach, and (5) communicating with other group members for support. The group feature allows users to post personal challenges and successes, receive feedback from other users, and respond to others' challenges. The participants were encouraged to use the group as much or as little as they wished. The coaches also participated in the group in response to posts and comments. Additional features of the app include a recipe section and the ability to log mood, sleep, glucose, and blood pressure.

Coach Role

Noom assigns users to a health coach who reviews participant entries in the app and works with participants to make changes in response to information entered in the app and communications between coach and participant via direct message. Weekly, the coaches reached out to users to help them identify individual goals, make and adhere to healthy changes, promote happiness and wellness, troubleshoot weight loss barriers, individualize feedback, find ways to adapt to lifestyle changes, and increase motivation [50]. Coaches used the chat feature to check in with participants through a private direct messaging system. They reached out to chat with each participant weekly to help set goals, resolve roadblocks, and

provide support. Each week, coaches encouraged participants to establish weekly mini goals to help users reach their overall weight loss goal (eg, replacing afternoon snacks with a fruit or vegetable 5 days per week or going to the gym 4 times). After helping to establish goals, coaches used subsequent weekly contacts to check progress and set new goals. Coaches initiated conversations at the beginning of the intervention; however, participant-initiated contacts were welcome as well. There was no limit to the frequency of communication with the coach. The coach used motivational interviewing techniques during all conversations to establish actionable steps, set realistic expectations, encourage reflections, and identify the source of potential setbacks (eg, When was the last time you felt motivated? What has changed since then?). These conversations are geared toward promoting lifestyle changes aligned with the DPP. These techniques helped focus on communication by providing support, encouraging self-efficacy, promoting healthy changes, and helping to solve difficult situations.

Curriculum Content

The content provided during the intervention was based on the DPP and aimed to help users develop and maintain healthy eating patterns, increase physical activity, and foster skills to navigate their environment and overcome barriers. Topics include learning about calorie balance and the importance of sticking to daily calorie goals for weight loss, being active and finding time to be active daily, coping with situations or cues that create unhealthy behaviors, finding support in their environment from friends or family, and how to stay focused on adhering to changes [4]. Dietary changes include reducing fat and calorie intake, replacing snacks with healthy alternatives, and healthy choices while eating out [4], which is displayed in the logging feature of the app using a red light or green light system (ie, options with higher calories or fats are red). In addition, the content promotes other aspects of well-being, including regular eating, sleep (8 hours per night), and stress management. The intervention program delivers this content over the app in short, easily digestible daily material, and the control program provides this information over the app in weekly newsletters, with all content for that week provided in each newsletter.

Noom Healthy Weight Program

Participants are encouraged to use the features of the Noom app daily, including daily logging (diet, exercise, weight, mood, sleep, blood pressure, or glucose), reading daily curriculum material, viewing the recipe section, talking to a coach when applicable, and communicating with the group. As participants reach the 6-month mark of this intervention, there is a gradual transition from weight loss–focused content to maintaining weight loss, encouraging the diet and exercise changes that were made to become lifelong habits. Participants receive a one-to-one coaching call to evaluate the progress and re-establish goals for maintaining gains. In months 7 to 12, coaches continue to reach out once a week and conduct maintenance check-ins with participants to check the progress and resilience of changes (eg, brief and intense reinstatement of practices such as self-monitoring of food choices).

Noom Healthy Weight Control

Noom Healthy Weight Control is a version of the Noom program with limited features. This version includes the option to read the same curriculum material as the Healthy Weight Program, but presented in a weekly newsletter format, in addition to daily logging (same as the intervention, with the exception of mood and sleep logging) and the inclusion of a recipe section. The primary difference in this program is the lack of access to the coach or group, limited logging options, and the presentation of weekly curriculum materials instead of daily educational content. The maintenance phase for the control condition prompts users to continue to use exercise and dietary recommendations and to deliver new content based on these goals to keep users engaged.

Treatment Fidelity

Coaches are trained in the areas of physical activity, nutrition, psychology, and behavioral health changes [50]. Coaches complete a health and wellness training program through Noomiversity, which teaches evidence-based strategies for weight loss and sustainability. Coaches complete an initial minimum level of training, including 75 hours of instructional content, mock scenario skill building, and 200 hours of direct user contact, and receive supervision from a research manager to ensure adherence to the intervention protocols. Research managers review coach transcripts every 4 to 6 weeks to provide guidance on nonadherence [50]. Coaches will be aware of users joining as part of this research project and will report any safety concerns to the study team. The user data will be shared with the investigators to perform adherence analyses.

Assessments

Follow-up assessments will take place for all participants at months 1, 4, 6, 12, 18, 24, and 30 via a REDCap [47] survey link, and weight will be collected over Zoom using the participants' scale. Participants will receive US $20 compensation for each follow-up assessment (approximately 60 minutes). The study team will monitor the adverse events that arise during these assessments. Should any conditions present harm to the participant if they continue with the intervention, they will either be withdrawn from the intervention or asked to take a break from the intervention until the condition subsides. These conditions will be assessed on a case-by-case basis, with the principal investigator (TH) making the final decision. All participants will be reached for follow-up unless they express directly to the study team that they would like to withdraw from the study and all future assessments. All adverse events, protocol deviations, and reportable information will be entered into the REDCap database.

Anthropometric Data

Participants will report their height at baseline and their weight at all assessment points. Considering that data collection occurs remotely, all participants will use their own scale to weigh themselves while on a Zoom call with a member of the research team, who will view the scale through the screen and record it in REDCap. Participants may schedule their Zoom call at any time of the day and wear any clothing that they prefer. There was no standardization of the scale used to measure the weight.

The primary outcome of weigh-ins during assessments is to determine (1) the difference in weight from baseline to 6 months and (2) baseline to the 2-year follow-up, measured using BMI. The difference between the highest lifetime weight and current weight at baseline will be tested as a potential predictor of treatment response. Weight is collected at all assessment points.

Measures of Eating and Physical Activity

24-Hour Recall Interview

The Automated Self-Administered 24-Hour (2020) [51], developed by the National Cancer Institute, is a self-administered dietary recall that evaluates foods and beverages consumed during a 24-hour period. Participants will complete one recall per assessment, which will be emailed to them during the baseline and follow-up windows for 8 administrations. The call can be completed on the day and time of the participants choosing. The difference in total caloric intake evaluated by the Automated Self-Administered 24-Hour from baseline to the 2-year follow-up is a secondary outcome.

Eating Disorder Examination Questionnaire

The Eating Disorder Examination Questionnaire [52] is a 28-item questionnaire assessing symptoms of eating disorder, with subscales for dietary restraint, eating, shape and weight concerns, and a global score. The difference in the global score from the baseline to the 2-year follow-up was a secondary outcome.

International Physical Activity Questionnaire

The International Physical Activity Questionnaire [53] is a 27-item self-report measure that evaluates the average time spent completing different levels of activity and generates a total activity in metabolic equivalents (MET) value for vigorous and moderate physical activity, walking, and sitting. The difference in METs from baseline to 2-year follow-up was a secondary outcome.

Psychosocial Measures

Depression Anxiety Stress Scales

The Depression Anxiety Stress Scales [54] is a 42-item self-report measure of negative emotional states with subscales for depression, anxiety, and stress symptoms. The difference in each of these subscales from baseline to the 2-year follow-up period was a secondary outcome.

Short Form-36 Health Survey

The Short Form-36 Health Survey [55] is a 31-item self-report measure of health-related quality of life that generates 2 scores: a mental composite score and a physical composite score. Scores are calculated using subscales of physical functioning, limitations, energy, emotional well-being, social functioning, pain, and general health. The difference in scores from the baseline to the 2-year follow-up was a secondary outcome.

Patient-Reported Outcomes Measurement Information System Sleep Related Impairment

The Sleep Related Impairment (version 1.0) [56] is a 16-item measure of perceived functioning during waking hours in relation to tiredness and trouble sleeping. A raw score of the items was translated into a *t* score with SE. The difference in the total score from the baseline to the 2-year follow-up was a secondary outcome.

Diet Self-Efficacy Scale

The Diet Self-Efficacy Scale [57] is a 12-item self-report measure of self-efficacy for healthy eating specific to physical activity, healthy eating, and weight loss. The change in the total score (sum of all items) during the initial treatment period (6 months) and follow-up period (30-month outcome) was the primary outcome.

Self-reported Health Status

Health status is assessed using an adapted Centers for Disease Control National Center for Health Statistics National Health Interview Survey [58]. This measure includes questions about the type and frequency of health care sought. The frequency of provider visits will be calculated to determine the use of health care from baseline to 2-year follow-up as a secondary outcome.

Concomitant Weight Loss Intervention Measure

The use of any weight loss resources outside the study intervention will be measured at each follow-up. Resource types could include tracking progress toward a goal, communicating with a professional, sharing weight loss experiences with others, connecting with others about a weight loss experience, and reading articles or information to learn about weight loss, healthy eating, or exercise.

Noom Inc Use Data

Adherence

Both local and global adherence will be measured during the 6 months of the intervention, which will allow the evaluation of whether program activities were implemented as intended. Local adherence will include the percentage of completed versus expected activities in each of the available features of the Noom intervention (ie, the number completed/the number expected × 100%). Features measured for the Noom Healthy Weight Program included self-monitoring of diet, physical activity, weigh-ins, engagement with group members, coach communication, and reading psychoeducational materials. The expected engagement is determined by the treatment algorithm and varies by event and week. The data were collected passively within the app. Self-monitoring of diet will be calculated as the average of daily logged meals (user input)/5 (the number of times per day that a person is expected to eat) × 100%. Global adherence will be measured using a similar calculation for completion of scheduled coach check-ins. Features measured for Noom Healthy Weight Control included self-monitoring of diet, physical activity, weigh-ins, and reading psychoeducational materials.

Attrition

Formal withdrawal from the study or failure to complete scheduled assessments constituted a dropout for the study.

Compatibility

We will capture and categorize the types of technological problems encountered by participants during the intervention and document any fixes required. The percentage of successful

fixes during the first 12 months will be our compatibility measure.

Regular Eating

Daily regular eating will be defined by evidence of recorded 3 meals and 2 snacks within the app that were separated by >3 and <6 hours. Weekly metrics for the frequency of regular eating will be derived from these self-reported data and used in the time-series models described below.

Data Analytic Plan and Sample Size Considerations

Sample Size Considerations

To determine the statistical power, we conducted Monte Carlo simulation studies [59] with 10,000 draws to estimate (1) the effect of treatment on latent growth over treatment ($slope_{tx}$) and posttreatment follow-up ($slope_{FU}$). We studied a model with 6 time points and 2 growth processes ($slope_{tx}$/$slope_{FU}$). The power to detect 1 unit difference in outcome, assuming (SD 4.5) of the treatment effect (β_{tx}) on each growth process ($slope_{tx}$, $slope_{FU}$) was 0.92 to 94 with sample (N=600) and assuming (Cronbach α=.05). We varied patterns of missing data from 10% to 30%, increasing linearly over time, and retained >80% power to detect a 1.2-unit difference (SD 4.5) with the same sample size at 30% missing data. For within-treatment change, power with the same sample size was estimated at 90% to 98% power for a 2.5-unit change (SD 5) and a correlation of 0.5 between repeated measures. All the estimates assumed an α level of .05. Consequently, we were able to detect a difference of 1 BMI (SD 4.5) at the end of treatment and 1.2 BMI (SD 4.5) at follow-up, assuming a possibility of 10% to 30% attrition.

The power of the aim 2 moderator models involved adding latent variables based on 12 indicators. Using the above model with inclusion of an interaction term between latent moderator (M*) and treatment, we estimated 0.85 to 0.93 power to detect significant interaction assuming an effect size of 0.20 SD units for interaction above the 0.20 SD units attributable to the intervention and an α level of .05. For aim 3, power analyses were based on adherence measurements adapted from a previous project using Noom with binge eating [60] and assumed a network efficiency of 0.75. The adherence measurements included 13 data points extracted from the Noom app. We plan to examine the relationship between network entropy and outcomes, with statistical power for regression prediction at 100% for each outcome. A mediation model of weekly regular eating is a time-series mediation model and assumes that latent measures of meal-snack adherence mediate changes in weight. The calculation is based on effect size goals of 0.25, 0.50, and 0.75. The results of simulations suggest that the power for the smallest effect size (0.25) is approximately 0.80 with 10% missing data or less and moderate correlations between time and change in regular eating (0.35) and moderate correlation between regular eating and weight outcome (0.35).

Analysis and Statistical Methods

All available data will be used in outcome analyses. Missing data will be initially modeled as missing at random, and we will follow-up the parameter estimation of hypothesized effects with a sensitivity analysis comparing estimates to missing not at random models and imputation models.

Specific Aim 1

The primary and secondary end points included testing the comparative efficacy of the intervention versus control for weight loss, quality of life, psychosocial functioning, and self-reported health status. Weight loss was the primary end point, while quality of life, psychosocial functioning, and self-reported health status were secondary end points.

- Hypothesis 1: intervention users will show a significant advantage in the 6-month efficacy relative to the control for weight loss—after the intervention.
- Hypothesis 2: intervention users will show long-term (30 months) efficacy relative to the control program.

Our primary model will include 2 sequential latent growth curves modeled on the weight loss phase (0, 1, 4, and 6 months) and maintenance phase assessments (12, 18, 24, and 30 months). Latent growth curve modeling offers an advantage in terms of statistical power, as it accounts for measurement errors. In addition, this method capitalizes on the features of structural equation modeling and can examine variables simultaneously as independent and dependent variables, allowing for complex representations of growth and correlates of change [61]. The details of the model are described as follows [62]: Randomization variables (intervention vs control) are exogenous to the model and conditioned on each latent slope. The hypotheses that $\beta_{treatment}\neq0$ and $\beta_{maintenance}\neq0$ will be tested in the same model. We will test linear and nonlinear constraints on slope parameters to ensure an adequate fit and choose the best-fitting model using the Bayesian information criterion, Akaike information criterion, and root-mean square error of approximation. We will use the same modeling procedure for each of the primary outcomes.

Specific Aim 2

The secondary end point includes comparing potential moderators of treatment response in the intervention and control groups.

- Hypothesis 1: the clinical profile (composite moderator) will show a significant interaction with treatment condition, demonstrating that individuals with a more severe profile (older age, less support, more health conditions, and more psychosocial problems) will benefit more from the intervention than the control.
- Hypothesis 2: the difference between the lifetime highest and current weight will moderate the efficacy of the intervention or control. (Weight suppression has a larger negative impact on the control condition).

We will follow the 2-step procedure outlined by Kraemer [35] to generate a composite moderator derived from demographic and baseline severity data and participant baseline data to data reduction through principal component analysis while examining loadings to assess fit with the single severity or vulnerability profile. If evidence of multiple latent profiles exists, we will adapt our model accordingly, although our data reduction strategy will favor single-factor (eg, principal components vs

geometric rotation) methods. The candidate variables include age, sex, race or ethnicity, medical conditions, medication use, and psychosocial measures included in the assessments section. Only those variables with >0.5 factor loadings will be retained for the final latent variable, and we will then incorporate the latent moderator variable into the piecewise growth models and test the interaction between the moderator and treatment. For hypothesis 2, we will use the same general approach to examine the interaction effect of the difference between the highest weight and current weight, and treatment on the proposed outcomes.

Specific Aim 3

This exploratory aim intends to identify the treatment mechanisms of change in Noom's behavior change program, using a repeated-measures Bayesian belief network to establish adherence within the Noom Healthy Weight Program and examine changes over time.

- Hypothesis 1: the time-series Bayesian belief network model of adherence predicts study dropout, successful weight loss, and quality of life.
- Hypothesis 2: regular eating will mediate treatment effects of weight loss over time
- Hypothesis 3: self-efficacy of weight loss will mediate Noom Healthy Weight Program (intervention) or Noom Healthy Weight Control effects after the treatment and at the 12-month follow-up.

We will build an adherence model according to the local or global structure, as noted earlier, and test models via cross-validation on an 80/20 split of data before model building. The structural and individual parameter weights of the nodes and their stability over time will describe adherence, and the predictive accuracy will evaluate the utility of the model in practice. We will examine individual network performance metrics as mediators in a time-series estimate of causal effects in hierarchical within-participants models [63].

Exploratory hypotheses 2 and 3 will use measures of regular eating and weight loss self-efficacy during the first 3 months of treatment as mediators. Each model will use bias-corrected bootstrapped estimates of the indirect effect as our test of mediation [64].

Statistical Analysis: General Approach

We are using a latent growth curve model (piecewise) to model the separate change processes assumed during weight loss and after intervention [64,65]. All models will be examined for goodness of fit, normality assumptions, and linear versus nonlinear changes. Best-fit models will be interpreted for treatment effects (primary aim), and moderator models will be explicitly tested by integrating the latent variable into a best-fitting model.

With regard to baseline descriptive statistics, baseline variables (demographics and anthropometrics) will be compared using chi-square and *t* tests to determine if pretreatment bias exists in randomization. Data will be examined for robust outliers (ie, values that are not plausible, such as a BMI change of 60 kg/m^2 between assessments), and extreme values will be monitored and validated if they exist within the range of physiology or the scale of the measures. All data cleaning and analysis will be performed without knowledge of the conditions. The principal investigator will be responsible for the analysis and will be blinded to the conditions in any study reports throughout the project. Blinding will be broken only after the analysis for the specific aim has closed. All other staff will not be blinded to the condition.

Results

Enrollment began in March 2021, and the 6-month intervention phase ended in March 2022. Data collection for the final assessment will be completed in March 2024.

Discussion

Principal Outcomes

This study provides a description of the rationale, design, and procedures for testing the efficacy and mechanisms of change in a digital health intervention for individuals with overweight and obesity. We anticipate that overall benefits, and specific improvements for individuals in the higher-risk profile will be observed after the intervention in the Noom Healthy Weight Program compared with Noom Healthy Weight Control. The design allows an examination of 6 months of intervention and 24 months of maintenance outcomes to answer a fundamental question about the long-term value of digital weight loss interventions. To test the hypothesized long-term efficacy of the Noom Healthy Weight Program (intervention), the Noom Healthy Weight Control (control) retains the same digital format, access, and fundamental components of behavior change, with the exception of prescribed weekly advice delivered via articles rather than by a Noom coach, availability for group communication, and limited logging features. Consequently, inferences about intervention effects will be more closely linked to the mechanistic hypotheses embedded in the intervention and control designs.

Expected Novel Contributions From the Research

Adherence to weight loss interventions is an important factor to consider when evaluating the efficacy of an intervention. There is limited knowledge about the level of adherence needed for successful weight loss and few standard measures of adherence [22,66,67]. Adherence is difficult to track with the complex elements of a lifestyle intervention such as didactic information delivery, level and frequency of daily monitoring, length and quality of coach contact, and the participant's choice of meaningful changes. Smartphones provide a greater opportunity to model individual variability in specific behaviors prescribed by lifestyle interventions. Tracking how users interact with each feature in the program allows for the ability to measure use (eg, frequency of logging) and the application of intervention lessons (eg, Did coach interactions indicate that the participant was using intervention components?). Furthermore, self-efficacy plays a critical role in weight loss, as the way an individual thinks, behaves, and perceives success contributes to improved weight loss, better health choices [68], and confidence in making healthy decisions. The ability to

successfully solve weight loss barriers contributes to successful long-term weight loss maintenance [69,70] and better adherence to intervention protocols [71]. This project will allow us to parse out the effects of the Noom Healthy Weight Program on adherence, self-efficacy, and regular eating from the common general effects of digitized behavioral weight loss such as support, goal setting, and logging [16].

In addition, this design introduces a new approach to studying moderator effects, aiming to profile individuals by demographic and severity indicators at baseline, allowing for the collective sum of smaller potential moderators to contribute to potentially important and clinically meaningful differences in response to these treatments.

Limited information exists regarding the long-term effectiveness of digitally delivered behavioral weight loss programs [24]. Weight loss maintenance has been achieved through in-person programs using continued access to coaches and logging [19,30]. However, in-person treatment is often too costly or uncovered by insurance and remains inaccessible for many people [30,72]. Participants providing feedback in other weight loss trials reported that weight loss success would be greater if access is provided to these intervention components for long term and at no cost or low cost [20,73]. Mobile apps provide a viable and cost-effective alternative. Testing the logging, coaching, and group features of Noom over the long term will provide important information about the association between the use of digitally delivered behavioral strategies and maintenance of weight change.

Alternative Design Considerations

We considered alternative digital platforms for comparison with our intervention condition; however, the constant evolution of commercial and noncommercial alternatives increased the risk that interventions could be contaminated in the case of a substantial change in delivery. Furthermore, using 2 different versions of Noom Inc will ensure a similar user experience with visual presentation, design, and functionality, thus reducing the possibility of group differences resulting from differences between programs. Recruiting users directly from Noom Inc allows us to target individuals interested in using digital interventions for weight loss and users motivated to lose weight. Local sampling (eg, from hospital programs or local environments) and stratified sampling strategies were considered but posed threats to generalizability. Selecting individuals seeking intervention from Noom Inc allows us to provide the most robust test of the existing platform, which has adapted the experience with its consumer base. Therefore, our national recruitment kept our sampling as wide as possible by enrolling those who focused on general app weight loss and minimalizing exclusion criteria. However, we recognize that the choice of a non–coach control condition limits full control of the active ingredients of the experimental condition and generalizability of the effects to Noom Inc's noncoaching products.

Limitations

The limitations of this study include potential for intervention contamination and self-directed weighing. It is possible that study participants could use weight loss resources outside of what is specifically delivered via the study intervention; however, we will be able to measure concomitant treatment use at study follow-up as a potential confounder. Owing to feasibility, timeline, and cost, weight will not be measured via a standard scale or with scales that have similar specifications.

Conclusions

Our study will use the technology of the Noom platform to overcome obstacles to weight loss and long-term weight loss maintenance, such as accessibility and the use of digitally delivered evidence-based features. In addition, this platform provides us with the opportunity to measure adherence to a digitally delivered behavioral intervention while exploring the role of each feature.

Acknowledgments

This study is funded by Noom Inc.

Data Availability

At the end of the trial, results will be posted on ClinicalTrials.gov, and data that support the findings of this study will be available from the corresponding author (RS) upon reasonable request.

Authors' Contributions

Lead investigators (principal investigator [TH] and coinvestigator [RS]) contributed to trial design, final approval of protocols and tracking systems, direction and supervision of the study team (JB, AB, and KC), data management, analyses, data interpretation, and manuscript preparation.

Trial management (project manager [JB]) included protocol development and adherence, staff management, budget monitoring, randomization, organization of study procedures, records, timelines, report development, and progress reports (recruitment, retention, data collection, budget, etc).

Participant contacts (research coordinators [AB, KC, and AS] and project manager [JB]) included recruitment, consenting, and following up with the participants.

Data management (research coordinators [AB and KC] and project manager [JB]) involved developing, testing, and maintaining the tracking and survey programs, data cleaning, and organization.

Conflicts of Interest

TH serves as the advisory board of Noom Inc. TH and RS have equity ownership in Noom Inc, the study sponsor and the manufacturer of the Noom Health platform. AM and ESM were employed by Noom Inc.

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Abbreviations

DPP: Diabetes Prevention Program

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Protocol

A Group Videoconferencing Intervention (C@nnected) to Improve Maternal Sensitivity: Protocol for a Randomized Feasibility Trial

Victoria Binda[1], MD; Marcia Olhaberry[2], PhD; Carla Castañon[1], MD; Constanza Abarca[2], MSc; Catalina Caamaño[2], MSc

[1]Deparment of Family Medicine, Medicine Faculty, Pontificia Universidad Católica de Chile, Santiago, Chile

[2]School of Psychology, Social Sciences Faculty, Pontificia Universidad Católica de Chile, Santiago, Chile

Corresponding Author:
Victoria Binda, MD
Deparment of Family Medicine
Medicine Faculty
Pontificia Universidad Católica de Chile
Av. Vicuña Mackenna 4860, Macul
Santiago, 7820436
Chile
Phone: 56 223548535
Email: vbinda@uc.cl

Abstract

Background: Early childhood development is highly dependent on the sensitive care provided by caregivers, and interventions focused on supporting parents to improve their sensitivity have shown to be effective. The COVID-19 pandemic has had a significant impact on mental health, with pregnant women and mothers of infants being an especially vulnerable group and maternal sensitivity particularly affected. However, access to face-to-face interventions is restricted; thus, it is important to have remote interventions to support this group of mothers.

Objective: The objective of this study is to evaluate the feasibility and acceptability of C@nnected, a group videoconferencing intervention to improve maternal sensitivity aimed at mother-infant dyads attending primary health care centers in vulnerable areas of Santiago, Chile.

Methods: This is a randomized feasibility single-masked (outcome assessor) study with a qualitative component. It will involve a block randomization procedure to generate a 3:2 allocation ratio (with more people allocated to the intervention arm). The intervention consists of 4 group videoconferencing sessions adapted from a face-to-face intervention with proven effectiveness. The control group will receive treatment as usual, along with educational brochures. The feasibility and acceptability of this study will be quantitatively and qualitatively assessed. Changes in clinical outcomes relating to maternal sensitivity, depressive symptoms, postpartum maternal attachment, and infant socioemotional development will also be evaluated.

Results: We finished adapting the face-to-face intervention to the videoconferencing format in July 2021. The study began recruitment in August 2021, and enrollment is expected to end in August 2022, with final study results expected in December 2022.

Conclusions: This study will contribute evidence for the use of eHealth interventions to promote maternal sensitivity. It will also inform the design and implementation of a future randomized clinical trial.

Trial Registration: ClinicalTrials.gov NCT04904861; https://clinicaltrials.gov/ct2/show/NCT04904861

International Registered Report Identifier (IRRID): DERR1-10.2196/35881

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KEYWORDS

maternal sensitivity; group intervention; primary care; eHealth; responsive caregiving; videoconferencing; Early childhood; caregiver; eHealth intervention; health intervention; parenting; children; peer-support

Introduction

Background and Rationale

Ensuring adequate early childhood development is necessary for countries to move forward in an equitable and sustainable way; therefore, interventions to support early childhood development are essential to realize the United Nations Sustainable Development Goals [1]. The experience that best facilitates adequate child development is responsive caregiving provided by parents or primary caregivers [2], and one of the most relevant predictors of child development is the quality of the mother-child interaction [3]. The more sensitive, responsive, attentive, and cognitively stimulating the mother is, the better the results in her child. The main risk factors associated with the presence of low maternal sensitivity are maternal depression [4-6], low socioeconomic status, and other psychosocial risk factors [7], which are mediated by the high levels of stress experienced by these families [8].

Before 2020, mental health disorders were leading causes of global health-related burdens. With the emergence of the COVID-19 pandemic, mental health disorders have greatly increased across the world [9], especially in high-risk populations [10]. Pregnancy and postpartum are periods of special vulnerability for mental health. There are short- and long-term negative consequences to the physical, cognitive, and psychological development of children associated with prenatal and postpartum stress, anxiety, and depression [11], which are mainly due to a decrease in the quality of mother-child interactions. A recent Canadian study [12] carried out in pregnant women and those with children under 1 year of age showed an increase in anxiety symptoms from 29% to 72% after the COVID-19 pandemic and postpartum depression symptoms from 15% to 47%. The risk of mental health problems in pregnancy and the first year postpartum in the context of the pandemic has increased due to concerns related to the well-being of the child and aggravated by the consequences of preventive measures such as confinement, physical distance, reduced health checks, and difficulty obtaining support from the usual networks [13]. Moreover, these mental health problems are present at a greater extent in women of low socioeconomic status. Countries are recommended to implement mitigation strategies to reduce the mental health burden imposed by COVID-19, considering their local context and vulnerable populations [9].

For mothers to provide the responsive caregiving that their children need, they must have adequate mental health and a support network. Early interventions focused on supporting parents in providing responsive caregiving have proven to be effective [14-16]. Health services provide a critical starting point for these interventions, given their reach to pregnant women, families, and young children [16,17]. Thus, it is imperative to implement supportive interventions for pregnant and postpartum women that promote adequate sensitivity toward their children.

Global lockdown measures have disrupted routine health care for non–COVID-19 patients, so telemedicine has been escalated to reduce the risks of disease transmission [18]. Electronic mental health care is one of the most widely offered methods of health care, with evidence of applicability and efficacy in a wide range of formats [19]. A systematic review showed that group video conferencing interventions are feasible, improve access to health care, and have results similar to those obtained in face-to-face groups [20]. There is an interest in retaining or further incorporating virtual components devised in response to the COVID-19 pandemic into the standard delivery of interventions in the future [21]. In this context, it is important to implement remote interventions in primary health care (PHC) for mothers of children under 1 year of age that promote responsive caregiving.

Chilean Context

Chile is a Latin American country that presents an important burden of mental health problems. The World Health Organization places Chile among the countries with the highest burden of morbidity from psychiatric diseases [22], and it has the world's highest rates of postpartum depression [23,24] and preschool mental health problems [25]. Despite this, only 38.5% of those diagnosed receive some type of mental health service [22]. Chile has a comprehensive protection system for children from the prenatal period to 4 years of age known as Chile Crece Contigo (translated as "Chile Grows With You") that aims to help all children reach their full potential for development through universal and targeted support services [26]; however, no specific interventions are offered to promote maternal sensitivity.

In 2 previous research projects, we developed and evaluated a face-to-face group intervention to promote maternal sensitivity during the child's first year of life [27]. The results, which will be published soon, showed positive effects on maternal sensitivity in mother-infant dyads attending PHC centers but low adherence rates. We also found a significant reduction in maternal depression symptoms and infant socioemotional development difficulties of resident dyads at Chilean female penitentiary centers [28].

Objective

The primary aim of this paper is to report on the protocol comprising a pilot randomized feasibility trial to evaluate the feasibility and acceptability of C@nnected, a group videoconferencing intervention that aims to improve maternal sensitivity in mother-infant dyads attending PHC centers in Chile. Along with detailing the intervention, this paper provides an account of the plan to collect both quantitative and qualitative measurements of outcomes.

The secondary aims are to (1) to estimate the effect size in clinical outcomes between the groups after the intervention in terms of maternal sensitivity, postpartum depressive symptoms, postpartum attachment, and socioemotional development; and (2) identify the key parameters for the implementation and evaluation of the intervention, which will enable the design of an effectiveness study in the future.

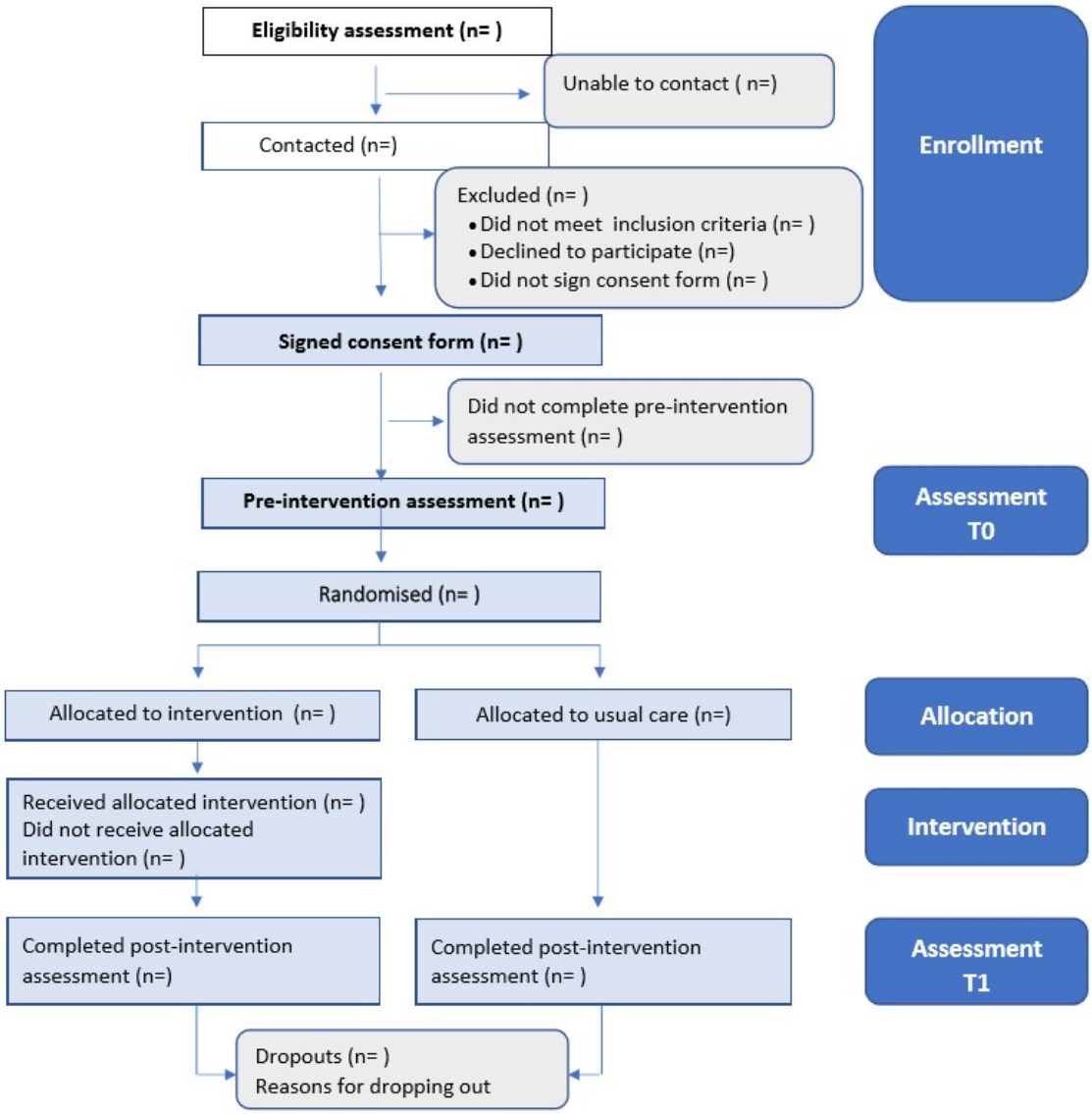
Methods

Trial Design

This is a data analyst–blind, superiority, pilot feasibility study with a mixed design. The quantitative component is a 2-arm randomized parallel group of 50 mothers of infants aged 6-12 months who receive health care in 2 PHC centers in Santiago, Chile. Mothers will be randomized into the intervention or control group in a to 3:2 ratio (with more people allocated to the intervention arm). Both groups will receive the usual treatment and educational brochures provided by the PHC center, with the intervention group also receiving the C@nnected videoconferencing intervention. The qualitative component will consist of semistructured interviews with intervention providers to identify possible improvements and core components of the intervention as well as focus groups with mothers participating in the intervention to evaluate user acceptability and satisfaction with the implementation.

This type of study is suggested by the literature as an initial requirement for the implementation of an innovative intervention before applying it on a larger scale. It is also recommended to use quantitative and qualitative methodologies to evaluate feasibility and acceptability [29]. This clinical trial protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and [30] and CONSORT (Consolidated Standards of Reporting Trials) guidelines [31]. Figure 1 provides a flowchart of the study process.

Figure 1. Flowchart of participants. T0: preintervention assessment; T1: postintervention assessment.



Study Setting

This study will be conducted at 2 PHC centers located in La Pintana and Puente Alto, 2 counties in Santiago, Chile, with low socioeconomic status. These counties have higher levels of poverty, overcrowding, and illiteracy than the national average.

Eligibility Criteria

The population eligible for this study will be mothers with infants between 6 and 12 months of age attending either of the

participating PHC centers. This age group was chosen because in the meta-analysis of the effectiveness of interventions to improve maternal sensitivity by Bakersman-Kranenburg et al [14], better results were observed with infants aged between 6 and 12 months than those under 6 months of age.

Inclusion Criteria

The inclusion criteria are mothers of infants between 6 and 12 months who (1) attend 1 of the participating PHC centers, (2) are older than 18 years, (3) can speak Spanish fluently, and (4) have an electronic device that allows videoconferencing (ie, computer, tablet, or smart cell phone). In the case that a participant does not have internet access at home, we will consider supplying them with a prepaid card with internet gigabytes.

Exclusion Criteria

The exclusion criteria are mothers with severe intellectual deficits or current psychotic symptoms and those participating in another early intervention at the PHC center.

Interventions

Control Arm (Treatment as Usual Plus Educational Brochures)

Participants of this study are patients of the Chilean public health system and are supported by the Chile Crece Contigo national comprehensive child protection system. Some of the benefits are health checks during pregnancy, care during labor and delivery, child health checks, delivery of material for early stimulation, and detection and timely treatment of developmental delays [26].

In addition to receiving treatment as usual (TAU) at their PHC center, the control group will receive digital brochures with information on early parenting (once a week for 4 weeks). These brochures will summarize the content of each workshop session and the homework to be complete as a family. These are the same brochures handed out after each session in the intervention group.

Intervention Arm (TAU Plus C@nnected Group Videoconferencing Intervention)

The intervention group will participate in C@nnected, a group videoconferencing intervention adapted to the e-mental health format from a face-to-face brief attachment–based intervention that was previously designed, piloted [27], and evaluated through a randomized controlled trial (RCT) (results not yet published) to promote maternal sensitivity in mother-child dyads attending PHC centers. The face-to-face intervention was developed in 2012 following the framework proposed by the UK Medical Research Council for the development and evaluation of complex interventions [32] by the first 2 authors (VB and MO) of this study, considering the available evidence and local qualitative information. The core components obtained from the evidence were recommendations of the systematic review by Bakersman-Kranenburg et al [14] on effective interventions to improve parental sensitivity. The review shows that interventions that are carried out after 6 months of life, are of brief duration, and incorporate a second caregiver are more effective. From local qualitative research obtained through focus groups with both the possible users and providers of the intervention, different topics considered relevant by the participants and ideas on the best way to deliver the intervention were incorporated.

The general objective of the intervention is to enhance maternal sensitivity and promote skills in reading infant cues and responding sensitively, given that the inclusion of this variable in interventions, specifically in conditions of vulnerability, is associated with favorable results [33]. Each intervention session defines themes and objectives, worked through experiential activities, and immediately puts into practice the presented topics. In 1 of the sessions, another primary caregiver is actively invited to participate. At the end of each session, educational brochures with key concepts and homework are handed out to the participants to share and practice the new skills at home with the rest of the family.

The intervention is aimed at mother-infant dyads and consists of 4 sessions delivered over the course of 4 weeks, at 2 hours per week. Each group will include a minimum of 3 and a maximum of 6 dyads per group led by a trained provider. The activities are protocolized in a manual and are designed to be carried out with the infant. The manual specifies the structure and content of each session, the details of the materials to be used, relevant aspects to be emphasized during the activities, and additional information that delves more deeply into the issues addressed in the workshop. This aims to ensure the comprehensive replication of the intervention, which has been associated with the best effectiveness in this type of intervention [34]. Table 1 shows the main components of the intervention.

The adaptation to the video conferencing format was carried out between May and July 2021 by 2 authors of the face-to-face intervention in conjunction with a designer experienced with digital interventions. We used the recommendations of the Early Intervention Foundation [21] to achieve good results in virtual interventions as a frame of reference, which include the use of engagement elements and mechanisms to improve adherence and flexibility.

We reviewed the complete content of the workshop, adjusted the sessions to 1.5 hours, and adapted the training manual and all the activities for use in a web-based group environment. We aim to provide lighthearted and interactive activities to allow all participants to understand and share their experiences. In addition, we have included some activities associated with the impact of the COVID- 19 pandemic. Figure 2 is a screenshot showing an example of a videoconference session, and Figure 3 shows 4 examples of activities that will take place in the workshop.

Table 1. Main components of the intervention with the objectives and activities of each session outlined.

Session	Name	Objectives	Examples of activities
1	"Knowing each other around attachment"	• Achieve group cohesion • Provide knowledge about attachment • Recognize expected affective behaviors in an infant	• Dynamics of presentation • Difficulties in motherhood • Common myths on attachment and parenting
2	"What does my baby need?"	• Recognize crying as a signal of communication • Recognize different expressions of emotions in babies • Understand importance of responding to infant's needs	• Recognize sensitive responses in caregivers • Work with different emotions and expressions in infants
3	"Massages and agreements in parenting style" (Another relevant caregiver is invited)	• Work on parental sensitivity through massage • Involve another caregiver in the concept of attachment • Achieve consensus among caregivers in some relevant issues of parenting	• Infant massage with emphasis on sensitive interaction • Watch locally made videos showing different parenting situations (eg, infant´s signs, safe exploration, talking and reading to children, and challenges in parenting)
4	"Boundaries and positive parenting"	• Understand the importance of setting boundaries with respect and love • Have strategies to set boundaries • Resolve doubts regarding child abuse • Recognize behaviors associated with positive parenting • Know children's rights	• Invent a story from an image that shows a difficulty in parenting • Comment on experiences related to child abuse • Express any doubts regarding the proper way to treat children • Provide reflections on children's rights

Figure 2. Screenshot of a videoconference session.

Figure 3. Screenshots illustrating different intervention activities. (A) Common myths in attachment and parenting; (B) working with different emotions and expressions in infants; (C) watching videos showing different parenting situations; (D) inventing a story from an image that shows the challenges of parenting.

In this study, each workshop will be led by a provider who is also a psychologist. Before conducting the intervention, the providers will receive a half-day training from the authors of the intervention. The video conferences will be recorded to guarantee the fidelity of the intervention and used later to perform a qualitative analysis of the change process [35].

To ensure internet connection during the evaluations and videoconferencing sessions, participants who do not have regular internet access will receive a prepaid card with internet gigabytes. To improve adherence to video conferencing sessions, the participating mothers will agree on the most convenient day and time for them to be held. In addition, a telephone chat group will be created to remind participants of the upcoming session and homework 1 day prior. If a participant cannot attend a videoconference session, they will be contacted by telephone by the provider to summarize the most important information of the session. This call will last between 15 and 20 minutes, and the main ideas and content of the session will be discussed, reinforcing the importance of positive interactions between mother and baby, sensitive care, and participation in the subsequent group sessions. For each participant to be considered to have received the intervention, they must attend at least 2 group videoconference sessions and 2 telephone calls or attend at least 3 of the 4 group video conference sessions.

Outcome Measures

Primary Outcome Measures

The primary outcome measures are listed as follows.

Feasibility of the Intervention

Feasibility will be evaluated in terms of the following factors: (1) eligibility rates, referring to the proportion of mothers who meet inclusion criteria compared with the total number of mothers contacted by telephone; (2) recruitment rates, meaning the proportion of mothers who accept the invitation to participate in the study with respect to those who meet eligibility criteria; (3) adherence to group intervention, meaning the proportion of participating mothers in the intervention arm that receive the intervention (at least 2 group video conference sessions plus 2 telephone calls) and the average number of online sessions attended; and (4) follow-up rates by treatment condition, which refers to the proportion of participants that completed the postintervention assessment

Acceptability of the Intervention (Quantitative Assessment)

Satisfaction with the intervention will be measured with the Spanish version of the Credibility/Expectancy Questionnaire (CEQ) [36] at the preintervention assessment (t0) and 2 to 3 months later in the postintervention assessment (t1) for both arms of the study. This is a self-report instrument that comprises 6 items scored on a 9-point Likert-type scale ranging from 1 (not at all) to 9 (very) as well as 2 factors (credibility and expectation) that explain 82.46% of the variance. In terms of reliability, the total questionnaire showed a Cronbach α of .8, and scores range from 0 to 100, with higher scores indicating higher acceptability of the intervention.

Acceptability of the Intervention (Qualitative Assessment)

This measure will evaluate the experience of all participants of the intervention, both those providing the intervention and the mothers participating in the workshops, to determine which factors are associated with acceptability, barriers, and facilitators to implementation. This will be carried out as follows:

First, semistructured interviews will be conducted with the providers of the intervention. These interviews will inquire about the changes, achievements, and learning observed in the participants, the most and least valued topics and methodologies, difficulties in implementation and how it could be integrated into standard practice, possible improvements to the intervention, and core components of the intervention.

Second, focus group interviews with mothers participating in the intervention will be carried out. Two focus groups, each including 4 to 6 mothers, will be asked about their opinions regarding the usefulness of the intervention, changes, achievements, learning experiences, satisfaction, most and least valued topics and methodologies, and possible improvements. The aim of this focus group interview is to collect information on participants' experience and identify possible improvements and the core components of the intervention.

Secondary Outcome Measures

Clinical outcomes measures will be carried out to characterize the sample and estimate how the intervention could guide the sample size of the next effectiveness study. These clinical outcome measures will be assessed at the preintervention assessment (t0) and 2 to 3 months later in the postintervention assessment (t1). Table 2 shows the schedule of enrollment, interventions, and assessments, and Figure 4 shows the study design schema.

Table 2. Schedule of enrollment, interventions, and assessments.

Scheduled items	Study period				
	Enrollment	Preintervention assessment	Allocation	Intervention	Postintervention assessment
Time point	t0	t0			t1
Enrollment					
Eligibility screen	✓				
Informed consent	✓				
Initial evaluation		✓			
Allocation			✓		
Interventions					
Intervention group (TAU[a] + group videoconference intervention)				✓	
Control group (TAU + educational brochures)				✓	
Assessments					
Feasibility	✓	✓		✓	✓
Acceptability: quantitative evaluation (CEQ[b])		✓			✓
Acceptability: qualitative evaluation					✓
Clinical outcomes (ESA[c], EPDS[d], ASQ:SE-2[e], MPAS[f])		✓			✓

[a]TAU: treatment as usual.

[b]CEQ: Credibility/ Expectancy Questionnaire.

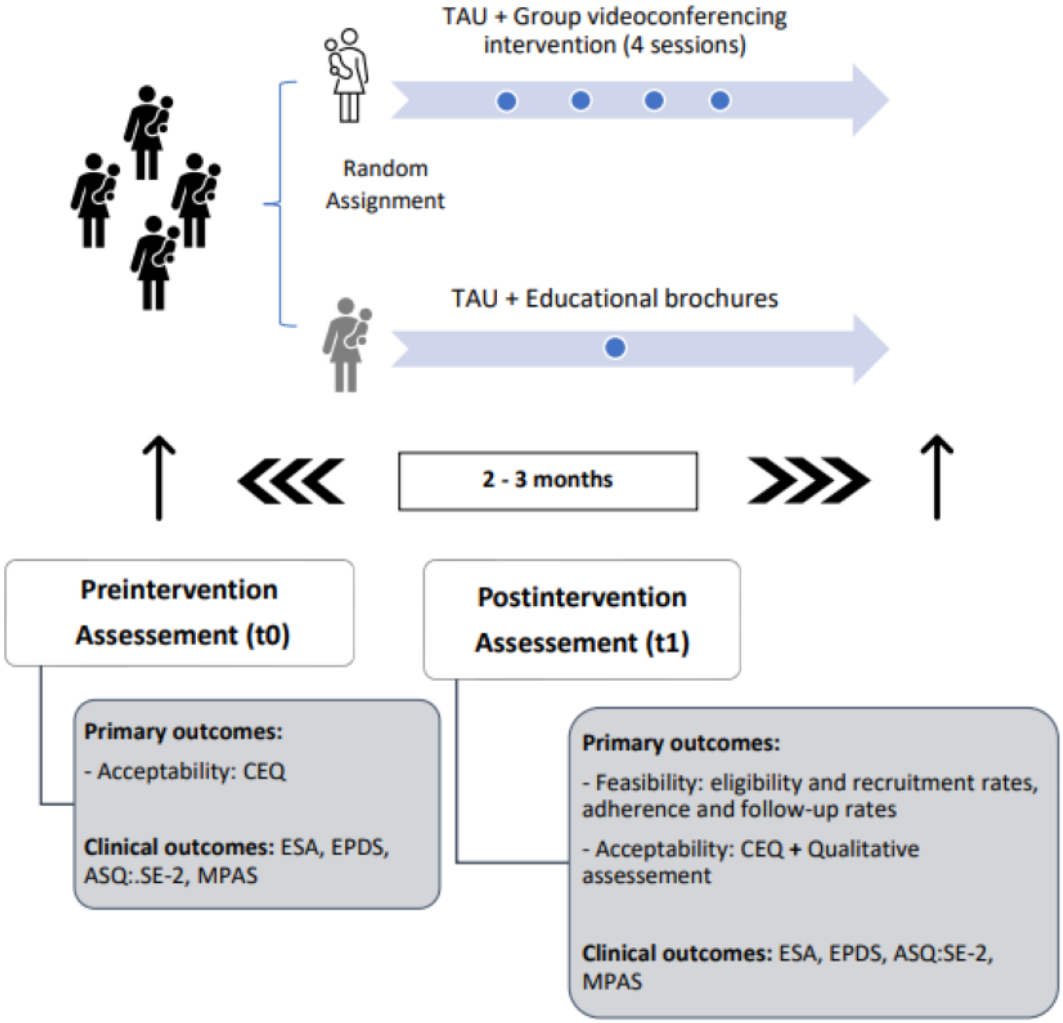
[c]ESA: Escala de Sensibilidad del Adulto (Adult Sensibility Scale).

[d]EPDS: Edinburgh Postnatal Depression Scale.

[e]ASQ:SE-2: Ages and Stages Questionnaire: Social-Emotional.

[f]MPAS: Maternal Postnatal Attachment Scale.

Figure 4. Study design schema. ASQ-SE-2: ages and stages questionnaire, social -emoaitonal; CEQ: measurement of credibility/expectancy questionnaire; ESA: adult sensibility scale; EPDS: Edinburgh postnatal depression scale; MPAS: maternal postnatal attachment scale; TAU: treatment as usual.



The secondary outcome measures are listed as follows.

Changes in Maternal Sensitivity

Changes in maternal sensitivity will be measured with the Escala de Sensibilidad del Adulto (ESA), also known as the Adult Sensitivity Scale [37]. Maternal sensitivity is the primary outcome that will also be measured in the effectiveness study since the objective of the intervention is to improve maternal sensitivity. This scale assesses an adult's sensitivity in their interaction with children between 6 and 36 months of age. The mother and child are filmed for 5 minutes during free play interaction. The only instruction given is "do what you always do." The coding system considers a rubric with 19 indicators that are related to different aspects of the sensitivity response. Each indicator is given a score between 1 and 3, with a higher score indicating higher sensitivity. In terms of reliability, the Cronbach α of the instrument is .93. The coders will be external to the research and blind to the randomized group, sociodemographic variables, and results of the different measurements. The Cohen kappa coefficient between the encoders will be obtained for the first 20 videos.

Changes in Maternal Depressive Symptoms

The measurement of postpartum depressive symptoms is of great relevance given its important association with low maternal sensitivity. This will be measured with the Edinburgh Postnatal Depression Scale (EPDS) [38], which is globally used to screen for maternal depression [39]. It consists of a self-administered questionnaire containing 10 multiple-choice questions, with 30 points as the maximum score and higher scores indicating higher depressive symptomatology. The scale has been validated in Chile [40] and has a sensitivity of 100%, a specificity of 80%, and adequate internal consistency (Cronbach α=.77). We will use the cutoff point of ≥10 to consider the presence of postpartum depressive symptoms.

Changes in Infants' Socioemotional Development

The measurement of socioemotional development will allow for a more direct evaluation of the effects of the intervention on the participating infants. These will be measured with the Spanish version of the Ages and Stages Questionnaires: Social-Emotional (ASQ:SE-2) [41]. Several studies have consistently supported the precision and ease of use of ASQ-SE-2, which has been used widely in early mental health intervention programs [42]. We will use the 6- and 12-month versions. A higher score indicates worse socioemotional development. Each version has its specific cutoff score, and those with scores higher than the cutoff are considered to be "at risk for socioemotional development delay."

Changes in Postpartum Maternal Bonding

The measurement of maternal bonding will allow us to chracterize the sample and evaluate possible changes to this parameter due to the intervention. We will use the Spanish version of the Maternal Postnatal Attachment Scale (MPAS) [43], a self-report measure that has 19 items ranging from 1 (low bonding) to 5 (high bonding) and is divided into 3 factors: quality of bonding, absence of hostility, and pleasure in interaction. Psychometric properties of the original version of the scale have shown an adequate internal consistency (Cronbach α=.78).

Participant Timeline

The study duration for the participants will be 3 months, regardless of study arm allocation. This study does not have a follow-up phase. The total trial data collection period will be approximately 14 months.

Sample Size

As this is a feasibility study, no hypotheses will be tested, and a formal power calculation is not required [44,45]. However, the evidence suggests a sample size of 25 people per arm for a small effect size of 0.2, which is suitable for clinical feasibility trials [45]. Therefore, a sample size of 50 participants was established, and the 3:2 allocation was chosen considering possible partial adherence to the intervention.

Recruitment

Potential study participants will be identified from a list provided by each PHC center. Two research assistants (Rs), both clinical psychologists, will be in charge of calling the mothers included in the list, verify by telephone whether they meet the inclusion criteria, and explain the study in detail. Mothers who meet the inclusion criteria and are interested in participating will be sent an online protocol that will include informed consent. Mothers who do not wish to participate will be asked for the reasons. Once the mother provides electronic consent, the initial evaluation scales (EPDS, ASQ:SE- 2, MPAS, and CEQ) and a sociodemographic survey will be sent to her electronically. Finally, the mother and RA will agree upon at a time to make a video call to record 5 minutes of free play required by the ESA.

Assignment of Interventions

Sequence Generation

To generate the random allocation sequence, we will use a computer software program called Studyrandomizer using permuted block randomization with a block size of 5 in a 3:2 ratio.

Concealment Mechanism

Allocation concealment will be ensured because the randomization code will not be released until all patients have been recruited and all initial measurements have been completed.

Implementation

After each participant signs the informed consent and performs baseline measurements, the RA recruiting the participant will contact another investigator to request the arm to which the participant has been randomized (intervention or intervention plus TAU). Thus, the enrollment of the participants will be performed by a different RA from the one who will generate the randomization sequence. The investigator will not be aware of the results of the initial evaluation. After completing the initial evaluation, the RA, who is blind to the random allocation sequence, will notify the participants of the type of intervention to which they will be assigned.

Blinding

Trial participants will be blinded to the conditions of the 2 arms; they will know the type of intervention to which they are assigned, but they will not know which of the interventions is considered the control. The intervention providers will be instructed not to disclose the treatment that participants are receiving. Follow-up measurements will be taken blindly for the assigned group. The assessments of outcome variables will be conducted by RAs who are blind to the treatment allocation.

Harms

No harm or risk to participants from this study is expected to occur. In cases where any alteration is detected in the postpartum depression and socioemotional development assessment scales, the mother will be informed and, with her consent, referred for management at her PHC center.

Data Collection

Data obtained from the sociodemographic survey and the quantitative evaluations will be stored electronically and will not be linked to the identities of the participants. The data will be in a different spreadsheet than the one with personal data, which only 1 RA has access to, thus ensuring that the identity of the participants is protected.

Once the intervention is complete, both groups will complete the scales again (EPDS, ASQ:SE- 2, MPAS, and CEQ), and a new video recording (ESA) will be made by an RA different from the one who provided the intervention. Finally, the qualitative evaluation of the process will be carried out.

Data obtained from the qualitative information (the interviews and focus groups) will be recorded, transcribed, and assigned codes that will ensure the anonymization and protection of the participants' identities.

Data Analysis

For the quantitative analysis, descriptive statistics will be used for the clinical and sociodemographic variables of the groups, eligibility rate, recruitment, and adherence. Analysis of covariance (ANCOVA) will be used to determine differences in clinical outcomes between the groups. Data analysis will be conducted using SPSS Statistics 27 software (IBM Corp).

For the qualitative analysis, interviews and focus groups will be analyzed considering the conceptual basis of the Framework Analysis Approach [46], which is commonly used for thematic analysis of semistructured interview transcripts. It allows for the identification of commonalities and differences in qualitative data to draw descriptive and explanatory conclusions grouped around themes. It is different from Grounded Theory, which involves making systematic comparisons between cases to refine

each topic and is aimed at generating social theory [47]. The Framework Analysis Approach is best suited to research that has specific questions, a limited time frame, a predesigned sample (eg, mothers and professionals participating in the intervention), and a priori issues (eg, evaluation of implementation of an intervention)

Ethics Approval

All procedures and informed consent were approved by the Scientific Ethics Committee of Health Science of Pontificia Universidad Católica de Chile. The study was approved on March 11, 2021, and renewed on January 6, 2022, with validity of 1 year (# 200813008).

Incentives

The participants will not receive any incentive for participating in this study. An incentive equivalent to US $12 will be offered to participants who complete the postintervention assessment.

Results

The adaptation of the face-to-face intervention to the eHealth format was carried out between March and July 2021, and enrollment began in August 2021. Enrollment and data collection will continue until 50 participants have been enrolled and their data collected. We expect to complete the enrollment in August 2022 and for the primary impact analysis to be conducted in December 2022.

Discussion

Expected Findings

The objective of this study is to assess the feasibility and acceptability of the C@nnected group videoconferencing intervention, which aims to improve maternal sensitivity in mother-infant dyads attending PHC centers in Chile and was adapted from a face-to-face intervention. We expect to find an adequate feasibility of this intervention in terms of achieving good recruitment rates (around 60% mothers will accept the invitation to participate in the study with respect to those who meet eligibility criteria), good adherence to group intervention (around 60% in the intervention arm will receive the intervention), and adequate adherence to the sessions (the average expected attendance is 3 out of 4 sessions). We expect to find a very good acceptability of the intervention with high scores in the satisfaction questionnaire and positive evaluation in the qualitative assessment. We also expect to find favorable results of the intervention in terms of clinical outcomes, especially relating to maternal sensitivity, which will allow us to estimate the sample size for the future RCT to evaluate effectiveness. The results of this study will inform the key parameters for the implementation and evaluation of the intervention and facilitate the design of an effectiveness study in the future.

The COVID- 19 pandemic has led health teams to adapt some interventions to the eHealth format, and it is likely that many of these interventions will remain in this format even after the pandemic is over. Nevertheless, we should not assume that interventions will work equally as well when delivered through virtual methods. Existing interventions must be carefully adapted and include a focus on identifying the core components that must be maintained [21].

Internationally, there are some group parenting interventions with proven efficacy to increase maternal sensitivity; however, one of the main problems of this type of intervention is low adherence [48]. The development of eHealth interventions may improve the accessibility and flexibility of group-based interventions, which are important for parents. If this group intervention delivered by videoconference is shown to be feasible, it will be particularly useful for mothers that face barriers to attending face-to-face interventions.

Limitations

This is a small pilot study in a highly vulnerable area of Santiago, Chile, so its results cannot necessarily be extrapolated to other contexts.

Strengths

The main strengths of this study are as follows: 1) the intervention has proven effectiveness and was designed locally using a framework that was later adapted for the electronic format; 2) it will evaluate the acceptability and feasibility of the intervention both quantitatively and quantitatively; and 3) it will evaluate clinical outcomes. In our opinion, these are essential steps to take before conducting a randomized controlled study, and they will subsequently allow us to scale up this intervention in similar contexts once its effectiveness is evaluated.

Conclusions

This study will lay the foundation for a randomized clinical trial to examine the effectiveness of an intervention to improve maternal sensitivity in mothers attending PHC centers.

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Data Availability

In keeping with transparency recommendations, data will be made publicly available after primary analyses in a public data repository. To promote dissemination of the study findings to potential end users, patients, and clinicians, as well as the scientific

community, the findings will be published in academic journals presented at conferences. Primary health care center directors will also receive the manuscripts.

Authors' Contributions

VB is the primary investigator. MO provided guidance on methodology and optimization of study design. C Castañon drafted the manuscript. CA and C Caamaño will be primarily responsible for data collection and provide oversight to ensure the protocol is adhered to during participant recruitment and data collection.

Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
ASQ: SE- 2: Ages and Stages Questionnaires: Social-Emotional
CEQ: Credibility/ Expectancy Questionnaire
CONSORT: Consolidated Standards of Reporting Trials
EPDS: Edinburgh Postnatal Depression Scale
ESA: Escala de Sensibilidad del Adulto
MIDAP: Millennium Institute for Research on Depression and Personality
MPAS: Maternal Postnatal Attachment Scale
PHC: primary health care
RA: research assistant
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: treatment as usual

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Protocol

Testing Behavioral Nudges and Prompts in Digital Courses for the Self-guided Treatment of Depression and Anxiety: Protocol for a 3-Arm Randomized Controlled Trial

Renante Rondina[1*], PhD; Trevor van Mierlo[2*], MScCH, MBA, GEMBA, MScBMR, DBA; Rachel Fournier[2*], MSc

[1]Rotman School of Mangement, University of Toronto, Toronto, ON, Canada

[2]Evolution Health Systems, Toronto, ON, Canada

[*]all authors contributed equally

Corresponding Author:
Renante Rondina, PhD
Rotman School of Mangement, University of Toronto
105 St George St
Toronto, ON, M5S 3E6
Canada
Phone: 1 647 212 7209
Email: renante.rondina@rotman.utoronto.ca

Abstract

Background: Despite showing strong evidence of positive outcomes, a common problem in the field of digital health is poor engagement and adherence. Non–health care, for-profit digital ventures, such as Facebook, LinkedIn, and Twitter, conduct behavioral experiments to increase user engagement. To our knowledge, digital health organizations have not published similar types of experiments in ad libitum environments, and there are limited published data indicating whether nudges and prompts can be leveraged to increase engagement with digital health interventions.

Objective: The main objective of our 3-arm randomized controlled trial is to test whether registered members in two well-established digital health courses for anxiety and depression will engage with four different types of nudges and prompts, and whether engaging with nudges and prompts increases engagement within the courses.

Methods: New members who register for the self-guided anxiety and depression courses on the Evolution Health platform will be randomized into 1 of 3 arms. The first control arm will feature a member home page without any behavioral nudges or prompts. The second arm will feature a member home page with a *Tip-of-the-Day* section containing directive content. Arm 3 will feature a member home page with a *Tip-of-the-Day* section containing social proof and present bias content. The third arm will also feature a to-do item checklist.

Results: The experiment was designed in August 2021 and was launched in November 2021. Initially, we will measure engagement with the tips and the to-do checklist by calculating the frequency of use by age and gender. If members do engage, we will then, according to age and gender, examine whether nudges and prompts result in higher course completion rates and whether specific types of prompts and nudges are more popular than others.

Conclusions: Our 3-arm randomized controlled trial will be the first to compare four distinct types of behavioral prompts and nudges in two self-guided digital health courses that were designed to treat mental health issues. We expect the results to generate insights into which types of behavioral prompts and nudges work best in the population. If they are shown to increase engagement, the insights will then be used to apply prompts and nudges to the platform's addiction-focused courses. Based on the results of the experiment, the insights will be applied to using artificial intelligence to train the platform to recognize different usage patterns and provide specific engagement recommendations to stratified users.

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KEYWORDS

behavioral economics; digital health; attrition; engagement; nudges; mood disorder; anxiety; depression; depressive disorder; mental health; nudge; prompt; behavior change; randomized controlled trial; present bias tip; future gain tip; health platform; mental illness

Introduction

Background

From its inception in the mid-1990s, digital health promised personalized treatments that patients could access from home. It was anticipated that such treatments would have a broad reach, resulting in improved health outcomes and decreased costs [1-3]. Over the past 2 decades, research examining the efficacy of self-guided digital health interventions has intensified. These studies have shown evidence of efficacy, especially for individuals with mental health concerns [4-6].

Although digital health interventions appear to be effective, patterns that have remained consistent in research are poor adherence and a lack of compliance [7-9]. These patterns were first recognized in 2005 and deemed *The Law of Attrition* [10].

As early as 2009, systematic reviews have identified poor adherence and a lack of compliance as an issue that needs to be addressed [11]. This issue persists in a recent meta-analytic review on digital interventions for depression that illustrate efficacy but highlight compliance as a major challenge [12].

This issue of adherence and compliance is complex and is rooted in a number of systemic and individual factors [13-18]. However, it is an important topic, as evidence indicates that higher levels of engagement are associated with improved health outcomes [19,20].

Digital health interventions are becoming increasingly common and accessible. Patients' use of and trust in these interventions have been intensified by the COVID-19 pandemic. The use of digital health interventions for mental health concerns is growing [21,22], and there is a shortage of professionals that can meet this growing demand. As such, it is important to determine how to increase engagement in digital health programs to maximize their efficacy.

Behavioral Economics

Behavioral economics leverages psychological experimentation to develop theories about human decision-making, and this field has identified a range of biases around the way people think and feel [23,24].

The utility of behavioral economics is vast, and digital health has leveraged the discipline, allowing researchers to investigate how people use digital health programs and obtain insights on the characteristics of people who use them. Several digital health studies have investigated the use of several strategies, including the use of cooperative games and incentives [25], gamification [26,27], serious games [28,29], and positive behavioral support [30,31].

Our Use of Behavioral Economics

In our study, we will be examining the effectiveness of nudge theory and behavioral prompts in two ad libitum, self-guided digital behavior change courses.

Nudge Theory

Nudge theory, which was popularized in the 2008 book *Nudge: Improving Decisions About Health, Wealth, and Happiness* [24], leverages indirect, positive suggestions to influence decision-making and behavior.

There is a paucity of quality research that analyzes the use of nudges in digital health. A 2019 scoping review examined the use of nudges in both web-based and real-world physical activity interventions [32]. In the 35 publications reviewed, 8 were web-based studies. The authors concluded that although nudging may be an effective approach to promoting physical activity, there are large gaps in research, and further studies are needed that are explicitly based on nudge insights.

A 2020 editorial in *Personalized Medicine* addressed the meaningful adoption of nudges in digital health [33]. The authors acknowledged that the use of nudges in digital health interventions is rare and advocated for the use of nudges to promote positive behavior change.

Behavioral Prompts

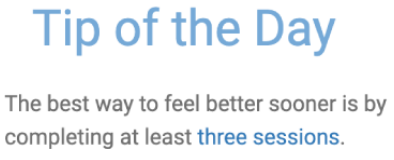
In applied behavioral analysis, behavioral prompts are cues that are specifically designed to encourage individuals to perform a specific task [34]. In our study, we will be employing the following two types of behavioral prompts, which are anchored in nudge theory: daily tips and a to-do checklist (Table 1).

Figure 1 is an example of a present bias tip that could randomly appear on a member's main home page.

Table 1. Example nudges and prompts.

Delivery format	Content type	Text example from our study
Tip	Directive content	"Express yourself by uploading your own image!"
Tip	Social proof	"Many members have similar goals as yours. Reviewing other members' goals can help you reach your own."
Tip	Present bias	"Feel better sooner by learning from others. Read what others have posted on the community."
Prompt	To-do checklist	"Watch the Getting Started Video"

Figure 1. Present bias tip.



We have not observed sufficient evidence for determining whether nudges and behavioral prompts can be strategically applied to increase engagement and decrease attrition in courses for depression and anxiety [35]. This is hypothesized in digital health that greater overall engagement may lead to better health outcomes [19,20,36].

Engagement experiments in popular, non–health care digital platforms are common. Although they are scientific in nature, they are not typically published. This makes sense, as they are conducted within private companies and are associated with trade secrets. For example, social network sites, such as Facebook, LinkedIn, and Twitter, generate revenue based on page views and the time users spend on the site. In a 2015 presentation, it was revealed that LinkedIn has over 400 controlled experiments being conducted per day [37]. Similar studies with an ad libitum population are required in digital health, and our study is an attempt to fill this gap.

Objective

The main objective of our 3-arm randomized controlled trial is to test whether registered members in two well-established, self-guided digital health courses for anxiety and depression will engage with four different types of nudges and prompts, and whether engaging with nudges and prompts increases engagement within the courses.

Methods

Digital Health Platform

The digital health platform that will be used in the study is managed by Evolution Health—an evidence-based digital health content provider that features courses based on behavior change techniques, including cognitive behavioral therapy, stages of change, structured relapse prevention, harm reduction, and quizzes based on brief intervention.

The platform offers interactive courses and quizzes for mental health issues, addiction issues, and obesity. The platform contains a moderated community that is based on social cognitive theory.

Memberships are available to individuals who register through the organization's free-to-consumer program, as well as white-label versions that are licensed by employers, insurance companies, employee assistance programs, educational institutions, nonprofit organizations, for-profit health care organizations, and individual therapists.

The Interventions

The two interventions in the study contain self-guided, interactive behavior change treatment courses based on state-of-the-art best practices, and both have been examined extensively in the literature [8,38-46].

In the literature, the Overcoming Depression course was previously known as *The Depression Center*, and the Overcoming Anxiety course was known as *The Panic Center*. Both had separate URLs. In 2019, they were each placed onto a single platform, along with other Evolution Health courses and brief interventions.

The two interventions have undergone several iterations since their onset. For example, The Panic Center is the first intervention noted in Eysenbach's [10] *The Law of Attrition* article. In that iteration, the course contained a tunnel design with 12 successive sessions. The course now has a gamified, free-form matrix design.

Table 2 outlines each course's current theoretical constructs and evidence base, and Table 3 outlines the main course components.

Table 2. Theoretical constructs and evidence base.

Theoretical construct	Overcoming Depression course	Overcoming Anxiety course
Brief intervention	✓	✓
Cognitive behavioral therapy	✓	✓
Gamification	✓	✓
Health belief model	✓	✓
Motivational interviewing	✓	✓
Social cognitive theory	✓	✓
Targeting and tailoring	✓	✓

Table 3. Main course components.

Course component	Overcoming Depression course	Overcoming Anxiety course
Avatar upload	✓	✓
Course completion certificate	✓	✓
Course worksheets	✓	✓
Gamified cognitive behavioral therapy course	✓	✓
Getting Started video	✓	✓
Goals exercise	✓	✓
Moderated community	✓	✓
Private messaging	✓	✓
Statistics extranet (for corporate clients)	✓	✓
Tailored depression and anxiety test	✓	✓
Therapist extranet	✓	✓

Ethical Considerations

All data collection policies and procedures adhere to international privacy guidelines [47-49]. At registration, all members tick a checkbox to confirm that they consent to having their data used for research purposes and approve of the platform's privacy policy.

The platform does not collect personally identifiable information except a user's email address, which is required for registration confirmation and the retrieval of lost passwords. Email addresses are encrypted in a separate database and are not included in data reports.

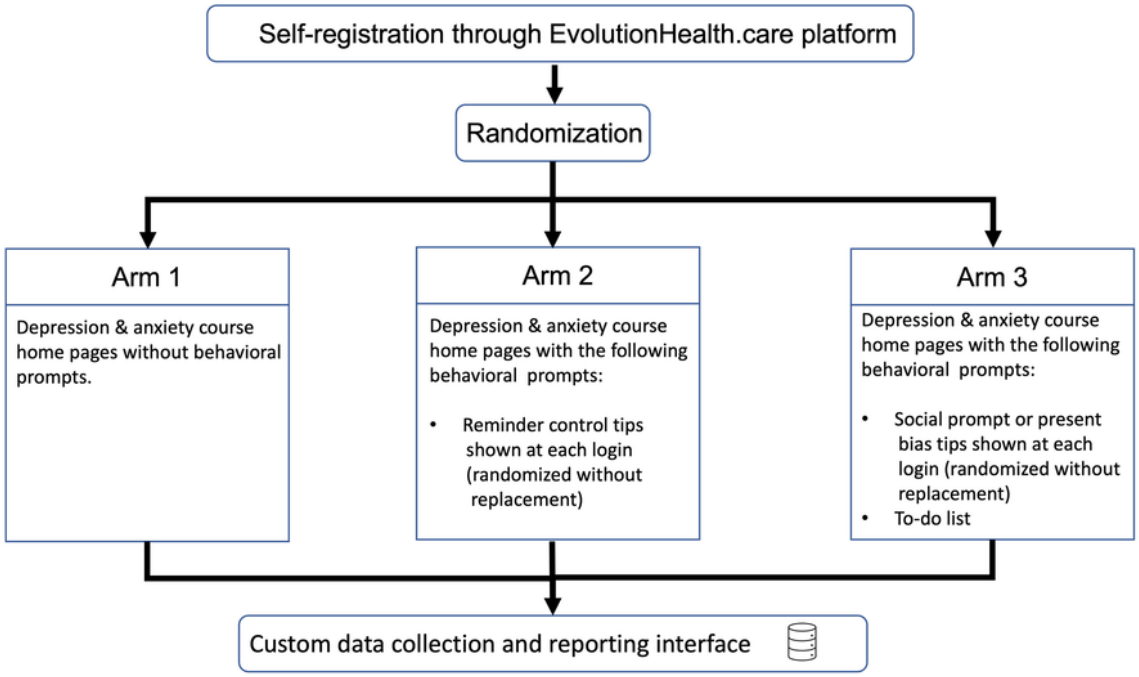
Power and Sample Size

Our goal is to obtain 0.95 power to detect a significant difference in the proportion of users who complete at least 1 cognitive behavioral therapy session between the two treatment groups (arm 2 vs arm 3). Based on a preliminary analysis of an early subsample of users from November 1 to December 9, 2021 (arm 1: n=510; power=3.14%; arm 2: n=484; power=5.79%) and a conventional α level (.05) for statistical significance, we would require a sample of 4224 users, with 1414 users in each treatment group. Multimedia Appendix 1 shows our study's CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [50].

Randomization

During the registration process, by using a random number generator, new members will be assigned into 1 of the 3 arms (Figure 2). Randomization will be conducted by using simple randomization.

Figure 2. Study flow.



Intervention Groups

Members allocated to the first arm will be presented with a member home page that contains no behavioral prompts. Figure 3 is a screenshot of an arm 1 homepage for a member who chooses to engage with the depression course.

Members allocated to the second arm will be presented with a member page that contains a *Tip-of-the-Day* section containing directive content. The randomization strategy for the 35 directive tips is randomization without replacement. Figure 4 is a screenshot of an arm 2 homepage for a member who chooses to engage with the depression course.

Members allocated to the third arm will be presented with two sections that contain interactive prompts. The first is a *Tip-of-the-Day* section containing social proof and present bias content. At each log in, members will see a new tip. The randomization strategy for the tips is randomization without replacement. There are 15 social proof tips and 15 present bias tips.

In addition to the tips of the day, the third arm will also feature a to-do checklist that lists interactive course components. When a member clicks on an interactive component, they will be brought to the exercise. When they complete the exercise, the item is marked as complete with a check mark. Figure 5 is a screenshot of an arm 3 homepage for a member who chooses to engage with the depression course.

Figure 3. Member home page for arm 1.

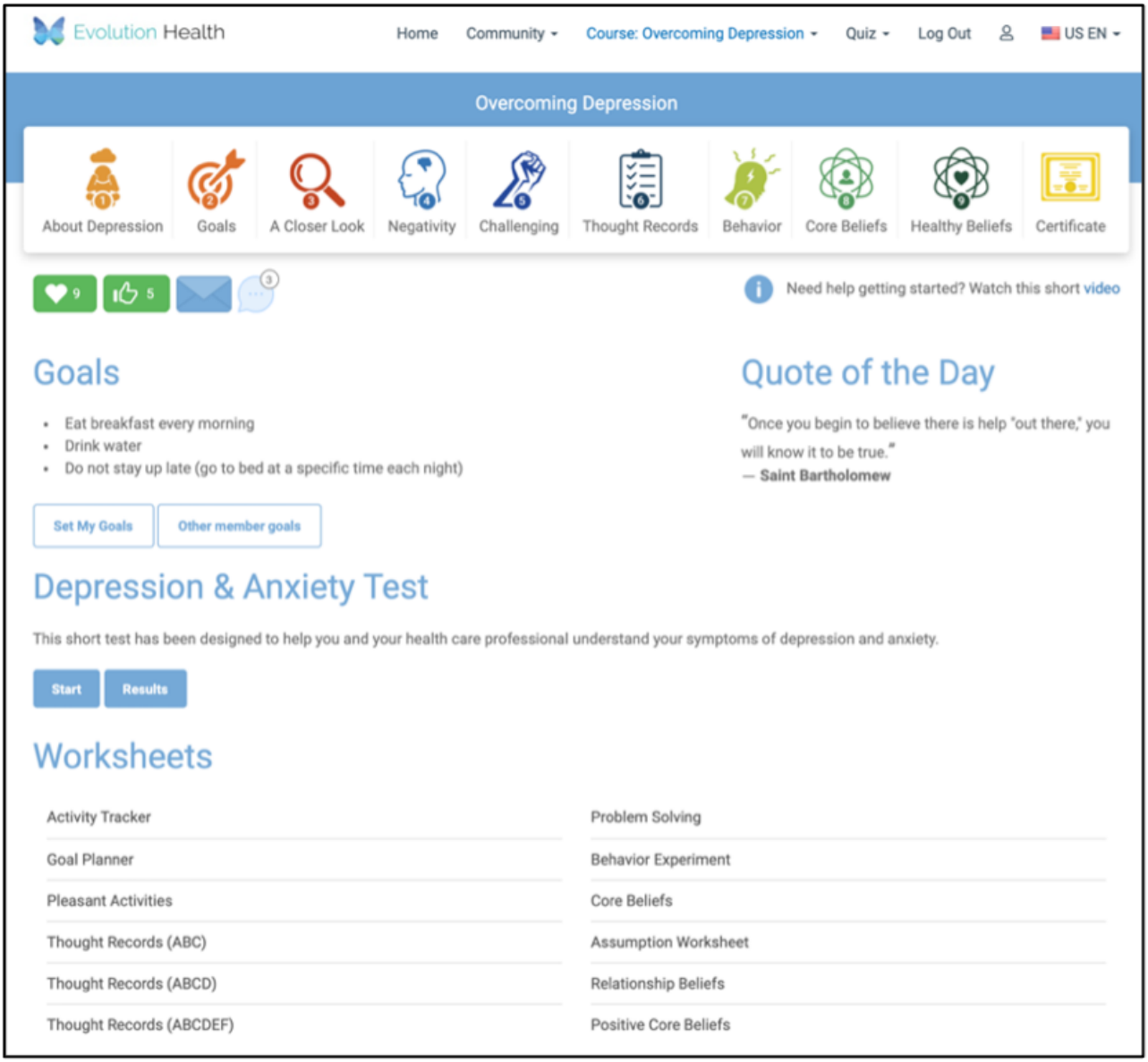


Figure 4. Member home page for arm 2.

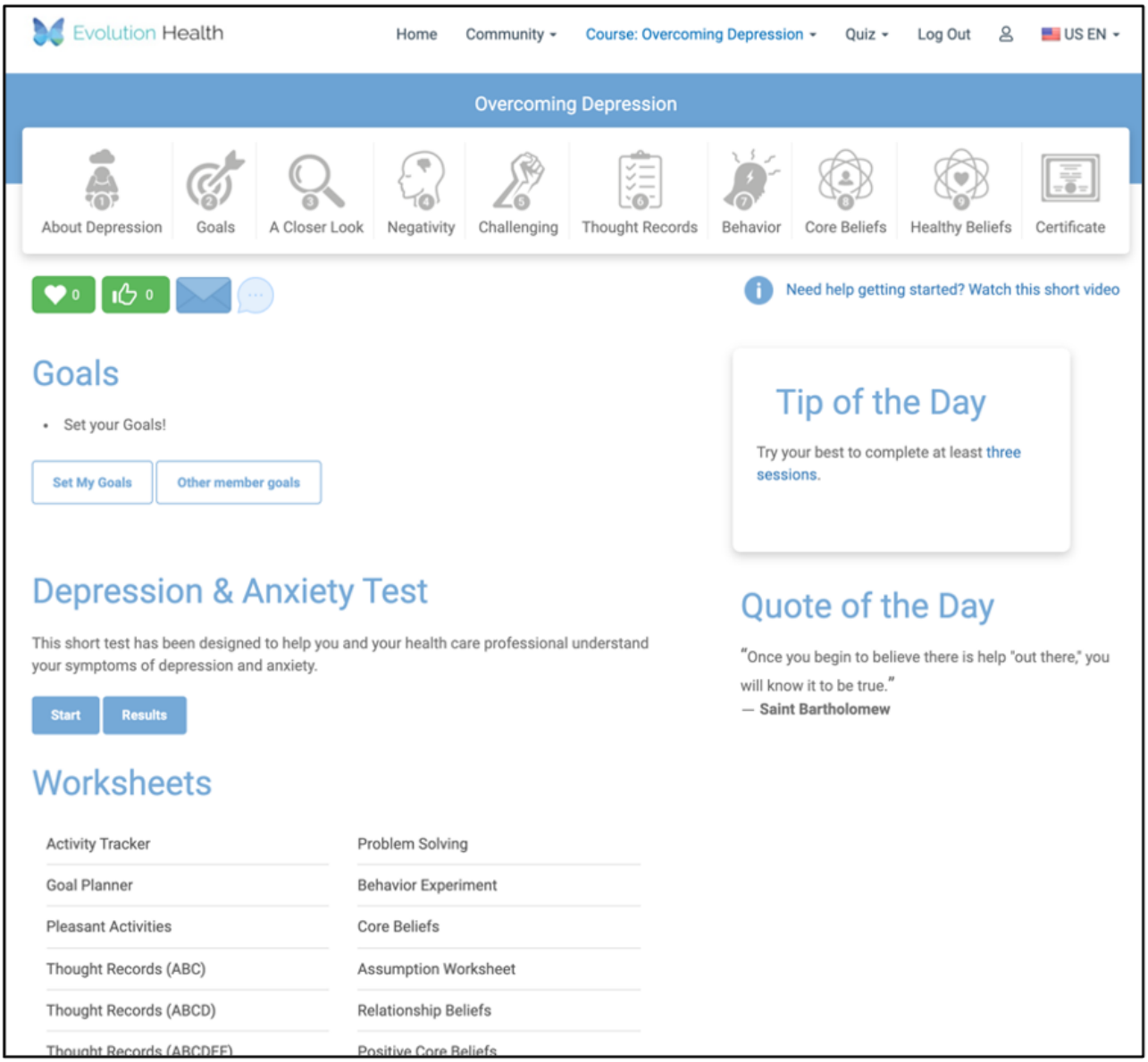
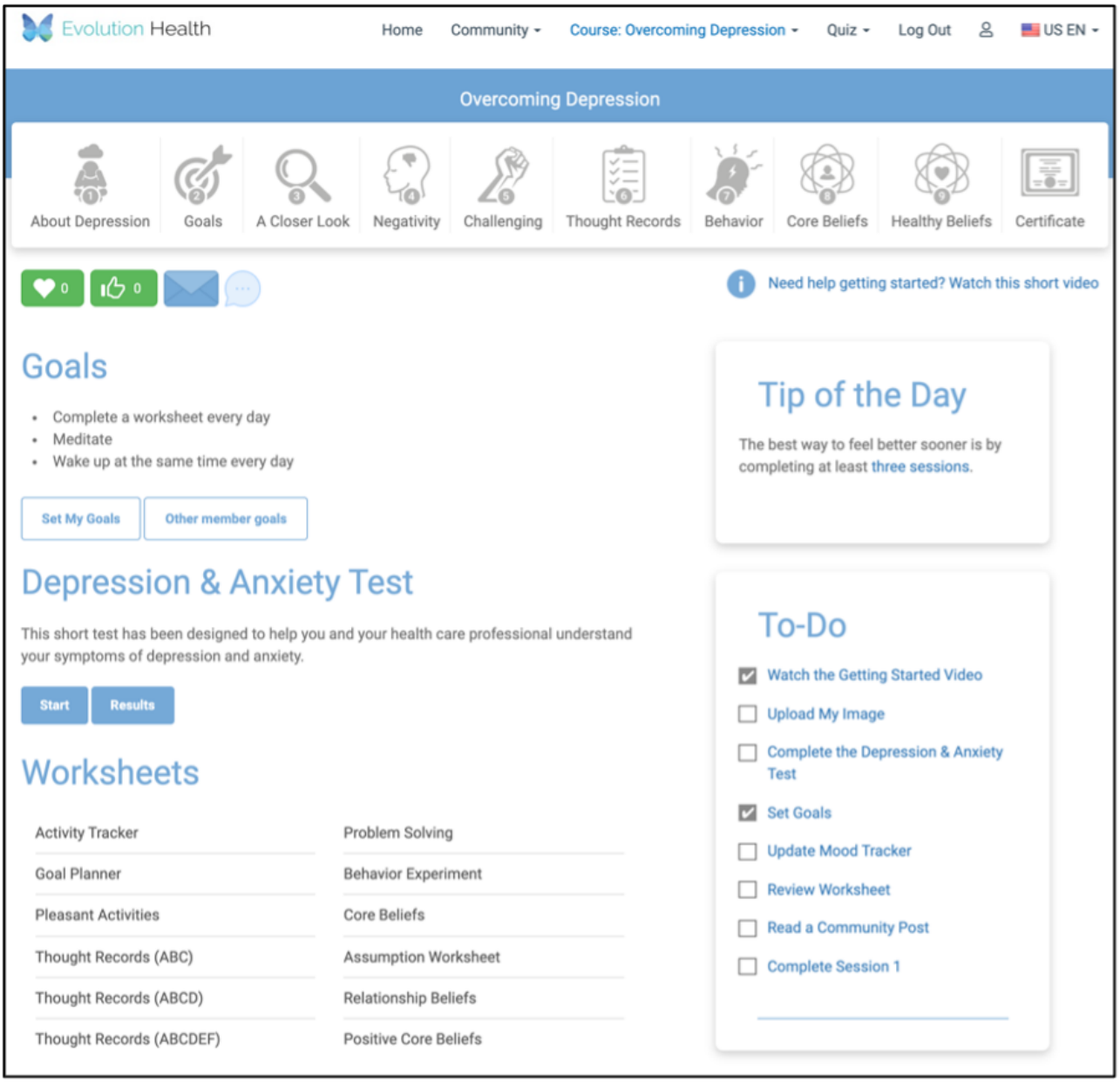


Figure 5. Member home page for arm 3.



Data Collection

Evolution Health developed a custom data collection interface and reporting mechanism. Data will be collected for each member who is randomized into the experiment. Data on age and gender will be collected at registration or at secure sign-on in various white-label versions. The course components that will be promoted by the tips and to-do items are listed in Table 4.

The following behaviors are tracked in the custom database for each tip and to-do item that is randomly presented to a user: whether a tip was shown, whether a tip was clicked on, and whether a user completed the course component described in a tip or to-do item.

It is possible for a single member to participate in both courses. However, the study was designed to test behavioral economics prompts, not courses. Participants will be randomized to an intervention arm in which behavioral nudges and prompts are consistent across courses.

Table 4. Course components tracked for engagement.

Action code	Course component
1[a]	Uploading a personal image to their profile
2[a]	Completing cognitive behavioral therapy session 1
3[a]	Use of the program's diary
4[a]	Read a community post
5	Review another member's profile
6	Posting in the community
7[a]	Review a course worksheet
8[a]	Set personal goals
9	Read other members' goals
10[a]	Complete the depression and anxiety test
11[a]	Watch the *Getting Started* video
12	Give a community member a thumbs-up
13	Encourage a community member by clicking their "show support" icon
14	Private message a community moderator

[a]Item in the to-do checklist.

Primary Outcome: Engagement With Tips and To-do Items

We will first measure engagement with the tips and to-do items in arms 2 and 3. We will compare the frequency of engagement with each nudge and behavioral prompt by age and gender. A member's engagement with tips will be measured as the proportion of tips that were clicked. Specifically, it will be a value between 0 and 1, calculated as the number of tips that a member clicked divided by the number of tips that were presented to the member. Engagement with to-do items will be measured as the number of to-do items that a member clicked, and course component completion rates will be measured as the number of course components that a member completed. All comparisons between arms 2 and 3 will be conducted by using an independent sample 1-tailed *t* test; a conventional α level (.05) for statistical significance will be used.

Secondary Outcomes: Completion of Course Components

A secondary outcome of this experiment is to test whether the presentation of tips and to-do items increases the overall completion of course content. We will achieve this by comparing course component completion rates in arm 2 and arm 3 via a 1-way ANOVA in which the types of tips are used as the independent variable. We will then assess if age and gender predict which type of tip is the most engaging by using multiple regression.

Tertiary Outcomes: Engagement With Types of Tips

Another outcome of this experiment is to determine what types of tips are most engaging (directive, social proof, or present bias tips). We will assess this by comparing engagement with the tips in arm 2 and arm 3 via a 1-way ANOVA in which the types of tips are used as the independent variable. We will then assess if age and gender predict which type of tip is the most engaging by using multiple regression.

Results

This protocol was originally designed in August 2021. Alpha and beta testing on Evolution Health's staging environment began in October 2021. The protocol was revised in October 2021, and the experiment was pushed live in November 2021. We exceeded the sample size requirements in each arm and concluded data collection in May 2022.

Discussion

Hypotheses

We hypothesize that members will engage with the prompts and nudges. We also hypothesize that the secondary results will generate insights on the types of prompts and nudges that are the most likely to result in engagement among members. This finding may be important, as dose-response relationships have been observed in digital health interventions [8,51].

Practical Implications

If we learn that the prompts are used by members, the arm 2 or arm 3 home page will become the default user home page for all new and existing members.

Strengths and Limitations

A strength of this experiment is that it will be conducted in an ad libitum environment. Unlike most digital health studies, ours will not be conducted with a small population in a controlled environment. Further, members will not be aware of the

experiment, which will limit participant bias and the Hawthorne effect.

A limitation of this experiment is that, especially due to the anonymity of members, we have no way of knowing who members are. We have no way of knowing whether registrants are people with depression or anxiety who are seeking help, or are browsing for other reasons. However, we have exceeded sample size requirements and believe that the large number of subjects should dampen these effects on the results.

A final limitation is that not all white-label clients license all course components. For example, some community tools and the depression and anxiety test are feature flags that are not used by all white-label clients. As the primary purpose of this experiment is to test whether members engage with prompts and nudges, we do not expect this particular limitation to hamper the overall results.

Future Directions

Although the content is different, the platform's addiction courses have user home page interfaces that have the exact same layout as that of the arm 1 home page interface. If the results from our study indicate that members engage with the prompts and nudges in arm 2 and arm 3, we will replicate this experiment with new members who register for these courses. Although the addiction courses focus on problem drinking and smoking cessation, the use of nudges and prompts to increase engagement may be generalizable to many digital health courses that focus on addictions and mental health.

The secondary and tertiary outcomes will help shape the development of future nudges and prompts. If specific types of nudges and prompts are appealing to specific gender and demographic groups, we will customize the content for these groups and analyze their effectiveness in future studies.

We are currently employing natural language processing to analyze identifiable contexts (ie, change talk) in our communities [52]. We will apply the findings from that experiment to the member-generated content from the goals and diary tools to better determine the types of prompts and nudges that result in engagement among members. The overall goal will be to use artificial intelligence to train the platform to recognize different usability patterns and show specific engagement prompts and nudges to stratified populations.

The goal of the courses is to promote wellness and increase access to efficacious, self-guided support for people with depression and anxiety. The focus of the study is restricted to testing whether nudges and prompts increase engagement. If the study is successful, future research will need to determine if nudges and prompts contribute to decreases in depression and the frequency and intensity of panic attacks.

Acknowledgments

We acknowledge financial support from the Behavioural Economics in Action at Rotman research center and from a partnership grant from Social Sciences and Humanities Research Council, which was granted to the Behaviourally Informed Organizations partnerships.

Data Availability

Allowing the data set from our study to be publicly available would violate the platform's data privacy policy, terms of use, and user agreement. However, researchers interested in accessing the data set or other platform data sets for noncommercial purposes are encouraged to contact Evolution Health.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 37389 KB - resprot_v11i8e37231_app1.pdf]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth

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Protocol

A Gambling Just-In-Time Adaptive Intervention (GamblingLess: In-The-Moment): Protocol for a Microrandomized Trial

Nicki A Dowling[1,2], PhD; Stephanie S Merkouris[1], PhD; George J Youssef[1], PhD; Dan I Lubman[3], PhD; Kathleen L Bagot[4], PhD; Chloe O Hawker[1], DPsych; Hannah J Portogallo[1], BPsych (Hons); Anna C Thomas[1], PhD; Simone N Rodda[1,5,6], PhD

[1]School of Psychology, Deakin University, Geelong, Australia

[2]Melbourne Graduate School of Education, University of Melbourne, Melbourne, Australia

[3]Turning Point and Monash Addiction Research Centre, Eastern Health Clinical School, Monash University, Melbourne, Australia

[4]Data Drawer Consulting, Sandringham, Australia

[5]Psychology and Neuroscience, Auckland University of Technology, Auckland, New Zealand

[6]School of Population Health, University of Auckland, Grafton, New Zealand

Corresponding Author:
Nicki A Dowling, PhD
School of Psychology
Deakin University
1 Gheringhap St
Geelong, 3220
Australia
Phone: 61 3 9244 5610
Email: nicki.dowling@deakin.edu.au

Abstract

Background: The presence of discrete but fluctuating precipitants, in combination with the dynamic nature of gambling episodes, calls for the development of tailored interventions delivered in real time, such as just-in-time adaptive interventions (JITAIs). JITAIs leverage mobile and wireless technologies to address dynamically changing individual needs by providing the type and amount of support required at the right time and only when needed. They have the added benefit of reaching underserved populations by providing accessible, convenient, and low-burden support. Despite these benefits, few JITAIs targeting gambling behavior are available.

Objective: This study aims to redress this gap in service provision by developing and evaluating a theoretically informed and evidence-based JITAI for people who want to reduce their gambling. Delivered via a smartphone app, *GamblingLess: In-The-Moment* provides tailored cognitive-behavioral and third-wave interventions targeting cognitive processes explicated by the relapse prevention model (cravings, self-efficacy, and positive outcome expectancies). It aims to reduce gambling symptom severity (*distal outcome*) through short-term reductions in the likelihood of gambling episodes (*primary proximal outcome*) by improving craving intensity, self-efficacy, or expectancies (*secondary proximal outcomes*). The primary aim is to explore the degree to which the delivery of a tailored intervention at a time of cognitive vulnerability reduces the probability of a subsequent gambling episode.

Methods: *GamblingLess: In-The-Moment* interventions are delivered to gamblers who are in a state of receptivity (available for treatment) and report a state of cognitive vulnerability via ecological momentary assessments 3 times a day. The JITAI will tailor the type, timing, and amount of support for individual needs. Using a microrandomized trial, a form of sequential factorial design, each eligible participant will be randomized to a tailored intervention condition or no intervention control condition at each ecological momentary assessment across a 28-day period. The microrandomized trial will be supplemented by a 6-month within-group follow-up evaluation to explore long-term effects on primary (gambling symptom severity) and secondary (gambling behavior, craving severity, self-efficacy, and expectancies) outcomes and an acceptability evaluation via postintervention surveys, app use and engagement indices, and semistructured interviews. In all, 200 participants will be recruited from Australia and New Zealand.

Results: The project was funded in June 2019, with approval from the Deakin University Human Research Ethics Committee (2020-304). Stakeholder user testing revealed high acceptability scores. The trial began on March 29, 2022, and 84 participants have been recruited (as of June 24, 2022). Results are expected to be published mid-2024.

Conclusions: *GamblingLess: In-The-Moment* forms part of a suite of theoretically informed and evidence-based web-based and mobile gambling interventions. This trial will provide important empirical data that can be used to facilitate the JITAI's optimization to make it a more effective, efficient, and scalable tailored intervention.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12622000490774; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380757&isClinicalTrial=False

International Registered Report Identifier (IRRID): PRR1-10.2196/38958

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KEYWORDS

mobile health; mHealth; just-in-time adaptive intervention; ecological momentary intervention; microrandomized trial; gambling; addiction; treatment; intervention; protocol; relapse; mobile phone

Introduction

Background

Gambling disorder (formerly pathological gambling) has been reclassified in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) as an addiction and related disorder alongside alcohol and substance use disorders [1]. Consistent with public health frameworks that conceptualize gambling problems across a continuum of risk [2], many jurisdictions, including Australia and New Zealand, use the term problem gambling to refer to gambling that results in adverse consequences for gamblers, families, and communities [3]. Internationally, estimates of past-year problem gambling have ranged from 0.1% to 5.8% over the past decade [4]. Specifically, Australian and New Zealand national estimates suggest that past-year problem gambling affects 0.4% to 0.7% of adults, with a further 2% to 11% displaying moderate-risk gambling and 3.0% to 7.7% displaying low-risk gambling [5-7]. Despite relatively low prevalence estimates, problem gambling is associated with a high burden of harm [8], which can include financial strain and loss, relationship breakdown, emotional and psychological distress, health decline, cultural upset, reduced work or study performance, and social deviance [9]. Problem gambling is also highly comorbid with a range of mental health issues, including mood, anxiety, alcohol and substance use, and personality disorders [10-12].

The Relapse Prevention Model

The relapse prevention model [13], a prominent and influential social-cognitive theory originally developed to explain relapse in substance use disorders, classifies factors or situations that can precipitate or contribute to relapse. Generally, these factors can be immediate determinants (high-risk situations, coping skills, outcome expectancies, and the abstinence violation effect) or covert antecedents that indirectly influence relapse (lifestyle imbalances, rationalizations, denial, apparently irrelevant decisions, and urges or cravings). A basic assumption of this model is that lapses are immediately preceded by a high-risk situation, broadly defined as any context that confers vulnerability to engaging in the target behavior, such as negative emotional states, interpersonal conflict, social pressure, testing of personal control, and nonspecific cravings. The model posits that positive outcome expectancies become particularly salient in high-risk situations, whereby the immediate positive effects of addictive behavior may be anticipated, and the possible delayed negative consequences of addictive behavior are ignored or discounted [13]. It also highlights that effective behavioral and cognitive coping in response to high-risk situations enhances self-efficacy, thereby reducing the probability of relapse [13,14].

The relapse prevention model has been reconceptualized [15] to emphasize the multidimensional, complex, nonlinear, and dynamic interaction among various precipitants that act jointly and interactively within high-risk situations to determine the likelihood of relapse. This model also incorporates the interaction among background factors (eg, years of dependence, family history, social support, and comorbid psychopathology), physiological states (eg, physical withdrawal), cognitive processes (eg, self-efficacy, outcome expectancies, craving, motivation, and abstinence violation effect), affective states, and coping skills. However, responding to a high-risk situation is related to both distal and proximal risk factors operating within both tonic processes and phasic responses. Tonic processes are distal risks or stable background factors that determine the *set point* or initial threshold for relapse. These processes, which indicate chronic vulnerability to relapse, often accumulate and lead to the instigation of a high-risk situation, providing the foundation for the possibility of relapse. In contrast, phasic responses are situational cognitive, affective, or physical states that can fluctuate across time and contexts and serve to activate lapses. Momentary coping responses can also serve as phasic events that determine whether a high-risk situation culminates in a lapse. The model predicts feedback loops, whereby lapse episodes can have reciprocal effects on the same factors (cognitive processes, affective states, and coping behavior) that contribute to the lapse. There is considerable empirical support for relapse prevention models across addictions [15,16].

In this model, cognitive processes that are relatively stable over time, such as outcome expectancies and global self-efficacy, are conceptualized as tonic processes, whereas cognitive processes that fluctuate over contexts and time, such as urges or cravings, as well as transient changes in outcome expectancies and self-efficacy, are conceptualized as phasic responses.

Because it emphasizes the importance of nonlinear relationships and the timing or sequencing of events, the model does not articulate the temporal relationships between each of these cognitive processes. For example, a momentary reduction in self-efficacy in a high-risk situation could have a disproportionate influence on other cognitive processes, such as outcome expectancies [15]. There is emerging evidence of the role that cognitive processes play in gambling behavior and relapse as tonic processes; however, there is less evidence in relation to the role they play as phasic responses.

Gambling Craving

Craving is a central phenomenon in addiction science. Despite the abundance of theoretical models, there is little consensus about its definition, etiology, and maintenance, and the terms craving and urge are often used interchangeably [17,18]. In the relapse prevention model, cravings are defined as the subjective desire to experience an appetitive target and urges are described as relatively sudden behavioral intentions or impulses to seek out and engage in an appetitive target [13,14]. This conceptualization is consistent with the integrative elaborated intrusion theory of desire [19,20], in which craving is defined as intense subjective desires for an appetitive target and urges are defined as specific desires for positive or negative reinforcement from an appetitive target [17]. Recent empirical studies attempting to delineate between gambling cravings and urges suggest that gambling craving is a higher-order and multifaceted construct, which is characterized by mental imagery, desire thoughts, and physiological sensations and triggered by various stimuli, including positive affect, negative affect, external cues, mental imagery, and desire thoughts [21]. In contrast, urges are a more narrowly defined construct comprising 2 core dimensions: intent and desire to gamble (due to expectations of positive reinforcement) and relief (due to expectations of negative reinforcement) [17].

Despite this conceptual confusion, the emerging cross-sectional literature highlights the important role that craving plays in the maintenance, exacerbation, and relapse of gambling problems. Specifically, findings suggest that gambling cravings are positively associated with problem gambling severity [22,23] and gambling relapse [24], negatively associated with abstinence [24,25], and are among the most frequent precipitants of relapse [26]. These findings are supported by qualitative research in which gambling cravings have been identified as a key construct associated with an increased risk of gambling relapse [27,28]. There is growing evidence that gambling cravings are relevant and useful intervention targets and potential mechanisms of change in both cognitive behavioral and mindfulness-based gambling interventions. Craving has predicted outcomes following cognitive behavioral treatment [29], and interventions that include craving management components have demonstrated efficacy in reducing cravings [27,28,30-43]. These studies typically targeted cravings using cognitive behavioral techniques, such as self-monitoring, psychoeducation, development of alternative responses, behavioral exposure exercises, and relapse prevention strategies, as well as mindfulness-based strategies such as urge surfing and guided breathing or body scan meditations.

Gambling Self-efficacy

Self-efficacy, an important construct within social-cognitive theory, refers to feelings of confidence and capability to perform a behavior in a specific situational context to produce a desired outcome [44]. Addiction science has predominantly conceptualized self-efficacy in terms of perceived confidence to resist engaging in addictive behaviors in high-risk situations, but self-efficacy measures frame such resistance slightly differently, including confidence in *controlling* addictive behavior [45], *resisting the urge* to engage in addictive behavior [46], *avoiding* addictive behavior [47], *refusing* to engage in addictive behavior [48], or *abstaining* from addictive behavior [49]. Regardless of how resistance is framed, cross-sectional studies have consistently found that self-efficacy is negatively associated with both gambling behavior and problem gambling severity [22,23,45,47,49-53] and accurately discriminates between nonproblem and problem gambling samples [48,52]. Qualitative research supports these findings, suggesting that self-efficacy is a key construct in preventing relapse, which in turn increases motivation and commitment to maintain abstinence over time; however, the protective effect of self-efficacy weakens once relapse has occurred [27,28]. Similarly, there is some evidence that self-efficacy plays a protective role in preventing cravings from transitioning to gambling behavior but not when cravings are intense [23]. These findings highlight the potential of self-efficacy as an important intervention target and mechanism of change in treatment. Furthermore, self-efficacy has been demonstrated as an important predictor of treatment outcomes for gambling across several studies [54-56], and there is a small but growing body of literature reporting improvements in self-efficacy following interventions incorporating relapse prevention, cognitive behavioral, and motivational interviewing strategies [39,41,43,52,57-62].

Positive Outcome Expectancies

Positive outcome expectancies are typically described as higher expectations or anticipation of the positive effects of future experience [13,14,44]. Theoretical conceptualizations suggest that outcome expectancies are associations among mental representations in long-term memory that are automatically activated under specific circumstances [63]. There is now growing cross-sectional evidence that global positive outcome expectancies [64-68] and specific positive outcome expectancies, such as financial, excitement, escape, ego enhancement, and social expectancies [69-78], are positively associated with problem gambling severity and related harm. Although few studies have explored the degree to which these expectancies change during treatment or are predictive of treatment outcomes, one study has found clinically and statistically significant reductions in global positive outcome expectancies from pre- to postresidential gambling treatment [79].

Ecological Momentary Assessment of Cravings, Self-efficacy, and Positive Outcome Expectancies

These predominantly cross-sectional studies, which are subject to recall bias, treat cravings, self-efficacy, and gambling outcome expectancies as stable and enduring traits rather than transient or phasic states [80-82]. However, the reformulated

relapse prevention model posits that transient changes in these cognitive processes can constitute phasic responses that interact with tonic processes and determine the likelihood of relapse [15]. Ecological momentary assessment (EMA), an event-level longitudinal methodology, overcomes the limitations of cross-sectional research by repeatedly measuring symptoms, emotions, behavior, and thoughts in real time and in natural environments [80]. Although there is now substantial EMA evidence that momentary cognitive processes (cravings, self-efficacy, and positive outcome expectancies) predict the occurrence of tobacco, alcohol, and substance use [83-89], few EMA studies have explored the associations between these processes and gambling behavior [90-92]. In the available studies, momentary cravings and self-efficacy, but not positive outcome expectancies, have predicted the likelihood of a subsequent gambling episode [90-92]. Moreover, all of these momentary cognitive processes constitute situational determinants of gambling behavior when they interact with other factors implicated in the relapse prevention model, such as high-risk positive reinforcement situations, self-efficacy, coping motives, cravings, positive emotional states, and coping styles [90-92].

Just-in-Time Adaptive Interventions

These findings, which support the relapse prevention model, suggest that cravings, self-efficacy, and positive outcome expectancies constitute phasic precipitants of gambling behavior, although this may only occur for positive outcome expectancies when they interact with tonic precipitants, such as problem gambling severity [90]. The presence of these discrete but fluctuating precipitants, in combination with the complex and dynamic nature of gambling episodes or lapses, calls for the development of tailored interventions delivered in real time, such as just-in-time adaptive interventions (JITAIs). JITAIs are mobile health (mHealth) interventions that address dynamically changing individual needs by providing the type and amount of support required at the right time and only when needed [93-97]. They are *push* interventions, in which decisions about when and how support is provided are initiated by intervention protocols via computer algorithms rather than *pull* interventions initiated by individuals when they feel they require support [97,98]. mHealth interventions characterized by *just-in-time* (provision of the right type, timing, or amount of support) and *adaptive* (use of dynamic information from the individual to repeatedly select the type, timing, or amount of support) components have also been described as ecological momentary interventions, as long as they are dynamically and individually tailored [99].

The overall aim of JITAIs is to prevent negative health outcomes and promote the adoption and maintenance of positive health outcomes [94-98]. They are designed to provide support when individuals are in a *state of vulnerability* (a period of susceptibility to negative health outcomes) or a *state of opportunity* (a period of susceptibility to positive health behavior change), as well as a *state of receptivity* (able and willing to receive, process, and use the provided support) [94,95]. JITAIs identify how and when support should be offered by continuously monitoring dynamic internal states and ecological contexts in real time and in the natural environments of individuals using mobile and wireless technologies, including smartphone-embedded or wearable sensors and smartphone-delivered EMAs [93-96,98].

Nahum-Shani et al [94-96] have developed a comprehensive organizing scientific framework to guide the design of JITAIs. This framework describes the four key components that play an important role in JITAI design: (1) *decision points* (points in time at which intervention decisions are made), (2) *intervention options* (potential type, dose, timing, and delivery mode of support that can be delivered at any given decision point), (3) *tailoring variables* (data about the individual's internal state or ecological context that is used to decide when and how to intervene), and (4) *decision rules* (a specification of which intervention option to offer, for whom, and when at each level of the tailoring variables). These components are guided primarily by the ultimate, long-term goal of the intervention (*distal outcome*) but also by the clearly defined near-time, short-term goals that the intervention is intended to achieve (*proximal outcomes*) [94]. JITAIs have been effective in supporting behavior change across a range of health behaviors, including addictive disorders, such as smoking, binge drinking, heavy drinking, and alcohol use disorders [93,94,96,99,100].

Similar to other mHealth interventions, JITAIs are characterized by high availability and accessibility, convenience, anonymity, portability, cost-effectiveness, and low burden, as well as the potential for real-world translation, scalability, and accurate data recording [93,97,99,101-103]. They also have the potential to reach underserved populations, including those who are unable or unwilling to participate in other interventions [99,101,102]. This is particularly important for gambling populations, given evidence that only a small proportion of people with problem and moderate-risk gambling (1 in 5 and 1 in 25 in Australia, respectively) access specialist face-to-face gambling services [104], despite an established evidence base indicating their efficacy [105-107]. These findings imply that face-to-face gambling treatment delivery does not provide sufficient access to evidence-based treatment [108]. The barriers to accessing face-to-face gambling treatment, which are now well-documented [109-111], include personal factors (eg, denial, shame, stigma, embarrassment, and a desire to deal with one's own problem), resource limitations (eg, a lack of available services and trained clinicians), geographic inaccessibility, low awareness of treatment options, treatment costs, time commitments, childcare requirements, and reluctance to engage in treatments with a prespecified goal of abstinence. JITAIs overcome many of these barriers by leveraging mobile and wireless technologies to provide immediate, cost-effective, and low-burden treatment in moments of need.

Despite these clear benefits, the development of JITAIs targeting gambling behavior has been slow. Two smartphone apps that send notifications in response to the detection of proximity or entry into gambling venues by passive assessments using geolocation sensors to collect automated data (GPS, accelerometer, gyroscope, and magnetometer) have been developed: a smartphone-based problem gambling evaluation and technology testing initiative (*SPGeTTI*) [112] and *Don't Go There* [113]. *SPGeTTI* also includes *pull* features that can

be accessed on demand (self-monitoring gambling diary, relapse prevention tips, and help service contacts), whereas *Don't Go There* allows an elected health professional to access the individual's information. Despite low recruitment rates for a planned randomized controlled trial of *SPGeTTI*, focus group interviews revealed that gamblers reported high interest in the app. However, specific issues with *SPGeTTI* have been identified, such as excessive battery drainage. *Don't Go There* is yet to be evaluated, with a usability study currently underway.

Two other gambling JITAIs that use active assessments via smartphone-delivered EMAs to collect data on internal states have been developed: *Jeu-contrôle* [114] and *GamblingLess: Curb Your Urge* [115,116]. Yet to be evaluated, *Jeu-contrôle* is a publicly available JITAI that uses EMAs to provide personalized feedback in relation to goal limits, with a view to supporting adherence to expenditure and time limits. In contrast, *GamblingLess: Curb Your Urge* is informed by the relapse prevention model and aims to reduce gambling cravings to prevent subsequent gambling episodes. This intervention, which was adapted from *GamblingLess*, an evidence-based web-based self-directed gambling program [41,43,115-120], tailors craving management activities to EMAs evaluating craving intensity and also provides these activities on demand. Key stakeholders rated the intervention content, helpfulness, acceptability, and usability highly and indicated that they would recommend the app to gamblers given its potential to increase gambling knowledge, attitudes, awareness, behavior change, intention to change, and help-seeking [115,116]. A pilot study of this JITAI [116] revealed promising findings, with more than a 70% reduction in the average number of gambling episodes and craving occurrences during the intervention period and a 10% decrease in momentary craving intensity immediately after a recommended intervention. There were also significant medium-to-large reductions in gambling symptom severity, gambling frequency, gambling expenditure, cravings, and self-efficacy at the postintervention and 1-month follow-up evaluations. At the 1-month follow-up evaluation, nearly half of the participants (10/21, 48%) reported recovery or improvement in the severity of gambling symptoms.

Research Questions

This project aims to redress the gap in existing gambling service provision by evaluating a theoretically informed and evidence-based JITAI that builds on pilot data provided by the evaluation of *GamblingLess: Curb Your Urge* [115,116]. *GamblingLess: In-The-Moment* is a smartphone-delivered JITAI for people who want to quit or gamble less. It uses EMAs to collect comprehensive and accurate data on the dynamic cognitive processes articulated by the relapse prevention model. The JITAI uses *decision rules* specifying that individuals who are in a state of receptivity (available for treatment) and report a state of cognitive vulnerability characterized by high craving intensity, low self-efficacy, or positive outcome expectancies (*tailoring variables*) in EMAs sent during 3 semirandom times a day (*decision points*) are delivered tailored cognitive behavioral and third-wave interventions targeting these cognitive processes (*intervention options*). The intervention aims to reduce gambling symptom severity in the long term (*distal outcome*), and reduce the likelihood of gambling episodes (*primary proximal outcome*) in the short term via improved craving intensity, self-efficacy, and positive outcome expectancies (*secondary proximal outcomes*). The JITAI is intended for use as a stand-alone or adjunctive treatment during periods of active gambling behavior or as a relapse prevention tool during recovery.

A microrandomized trial (MRT), a form of sequential factorial design in which every participant serves as their own control, will be used to inform the optimization of this JITAI [93,98]. In this MRT, each participant will be randomized to a tailored intervention condition or no intervention control condition at each decision point across a 28-day period [121,122]. The primary aim of the MRT is to explore whether it is worthwhile to deliver a tailored intervention option at a time of cognitive vulnerability. Specifically, the aim is to explore whether, compared with the delivery of no intervention, the delivery of a tailored intervention reduces the probability of a subsequent gambling episode (primary proximal outcome) and improves craving intensity, self-efficacy, and positive outcome expectancies (secondary proximal outcomes). It is hypothesized that the delivery of a tailored intervention will be more effective than no intervention in reducing the probability of a gambling episode and improving craving intensity, self-efficacy, and positive outcome expectancies by the subsequent EMA. Should data allow, secondary exploratory research questions include the following:

1. *Which type of intervention option is most beneficial at a time of cognitive vulnerability?* Is the delivery of one intervention option (targeting cravings, self-efficacy, or positive outcome expectancies) more likely to reduce the probability of a subsequent gambling episode than the other intervention options?
2. *Under what conditions is the delivery of an intervention option most beneficial?* How do time-variant (EMA) factors (time of day, time of week, craving intensity, self-efficacy, positive outcome expectancies, psychological distress, impulsivity, subjective alcohol intoxication, readiness to change, gambling availability [financial and location], and social context) and time-invariant (preintervention survey) factors (gambling symptom severity, gambling frequency, gambling expenditure, gender, and age) influence the intervention effect on the probability of a subsequent gambling episode?
3. *How do the proximal effects of intervention options change over time as the treatment progresses?* How does the effect of a tailored intervention on the probability of a subsequent gambling episode change over the course of the 28-day MRT?

Methods

Ethics Approval

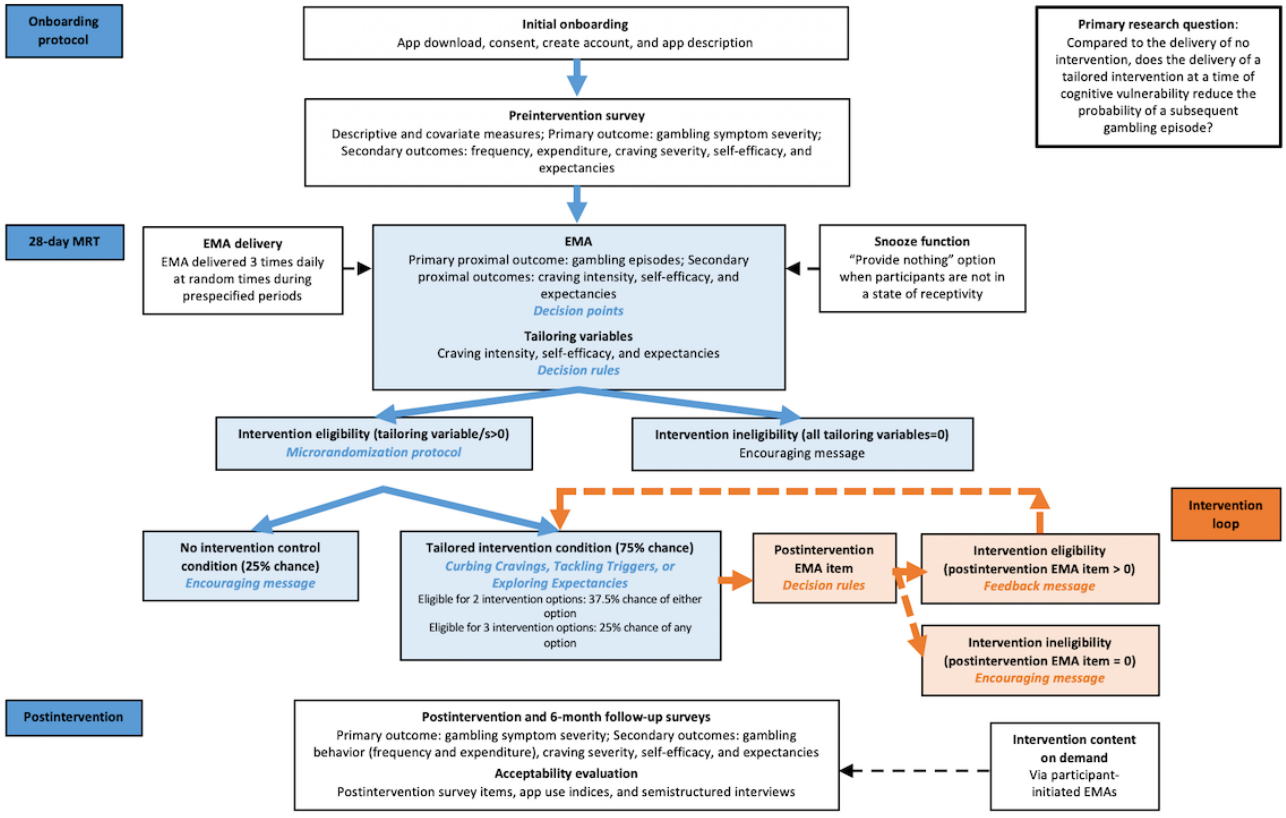
This trial has been approved by the Deakin University Human Research Ethics Committee (2020-304) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622000490774).

Trial Design

MRTs have significant advantages over randomized controlled trials as participants act as their own control group, providing a strong capacity for causal inferences and increased power to detect treatment effects [98]. Moreover, they are designed to facilitate the optimization of JITAIs, which involves determining how a JITAI should be adjusted to make it more effective, efficient, and scalable [98,122,123]. Participants will participate in a 28-day MRT, in which they will be prompted via push notifications on their smartphones to complete a time-based EMA 3 times daily (*decision points*). In this EMA, *tailoring variables* used to determine intervention eligibility include momentary craving intensity, self-efficacy, and positive outcome expectancies. *Decision rules* based on EMA item cut points will determine eligibility for a tailored intervention, which could consist of a craving, self-efficacy, or positive outcome expectancy *intervention option*. Participants will be randomly allocated to either a tailored intervention condition or no intervention control condition at each *decision point* across the 28-day trial period. To maintain the integrity of the MRT evaluation, the JITAI will be evaluated as an entirely *push* intervention during the 28-day MRT period [97,98]. This trial will provide important empirical data that can be used to facilitate the optimization of the JITAI to make it a more effective, efficient, and scalable intervention.

The MRT will be supplemented with (1) a within-group follow-up evaluation to explore the long-term outcomes of the intervention in relation to the primary (gambling symptom severity) and secondary (gambling frequency, gambling expenditure, cravings, self-efficacy, and positive outcome expectancies) outcomes from the preintervention evaluation to the postintervention and 6-month follow-up evaluations as well as the predictors of long-term treatment outcomes and (2) an evaluation of the acceptability of the JITAI using postintervention surveys, app use and engagement indices, and semistructured interviews. An overview of the trial design is shown in Figure 1.

Figure 1. Overview of the *GamblingLess: In-The-Moment* trial design. EMA: ecological momentary assessment; MRT: microrandomized trial.



Participant Recruitment and Reimbursement

Participants will be recruited across Australia and New Zealand, using a range of strategies, such as web-based advertising (eg, Google Adwords), social media (eg, Facebook and Instagram), gambling-related websites (eg, GambleAware, Gambling Helpline, Gambling Help Online, and Australasian Gaming Council), and advertisements in public places (eg, universities, general practices, health services, mental health services, and alcohol and other drug services). Gambling counseling services and gambling venues may also be requested to assist with participant recruitment. The eligibility criteria will include (1) current Australian or New Zealand residence, (2) ≥18 years of age, (3) installation of the app from an internet-enabled smartphone, (4) willingness to receive notifications from the app, (5) fluency in the English language, and (6) seeking support for one's own gambling. The target population for *GamblingLess: In-The-Moment* comprises people who want to quit or gamble less. Consistent with a pragmatic design, the intervention will be available to any interested gambler, regardless of the level of gambling symptom severity or whether they are seeking other forms of support or treatment [124]. Moreover, consistent with a harm minimization approach, participants can select abstinence or nonabstinence treatment

goals [125-127]. Participants in the trial will be compensated for their time in e-gift vouchers: US $0.70 for each EMA completed and a US $14 bonus if >75% of the EMAs are completed (to a maximum of US $70), US $35 for completion of the postintervention survey, US $50 for completion of the 6-month follow-up survey, and US $35 for the optional semistructured interview.

Onboarding Protocol

Participants will be required to download *GamblingLess: In-The-Moment* from app stores and provide explicit agreement to the trial plain language statement, as well as the app platform's terms of use and privacy policy. By agreeing to the terms and privacy policy, participants declare that they have read and understood the plain language statement, are freely participating in the trial according to this statement, meet the eligibility criteria, and understand their privacy rights. They will be required to create an account on the platform by providing the requisite details for the app platform (username, email address, password, and display name). The in-app onboarding protocol will then require participants to read a brief app description and information about how to use the app. They will then be required to indicate whether they are gamblers, family members, or stakeholders in order to complete the preintervention survey (see *Within-Group Follow-up Evaluation*). Finally, they are required to record their mobile number, indicate their interest in being contacted for further research, and indicate their interest in participating in the semistructured interviews. Following this onboarding protocol, the participants will be encouraged to complete their first EMA.

Distal and Proximal Outcomes

The *distal outcome* of *GamblingLess: In-The-Moment* is the severity of gambling symptoms. The *primary proximal outcome* is reduced probability of a subsequent gambling episode (measured at the subsequent EMA). This outcome will be measured in the EMA using the item, "Have you gambled since the last time you checked in?" with a binary response option (yes or no). The secondary proximal outcomes are improvements in subsequent craving intensity, self-efficacy, and positive outcome expectancies (measured at the subsequent EMA).

EMA Features

Overview

GamblingLess: In-The-Moment will use an EMA protocol (Multimedia Appendix 1) employing in-app time-based sampling (ie, semirandomly prompting individuals to input internal states and ecological contexts), which will incorporate event-based sampling (collecting data around specific and discrete gambling episodes). Each EMA, which will take approximately 1 minute to complete, will comprise 10 items measuring momentary internal states and ecological contexts (including the tailoring variables), most of which are recorded on varying 5-point response scales presented in a multiple-choice format. To ensure an accurate record of gambling events, participants will also be administered an event record (Multimedia Appendix 1) in each EMA, in which they will record gambling episodes (primary proximal outcome) and associated expenditure using single items that have been used in previous EMA and ecological momentary intervention gambling research [90,92,115,116].

Decision Points

During the 28-day MRT, participants will be prompted via push notifications to complete an EMA delivered through the app 3 times daily at random times during the prespecified periods: morning (8:30 AM-11 AM), afternoon (1 PM-3:30 PM), and evening (5:30 PM-8 PM; Figure 1). At each EMA notification, participants can auto-launch the EMA via the notification or app. Participants will be allowed 2 hours to complete an EMA to preserve the momentary nature of the intervention while accommodating the potential for possible unavailability (eg, driving and working) of the participant at the initial prompt time [98,128].

Tailoring Variables

The tailoring variables for *GamblingLess: In-The-Moment* include momentary craving intensity, self-efficacy, and positive outcome expectancies measured during each EMA (Multimedia Appendix 1). The craving item was adapted from the first item of the Gambling Symptom Assessment Scale [129], the self-efficacy item was adapted from the Brief Situational Confidence Questionnaire-Gambling [130], and the positive outcome expectancy item was adapted from the Gambling Outcome Expectancy Scale [69]. The JITAI will tailor the type, timing, and amount of support to individual needs [94-96,99,100] (Figure 1). The tailoring variable data received from each participant will be used to individualize treatment by repeatedly selecting the *type* of intervention content (craving, self-efficacy, or positive outcome expectancies). The flexible collection of tailoring variable data will allow for the *timely* individualization of intervention options at specific moments when individuals are especially in need of support but not when they do not need support or are unreceptive to support. Finally, the dosage or *amount* of support will be tailored to individual needs via an intervention loop, whereby participants who continue to require support after completing an intervention activity will be offered additional support.

Additional EMA Items

Additional single items measuring other momentary internal states and ecological contextual factors highlighted by the relapse prevention model [13,15] will be included in each EMA to explore the conditions under which the JITAI is most effective: psychological distress (based on the distress thermometer: Psychosocial Distress Practice Guidelines) [131], readiness to change (based on the gambling readiness ruler) [132], subjective alcohol intoxication (based on the Subjective Effects of Alcohol Scale) [133], impulsivity (based on an EMA item from the Momentary Impulsivity Scale) [134], social context (based on an EMA item measuring social context for alcohol use) [135], financial gambling availability (based on an EMA item assessing money for preferred products) [136], and location gambling availability (based on an EMA item assessing cigarette availability [137]) (Multimedia Appendix 1).

Welcome and Reminder Protocol

The following contact protocol will be adopted to enhance EMA compliance during the 28-day MRT: (1) an automated welcome

email to all participants following onboarding, (2) a reminder email to participants who fail to complete onboarding or fail to complete an EMA for more than 48 hours following onboarding, and (3) a reminder telephone call by clinically or qualitatively trained research fellows to participants who still fail to complete onboarding or an EMA in the subsequent 48-hour period (with a follow-up SMS message if no answer or second follow-up email if no valid phone number was provided). Participants who fail to complete an EMA following this protocol will receive no further contact but (as long as they complete onboarding and at least one EMA and have some engagement with app-intervention activities) will be contacted to request completion of the postintervention and 6-month follow-up surveys.

Intervention Options

Tailored Intervention Condition

The intervention options in *GamblingLess: In-The-Moment* are informed by the relapse prevention model [13,15] as well as data from the *GamblingLess* program of research [41,43,115-120]. The intervention options were designed to target the cognitive processes that mark a state of cognitive vulnerability (cravings, low self-efficacy, and positive outcome expectancies) (secondary proximal outcomes) for the occurrence of a gambling episode (primary proximal outcome). The resulting program comprises 53 activities across three tailored intervention options (modules): (1) *Curbing Cravings*, (2) *Tackling Triggers*, and (3) *Exploring Expectancies*. Consistent with more recent conceptualizations of coping strategies explicated by the relapse prevention model, these interventions include cognitive, behavioral, and third-wave (mindfulness and acceptance) strategies [13,15,138]. Cognitive behavioral treatments have the most established evidence base in both face-to-face and mobile treatment of problem gambling [105-107,139,140], with mindfulness-based interventions receiving emerging empirical support [141,142]. The activities in each of these modules are displayed in Multimedia Appendix 2.

The intervention activities were selected based on their appropriateness for repeated delivery, effectiveness in previous research, and previous acceptability feedback [41,43,115,116]. The selected activities were developed for smartphone delivery with a focus on engagement, interactivity, user preferences, participant literacy, inclusiveness, and ease of use, with the aim of encouraging autonomy and creating an aesthetically pleasing design. Activities involved user interaction and gamified using multimedia delivery strategies comprising a combination of video activities, audio activities, personalized feedback, quizzes, open-ended items, and multiple-choice items. All video-based activities were publicly sourced videos from YouTube, with written permission obtained from each creator. To assist participants in selecting an activity appropriate to their current environment or social situation, all activities are labeled as text, video, interactive, audio, or text and image on each menu. Consistent with the pilot study, *GamblingLess: Curb Your Urge* [115,116], most activities take <5 minutes to complete.

Intervention Option 1: Curbing Cravings

The *Curbing Cravings* intervention option includes a bank of 10 craving management activities, including psychoeducation, distraction, breathing exercises, progressive muscle relaxation, mindfulness meditation, urge surfing, imagery, cognitive reframing, decisional balance, and planning [13,14]. In the *GamblingLess* trial, participants reported the lowest self-efficacy for high-risk situations related to urges and temptations [41,43]. Despite the delineation between craving and urges described earlier, the term urges was used in all user-facing aspects of the intervention (ie, EMA items and activity content; the intervention title is not user-facing), given anecdotal evidence in the addiction field that this is the most understandable, accessible, and commonly used term in addiction science [143-145].

Intervention Option 2: Tackling Triggers

The *Tackling Triggers* intervention option contains 25 activities to improve self-efficacy across 5 types of high-risk situations: financial pressure, unpleasant emotions, social pressure to gamble, testing control over gambling, and conflict with others. Participants in the *GamblingLess* trial [41,43] reported the lowest self-efficacy in these situations (with the exception of urges and temptations, which are targeted separately in the *Curbing Cravings* intervention option). Each situation type comprises a bank of 5 activities designed to increase a sense of competency and mastery by teaching participants to identify, anticipate, plan for, and effectively cope with these high-risk situations [13,14]. These include behavioral (eg, self-monitoring, goal-setting, behavioral substitution, progressive muscle relaxation, psychoeducation, assertiveness training, conflict resolution training, lapse management, and planning), cognitive (eg, cognitive reframing, imagery, and decisional balance), and acceptance or mindfulness (eg, cognitive defusion and mindfulness meditation) strategies [13,14].

Intervention Option 3: Exploring Expectancies

The *Exploring Expectancies* intervention option contains 18 activities to redress 3 types of positive outcome expectancies: excitement, escape, and money. These positive outcome expectancies have consistently displayed positive associations with problem gambling severity and gambling-related harm, particularly in Australian adult samples [69,75,76]. Consistent with the relapse prevention model [13], the focus of intervention activities in this intervention was to explore the validity and reality of positive outcome expectancies by contrasting the possible immediate positive consequences with the delayed negative consequences of gambling [146]. Meta-analytic evidence supports the efficacy of such expectancy challenge interventions for alcohol abuse prevention [147]. Each type of expectancy comprises 6 activities, including behavioral (eg, self-monitoring, personalized normative feedback, psychoeducation, progressive muscle relaxation, and behavioral substitution), cognitive (eg, decisional balance, imagery, and expectancy challenging), and third-wave (eg, mindfulness meditation, and cognitive defusion) activities to redress these positive outcome expectancies.

No Intervention Control Condition

In the MRT, the no intervention control condition involves participants being delivered a brief encouraging message, after which their interaction with the app will end. This tailored message involves acknowledgment that participants have an urge, low self-efficacy in high-risk situations, or positive outcome expectancies, as well as encouragement to consider doing something to reduce their urge, avoid or cope with high-risk situations, or reduce their expectations. In this condition, the participants are not provided with any intervention activities.

Decision Rules

The decision rules are illustrated in Figure 1. At each decision point during the 28-day MRT, responses to EMA items assessing craving intensity (tailoring variable 1), self-efficacy (tailoring variable 2), and positive outcome expectancies (tailoring variable 3) are used to determine eligibility for the delivery of the tailored intervention, according to a set of predetermined decision rules (scoring >0 on each tailoring variable). At each decision point, participants who do not exceed the cut point for any of the tailoring variables are not eligible for any intervention. These participants will receive a brief encouraging message and their interaction with the app will end. In contrast, participants who exceed the cut point on one or more of the tailoring variables are eligible for a tailored intervention (ie, curbing craving, tackling triggers, *or* exploring expectancies).

Microrandomization Protocol

The microrandomization procedure will then be applied, whereby eligible participants will be microrandomized to a tailored intervention condition or no intervention control condition (Figure 1). Overall, the microrandomization procedure will involve eligible participants having a 75% chance of being microrandomized in the tailored intervention condition and a 25% chance of being microrandomized in the no intervention control condition. However, because the reformulated relapse prevention model does not presume that certain factors are more influential than others [15], participants exceeding the cut point on more than one of these tailoring variables will be randomly allocated to a relevant intervention option (curbing cravings, tackling triggers, or exploring expectancies). Specifically, participants who are eligible for 2 intervention options will have a 37.5% chance of receiving either intervention option, and those who are eligible for 3 intervention options will have a 25% chance of receiving any of the intervention options. This microrandomization protocol is fully automated, which guarantees that the administration of treatments and assessment of outcomes are blinded.

Following completion of each EMA, participants who are microrandomized to the no intervention control condition will be sent an encouraging message, and their interaction with the app will end. Participants microrandomized to the tailored intervention condition will be sent to the relevant intervention dashboard, which comprises a menu of intervention activities from which they can select. Specifically, participants who are allocated to the craving intervention will be taken to the craving intervention dashboard and asked to select an intervention activity. In contrast, participants who are allocated to the self-efficacy and expectancies interventions will be asked to select a specific type of trigger or expectation, administered an EMA item specific to their selected trigger or expectation (Multimedia Appendix 3), then taken to the relevant intervention dashboard, and asked to select an intervention activity.

Intervention Loop

Following the completion of an intervention activity, participants are asked to complete the specific EMA item associated with the intervention group to which they were allocated (postintervention EMA item; Multimedia Appendix 3). Their response to the postintervention EMA item is then subjected to the same decision rules used for the time-based EMA. Participants who fail to reach the cut point on this postintervention EMA item will be presented with an encouraging message, and their interaction with the app will end. Participants who exceed the cut point (ie, score one or more) on the specific EMA item will be presented with a feedback message in which their response to their postintervention EMA item is compared with their time-based EMA response on the same item, encouraged to select another intervention activity, and returned to the relevant intervention dashboard. This intervention loop continues until the participant fails to exceed the cut point or closes the app (Figure 1). At several locations within the app, as well as in the welcome email and trial plain language statements, participants are informed that they can stop the loop at any time by closing the app to ensure that they do not adjust their response to break the loop.

Provide Nothing Option

Importantly, a *provide nothing* option is provided for situations in which the participant is unreceptive, support is not required, or the provision of support may be unsafe, inconvenient, or unethical [94-96,98]. Specifically, support will not be offered if participants ignore the push notification prompting EMA completion or press the *snooze* function to indicate that they are currently unable to complete the EMA (which suggests that they are not in a state of receptivity).

Other App Features

The home dashboard includes quick links to the *Check In Here*, *Get More Support*, and *More* features. The *Check In Here* quick link allows participants to complete an EMA within the allowed 2-hour period and provides an encouraging message when participants attempt to complete an EMA if more than 2 hours have passed since the last notification. The *Get More Support* quick link, which is also available on each of the intervention activity menu dashboards, provides click-to-call and click-to-email functions to Australian and New Zealand helpline and web-based specialist gambling services. This feature allows participants to escalate the support they receive, including immediate crisis support [101]. The *More* quick link provides information about the app, the trial, contact details, the platform's privacy policy, the plain language statement, profile information, account details, and sign out. Other app features include the *Did You Know?* feature, which delivers brief passive psychoeducational messages related to cravings, self-efficacy, and positive outcome expectancies before the delivery of every

intervention activity and the *Pick For Me* feature on each intervention activity menu, whereby the app randomly selects one of the intervention activities on the menu for participants.

Within-Group Follow-up Evaluation

A within-group evaluation of outcomes over a 6-month follow-up period will supplement the MRT to (1) evaluate within-group change over a longer period and (2) explore predictors of longer-term treatment outcomes (including app use over the 6-month follow-up period). Although the preintervention survey will be automated via the app before beginning the 28-day MRT period, participants will be prompted by email to complete the postintervention and follow-up surveys via Qualtrics (Qualtrics XM). Descriptive and covariate measures will include participant type (gambler, family member or friend, and clinician, researcher, or policy maker), sociodemographic characteristics, problem gambling activities, intended gambling behavior (measured using the Timeline Follow-Forward, a novel adaptation of the Timeline Follow-Back [148]), and other help-seeking (measured using the Help Seeking Questionnaire [149]). The primary outcome will be gambling symptom severity (measured using the Gambling Symptom Assessment Scale [129]), and secondary outcomes will include gambling frequency and expenditure (measured using a timeline follow-back at the preintervention evaluation, the EMA event record data at the posttreatment evaluation, and single items at the 6-month evaluation) and the cognitive processes targeted by the intervention: craving severity (measured using the Penn Gambling Craving Scale [25]), self-efficacy (measured using the Brief Situational Confidence Questionnaire-Gambling [130]), and positive outcome expectancies (measured using the Excitement, Escape, and Money subscales of the Gambling Outcome Expectancies Scale [69]; Multimedia Appendix 4). Each evaluation will be completed in approximately 10 to 15 minutes. Ideally, follow-up evaluation surveys will also be conducted 12 and 24 months after the intervention, but this will be dependent on obtaining additional funding.

A follow-up protocol will be implemented to enhance the completion of the postintervention and 6-month follow-up surveys: (1) an email requesting survey completion, (2) a reminder email requesting survey completion within a week to participants who fail to complete the survey in the subsequent 1-week period, and (3) up to 2 reminder telephone calls by clinically or qualitatively trained research fellows to participants who fail to complete the survey in the subsequent 3-week period (with a follow-up SMS text message if no answer or a further follow-up email if no valid phone number was provided). An advance notice email will also be sent 1 week before the 6-month surveys are sent. At each time point, the option to complete the survey over the phone with a trained research fellow will be offered. Participants who fail to complete the surveys following this protocol will receive no further contact, but participants failing to complete the postintervention survey will be contacted to request the completion of the 6-month follow-up survey.

During the 6-month follow-up evaluation period, tailored intervention content will be available to participants on demand. Although Nahum-Shani et al [94] defines JITAI designs as a *push* intervention approach, participant-determined features may accommodate conditions in which participants know when and what type of support is required, promote autonomy by facilitating agency and control, reduce waste and disruption, generalize learned skills, and maintain therapeutic gains [94,97-99,101,150]. During this period, participants will not receive push notifications to complete EMAs and the microrandomization protocol will not be applied (ie, all participants will be allocated to the tailored intervention condition, with the no intervention control condition turned off). However, they will be able to access tailored intervention content via participant-initiated EMAs (ie, they can complete an EMA at any time, which will direct them to tailored intervention content). This approach has been adopted to encourage participants to incorporate coping skills in their everyday lives when they recognize states of vulnerability or opportunity and are motivated to initiate access to support [97-99,101]. The degree to which app use across the 6-month follow-up period influences longer-term treatment outcomes will be explored.

Acceptability Evaluation

The acceptability of *GamblingLess: In-The-Moment*, operationalized as a multifaceted construct that reflects the extent to which participants consider the intervention to be appropriate based on the cognitive and emotional responses they have to the intervention [151], will be explored using multiple methodologies. *Postintervention surveys* will evaluate the subjective quality and perceived impact of the JITAI using the 4-item subjective quality and 6-item perceived impact subscales of the Mobile App Rating System [152], as well as the perceived helpfulness of additional features (eg, in-person support, web-based discussion boards, motivational messages, feedback, and push and pull features), EMA frequency, and program duration. *App use and engagement indices* will be used across the 28-day MRT and 6-month follow-up period to explore download information, onboarding information, app use information (eg, EMA compliance, intervention eligibility, intervention compliance, participant retention, and intervention activities selected), and the use of specific app features (eg, intervention loop, *Pick For Me*, and *Get More Support*). *Semistructured interviews* will be conducted with a minimum of 10 participants from the MRT to explore the reasons for using the app, program duration, EMA frequency and timing, perceived helpfulness of the intervention activities and specific features, perceived helpfulness of additional features, impact on behavior change, the app's look and feel, and areas for improvement. Given the funding source, participants from New South Wales will be prioritized and stratified according to gender and app use. These interviews, which will be conducted at the end of the 28-day MRT, will be conducted by clinically or qualitatively trained research fellows via video conferencing or telephone. Interviews will be audio recorded for transcription and data analysis purposes, and data will be analyzed using thematic analysis at a semantic level based on the guidelines by Braun and Clarke [153].

Statistical Analyses

To assess the research questions, the method of generalized estimating equations (GEE) will be used, with an appropriate link function for the outcome of interest (eg, identity and logit). Although the intention is to use an exchangeable working correlational structure for analyses, alternative correlational structures based on the observed within-person correlation pattern over the course of the study (eg, independent or autoregressive) will be considered. For all MRT analyses, the (lagged) outcome of interest (eg, gambling episode at $Time_{t+1}$) will be regressed on to a variable denoting the intervention received (eg, intervention options 1, 2, and 3 or no intervention) at $Time_t$, as well as covariates (including unbalanced time, time since prior assessment, and other forms of help-seeking). To assess the primary research question and secondary research question 1, the analyses will examine the effects of the tailored intervention versus no intervention control on the probability of a subsequent gambling episode, stratified analyses focusing on each intervention option separately versus no intervention control (on the specific outcome related to each intervention option; ie, craving intensity, self-efficacy, and positive outcome expectancies), and formal tests comparing the magnitude of each intervention with the no intervention condition on the probability of a subsequent gambling episode. Secondary research questions 2 and 3 will be examined by specifying the interaction terms between the intervention variable and the interaction variable of interest (eg, psychological distress and time). Consideration will be given to making appropriate adjustments in line with modern causal methods for assessing effect moderation [154].

To explore the long-term outcomes of the intervention (within-group follow-up evaluation), distal outcomes will be assessed using GEE by regressing the outcome of interest (eg, gambling symptom severity) on a variable denoting time (ie, preintervention, postintervention, 6-month follow-up variables) and covariates. The factors associated with longer-term treatment outcomes will also be explored using GEE by regressing the outcome of interest (eg, clinically significant change in gambling symptom severity) with selected preintervention, postintervention, and app use variables (eg, the number of participant-initiated EMAs completed in the 6-month follow-up period). Where appropriate, missingness will be addressed using multiple imputation, with appropriate accounting for the multilevel nature of the data (eg, see multilevel multiple imputation [155]).

Clinical Significance

Supplementary analyses will consider the clinical significance of any effect (ie, meaningful changes in the participant's life) [156]. Effect sizes will be calculated for all primary and secondary outcomes. These group-level examinations of effectiveness will also be supplemented by metrics of individual-level change for all primary and secondary outcomes. A reliable change index will be used to assess changes beyond those attributable to chance or measurement error [157]. Clinically significant change, as outlined by Jacobson and Truax [156], will subsequently be calculated using functional score ranges where possible (Gambling Symptom Assessment Scale score of ≤20) or a convention of at least a 25% change in scores in the positive direction [158]. At the posttreatment and 6-month follow-up evaluations, each participant's status will be defined as *recovered* (final score falls into the functional range and corresponds to a reliable change), *improved* (final score falls into the dysfunctional range and corresponds to a reliable change), *unchanged* (final score does not correspond to a reliable change), or *deteriorated* (final score corresponds to a relative change in the negative direction).

Sample Size

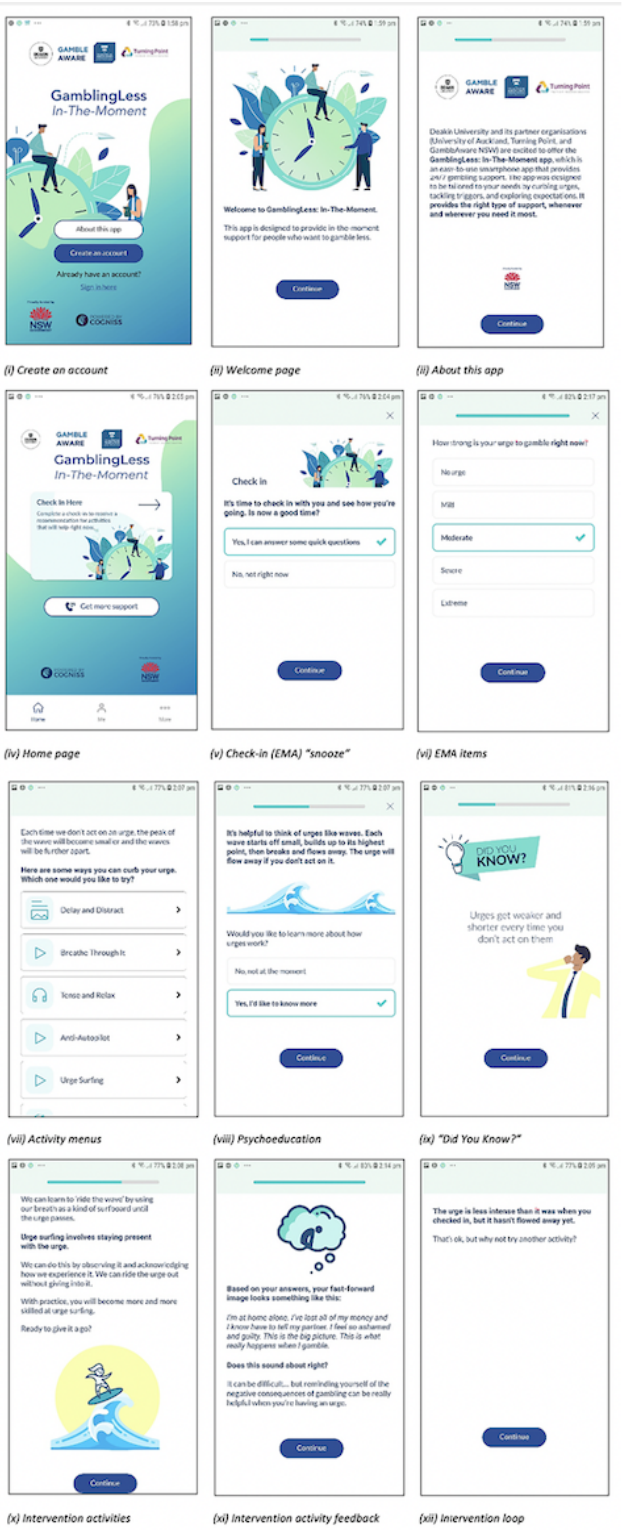
The project aims to recruit a sample of 200 participants. A sample size of 120 participants would provide >80% power to detect a small true intervention effect size for the primary binary outcome (ie, gambling episode) of relative risk=1.21 (at Cronbach α=.05; availability parameter=0.3; randomization P=.25; outcome without intervention P=.25) [159,160]. In *GamblingLess: Curb Your Urge*, attrition was 39% when considering participants who completed the baseline measures and 19% when considering participants who downloaded the app after completing the baseline measures [116]. As such, this project will provide sufficient power to detect true effects even under a conservative attrition rate of 40% from the original sample of 200 participants at baseline.

Results

Development of GamblingLess: In-The-Moment

Development and evaluation of *GamblingLess: In-The-Moment* was funded in June 2019 by the New South Wales Government's Responsible Gambling Fund. The development of *GamblingLess: In-The-Moment* involved a multidisciplinary team comprising behavior change expertise from clinical and social psychology, implementation science, biostatistics and research design, and technology developers, consistent with recommendations for technology development [94]. *GamblingLess: In-The-Moment* is part of a suite of theoretically informed and evidence-based web-based and mobile gambling interventions (*GamblingLess*). The development of the treatment content was led by the NAD, a clinical psychologist, and the app was hosted on the Cogniss behavior change platform, which was created by 2and2, specialist developers of custom tech solutions for learning, health, and behavior change. Illustrative screenshots of JITAI are displayed in Figure 2.

Figure 2. Illustrative screenshots of *GamblingLess: In-The-Moment*.



User Testing of GamblingLess: In-The-Moment

Following its development, *GamblingLess: In-The-Moment* was subjected to user testing with 13 gambling stakeholders from June 2021 to July 2021, including 5 gambling clinicians, 5 gambling researchers, and 3 gambling consumers, who had scores in the problem gambling range of the Problem Gambling Severity Index (mean 18.7, SD 10.6). These user-testing participants comprised 5 men and 8 women, who tested the app on both Android (4/13, 31%) and Apple (9/13, 69%) devices. They were reimbursed with a US $35 e-gift voucher to download the app, create an account, test that the app functions as intended over a 3-day period, and evaluate the acceptability of the app via a Qualtrics XM survey (Multimedia Appendix 5). Participants completed the Mobile App Rating Scale [152], which comprises 23 items across 4 subscales measuring the overall quality of the app, the subjective quality of the app, and the perceived impact of the app [152].

Participants rated the user-testing version of *GamblingLess: In-The-Moment* over a minimum acceptability score of 3 for all Mobile App Rating Scale subscales, suggesting that the app can be recommended for reducing gambling symptom severity [161]. All tailored interventions were rated highly in terms of ease of completion (>8 out of 10) and helpfulness (>7 out of 10). Users also rated specific features highly (out of 10), particularly the helpfulness of the *Click to Call/Email* (mean 8.9, SD 1.3), *Pick for Me* option (mean 8.6, SD 1.8), and *Did You Know?* messages (mean 8.5, SD 1.3). Qualitative data were also generally positive, with positive comments relating to comprehensive, accurate, and concise information; ease of use; strategy range; helpfulness, practicality, and interactivity; the customization of feedback based on participant responses; the use of accessible and respectful language; the look and feel of the app, including graphics, multimedia, and interactivity; and the *Pick For Me* function. Participants generally indicated that the app would be a great resource, both as a stand-alone and adjunct intervention. Although few content or flow issues were identified, participants commented on several technical issues, predominantly in relation to notification frequency, the functionality of the deep link from the notification to the EMA, the accuracy of the check-in duration windows, and loading times (particularly in relation to Timeline Follow-Back and Timeline Follow-Forward calendars). These issues were resolved before the app was released for evaluation.

Trial Progress

GamblingLess: In-The-Moment is available for download during this trial on Apple (App Store) and Android (Google Play Store) devices. Following advertising on March 22, 2022, a total of 3 pilot participants were recruited to ensure that the app and evaluation protocols functioned as intended. Advertising for the trial began on March 29, 2022. As of June 24, 2022, a total of 84 participants had been recruited for the trial. The results are expected to be published mid- to late-2024.

Discussion

Overview

This project aims to redress the gap in existing service provision by developing and evaluating a theoretically informed and evidence-based JITAI for gamblers who want to quit or gamble less. Consistent with JITAI development recommendations [94], *GamblingLess: In-The-Moment* was developed by a multidisciplinary team involving clinical and social psychology, implementation science, biostatistics and research design, and technology development. It uses *decision rules* specifying that individuals who are in a state of receptivity (available for treatment) and report a state of cognitive vulnerability characterized by high craving intensity, lowered self-efficacy, and positive outcome expectancies (*tailoring variables*) in time-based EMAs sent 3 semirandom times a day (*decision points*) are delivered tailored cognitive behavioral and third-wave interventions targeting these cognitive processes (*intervention options*). The JITAI will tailor the type, timing, and amount of support for individual needs.

The evaluation of the JITAI will involve a 28-day MRT, in which the JITAI will be evaluated as an entirely *push* intervention approach. Information from the MRT will be used to optimize *GamblingLess: In-The-Moment* to make it a more effective, efficient, and scalable intervention. This trial will provide important empirical data to identify more refined decision rules specifying which intervention options should be delivered as well as to explore when and for whom the intervention is effective [97,98]. This may involve discarding less effective or more burdensome options, delivering the intervention during specific internal states and ecological contexts, or modifying the timing and cut points for each tailoring variable [96-98].

Evaluations of JITAIs, particularly those using MRTs, generally preclude evaluations of long-term outcomes. Therefore, MRT will be supplemented with a 6-month within-group follow-up evaluation to assess and predict long-term outcomes. During this 6-month period, participants will be able to access the intervention content on demand via participant-initiated EMAs when they recognize states of vulnerability or opportunity and are motivated to initiate access to support. Unlike many other JITAI evaluations [99], within-group follow-up evaluations will also facilitate the consideration of the clinical impact of *GamblingLess: In-The-Moment* in addition to the statistical significance of the findings.

Consistent with recommendations [99,162], the development of *GamblingLess: In-The-Moment* used an iterative and user-centered approach to its design. The intervention has been subject to stakeholder user testing, which suggests that the JITAI is an acceptable gambling intervention, and subsequent consideration of user-testing feedback. The acceptability of the intervention will also be explored in the trial, using both qualitative and quantitative methods. This information can be used to evaluate participants' perceptions related to the app's subjective quality and perceived impact. It will also inform the future development of the app by providing information relating to individual intervention activities, the app's specific features, and additional features that could be included in future iterations of the app. For example, it may be that participants indicate a preference for a more traditional *pull* approach, in which they initiate intervention access when they require support, or the addition of some *participant-determined* features or *on-demand* intervention content to this JITAI [94]. The addition of such features may accommodate situations in which individuals recognize states of vulnerability, thereby maintaining therapeutic gains by encouraging coping skills in everyday life, enhancing generalization of learned skills, promoting autonomy by facilitating agency and control, and involving less disruption and burden [94,97-99,150]. Similarly, participants may indicate a preference for the addition of human support via the involvement of clinicians, guides, coaches, or peers [103,162-164] or digital avatars in the form of personal coaches and assistants [165], which may enhance motivation, engagement, and adherence to the requirements of the intervention [163]. The acceptability evaluation will also offer the opportunity to explore participant preferences for program duration, as well as the frequency and timing of EMAs. For example, there is a risk that 3 EMAs each day are an obstacle to sustained engagement or that restricting the timing of the EMAs to daytime hours is not aligned with high-risk situations

occurring outside these hours. This information is therefore particularly important to inform the limited evidence base regarding transitory changes in the presence of urges or cravings, self-efficacy in high-risk situations, or positive outcome expectancies.

This study will be one of the first to examine the effectiveness of real-time support for reducing gambling behavior and the first to achieve this by comprehensively addressing the cognitive processes underlying gambling lapses and relapses, as articulated by the highly influential relapse prevention model. Given that JITAI development and evaluation of gambling problems is an emerging area of research, this study can establish an evidence base for future research using optimized interventions. For example, future research could establish the efficacy of interventions when human support is added [103,162-164], with an emphasis on when and for whom human support adds value given the effectiveness and lower cost of unguided interventions [162,166]. As recommended by Nahum-Shani et al [94], future research is required to explore how best to add *participant-initiated* or *on-demand* features to this JITAI to ensure that personal volition is balanced with planned, externally initiated support. Future iterations of *GamblingLess: In-The-Moment* could also combine EMA data with tailoring variables from passive assessments from sensors or other technologies to provide additional contextual information, lower user burden, and enhance user awareness of behavior [102,128]. Future research using cost evaluation analyses that weigh the relative costs and outcomes of *GamblingLess: In-The-Moment* with other interventions could inform health care resource allocation decisions [100], and the efficacy of this intervention delivered as a transdiagnostic intervention to address the cognitive processes underlying all addictions could improve treatment efficacy, efficiency, and cost-effectiveness [167]. Finally, there is scope for harnessing machine learning approaches to develop accurate models identifying response patterns that predict the risk of unplanned gambling in real time, ideally with respect to targeting factors contributing to the risk of gambling for each individual [128].

Dissemination of Findings

The findings of this evaluation of *GamblingLess: In-The-Moment* will be disseminated in peer-reviewed journal articles, conference presentations, stakeholder forums, and professional development seminars. A summary of the findings of the trial will be available on the *GamblingLess* website when they become available [168].

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Authors' Contributions

The development of the *GamblingLess: In-The-Moment* intervention is led by NAD (Deakin University) and is part of a suite of theoretically informed and evidence-based web-based and mobile gambling interventions (*GamblingLess*). NAD, with support from SSM and SNR, conceived the project, developed the methodology, and acquired funding. NAD wrote the first draft of the manuscript, with statistical advice from GJY. All the authors contributed to the final draft of the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare in relation to this article.

The 3-year declaration of interest statement of this research team is as follows: NAD, SSM, GJY, DIL, ACT, SNR Delaware, KLB, and ACT received funding from multiple sources, including government departments and the Victorian Responsible Gambling Foundation (through hypothecated taxes from gambling revenue), and the International Center for Responsible Gaming, a charitable organization that derives its funding from multiple stakeholders (with funding decisions the responsibility of a scientific advisory board). SSM is the recipient of the New South Wales Office of a Responsible Gambling Postdoctoral Fellowship. None of the authors have received research funding from the gambling, tobacco, alcohol industries, or any industry-sponsored organization. The authors have no conflicts of interest to declare in relation to this article.

Multimedia Appendix 1
GamblingLess: In-The-Moment ecological momentary assessments items.
[DOCX File , 16 KB - resprot_v11i8e38958_app1.docx]

Multimedia Appendix 2
Overview of the GamblingLess: In-The-Moment intervention options.
[DOCX File , 14 KB - resprot_v11i8e38958_app2.docx]

Multimedia Appendix 3
GamblingLess: In-The-Moment intervention eligibility.
[DOCX File , 14 KB - resprot_v11i8e38958_app3.docx]

Multimedia Appendix 4
GamblingLess: In-The-Moment intervention eligibility.
[DOCX File , 21 KB - resprot_v11i8e38958_app4.docx]

Multimedia Appendix 5
GamblingLess: In-The-Moment user-testing scores.
[DOCX File , 15 KB - resprot_v11i8e38958_app5.docx]

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Abbreviations

EMA: ecological momentary assessment
GEE: generalized estimating equations
JITAI: just-in-time adaptive intervention
mHealth: mobile health
MRT: microrandomized trial
SPGeTTI: smartphone-based problem gambling evaluation and technology testing initiative

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Protocol

Association of Transcranial Direct Current Stimulation and Neurofeedback With Declarative Memory and Cerebral Arterial Flow in University Students: Protocol for a Double-blind Randomized Controlled Study

Leandro H Grecco[1,2,3*], MSc; Giuliano R Gonçalves[2,4], MSc; Bárbara Neiva Perri[2], BSc; Breno Alexander Bispo[2], BSc; Isabella Favilla Jorge Grandin[2], BSc; Paula Valentina Nunes Dias Gomes[2], BSc; André Alexandre Bocchi[2], BSc; Kennedy Martinez Oliveira[5], PhD; Diogo Correa Maldonado[1], PhD; Marcelo Cavenaghi Pereira da Silva[1,3*], PhD

[1]Department of Morphology and Genetics, Universidade Federal de São Paulo, São Paulo, Brazil

[2]Faculdade São Leopoldo Mandic, Campinas, Brazil

[3]Universidade Federal de São Paulo, São Paulo, Brazil

[4]Pontifícia Universidade Católica de Campinas, Campinas, Brazil

[5]Anatomy and Image Department, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[*]these authors contributed equally

Corresponding Author:
Leandro H Grecco, MSc
Department of Morphology and Genetics
Universidade Federal de São Paulo
Rua Botucatu, 682
São Paulo, 04021-001
Brazil
Phone: 55 11 5576 4848
Email: leandrohgrecco@gmail.com

Abstract

Background: The performance of a task depends on ongoing brain activity, which can be influenced by attention, excitement, or motivation. Scientific studies have confirmed that mindfulness leads to better performance, health, and well-being. However, these cognitive efficiency modulating factors are nonspecific, can be difficult to control, and are not suitable to specifically facilitate neural processing.

Objective: The aim of this study is to evaluate the effects of transcranial direct current stimulation associated with neurofeedback on declarative memory and cerebral blood flow in university students.

Methods: In this study, we will use transcranial direct current stimulation, a low-cost physical resource that is easy to apply, has few adverse effects, and is associated with a neurofeedback resource. This, in turn, has been shown to be a training program capable of improving working memory function.

Results: Participants will be recruited between July 2022 and December 2022. This study is expected to conclude in July 2023.

Conclusions: This study will provide preliminary results on the benefits of using the direct current neurostimulation and neurofeedback tools on the participants being analyzed.

Trial Registration: Brazilian Clinical Trials Registry RBR-7zs8b5; https://ensaiosclinicos.gov.br/rg/RBR-7zs8b5

International Registered Report Identifier (IRRID): PRR1-10.2196/36294

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KEYWORDS

transcranial direct current stimulation; neurofeedback stimulation; TDCS; memory; Doppler ultrasonography; arterial flow; brain stimulation; electrical stimulation; transcranial; neurofeedback; brain; neurology; cerebral; blood flow; cerebrum; declarative

memory; double-blind; controlled trial; RCT; randomized controlled trial; university; college; student; postsecondary; graduate; undergraduate

Introduction

As is well known, learning and memory involve explicit procedures (eg, declaratives) and implicit processes (eg, procedures), and improving one or both can contribute to improving learning [1]. Working memory refers to the temporary storage and manipulation of information needed for complex tasks such as language comprehension, attention, learning, and reasoning. One of the main goals of educational efforts is to develop techniques for improving learning and promoting better retention [1,2].

Today computer games are being developed not only for gamer entertainment but also in the field of health and education to improve one or more of the cognitive abilities of users. These games can improve problem-solving skills [3,4]. Brain events can be recorded in a noninvasive and flexible way through the electroencephalogram (EEG), and EEG-based applications were initially developed to help people with disabilities to communicate with machines; later they were used in video games as controllers and more recently as neurofeedback games [5]. Neurofeedback is a noninvasive, drug-free form of brain training reported to help with a variety of conditions, including pain, fatigue, depression, anxiety, sleep disturbances, and cognitive decline [6]. We can also include the implementation of a game to test the progress of trained individuals with a more flexible and interesting approach. It is a simple game application that uses visualization techniques to increase enthusiasm without being aware of being tested. As the system makes use of a participant's direct attention to control a game, it works on a feed-forward mechanism [7]. Neurofeedback offers the possibility of endogenously manipulating brain activity as an independent variable, making it a powerful neuroscientific tool [8]. Some areas of clinical research involve comparing or combining neurofeedback with other interventions such as pharmacotherapy, behavioral therapy, and neurostimulation (eg, transcranial direct current stimulation [TDCS]).

TDCS noninvasively induces plasticity-related changes in neural circuits in vivo and is experiencing increasing use as a potential tool to modulate brain function [9]. There is growing evidence that TDCS-related outcomes are likely to be influenced by an individual's brain state at the time of stimulation, that is, the effects show a degree of "state dependence" [10]. Fregni et al [11] demonstrated that anodic TDCS in the left dorsolateral prefrontal area leads to an increase in working memory performance, that is, increasing the accuracy of a task when compared to simulated stimulation of the same area. This study corroborates literature data showing TDCS as a tool that can significantly impact some aspects of knowledge [12].

TDCS is characterized by the administration of a single-phase electrical current of low intensity (0.5-2 mA) applied to the scalp through surface electrodes. This stimulation induces lasting changes in cortical neuronal excitability, both in animals and in humans [9]. TDCS-induced cortical modulation is dependent on the polarity of the applied current, and the effects are obtained by the movement of electrons. The poles of the electrodes used are the anode and cathode, with the anode being the positive pole and the cathode the negative pole. During the application of TDCS, the electrical current generated by the electrodes penetrates the skull, reaching the cortex [13]. Although most of the current dissipates between tissues superficial to the cortex, a sufficient amount of current reaches the cortical structures, thus modifying the membrane potential of the cells located there. It has been observed that anodic current increases cortical excitability, favoring neuronal membrane depolarization, while the cathodic current has an inhibitory effect by hyperpolarizing the neuronal membrane. TDCS has been shown to be a useful tool in the treatment of neuropsychiatric diseases and physical rehabilitation processes, being a safe and inexpensive form of noninvasive brain stimulation [10,11,14].

Some studies covering healthy individuals support the hypothesis that TDCS improves performance involving working memories, compared to simulated stimulation (placebo), and these effects can last up to 30 minutes after the end of the session. Nitsche et al [15] proposed general exclusion criteria for TDCS in healthy individuals: individuals must be free from unstable medical conditions or any disease that may increase the risk of stimulation, for example, neurological diseases such as epilepsy or acute eczema under the electrodes. Additionally, they must not have metallic implants near the electrodes. Side effects such as itchiness, a burning sensation, or a headache are common but usually mild and with no long-term impact. Thus, TDCS compares favorably with other therapeutic approaches such as antidepressants or transcranial magnetic stimulation [15].

Noninvasive neuromodulation has emerged as an alternative to replace other forms of treatment such as pharmacological treatments, which although effective, have a high rate of side or adverse effects. Among the different types, neurofeedback and TDCS have shown to be promising approaches that can modify brain wave oscillation and can be used in the development of skills for the self-regulation of brain activity [16]. However, no data were found in the literature associating these two features. The aim of this trial is to investigate the effectiveness of TDCS on the dorsolateral prefrontal cortex (DLPFC) associated with neurofeedback evaluating behavioral and physiological parameters of healthy college students. We hypothesize that there will be a significant increase in declarative memory responses and increased cerebral blood flow using the proposed protocol.

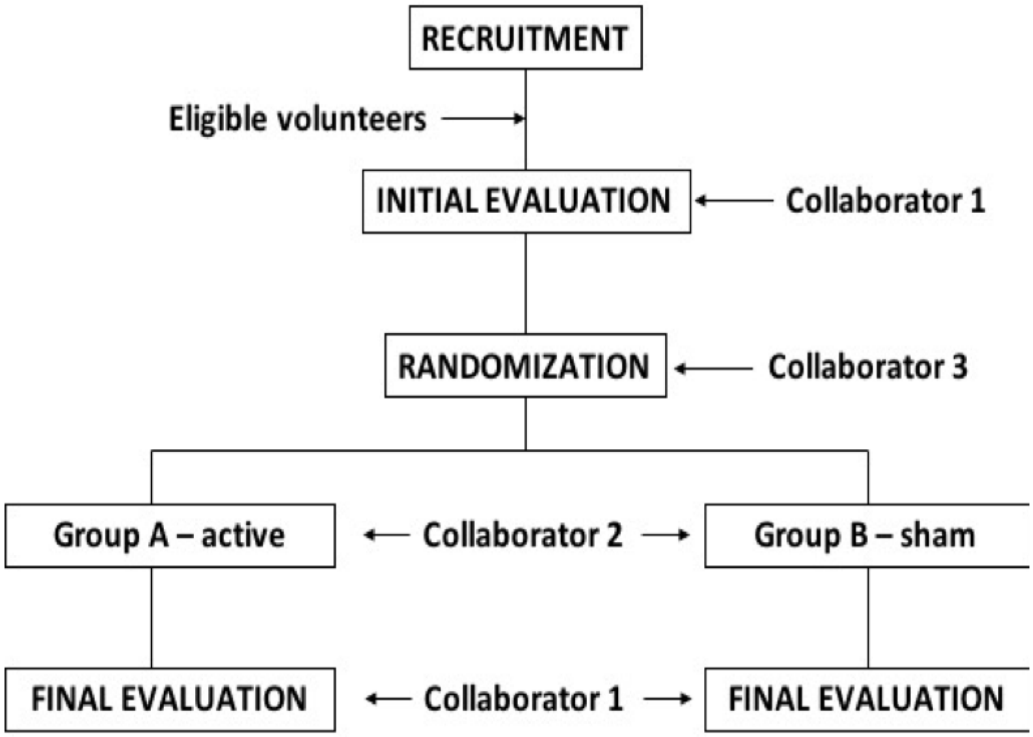
Methods

Study Design

This is a prospective, parallel, double-blind, randomized controlled, and 2-armed clinical trial. This study will be single center and carried out on the premises of Faculdade São Leopoldo Mandic/Campinas, São Paulo, Brazil.

After an initial evaluation carried out by a research collaborator (collaborator 1), the participant will carry out the research protocol with another collaborator (collaborator 2) according to the draw performed by this collaborator. At the end of the protocol, the participant will again undergo an evaluation that will be performed by collaborator 1. Only collaborator 2 will know if the participant performed active stimulation or placebo. Therefore, this procedure will allow blinding of the participant and collaborator 1 (evaluator) to the stimulation conditions (Figure 1).

Figure 1. Flowchart of study design.



Sample

The sample of 50 volunteers was calculated assuming a 40% difference in the proportion between the active TDCS and placebo groups in performance before and after the interventions. This calculation was performed using an online statistical program, considering an alpha of .05 and a power of 0.80, resulting in a sample of 25 individuals in each group (intervention and control). To approximate unexpected factors, we applied a 20% dropout rate, reaching a total sample size of 60 individuals.

Inclusion Criteria

Eligible volunteers for the study must meet all the following items prior to randomization: medicine and dentistry undergraduates in their first to eighth semester, duly enrolled in the institution; aged between 18 and 30 years; and without distinction of sex or gender.

Exclusion Criteria

Participants will be ineligible for the study if their medical history present psychiatric disorders, neurological trauma, epilepsy, seizures, or drug abuse in the last 6 months (including alcohol); if they are using medication that acts on the central nervous system by self-report or have any metallic implant in the head region; and if they are pregnant or planning to get pregnant in the next 2 months.

Randomization and Blinding

Once eligibility and consent have been approved and completed, randomization will occur using the random list generated by an automated web-based randomization program. Participants will be randomly assigned into 1 of the following 2 groups:

1. Group A: TDCS active + neurofeedback
2. Group B: placebo TDCS + neurofeedback

Participants randomized to receive placebo TDCS will have the opportunity to enroll in an open-label portion of the study upon completion of their participation in the randomized portion of the study.

This process will be carried out by a member of the research team (collaborator 3) who is not involved in the study recruitment or development process.

Ethical Approval

In accordance with the Declaration of Helsinki, this study strictly follows ethical principles in research involving human participants. All participants will be informed of the nature of the study and all procedures prior to registration. Following resolution 196/96 of the National Health Council (Brazil), only those who sign the free and informed consent form will be included.

This study was approved by the Ethics and Research Committee of Faculdade São Leopoldo Mandic/Campinas-SP under the opinion number 08051619.1.0000.5374. Furthermore, this study

was submitted to the Brazilian Registry of Clinical Trials and approved under the RBR-7zs8b5 protocol (Universal Trial Number U1111-1254-0883).

Assessments

Once eligibility and consent have been approved and completed, volunteers will undergo the Stroop test (based on the study by Campanholo et al [17]). This test consists of two tasks, one for reading and the other for naming the color. In both, the stimuli are color names printed in incongruous colors. The word-reading task gives an indication of reading fluency and serves to establish a benchmark for performance effectiveness relative to the color-naming task. The fact that there is an incongruity between the word name and the ink color causes an interference effect in the color naming. This interference is the Stroop color effect. Tests inspired by the Stroop effect are widely used in neuropsychology to measure individuals' executive control and concentration [17].

After performing the Stroop test, the participant will undergo an assessment of cerebral blood flow by means of a transcranial Doppler ultrasound examination of the middle cerebral artery. The protocol developed by Rogge et al [18] will be carried out. Color-coded transcranial Doppler ultrasound will be performed in combined color and power mode with an ultrasound system equipped with a 2.5 mHz multifrequency probe transducer. Transtemporal insonation will be performed through the temporal bone window using axial and axial insonation plans and coronal with the participant in the right dorsal decubitus position. No eco-enhancer contrast will be used. Peak systolic and end diastolic pressure velocities will be measured in pulsed wave mode. Flow velocity measurements will be performed without angle correction. The examiner was free to optimize the images by changing the pulse gain and repetition frequencies [18].

Interventions

Transcranial Direct Current Stimulation

A direct current will be applied by a pair of spongelike surface electrodes soaked in saline (35 cm^2) and supplied by a specially developed constant current stimulator with a maximum output of 10 mA. To stimulate the DLPFC, the anode electrode will be placed over F3 according to the international 10-20 system for EEG electrode placement. The cathode will be placed over the contralateral supraorbital area (Figure 2).

Figure 2. Transcranial direct current stimulation device.

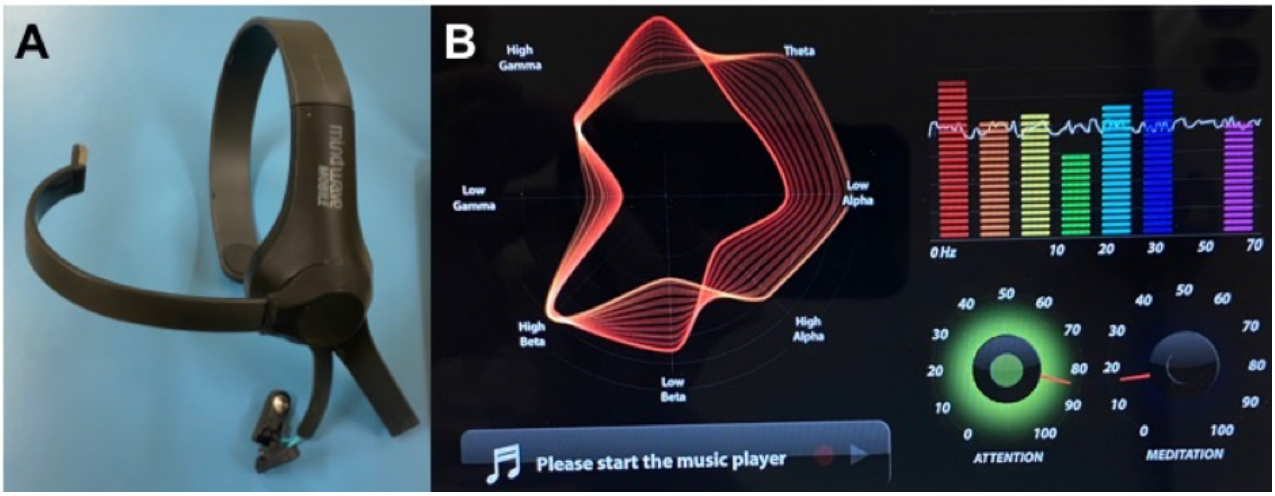
For simulated stimulation, the electrodes will be placed in the same position; however, the stimulator will turn off after 20 seconds as described above. Therefore, the individuals felt the initial itching sensation at first, but they received no current for the remainder of the stimulation period. This procedure will allow the individuals to be blinded to the conditions of stimulation. A total of 10 stimulation sessions will be held for 2 consecutive weeks, with an interval of 2 days between the weeks. The duration of each session is 20 minutes. The applied intensity will be 2.0 mA [11,12,14].

Possible adverse effects are a tingling sensation and redness at the electrode site after stimulation. Headaches and burns may rarely occur. Possible side effects will be evaluated on a daily basis using a previously prepared questionnaire.

Neurofeedback

In this study, we will use TuSion software to design the gaming environment and an EEG device and its Neurosky driver software. TuSion is free software designed to help improve cognitive skills while playing (Figure 3). The game design scheme was developed considering the following points: used hardware must be cheap and easy to handle, it should be simple to get a novice to get used to it in a short amount of time, and it should use neurofeedback to give a visual representation of attention levels and thus help improve it in a more attractive way. The ThinkGear software provided with the EEG device is used to connect the EEG device to the computer. It allows special apps and games to run according to the mental states detected by the EEG earplug with NeuroSky's ThinkGear sensor. It is provided as an executable for Mac OS X and Windows platforms. Hardware includes a laptop or smartphone and a Neurosky "Mindwave Mobile" EEG device. The hardware for acquiring brain waves consists of a sensor that touches the forehead to collect data centered on the frontal cortex, the contact, and the reference points located in the earlobe. Data is processed using the integrated chip included in it. Both the eSense Meter (meditation and attention) and raw brain waves are calculated on the ThinkGear chip. The EEG electrode is placed on the user's forehead (on the frontal cortex) during gameplay. The earplug safely measures and produces EEG power spectra (alpha waves, beta waves, etc), attention, meditation, and blink values. Attention and meditation are indicated and reported on a meter with a relative eSense scale from 1 to 100. This scale has a set of grouping schemes for the ranges of values, and a certain mental state is assigned to it. Values between 20-40 are reduced levels and 1-20 are considered a heavily reduced eSense. A value in the range of 40 to 60 is considered neutral. Values above 60 are considered values above normal or "high." Values in the range of 80-100 are considered high eSense levels. Attention as an unsigned 1-byte value indicates the intensity of the user's level of mental "focus" or "attention," as occurs during intense concentration and directed (but steady) mental activity. Its value ranges from 0 to 100 (Figure 1). Distractions, wandering thoughts, lack of focus, or anxiety decrease attention meter levels [19,20].

Figure 3. Electroencephalography device and its Neurosky driver software.



Statistical Analysis

For the sociodemographic and epidemiological description of the groups, we will use the usual procedures of descriptive statistics such as calculation of frequencies and measures of central tendency and dispersion. The Shapiro-Wilk test will be performed to assess the assumption of normality of the outcome variables.

For analysis of paired and independent samples using a *t* test for comparisons within and between intervention groups or applying equivalent nonparametric tests (according to the results of the Shapiro-Wilk test) before and after the intervention, *P* values <.05 will be considered significant. Data will be organized and tabulated using SPSS (IBM Corp).

Study Schedule

The schedule for the study is shown in Table 1.

Table 1. The schedule of enrollment, interventions, and assessments.

	Study period						
	Enrollment	Allocation	Postallocation				Close-out
	$-t_1$	0	t_1	t_2	t_3	t_4	t_x
Enrollment							
Eligibility screen	✓[a]						
Informed consent	✓						
Allocation		✓					
Interventions							
Intervention A			✓	✓	✓	✓	
Intervention B			✓	✓	✓	✓	
Assessments							
Stroop test/US Doppler	✓	✓					✓
TDCS[b] + neurofeedback				✓	✓	✓	

[a]Included at this time point.

[b]TDCS: transcranial direct current stimulation.

Outcome Variables

The guiding theme of this study is to use tools or strategies to improve learning and promote better retention. The primary expected result is a greater correctness of answers in two phases of the Stroop test (word reading and color recognition) and a decrease in test execution time.

Secondary variables are based on physiological responses of cerebral blood flow where we expect to find an increase in velocity and systolic and diastolic peaks. This hypothesis is based on functional magnetic resonance studies where the results show an increase in local blood flow after the use of TDCS.

Results

The trial and enrollment began in July 2022. The statistical analysis for the secondary outcomes are currently being performed.

Discussion

We believe that the resources used in this study can help improve some aspects of declarative memory, since learning and memory processes modify the brain. Strategies to enhance the acquisition, storage, and use of information must be able to sensitize (motivate) and involve volunteers in the learning process, thus clarifying their role.

The performance of a task depends on ongoing brain activity that can be influenced by attention, excitement, or motivation. Scientific studies confirm that mindfulness leads to better performance, health, and well-being. However, these factors that modulate cognitive efficiency are nonspecific, can be difficult to control, and are not suitable to specifically facilitate neural processing.

The first stages of memory consolidation involve the stabilization of structural and functional neural changes and other neural changes generated by learning. New methods of memory consolidation optimization are being suggested (authors) in the role of neuromodulation.

The human brain is a highly interconnected network with high information processing efficiency. This efficient processing network operates through specialized structures and functions [21]. Among the essential functions of humans, memory requires significant attention from researchers because it is the ability to store and evoke learned knowledge [2]. The storage and use of learned information in the brain are fundamental for the interaction and modulation of human behavior and the adaptation and interaction of individuals with their environment [22].

In recent years, there has been an increase in technological improvement and neuroscientific discoveries aimed at new forms of training focusing on increasing memory performance [23].

As already described, neurofeedback is a brainwave training technique used to improve performance in terms of creativity, attention, and memory [24]. It has also been used as a potential cognitive and behavioral adjuvant for healthy individuals [6,25]. However, the effectiveness of neurofeedback with healthy participants received criticism from the scientific community since most studies failed to provide evidence for changes in behavioral and electrophysiological measures, mainly due to methodological deficiencies such as the lack of a sham/control group [26]. In response to this lack of reliability, Wang and Hsieh [3] researched young and older adult individuals to investigate the effectiveness of the cortical activity training protocol on attention and working memory performance. The authors observed better performance in older adults, with a significant improvement in memory among the young [3].

Although recent discoveries are addressing and answering old and new questions, the current findings provide insights into the underlying mechanisms of neurofeedback training in

cognitive function. Furthermore, the results indicate that an intervention program protocol could be effective against cognitive aging and memory decline [3].

The future of neurofeedback research lies primarily in mobile recording and real-time feedback of the emotional and cognitive states of the individuals being evaluated. Due to volume conduction (the ability to measure electrical potentials at a distance from their source generators), single channels, regardless of where they are placed on the scalp, can capture a substantial fraction of all brain dynamics. Indeed, Rebolledo-Mendez et al [25] used attention levels as an input to interface systems between the brain and a computer, and found that the device provides accurate readings regarding attention since there is a positive correlation between measured and self-reported attention levels. However, setbacks observed by the authors included difficulties using the device due to the size of the head, interference with the hair, and no indicator for low batteries [25].

The primary reason for selecting this equipment is that it is a single dry electrode system, a type of EEG that does not require any substance or solution between the skin and the electrode. This feature makes the testing process more agile and reduces the individual's discomfort. Johnstone et al [27] reported that the results obtained with this type of EEG are comparable to other devices that use different sensors and conductive substances. Additionally, it is easy to use and access the data since the equipment communicates with a computer via Bluetooth, making analyses and treatment more efficient. Furthermore, this technology comes at a low cost. These characteristics facilitate research and allow acquisition by any individual without substantial training [27].

The other device suggested for applying this protocol uses TDCS. This technique has been shown to elicit lasting effects in different protocols and diseases. TDCS provided the beneficial effect of anodic direct current stimulation of increased excitability in simple reaction times and implicit motor learning when stimulating the primary motor cortex [28] and improved learning of a visual-motor coordination task by stimulating the primary motor area or the V5 visual area [29].

Regarding its action on working memory, Fregni et al [11] demonstrated that anodic stimulation in the left DLPFC improves working memory performance. This effect depends on the polarity of the stimulation and is specific to the stimulation site. The results of Fregni et al [11] were further corroborated by Javadi and Walsh [30], who performed two experiments involving 32 participants who performed a series of word memorization tasks. This task was performed during simulated anodic and cathodic stimulation to the left DLPFC. Participants in the first experiment performed the same task with anodic TDCS of the primary motor cortex (M1). The results indicated that active stimulation of the left DLPFC leads to an improvement or attenuation of verbal memorization depending on the polarity of the stimulation. For example, during encoding, anodic stimulation of the left DLPFC improved memory, while cathodic stimulation of the same area impaired memory performance in later recognition. Anodic stimulation of M1 did not affect later recognition [30]. Smirni et al [31] observed and confirmed the same results.

To date, we have not found scientific studies using the association of the two techniques. We believe that using neurofeedback in conjunction with TDCS can potentiate the effects of training and thus provide greater effectiveness and long-term effects on the memory of individuals. In the long term, we expect that our results might further comprehensive programs for these conditions.

Authors' Contributions

LHG and MCPdS conceptualized the study. LHG, GRG, and MCPdS were involved with the data curation and the formal analysis. LHG, BNP, BAB, IFJG, PVNDG, AAB, KMO, and DCM preformed the investigation. LHG developed the methodology and preformed the validation. LHG, BNP, BAB, IFJG, PVNDG, AAB, KMO, and DCM wrote the original draft. GRG and MCPdS reviewed and edited the paper. MCPdS supervised the study.

Conflicts of Interest

None declared.

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Abbreviations

DLPFC: dorsolateral prefrontal cortex
EEG: electroencephalogram
TDCS: transcranial direct current stimulation

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Protocol

Using Artificial Intelligence as a Diagnostic Decision Support Tool in Skin Disease: Protocol for an Observational Prospective Cohort Study

Anna Escalé-Besa[1], MD; Aïna Fuster-Casanovas[2,3], RPh, MSc; Alexander Börve[4,5], MD; Oriol Yélamos[6], MD, PhD; Xavier Fustà-Novell[7], MD; Mireia Esquius Rafat[7], MD; Francesc X Marin-Gomez[8], MD, PhD; Josep Vidal-Alaball[2,3,9], MPH, MD, PhD

[1]Centre d'Atenció Primària Navàs-Balsareny, Institut Català de la Salut, Navàs, Spain

[2]Unitat de Suport a la Recerca de la Catalunya Central, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, Sant Fruitós de Bages, Spain

[3]Health Promotion in Rural Areas Research Group, Gerència Territorial de la Catalunya Central, Institut Català de la Salut, Sant Fruitós de Bages, Spain

[4]iDoc24 Inc, San Francisco, CA, United States

[5]Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[6]Dermatology Department, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

[7]Fundació Althaia de Manresa, Manresa, Spain

[8]Servei d'Atenció Primària Osona, Gerència Territorial de Barcelona, Institut Català de la Salut, Vic, Spain

[9]Faculty of Medicine, University of Vic-Central University of Catalonia, Vic, Spain

Corresponding Author:
Aïna Fuster-Casanovas, RPh, MSc
Unitat de Suport a la Recerca de la Catalunya Central
Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina
C/Pica d'Estats 13-15
Sant Fruitós de Bages, 08272
Spain
Phone: 34 93 693 0040
Email: afuster.cc.ics@gencat.cat

Abstract

Background: Dermatological conditions are a relevant health problem. Each person has an average of 1.6 skin diseases per year, and consultations for skin pathology represent 20% of the total annual visits to primary care and around 35% are referred to a dermatology specialist. Machine learning (ML) models can be a good tool to help primary care professionals, as it can analyze and optimize complex sets of data. In addition, ML models are increasingly being applied to dermatology as a diagnostic decision support tool using image analysis, especially for skin cancer detection and classification.

Objective: This study aims to perform a prospective validation of an image analysis ML model as a diagnostic decision support tool for the diagnosis of dermatological conditions.

Methods: In this prospective study, 100 consecutive patients who visit a participant general practitioner (GP) with a skin problem in central Catalonia were recruited. Data collection was planned to last 7 months. Anonymized pictures of skin diseases were taken and introduced to the ML model interface (capable of screening for 44 different skin diseases), which returned the top 5 diagnoses by probability. The same image was also sent as a teledermatology consultation following the current stablished workflow. The GP, ML model, and dermatologist's assessments will be compared to calculate the precision, sensitivity, specificity, and accuracy of the ML model. The results will be represented globally and individually for each skin disease class using a confusion matrix and one-versus-all methodology. The time taken to make the diagnosis will also be taken into consideration.

Results: Patient recruitment began in June 2021 and lasted for 5 months. Currently, all patients have been recruited and the images have been shown to the GPs and dermatologists. The analysis of the results has already started.

Conclusions: This study will provide information about ML models' effectiveness and limitations. External testing is essential for regulating these diagnostic systems to deploy ML models in a primary care practice setting.

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KEYWORDS

machine learning; artificial intelligence; data accuracy; computer-assisted diagnosis; neural network computer; support tool; skin disease; cohort study; dermatology

Introduction

Health care systems in Western countries are increasingly exposed to new challenges: a high volume of demand, aging populations, chronic diseases, a high degree of comorbidity, and the global pandemic situation. These factors, together with the lack of professionals, particularly general practitioners (GPs), generate the need to find new solutions to improve the quality of care and the workflow of professionals [1].

Dermatological conditions are a relevant health problem, and skin disease is one of the principal reasons why patients visit their GPs. Every person has on average 1.6 skin diseases per year [2]. About 20% of all GP visits are related to a dermatological concern, and 15% of all telehealth visits are related to dermatology [3,4]. About 7.6% of the total population of Catalonia visit a primary care center (PCC) due to skin concerns every year, and around 35% are referred to a dermatology specialist [5,6]. Nowadays, in the health care area of central Catalonia, teledermatology consultations are commonly used to refer patients to a hospital-based dermatologist. It is estimated that more than 70% of all PCC patients with a skin problem can be effectively triaged with teledermatology and do not need a face-to-face visit with a dermatologist [7,8].

The use of computer-assisted diagnosis in medicine dates to the 1960s in radiology. The initial description of artificial intelligence (AI) in dermatopathology dates to 1987, when the text-based system TEGUMENT was produced [9]. TEGUMENT included a semantic tree with 986 potential diagnoses used to assist the dermatologist in the histopathologic differential diagnosis of diseases and tumors of the skin. Computer-aided melanoma diagnosis was introduced in the early 2000s in dermatology using rule-based classifiers, which use predefined features to classify images into desired categories [10].

The application of teledermatology worldwide has increased over the years. It is used in many PCC settings and has been well established and backed by extensive research that it is a viable method of triage, particularly for skin cancer lesions [11]. Studies comparing the general accuracy of face-to-face dermatology consultation versus teledermatology have different results. In general, face-to-face consultations achieve higher diagnostic accuracy than teledermatology. However, some studies did report the high accuracy of teledermatology diagnoses for skin cancer [12]. Nevertheless, it is necessary to first ensure that the clinicians have high interrater reliability; without this, it is difficult to tell whether the limited agreement in diagnoses is related to the use of the technology itself or differences in clinical opinion that ordinarily exist in practice. In this context, studies have compared the diagnostic agreement between GPs using telemedicine and dermatologists. The results of the studies showed an overall diagnostic agreement of 65.52%, showing that GPs tend to overdiagnose some diseases [13]. The concordance obtained for teledermatology was 94.7%. Even though this technique showed merits in triage quality, it presented low accuracy in inflammatory problems [13]. Teledermatology has the potential to increase access by facilitating referrals and offering convenience and decreased waiting times, as well as providing diagnostic support and improved satisfaction for both patients and providers [8,14-17]. To achieve the correct implementation of AI in primary care, it is important to know the real needs and developed an easy-to-use interface, which can help reduce resistance to change from traditional to touch-based interfaces in current clinical setups [18].

In recent years, AI has been developed, researched, and applied in many medical disciplines. Images are the most commonly used form of data for AI development, such as electrocardiograms or radiologic images [19-21]. Dermatopathology is particularly suited for deep learning algorithms, because pattern recognition in scanning magnification is fundamental for diagnosis [10,22-24]. Furthermore, machine learning (ML) is increasingly being applied to dermatology, particularly focused on skin cancer detection using image analysis with ML models that include deep convolutional neural networks (CNNs) [25,26]. Algorithms and models that include CNNs were introduced in the 1980s [23], but it was not until 2012 that the ImageNet competition demonstrated their potential for image analysis. Since then, CNN has become a popular ML approach in several disciplines including dermatology [27]. There are also ML studies that have investigated the use of a wider classification of skin diseases that could be used in primary health care [28]. The evolution in ML came around 2010 with deep learning [10], and it has revolutionized tasks such as image classification and segmentation and speech recognition.

Even though GPs see a lot of skin ailments [5,29], few studies have been conducted in primary health care settings prospectively. However, some studies have included GPs along with dermatologists as readers for the comparison group to compare the performance of ML with clinicians [11,28,30] and have concluded that AI tools could be used in primary care [28]. For all these reasons, the main objective of the study is to perform a prospective validation in real primary care practice settings of an ML model as a diagnostic decision support tool for the diagnosis of dermatological conditions in a rural area of Catalonia (Spain).

Methods

Study Design

Trial Design

This is a prospective study that aims to evaluate an ML model's performance, comparing its diagnostic capacity with GPs and dermatologists. A secure, anonymous, and stand-alone web interface that is compatible to any mobile device was integrated with the Autoderm application programming interface (API; iDoc24 Inc).

To conduct this study, the following procedure were carried out until the required number of samples was reached: (1) a suitable patient with skin concern was asked to participate and sign the patient study agreement; (2) GPs diagnosed the skin condition; (3) GPs took 1 good-quality image of the skin condition; (4) GPs sent the photograph as a teledermatology consultation following the current workflow; (5) the image were entered into the Autoderm ML interface; and (6) dermatologists diagnosed the skin condition.

The satisfaction of the health care professionals using the ML tool were assessed using 3 questions embedded in the questionnaire. The questions relate to the potential usefulness of the tool to help the diagnosis or consider further diagnosis not contemplated initially and the potential use of the tool to avoid a dermatology referral.

Study Population, Site Participation, and Recruitment

The study was conducted in PCCs managed by the Catalan Health Institute (the main primary care services provider in Catalonia) in central Catalonia, which includes the regions of Anoia, Bages, Moianès, Berguedà, and Osona. The reference population included in the study was around 512,050 habitants. The recruitment of prospective subjects was done consecutively.

Data Collection and Sources of Information

Patients, Data Collection, Sources of Information, and Intervention

GPs collected data from consecutive patients who met the inclusion criteria after obtaining written informed consent. The collected data were reported exclusively in a case report form.

The GP diagnosed the skin condition and filled in a questionnaire. For each patient, the GP used a smartphone camera to take a close-up good-quality image of the skin problem. The image is anonymous, as it is not possible to identify the patients. The GP then used the Autoderm ML interface to upload the anonymized image and filled in the questionnaire with the top 5 diagnoses generated by the ML model.

This evaluation study of the Autoderm API tool is intended as a validation study of a tool to support the diagnosis of skin lesions in real clinical practice conditions in primary care. Therefore, although the tool uses a closed source code, this study is intended to be a starting point to see if similar tools can be suitable for use as working tools in real clinical conditions. Autoderm is a research-backed, Conformité Européenne–marked dermatology search engine using ML technology to help provide faster and more accurate skin diagnosis. The current ML model can screen for 44 different skin disease types, which includes inflammatory skin diseases, skin tumors, and genital skin concerns, and can be accessed via an API. For this study, a user web interface was developed for the easy upload of images from the smartphone library or those taken with the smartphone camera. From just a smartphone photo, the model generates the top 5 ranked skin diseases in order of probability. The life cycle of this ML model is estimated to be around 3 months. After this period, the model will be upgraded to a more accurate model that will possibly include more skin diseases.

At its current stage, the ML model uses a 34-layer pretrained ResNet model provided by TorchVision (PyTorch) that is used for applications such as computer vision and natural language processing. In addition, the model has been trained using transfer learning on a proprietary data set of 55,364 images for the training set and 13,841 images for testing. The average accuracy of the model used is 31.7% for the top 1 diagnosis and 68.1% for the top 5. Some skin diseases have higher accuracy and some have lower accuracy, which is a consequence of the number of images the ML was trained on and the fact that some skin diseases are more distinct and certain anatomic locations make diagnosis more difficult. Before deployment, the ML model was also manually tested with a data set collected from various websites that provided images of skin disease taken with a mobile camera. The ML model was deployed when it was deemed to be robust. The 44 different skin disease classes represent about 90% of what the general public are concerned about and consults for.

To get a second opinion, the GP incorporated the anonymized image and an accurate description of the skin lesion into the patient's medical history following the current teledermatology workflow. The dermatologist then filled in the "Assessment by teledermatology" questionnaire after receiving the information. The response time was expected to be about 2-7 days.

In case of a dermatology referral, the GP filled in the "Assessment by in-person dermatologist" questionnaire by accessing the electronic health records as they become available. The average waiting time for a dermatology referral ranges from 30-90 days.

The questionnaire case number was predefined before the initiation of the data collection phase and was the same for all questionnaires, making it impossible to identify the patient.

Inclusion Criteria

Patients visiting for reasons related to a cutaneous disease at a participating PCC, who provided written informed consent and were aged ≥18 years, were included in the prospective study.

Exclusion Criteria

Patients with a cutaneous lesion that could not be photographed with a smartphone or had conditions associated with a risk of poor protocol compliance were excluded from the study. Images with poor quality were also excluded from the study.

Statistical Analysis

Calculation of Sample Size

To compare the performance of the ML model with those of the GPs and dermatologists, a sample size of 100 images of skin diseases from patients who meet the inclusion criteria is required. The proposed sample size is based on sample size calculation used in similar research studies [31-33].

Planned Analysis

The validation data set will include about 100 cases, consisting of an image and 3 or 4 assessments: the face-to-face assessment by a GP, the assessment made by teledermatology, the top 5 differential diagnoses from the ML model ordered by probability, and the assessment by the face-to-face dermatologist (in cases with a referral). The ML model assessment will be limited to 44 skin diseases classes. A confusion matrix will be used to calculate the precision, sensitivity (recall), specificity, and accuracy of the ML model. For each individual skin disease, the number of true positives, true negatives, false positives, and false negatives will be calculated. To evaluate the ML multiclass classifier, data will be treated as a collection of binary problems, 1 for each skin disease class. Area under the curve and receiver operating characteristics curve for N number of skin diseases classes will be calculated using one-versus-all methodology. Macro- and micro-averaging measures will be considered to highlight the performance of infrequent skin disease classes (weighted by prevalence). Precision, recall, and *F*-measure will be calculated independently for each skin disease class, and the results will be combined to obtain the average precision and *F*-score. The accuracy of the top 3 diagnoses of the ML model will be also calculated.

Ethics Approval

The Institut Universitari d'Investigació en Atenció Primària (University Institute for Research in Primary Health Care) Jordi Gol i Gurina ethics committee approved the trial study protocol (code 20-159P). Written informed consent was sought from all patients participating in the study.

Results

The results will be represented globally and individually for each skin disease class using a confusion matrix and one-versus-all methodology. The time taken to make the diagnosis will also be taken into consideration. The satisfaction of the professionals with the use of this ML tool will be assessed.

Patient recruitment began in June 2021 and lasted for 5 months. Currently, all patients have been recruited and the images have been shown to the GPs and dermatologists. The analysis of the results has already started. We hope that sufficient evidence can be obtained to validate this image analysis ML model. We believe the results will be used in clinical practice on patients with skin diseases to make a GP's workflow more efficient and safer for the patient. This study is a first approach to designing larger ML model validation studies.

It has to be considered that even if the ML model does not provide a better diagnosis than the doctor's, it is expected to help the practitioner consider other differential diagnoses.

Discussion

This study aims to perform a prospective validation of an ML model as a diagnostic decision support tool for the diagnosis of dermatological conditions. It would also assess the diagnostic accuracy and efficacy of a ML model in a PCC setting. In this context, this study may provide added value for both patients and primary care physicians, increasing the effectiveness and efficiency of the system, and will provide information about ML models' effectiveness and limitations. External testing is essential to regulate these diagnostic systems and deploy ML models in real PCC settings.

First, the most relevant limitation of this study is the number of image samples used for the evaluation of the performance of the ML model. As Autoderm assesses only 44 skin diseases and that the prevalence of a substantial number of these skin conditions represents less than 1% to 5% of the images, the sample data of each class may be unbalanced and some skin conditions may not be evaluated, causing an insufficient confidence level and therefore, less conclusive results for these specific conditions.

Second, due to the sample size and consecutive case recruitment, we will probably not obtain representative results for less common diseases. As class imbalance may be an issue in the 100 patients recruited, we will focus on the *F*-Score for the analysis, as otherwise having 90% of the most common skin lesions may overestimate the quality of the model when considering accuracy, sensitivity, and specificity. It has to be taken into consideration that this study will be done in real practice conditions, and we will not be able to select the patients.

Third, a diagnosis made with only 1 image with the most optimal composition may present inherent limitations compared to diagnoses made in a clinical setting. Our ML algorithm output was based on a single photograph, which differs from other ML algorithms that consider more than 1 photograph and even those with the same algorithm available for the general public that considers 2 images.

Fourth, another limitation is that our data will not include additional testing and only a subset of suspected malignancies will have a biopsy confirmation. Instead, our golden standard for each case is based on aggregating the differential diagnoses of a panel of dermatologists. Ambiguities in diagnosis do exist in clinical practice, which makes it challenging to evaluate the accuracy of clinicians and deep learning systems, especially for conditions such as rashes, which are not typically biopsied.

Fifth, our ML algorithm did not include additional clinical metadata (past medical history, symptoms, appearance, and the texture), which is a probable grievance when comparing ML versus physicians' diagnostic accuracy.

Lastly, the clinicians were requested to provide just the top 3 diagnosis, even if they had other potential options.

Data Availability

Our manuscript is based on confidential and sensitive health data. However, to support scientific transparency, we will publish deidentified data for reviewers or for replication purposes. The data will be deposited and made available in our publicly accessible Mendeley repository.

Authors' Contributions

All authors contributed to the design and content of the study protocol. AEB is responsible for the coordination of the study. AEB, JVA, AFC, and FXMG are responsible for the design and writing of the initial draft of the manuscript. AEB, OY, MER, and XFN are responsible for data collection, and AEB and JVA are responsible for data processing and exploitation. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

AB is the chief executive officer and majority shareholder of iDoc24 Inc and iDoc24 AB. He provided the technology but did not take part in the data collection or any clinical validation.

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Abbreviations

AI: artificial intelligence
API: application programming interface
CNN: convolutional neural network
GP: general practitioner
PCC: primary care center

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Protocol

Magnetic Resonance Imaging Angiography of Physiological and Pathological Pregnancy Placentas Ex Vivo: Protocol for a Prospective Pilot Study

Matthieu Dap[1,2], MD; Bailiang Chen[3,4], PhD; Claire Banasiak[4]; Gabriela Hossu[4], PhD; Olivier Morel[1,3], MD, PhD; Marine Beaumont[3,4], PhD; Charline Bertholdt[1,3], MD, PhD

[1]Obstetric and Fetal Medicine Unit, Centre Hospitalier Régional Universitaire of Nancy, Nancy, France

[2]Department of Foetopathology and Placental Pathology, Centre Hospitalier Régional Universitaire of Nancy, Nancy, France

[3]INSERM U1254, IADI, Vandoeuvre-lès-Nancy, France

[4]INSERM CIC-IT 1433 Innovative Technology, University of Lorraine and University Hospital of Nancy, Nancy, France

Corresponding Author:
Matthieu Dap, MD
Obstetric and Fetal Medicine Unit
Centre Hospitalier Régional Universitaire of Nancy
10, rue du docteur Heydenreich
Nancy, 54000
France
Phone: 33 630736896
Email: m.dap@chru-nancy.fr

Abstract

Background: Preeclampsia (PE) and intrauterine growth restriction (IUGR) are 2 major pregnancy complications due to abnormal placental vasculogenesis. Data on whole fetoplacental vasculature are still missing; hence, these pathologies are not well understood. Ex vivo magnetic resonance imaging (MRI) angiography has been developed to characterize the human placental vasculature by injecting a contrast agent within the umbilical cord.

Objective: The primary objective of this study is to compare the placental vascular architecture between normal and pathological pregnancies. This study's secondary objectives are to (1) compare texture features on MRI between groups (normal and pathological), (2) quantitatively compare the vascular architecture between both pathological groups (pathological IUGR, and pathological PE), (3) evaluate the quality of the histological examination in injected placentas, and (4) compare vascularization indices to histological characteristics.

Methods: This is a prospective controlled study. We expect to include 100 placentas: 40 from normal pregnancies and 60 from pathological pregnancies (30 for IUGR and 30 for PE). Ex vivo MR image acquisition will be performed shortly after delivery and with preparation by injection of a contrast agent in the umbilical cord. The vascular architecture will be quantitatively described by vascularization indices measured from ex vivo MRI angiography data. Comparisons of vascularization indices and texture features in accordance with the group and within comparable gestational age will be also performed. After MR image acquisition, placental histopathological analysis will be performed.

Results: The enrollment of women began in November 2019. In view of the recruitment capacity of our institution and the availability of the MRI, recruitment should be completed by March 2022. As of November 2021, we enrolled 70% of the intended study population.

Conclusions: This study protocol aims to provide information about the fetal side of placental vascular architecture in normal and pathological placenta through MRI.

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International Registered Report Identifier (IRRID): DERR1-10.2196/35051

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KEYWORDS

MRI; magnetic resonance imaging; placenta; IUGR; intrauterine growth restriction; preeclampsia; PE; uterine; intrauterine; pregnancy; vasculogenesis; pathology; physiology

Introduction

Placental dysfunction is a major cause of intrauterine growth restriction (IUGR) or preeclampsia (PE) and is responsible for maternofetal mortality and morbidity such as fetal death, preterm delivery, minor cognitive deficits, school problems, and metabolic syndrome in adulthood [1-3]. Normal placental development is an essential prerequisite for efficient placental function followed by fetal growth. Placental dysfunction is primarily due to a deficient remodeling of the spiral arteries in the myometrium during the first trimester [4]. These remodeling disorder leads to abnormal placental development with morphological and functional alteration of the placenta. The exploration of these alterations, functional and morphological, is important to not only understand the pathophysiology of IUGR and PE but also for screening or diagnostic techniques to improve antenatal care. Imaging tools are particularly suitable for this exploration.

As a consequence, some teams work on in vivo exploration of placental function using magnetic resonance imaging (MRI) or ultrasound imaging [5-7]. However, in vivo imaging has the disadvantage of having major difficulty in differentiating between the maternal and fetal sides, except for very advanced MRI techniques (DECIDE) for contrast-enhanced ultrasound imaging, which allows for the exploration of exclusively the maternal side and for MRI with gadolinium injection but is not allowed during pregnancy [8,9]. Besides, ex vivo studies seem to offer unique opportunities to explore placental physiology even outside the womb, where the placenta's normal state is modified [10]. Two main tools have been described: ex vivo microcomputed tomography (micro-CT) and ex vivo MRI [11-13]. Regarding ex vivo micro-CT, Junaid et al [11] published a comparative analysis of placental vascularization between IUGR and normal placentas and showed a significant decrease in vessel length in IUGR placentas compared to normal ones.

Regarding ex vivo MRI, several studies described an MRI-compatible perfusion chamber allowing the exploration of dynamic placental perfusion during MRI scanning [14,15]. Ex vivo MRI could also be used to explore placental function.

Other studies have described a protocol for ex vivo angiography of the fetal vessels, including Link et al [16] and Chen et al [17]. The described technique allows for imaging of the architecture of the whole fresh human placental vascular tree by injection of oil in the umbilical cord vessels. This protocol can reveal up to the sixth level of placental vascularization at a submillimeter quasi-isotropic resolution [17]. Link et al [16] recently compared IUGR and normal placental vascular trees using ex vivo angiography [16]. The main limitation of this work is that the understanding of placental structure and vasculature at different gestational stages is limited [18,19].

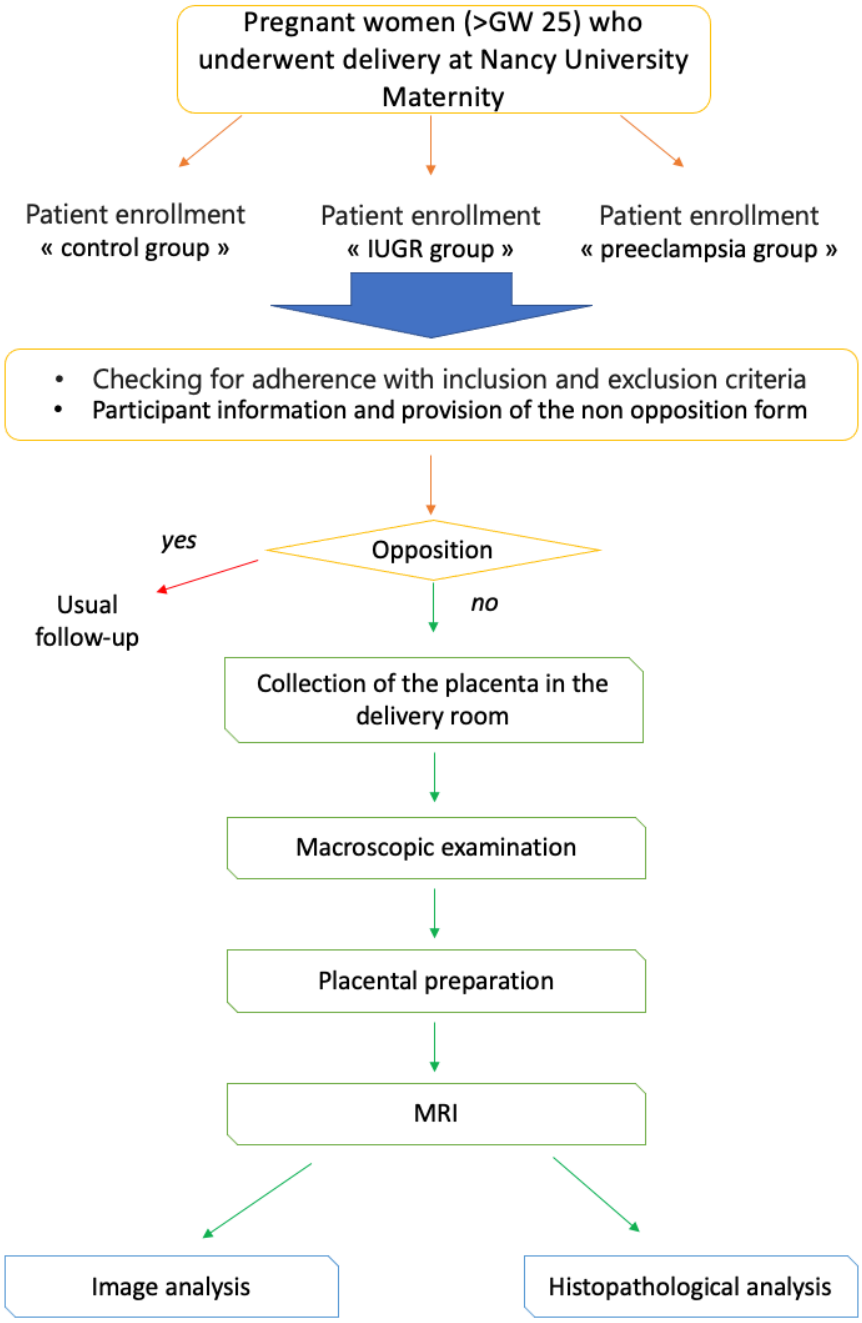
The main objective of our study is to compare the vascular architecture of the placenta in normal and pathological pregnancies; for example, PE and intrauterine growth restriction. Our secondary objectives are to (1) compare texture features on MRI between groups (normal and pathological), (2) quantitatively compare the vascular architecture between both pathological groups (pathological IUGR and pathological PE), (3) evaluate the quality of the histological examination in injected placentas, and (4) compare vascularization indices to histological analysis.

Methods

Trial Design

The MRI Angiography of Physiological and Pathological Pregnancy Placentas *Ex vivo* (MAPLE) protocol is a prospective, monocentric (Maternité du Centre Hospitalier Régional Universitaire [CHRU] de Nancy, France), open, controlled, nonrandomized pilot study conducted at CHRU de Nancy. Figure 1 presents the study flowchart.

Figure 1. Study flowchart. GW: gestational week; IUGR: intrauterine growth restriction; MRI: magnetic resonance imaging.



Study Population

Enrolled women will be distributed into 3 groups (normal, IUGR, and PE) in accordance with their pregnancy status. The participants in this study are pregnant women in their third trimester in order for us to obtain comparable gestational ages between groups. Textbox 1 presents the inclusion and exclusion criteria. IUGR is defined as a birth weight less than the third percentile of the French growth curve (Association des Utilisateurs de Dossiers Informatisés en Pédiatrie, Obstétrique et Gynécologie, Lyon, France). PE is defined as a systolic blood pressure of ≥140 mm Hg and a diastolic blood pressure of ≥90 mm Hg associated with proteinuria of >300 mg per 24 hours after 20 weeks of gestation. Before inclusion, women will be informed of the aim, procedures, and predictable risks of the study (no identified clinical risk) by the investigator. Patients' medical history, including smoking and obstetric history, will be collected. Medical information on the current pregnancy will also be collected (Textbox 2).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Already received complete information about the study and do not express any opposition to the use of their data
- Mandatory enrollment in a social security plan
- Gestational age of >25 weeks (and until at term)
- Having undergone either natural or Cesarean delivery and whose placenta is naturally completely separated
- For the normal group:
  - Normal fetal weight (between the 10th and 95th percentile for age)
  - No intrauterine growth restriction (IUGR) or preeclampsia (PE) suspected or confirmed
  - No Doppler (fetal and umbilical) abnormality
- For the pathological group:
  - Subgroup IUGR: IUGR defined by a fetal estimated weight of less than the third percentile of the antenatal curve, and confirmed in the postnatal stage; absence of associated PE
  - Subgroup PE: clinical diagnosis of PE (high blood pressure associated with significative proteinuria); absence of associated IUGR

Exclusion criteria:

- Younger than 18 years
- Newborn with congenital disease (either suspected at birth or already diagnosed)
- Presence of only one umbilical artery
- Presence of a maternal pathology: gestational diabetes, pre-existing autoimmune diseases, or cancer
- Do not speak French or inability to understand the given information of the study
- Manual delivery
- Incomplete placenta
- Person referred to articles L.1126-6 and L-1126-8 of the public health code

Textbox 2. Data collected.

Habitus:

- Smoking and addictions
- Drug consumption

Obstetric data:

- Gestational age, parity, and birth weight

Clinical data:

- BMI and age
- For preeclampsia: proteinuria, blood pressure (systolic and diastolic), and complications
- For intrauterine growth restriction: ultrasound data (biometry, umbilical artery Doppler, and estimated fetal weight)

Magnetic resonance imaging data:

- Morphological images of the placenta, vascularization indices, and texture indices

Histological data:

- Placental analysis (weight and morphological analysis)

Placenta Preparation for Perfusion

All human placentas will be immediately collected and prepared for acquisition after natural vaginal delivery or Cesarean delivery to reduce the occurrence of blood clotting. The preparation procedure was based on Rasmussen's procedure modified by Chen et al [17] to fit our requirements [20]. First, a gross macroscopic examination of the placenta will be performed as described by the Amsterdam Placental Workshop Group Consensus, including placental weight, dimensions, and descriptions of the umbilical cord, membranes, and lesions [21]. Next, fresh placentas will be placed in a water bath at 37 °C during preparation. The chorion and amnion will be trimmed and removed. The umbilical cord will be severed at a 5-cm length to its placental insertion point. Umbilical vessels will be catheterized. The placental vascular bed will be slowly rinsed with a water-based solution through catheters fixed to the artery. The wash will be stopped when the reflux from the vein catheter becomes completely clear. The contrast agent (B-oil for rotary vane pumps, Vacubraand) will be slowly injected through the umbilical arteries until outflow of the contrast agent in the vein is observed, to ensure microvessel filling. The arteries and veins need to be closed well at their entry points. The overall preparation time is 1 hour. The sealed cord will be placed within a plastic tube supporter (the residual umbilical cord part), which was dedicatedly designed and printed with a 3D printer (Figure 2). Within this holder, the umbilical cord was tightly attached and not compressed so that the primary level of the vein and artery vessel trees can be distinguished in the MR data for the subsequent vessel tree extraction algorithm, especially to be able to separate arteries and veins. After preparation, the placenta will be stored in a refrigerator at 4 °C.

Figure 2. Placenta prepared for magnetic resonance imaging. The placental vascular tree is filled with oil. The sealed cord is placed within a plastic tube supporter designed and printed with a 3D printer.

MR Image Acquisition

Prepared placentas will be taken out from the refrigerator and placed in the MR room for approximately 30 minutes before MR image acquisition in order to ensure a steady temperature during the whole acquisition procedure. It will be placed on top of a flat platform appropriate for placental size: one with a diameter of 22 cm, the other with a diameter of 22.5 cm. Both can be fitted inside a 20-channel head coil. Therefore, the placenta is well placed at the isocenter of the MRI bore so that the homogeneity of the magnetic field can be maximumly satisfied. The imaging protocol has been tuned and set up on a 3T Prisma Siemens MR scanner. A 3D Flash sequence is employed to acquire the data. The relevant parameters are 0.4 × 0.4 × 0.4 mm^3, TR/TE 8/3.5 milliseconds, 512×512 acquisition matrix, bandwidth of 390 Hz, and 14 NEX. The field of view and number of slices can vary from placenta to placenta, but all will be adjusted to achieve the aforementioned acquisition parameters, especially the isotropic resolution. Neither parallel imaging nor partial Fourier acquisition strategies have been adopted. The mean overall acquisition time was 1 hour 40 minutes. After MR image acquisition, the placenta will be immediately sent back to the pathology laboratory for histological processing, being always maintained at 4 °C.

Pathological Examination

After MR image acquisition, the entire placenta will be fixed in a 4% formaldehyde solution for approximately 1 month. Random samples of cord, membranes, and placental parenchyma will be submitted (4 blocks as a minimum and 1 block for each type of lesion) in accordance with the recommendations of the Amsterdam Consensus Statement and be subjected to histopathological evaluation [21]. Once the tissue block is embedded in paraffin wax, a 6-µm vertical section containing the entire thickness of the placenta will be taken and mounted for staining with hematoxylin and eosin.

Certified pathologists will read slides to establish a histopathological diagnosis. Gross and histological lesions of fetal and maternal vascular malperfusion will be reported. Fetal vascular malperfusion (FVM) will be classified as global/partial or segmental/complete, and high-grade FVM will be also reported [22,23]. Finding of maternal vascular malperfusion (MVM) we be classified into villous changes (infarcts, retroplacental hematoma, accelerated villous maturation, and

distal villous hypoplasia) and vascular lesions (acute atherosis, persistent muscularization of basal plate arterioles, basal decidual vessel thrombosis, and mural hypertrophy of membrane arterioles) [22]. MVM will be graded as global/partial or segmental/complete [23].

MR Image Analysis

All the placental data will be archived and managed by a local research image management system ArchiMed. A MATLAB program has already been developed to segment the acquired placenta data and extract the vessel tree structure [17]. Owing to the good contrast-to-noise ratio and signal-to-noise ratio of the MR images, a simple thresholding is sufficient to delineate the vessel tree. A fast-marching algorithm will be used to quantitatively characterize the placenta's vessel tree. Separation of the artery and vein tree structure will be achieved with a homemade software written in C++ as described by Kerrien et al [24]; the segmented placenta vessel data will be rendered in 3D, and its skeleton will be overlapped with its 3D model using this software. Morphological parameters including total vessel density, artery and vein density (per cm^3), and tortuosity and bifurcation density (per cm^3) will be calculated automatically or semiautomatically. Total vessel density is defined as the overall vessel density regardless of whether the vessel is an artery or vein. It is calculated as the vessel voxel volume divided by the whole placenta volume, while artery and vein vessel density are defined as artery and vein volume divided by whole placenta volume, respectively. The 3-vessel density will be calculated automatically by the software. Calculation of tortuosity and bifurcation density are computed semiautomatically as the branching of the vessel network and bifurcations need to be checked by observers. Tortuosity is defined as the curvilinear distance and Euclidean distance between the starting and the end of a vessel path (in this case, a vessel branch) [24]. Bifurcation density is defined as the number of detected bifurcations divided by the placental volume. Radiomics features, as described by Vallières et al [25], will also be extracted to quantify the differences among the 3 groups of placentas [25]. The quantitative parameters will be described by their mean (SD), median, maximum and minimum, and n (%) values. Mean values between groups will be compared using the Student *t* test or Mann-Whitney test, unpaired in accordance with whether the data are normally distributed, depending the type of data. Linear regression models will be used to test the group and the effect of gestational age on the parameters considered.

Outcomes

The primary outcome will be the vascular architecture, described by vascularization indices (total vascular density, arterial and venous density in cm^3, tortuosity index, and branching index) measured from ex vivo MRI in both groups (physiology and pathology).

The secondary outcome measures are the following:

- Secondary objective 1: measurement of texture indices as established by Vallières et al [25].
- Secondary objective 2: measurement of vascularization indices and texture based on the participant group.
- Secondary objective 3: number of placentas with an appropriate histological quality to be examined microscopically.
- Secondary objective 4: statistical comparison between vascularization indices achieved through MRI and histological evaluation (presence or absence of FVM, presence of absence of MVM, if present: grading of the lesions).

Follow-up

No specific follow-up has been planned for participants except for standard routine care. Any adverse events will be noted and reported.

Patient and Public Involvement

Patients and the public were not involved.

Sample Size Consideration

Given the exploratory nature of this study and in the absence of data allowing for sample size estimation, we consider it necessary to include 100 women: 40 women with a normal pregnancy and 60 women with a pathological pregnancy (30 women with an IUGR and 30 with PE).

In fact, to obtain a sufficiently precise characterization and to be able to use descriptive statistics applicable to large samples (mean, SD values), we will need to obtain at least 30 observations in each group.

Data Collection and Management

An electronic case report file (e-CRF) will be created for each woman. The women's anonymity will be ensured by mentioning to the maximum extent possible their research code number, followed by the first letters of the last name and first name of the participant on all necessary documents or by deleting their names by appropriate means (whiteout) from the copies of source documents intended to document the study.

The MRI data will be anonymized and transferred via a secure server for storage and archiving directly in the ArchiMed database, reported to the CNIL (CNIL report number 1410005) because they cannot be transcribed in the e-CRF. The clinical data of the women are shown in Textbox 2.

Statistical Analysis

Quantitative data will be described by their mean (SD), median, and maximum and minimum values. Qualitative data will be expressed as n (%) values. Between-group comparisons will be performed using the Student *t* test or the Mann-Whitney test, matched or unmatched, depending on the type of data. The chi-square test or the Fisher exact test will be used to compare the qualitative data between groups. The analyses will be performed with R software (R Foundation for Statistical Computing). No intermediary analysis is intended. The analyses will be performed on a per-protocol basis.

Quality Control: Right of Access to Data and Source Documents

Medical data of each patient will only be transmitted to the responsible party (CHRU de Nancy) or any person duly authorized by the responsible party and, where applicable, to

the authorized health authorities, under conditions guaranteeing their confidentiality.

The responsible party and the regulatory authorities may request direct access to the medical file for verification of the procedures and data of the clinical trial without violating confidentiality and within the limits permitted by laws and regulations.

For research purposes, processing of personal data of the study participants will be carried out. These data are collected and processed solely on the basis of the legal grounds provided for by statute and regulations in the context of the performance of the public interest missions of CHRU de Nancy, particularly those relating to ensuring and contributing to research and innovation (Article 6.1.e of the General Data Protection Regulation [GDPR]). The processing of personal data of the study participants is permitted by the exception provided for in Articles 9.2(i) and (j).

This data processing is part of the MR003 reference methodology that CHRU de Nancy has undertaken.

According to the GDPR, persons participating in research have the right of access to their data (Article 15), the right of rectification (Article 16), the right to erase their data (right to forget) under the conditions (Article 17), the right to limit the processing (Article 18), and the right to object to the processing of their personal data (Article 21). These rights are exercised with the Investigators, who will inform the research stakeholders as soon as possible.

The persons participating in the research also have a right to complain to the supervisory authority in France, namely, the Commission Nationale de l'Informatique et des Libertés (CNIL).

Study Monitoring

Each patient's e-CRF must be consistent with the source documents.

Data Management and Quality Control

Data management will be carried out by the clinical research team Centre D'investigation Clinical–Innovation Technological (CIC-IT) at CHRU de Nancy (INSERM CIC 1433). The MR imaging data will be automatically transferred to CIC-IT and be stored after verification in the ArchiMed database declared to the French authorities (CNIL declaration number: 1410005).

Patient Data Protection

Each patient must be identified on the e-CRF and placental specimen with her initials and ID number indicating her order of inclusion in the study. The investigators must maintain a list of all the patients, including their ID numbers and full names.

Patients must be informed in writing about the possibility of audits by authorized stakeholders and regulatory authorities, in which case the relevant parts of study-related hospital records may be required.

Patients will also be informed that (1) the results obtained will be computerized and analyzed, (2) local laws will be applied, (3) their confidentiality will be preserved, and (4) they are entitled to obtain any information concerning the data stored and analyzed by the computerized system.

Potential Risks Related to the Study

This study will comply at all times with the Good Clinical Practices defined by the Ministry of Health, France. In this study, only placental collection is intended to be performed. This study, therefore, does not expose any particular risk to the women.

Ethical Considerations

The stakeholders and all investigators undertake to conduct this study in accordance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Tokyo 2004) and its updates, the provisions of European Directive 2001/20-CE as transposed into French law by L. 2004-806 dated August 9, 2004, on public health policy and 2004-800 dated August 6, 2004, on bioethics and their implementation decrees, and to comply with the guidelines of Good Clinical Practices (ICH version 4 of May 1, 1996, and decision of November 24, 2006).

They undertake to adhere to all legislative and regulatory provisions that may concern the study. In accordance with Article L. 1123-6 of the Public Health Code, the responsible party has submitted the research protocol to the Nancy CHRU Ethics Committee (Comité d’éthique du CHRU de Nancy). The collection was declared to the Ministry of Education, Research and Innovation on October 3, 2019 (reference number DC-2019-3739). The study is registered under the number NCT04389099 on www.ClinicalTrials.gov.

The study will be conducted in accordance with the present protocol. The investigators undertake to respect the protocol in all aspects especially with regard to the information and delivery of an opposition form to each patient.

Information Letter and Opposition Form

Research participants will be informed of the objectives and constraints of the study, their rights to refuse to participate in the study, or to withdraw from the study at any time. When all essential information has been conveyed to the subject and the investigators have ensured that the patient has understood the implications of participating in the trial, the placenta can be collected in the absence of patient opposition.

Protocol Amendment

The responsible party must be informed of any proposed amendment to the protocol by the principal investigator. Changes, substantiative or not, must be described.

Final Research Report

The principal investigator and the mandated biostatistician will collaboratively write the final research report. This report will be submitted to each of the investigators for review. Once consensus has been reached, the final version must be endorsed with the signature of each of the investigators and sent to the responsible party as early as possible after the effective end of the study. A report prepared in accordance with the reference plan of the competent authority must be forwarded to the CHRU Ethics Committee within a year after the end of the study. This final report is made available to regulatory authorities.

Results

The enrollment of women began in November 2019. In view of the recruitment capacity of our institution and the availability of the MR images, recruitment should be completed by March 2022. As of November 2021, we enrolled 70% of the population.

Discussion

This study aims to evaluate whole human placental vasculature using ex vivo MRI in a normal and pathological population. We hypothesize that the placental vascular tree is altered in case of IUGR or PE compared to normal pregnancy. Our study data will provide information about uteroplacental physiology and pathophysiology by the exploration of the fetal placental side.

To our knowledge, this is the first prospective, comparative, controlled study comparing the architecture of the placental vascular tree between normal and pathological pregnancies at the same gestational age.

The groups have been selected strictly on the basis of gestational age and neonate size at birth to assess the comparison. This technique has been previously evaluated in a pilot study carried out by our team; however, only the fetal side can be analyzed with this technique.

The strength of our study is the large sample size compared to that in other studies and the control of confounding factors such as gestational age. Furthermore, our team comprises both obstetrics experts (MD, CB, and OM), who ensured the relevance of definitions of pathologies, and imaging experts with research engineers (BC and MB).

The main limitation of this study is the lack of clinical applicability of this technique. A promising recent study demonstrated the possibility to image the placental vascular tree in vivo [9]. Our results, combined with this technique, could provide to parents and obstetricians useful information during pregnancy. This trial is in accordance with the Standard Protocol Items: Recommendations for Interventional Trials checklist.

Acknowledgments

This study was partially funded by the University of Lorraine in 2020 and Centre Hospitalier Régional Universitaire of Nancy.

Data Availability

All data generated during the project will be made freely available via Centre D'investigation Clinical–Innovation Technological (CIC-IT), Nancy. Data obtained from this study will be deposited at CIC-IT, Nancy, where they will be maintained for a minimum of 15 years. There are no security, licensing, or ethical issues related to the expected data, and all data used in the study will be generated directly as a result of the project, without any pre-existing data being used.

Authors' Contributions

C Bertholdt and MD participated in study design and are carrying out, or will carry out, recruitment. BC and MB are in charge of MR image acquisition and image postprocessing, MD was responsible for histological analysis. MD, C Bertholdt, and BC drafted the manuscript. C Bertholdt and OM are the primary investigators for clinical assessment and study design. C Banasiak is the project manager for the study. GH is in charge of statistical analysis. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CHRU: Centre Hospitalier Régional Universitaire
CIC-IT: Centre D'investigation Clinical–Innovation Technological
CNIL: Commission Nationale de l'Informatique et des Libertés

e-CRF: electronic case report file
FVM: Fetal vascular malperfusion
GDPR: General Data Protection Regulation
IUGR: intrauterine growth restriction
MAPLE: MRI Angiography of Physiological and Pathological Pregnancy Placentas Ex vivo
Micro-CT: microcomputed tomography
MRI: magnetic resonance imaging
MVM: maternal vascular malperfusion
PE: preeclampsia

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Protocol

Reducing New Chlamydia Infection Among Young Men by Promoting Correct and Consistent Condom Use: Protocol for a Randomized Controlled Trial

Nicole Stone[1*], PhD; Rowena Bedford[1*], MSc; Katie Newby[2*], PhD; Katherine Brown[2*], PhD; Louise Jackson[3*], PhD; Stephen Bremner[4*], PhD; Leanne Morrison[1,5*], PhD; Nuala McGrath[5,6*], SCD; Tom Nadarzynski[7*], PhD; Jake Bayley[8*], MBChB; Nicky Perry[9*], MSc; Cynthia Graham[1*], PhD

[1]Department of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, United Kingdom

[2]Department of Psychology and Sports Science, Faculty of Life and Medical Sciences, University of Hertfordshire, Hertfordshire, United Kingdom

[3]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

[4]Department of Primary Care and Public Health, Brighton and Sussex Medical School, Brighton, United Kingdom

[5]School of Primary Care, Population Sciences and Medical Education, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

[6]Department of Social Statistics and Demography, Faculty of Economic, Social and Political Sciences, University of Southampton, Southampton, United Kingdom

[7]School of Social Sciences, University of Westminster, London, United Kingdom

[8]Barts Health NHS Trust, London, United Kingdom

[9]University Hospitals Sussex NHS Trust, Brighton, United Kingdom

[*]all authors contributed equally

Corresponding Author:
Cynthia Graham, PhD
Department of Psychology
Faculty of Environmental and Life Sciences
University of Southampton
University Road
Highfield
Southampton, SO17 1BJ
United Kingdom
Phone: 44 07871310526
Email: C.A.Graham@soton.ac.uk

Abstract

Background: The health, social, and economic costs of sexually transmitted infections (STIs) represent a major public health concern. Young people are considered one of the groups most at risk for acquiring and transmitting STIs. Correct and consistent condom use has been shown to be the most effective method for reducing STIs; however, condoms are often not used properly. Evidence shows that brief behavior change interventions that focus on skills, communication, and motivation to acquire safe sex practices should be adopted into routine care to reduce STIs. Funding for sexual health services in England has declined dramatically, so novel ways of reducing clinic attendance are being sought. The home-based intervention strategy (HIS-UK) to promote condom use among young men has shown promise in feasibility and pilot studies by demonstrating high acceptability of the intervention in participant and health professional feedback, including aiding men to find condoms they like and feel more confident when using condoms.

Objective: The aim of this study is to determine the effectiveness and cost-effectiveness of HIS-UK when compared to usual condom distribution care among young men.

Methods: The 3 trial arms consisting of “e-HIS” (HIS-UK delivered digitally), “ProHIS” (HIS-UK delivered face-to-face), and control condition (usual National Health Service [NHS] care) will be compared against the following 3 primary outcomes: the extent to which correct and consistent condom use is increased; improvement of condom use experiences (pleasure as well as fit and feel); and decrease in chlamydia test positivity. Eligibility criteria include men aged 16-25 years at risk of STIs through reporting of condom use errors (ie, breakage or slippage) or condomless penile-vaginal or penile-anal intercourse with casual or

new sexual partners during the previous 3 months. Prospective participants will be recruited through targeted advertisements and an opportunistic direct approach at selected sexual health and genitourinary medicine services and university-associated health centers and general practitioner practices. Community and educational establishments will be used to further advertise the study and signpost men to recruitment sites. Participants will be randomly allocated to 1 of 3 trial arms. A repeated measures design will assess the parallel arms with baseline and 12 monthly follow-up questionnaires after intervention and 3 chlamydia screening points (baseline, 6, and 12 months).

Results: Recruitment commenced in March 2020. Due to the COVID-19 pandemic, the study was halted and has since reopened for recruitment in Summer 2021. A 30-month recruitment period is planned.

Conclusions: If effective and cost-effective, HIS-UK can be scaled up into routine NHS usual care to reduce both STI transmission in young people and pressure on NHS resources. This intervention may further encourage sexual health services to adopt digital technologies, allowing for them to become more widely available to young people while decreasing health inequalities and fear of stigmatization.

Trial Registration: ISRCTN Registry ISRCTN11400820; https://www.isrctn.com/ISRCTN11400820

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KEYWORDS

condom fit and feel; condom use; pleasure; digital intervention; sexual behavior; health psychology; behavior intervention; chlamydia; sexual health; randomized controlled trial

Introduction

Background

Sexually transmitted infections (STIs) are a major public health concern. Individuals affected by STIs can face poor physical and psychological outcomes, and STI testing and treatment are a costly burden on limited health care service budgets [1,2]. The UK Department of Health and Social Care has prioritized the need to reduce STIs among those at greatest risk, including Black and minority ethnic populations, young heterosexual men and women, men who have sex with men, and among those residing in the most deprived areas in England [1,3]. Furthermore, the World Health Organization, the UK Department of Health and Social Care, and Public Health England all recommend that evidence-based preventative interventions should be used in primary care settings to help in the reduction of STI rates [4-6].

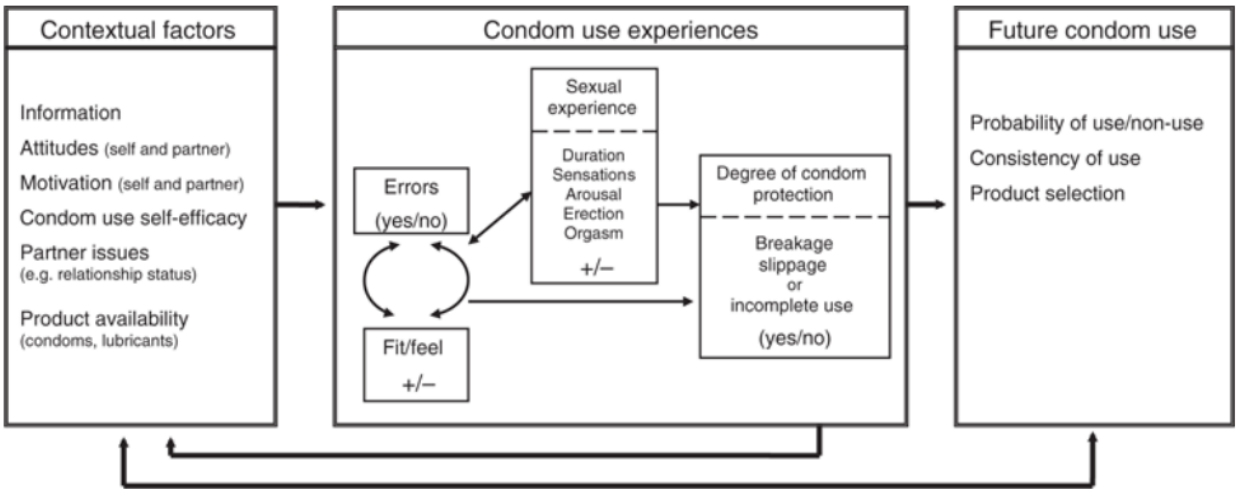
Male condoms, when used correctly and consistently (used from the start to the finish of every sex act), are highly effective in preventing STI transmission [7,8]. While being highly effective, there is substantial evidence to indicate that condoms are not used frequently, and if they are, they are often not used properly [9-11]. Research has shown there are several common errors and problems associated with condom usage, including not checking the condom for visible damage, not leaving room at the tip of the condom, and using oil-based lubricants, which could be detrimental to the condom material [10,12,13].

Behavior change intervention programs to promote condom use typically aim to improve knowledge and skills, reduce communication barriers, and improve partner negotiation. Research shows, however, that negative condom attitudes form a significant barrier to usage, often shaped through experience of decreased sensation and sexual pleasure, as well as erection difficulties during condom application and use [9]. Many interventions to date have failed to consider the promotion of pleasurable condom use and to address issues around the fit and feel of condoms, including condom size, texture, and thickness. One review found only 5 studies (out of the 123 condom promotion studies identified) focused on improving fit and feel [14], despite its positive association with use [15].

Intervention

A review of the evidence on safe-sex advice underlined the need for novel brief behavior change interventions focusing on skills acquisition, motivation (via affective or automatic attitudinal cognitive processes), and communication competencies to ensure the adoption of safer sexual behaviors [16]. Furthermore, the National Institute for Health and Care Excellence has emphasized the need to provide a range of condoms and lubricants when teaching young people to use condoms effectively and safely [17], with the National Health Service (NHS) of England also highlighting the importance of using digital technologies to deliver health care to help reduce costs, accessibility barriers, and clinical burden [18]. With these recommendations in mind, the home-based intervention strategy (HIS-UK) has been adapted from an intervention previously piloted in the US and Canada (The Kinsey Institute Homework Intervention Strategy [19,20]), guided by the condom use experience (CUE) model proposed by Sanders et al [13]. The CUE model acts as a framework for understanding the role of errors and problems in inadequate condom protection (Figure 1). In the model, contextual factors (eg, knowledge, skills, and self-efficacy), in conjunction with condom use experience (including issues of fit and feel as well as condom use errors and problems), affect the probability and consistency of future condom use either directly or as mediated through other aspects of the sexual experience, such as sensations, discomfort, and duration or intensity of intercourse. The model is dynamic, as the quality of the CUE (past and present) cyclically affects condom-related contextual factors during subsequent sexual encounters, which in turn affect CUE.

Figure 1. The Condom Use Experience Model (Sanders et al [13], 2012).



The HIS-UK intervention is novel in that it aims to increase condom use by enhancing the fit and feel of condoms and, thereby, increasing outcome expectancies related to enjoyment of sex while using condoms [21]. HIS-UK places the impetus for behavior change on the individual using home-based solitary condom and lubricant practice exercises ("homework") with focus on pleasurable use [22]. It comprises the following three key elements: (1) "Education & Training"—providing guidance on pleasurable condom use, the variety and types of condoms available (shape, size, texture, and material), how to find the best condom for optimal fit and feel, and the added benefits of using lubricant to sexual enjoyment; (2) "Practice & Experimentation"—the provision of a condom kit containing a wide variety of condoms and lubricants and home-based directed practice exercises in applying, using (masturbating with the use of additional lubricant), and removing condoms in "low pressure" situations (ie, not in the presence of a sexual partner); and (3) "Reflection": the completion of web-based rating forms about the individual's experience of the condoms and lubricants tested.

HIS-UK has been designed as an extension to the usual condom distribution care model currently practiced by health promotion professionals, which typically comprises the delivery of safe sex messages, a condom application demonstration, and the supply of generic condoms.

Two development and feasibility studies were conducted to inform the adapted design of the HIS-UK intervention, research methodology, and data collection tools [22-24]. The following 2 delivery models of the education and training component of HIS-UK were designed: (1) face-to-face delivery by a trained health professional (ProHIS) and (2) a digital intervention using an interactive website (e-HIS) and without the need for specialist provider contact. The first of the feasibility studies tested the viability, operability, and acceptability of the ProHIS version of the HIS-UK intervention with men aged 16-25 years. The second study tested the feasibility of e-HIS with men aged 18-69. The findings from both studies indicated the intervention was acceptable to men and health promotion professionals, and the research design, evaluative tools, and outcome measures were appropriate.

Objective

The aim of this trial is to assess the effectiveness and cost-effectiveness of HIS-UK delivered by the 2 intervention delivery models (ProHIS and e-HIS) to reduce chlamydia test positivity among men aged 16-25 years by enhancing condom use experiences and improving correct and consistent condom use, as compared to usual NHS condom distribution care. Intervention implementation, usability, acceptability, as well as mechanisms for impact will be assessed using a mixed-methods approach guided by our logic model and the intervention evaluation framework proposed by Saunders et al [25].

Methods

Trial Design

The HIS-UK study is a randomized, controlled, superiority trial with 3 parallel arms (2 intervention and 1 control arm, with a 1:1:1 allocation), with an internal pilot. A repeated measures trial design is being used with baseline measurement (T0) and monthly follow-up questionnaires (T1-12) after randomization and 3 STI screening points for chlamydia (T0, T6, and T12). Cost and outcome data are being collected to compare the resource use and cost-effectiveness of the 2 HIS-UK delivery models compared to usual condom distribution care. The protocol for this trial was registered with the ISRCTN Clinical Trials Registry in October 2019.

Recruitment and Participants

The trial is multicentered, delivered from NHS Trust sites across England. Participants are recruited through opportunistic direct approach and patient identification by trained site staff at integrated sexual health and genitourinary medicine services located within the participating Trust sites. Targeted advertising in sixth form colleges and youth advisory services and via social media platforms (eg, Twitter, Instagram, and Facebook) is also being used.

Eligible participants must have a penis, be aged 16-25 years, resident in England, and at risk of STIs through reporting either condom use errors (ie, breakage or slippage) or condomless

penile-vaginal or penile-anal intercourse with casual (nonregular) or new sexual partners during the previous 3 months. Those with a recognized latex allergy, restricted internet access, or limited proficiency in spoken English are excluded from the trial.

Baseline Data Collection and Randomization

The trial is delivered using *Lifeguide*, an interactive web-based intervention software platform and secure validated data management system designed to collect participant information and deliver digital interventions to support health behavior change [23,26]. The *Lifeguide* platform can be accessed via any internet-enabled device, and recruitment sites are provided with handheld tablet computers for recruitment purposes.

Following eligibility screening and the taking of informed online consent, participants are registered for the trial and complete a baseline questionnaire (T0). At baseline, participants are asked about their sexual behavior, condom attitudes, condom usage experiences, STI screening, demographics, quality of life (using standard measures), and any recent NHS and public sector resource use (ie, attendance at general practitioner clinics; see Secondary Process Indicators for further details). On submission of T0, participants are randomized to a trial arm (1:1:1) by an in-built *Lifeguide* algorithm to eliminate direct exposure of the allocation process by any members of the research team or recruitment site staff. The algorithm uses randomly permuted blocks of varying length to preserve concealment and maintain balance, with stratification by participant ethnicity and sexual risk. Site staff are informed of the randomization outcome (allocation either to ProHIS, e-HIS, or control arm) by an on-screen notification.

Participants randomized to the ProHIS arm receive a HIS-UK education and training consultation delivered by a health professional (approximately 10 minutes), and participants allocated to receive e-HIS are provided with log-in access to the e-HIS education and training website for them to access at their own leisure. The webpages of e-HIS are delivered and managed by *Lifeguide* using a series of intelligent “agents” (interaction, information, instruction, and evaluation). The purpose of the agents is to manage and monitor the learning of individuals by observing and recording e-learning behavior (ie, pages visited and instructional videos watched) to receive tailored prompts (through automated texts or emails) that guide and assist effective learning (eg, to visit further pages and to undertake tasks) and to ensure participants are exposed to a variety of learning elements.

HIS-UK participants (both ProHIS and e-HIS) are also provided with a condom kit containing 24 condoms (at least 8 different types, shapes, and sizes to demonstrate the wide range of condoms available), 12 lubricant sachets (at least 3 different types), a condom-measuring guide, and an instruction guide to home-based self-practice (Figure 2).

Figure 2. Contents of the home-based intervention strategy (HIS-UK) condom kit.

Participants randomized to the control arm receive information, advice, and supplies per usual condom distribution care (eg, per usual care at the recruitment site).

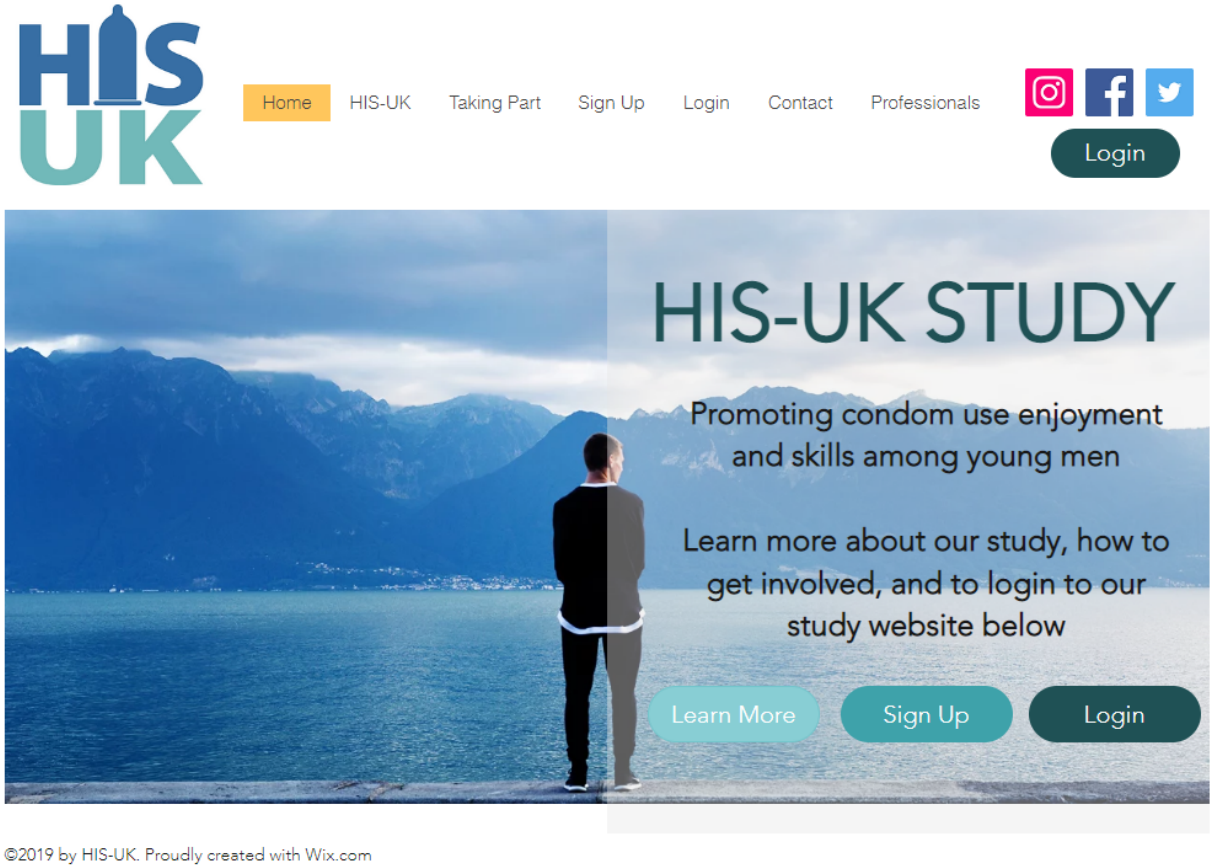
Individual trial participants are not blinded in the trial. Site staff are required to deliver all intervention arms and, as such, are also not blinded. To avoid bias and potential contamination between trial arms, in a 7% random selection of cases, the participant-staff interaction will be audio taped (with participant consent) and assessed for intervention fidelity. In addition, in all cases where ProHIS and usual care are delivered, participants are asked to complete a postintervention fidelity checklist and recall the topics covered during their intervention consultations.

At the baseline visit, participants are further required to undertake screening for chlamydia (the most commonly occurring STI among young men), as per usual clinical practice; a single urine sample is requested from men who report only sexual contact with women, and a triple test (urine sample, anal swab, and oral swab) from men who report sex with men. Sites are responsible for the collection and laboratory analysis of samples, and screening results are subsequently shared by site staff with the research team via the *Lifeguide* platform.

Post–COVID-19 Amendments

Due to the uncertain future of the COVID-19 pandemic and the need to reduce direct-contact exposure between site staff and participants, the following amendments to the original protocol were proposed and approved by the UK Health Research Authority in February 2021: (1) potential participants can self-refer to the study by completing a web-based expression of interest application via the study website (Figure 3). Eligible participants, who live within the catchment area of a recruiting NHS Trust site, are prompted to complete the web-based consent, *Lifeguide* registration, and T0 baseline questionnaire before being contacted by site staff to complete the final recruitment tasks (verbal reconfirmation of informed consent, chlamydia screening, and delivery of the intervention arm); (2) participants randomized to the control arm or to e-HIS are not required to attend in person to a recruitment site to complete the final recruitment tasks; these instead can be performed during a telephone consultation. For participants randomized to ProHIS, the recruitment tasks can be performed either using the web-based video-consultation software or in clinic. ProHIS cannot be delivered via a telephone consultation due to the requirement of a visual condom demonstration; (3) all HIS-UK condom kits can be mailed out to participants instead of being collected in person; (4) postal STI screening kits can be used to collect and return samples for chlamydia screening; and (5) the number of NHS Trust sites recruiting to the trial has been increased, with no upper limit proposed.

Figure 3. Home-based intervention strategy (HIS-UK) website.



HIS-UK Tasks and Data Collection

Following education and training, HIS-UK participants commence a 2-week condom and lubricant self-practice period using the contents of the supplied kits and guided home-based exercises (ie, applying, using, and removing condoms without partner presence). As young men try out each condom and lubricant, they are asked to think about what they like and dislike

about the products (texture, smell, thickness, shape, size, etc), and to focus on pleasurable sensations when using them to build positive associations between condom use and sexual enjoyment. After experimentation, participants are asked to complete a web-based rating and reflection form for each condom and lubricant used.

Automated emails or SMS text message reminders are sent to participants to complete their ratings. Those who complete at least three ratings over the 2 weeks can order 12 condoms of their choosing and 6 sachets of lubricant to receive by post.

Follow-up

All participants receive monthly automated text message or email notifications to complete a web-based questionnaire (T1-T12), as per T0.

HIS-UK participants who successfully complete a follow-up questionnaire, and who report sexual activity within the previous month, are offered the opportunity to order further supplies of condoms and lubricants of their choosing (12 condoms and 6 lubricants).

At T6 and T12, all trial participants are requested to provide samples for chlamydia testing and are offered the choice of using a postal screening kit or attending at their trial registration clinic. As per usual clinical practice, only participants reporting sexual activity in the previous 6 months are screened. Furthermore, if a participant has reported chlamydia screening within 4 weeks prior to the T6 and T12 testing period, the self-reported results of these tests are used, and no further samples are taken to minimize screening burden.

All participants receive electronic voucher payments totaling £50 (US $60) to compensate them for their time; £10 (US $12) after active participation for 3 months, £15 (US $18) after 6 months, and £25 (US $30) after 12 months.

Primary Outcome Measure

Chlamydia test positivity is measured at baseline (T0), 6 months (T6), and 12 months (T12) through biomarker testing and treatment, and at T1-T5 and T7-T11 through questionnaire self-report. The primary health end point is test positivity at 6 months. To examine longevity of intervention effect, test positivity is assessed again at 12 months after randomization.

Secondary Process Indicators

The following secondary process indicators (those through which the primary outcome is likely to be realized) are measured via web-based self-completion questionnaires using validated scales at baseline (T0) and at monthly intervals to 12 months (T1-T12)—the *Condom Barriers Scale* [27], with items including the effect of condoms on sexual experience (eg, “condoms reduce orgasm/climax”) and motivational barriers (eg, “I feel closer to my partner without a condom”); the *Condom Use Errors and Problems Survey* [28,29] to assess the possible errors (eg, putting condom on after starting sex) and problems (eg, breakage or slippage and erection difficulties) when using condoms; the *Correct Condom Use Self-Efficacy Scale* [30] to measure the efficacy of an individual to negotiate and correctly use condoms with their partner; the *UCLA Multidimensional Condom Attitude Scale* [31], in which items include “condoms can make sex more pleasurable/stimulating,” “use of condoms can improve foreplay,” “condoms can feel good for both partners,” and “condoms are fun”; and finally, the *Condom Fit and Feel Scale* [32], in which participants are asked to recall their recent condom use experiences and answer questions about fit and feel.

Additionally, participants are asked at baseline and monthly intervals about their sexual partners, frequency of intercourse, STI screening and test positivity, condom use motivation, use of contraception and condoms, and any episodes of condomless anal or vaginal intercourse.

Economic Evaluation—Outcome Data

Alongside the clinical outcomes collected in the trial and in line with guidance by the National Institute for Health and Care Excellence, quality-adjusted life years will be used as an outcome measure to assess the cost-effectiveness of HIS-UK as compared to usual condom distribution care [33]. Because sexual health interventions such as HIS-UK have an important psychosocial aspect, the following 2 validated measures of health-related quality of life, which ask about an individual’s self-perceived physical and psychological health status, are used: the SF-12 (12-Item Short Form Health Survey) instrument and the EQ-5D-5L questionnaire [34-36]. These questionnaires are administered to participants to compare changes in HRQL for the 3 trial arms, at baseline, 6 months, and 12 months after randomization.

Cost and Resource Use Data

Resource use data will be collected prospectively to estimate the costs associated with the 2 HIS-UK intervention arms, compared to usual care. Within the trial, the resource use and costs associated with delivering ProHIS and e-HIS and any follow-up care will be captured via trial reporting mechanisms. This will include the costs of condom kits, consultation costs, digital delivery costs, and other resource use associated with intervention delivery. The baseline and monthly questionnaires (T0-T12) further capture the wider NHS and public sector resource use by participants, including the use of medication, general practitioner and sexual health service visits, and other public sector resource usage. The monthly questionnaires also collect data on personal costs experienced by participants connected with their involvement in the trial (eg, travel costs, internet use, and other out-of-pocket expenses).

Sample Size

The clinical effectiveness of HIS-UK delivered by ProHIS and e-HIS will be analyzed with an overall Type I error rate of 5% (2.5% per comparison), comparing test positivity in each of the intervention arms with the control arm (usual care). Data published by the National Chlamydia Screening Programme suggest a test positivity of 11.9% in 2017 and 12.2% in 2018 among young men aged 15-24 years in England tested in specialist and nonspecialist (including community-based) services [37]. Our trial is powered to detect a 45% reduction in chlamydia test positivity among our intervention arms—from 11% to 6% at 6 months after randomization. Previous piloting suggests that the intervention is likely to be equally effective

across all stratification subgroups (deprivation, ethnicity, sexual orientation, and age) [22,23].

To have 85% power to obtain the projected difference in the outcome at T6, the study requires 476 participants in each of the arms (G*Power 3.1.9.2). To minimize risk to the trial and to reflect 36% attrition at follow-up (observed during feasibility testing) [22], a total of 2231 participants will be randomized.

It is estimated that it will take 30 months to recruit the target sample of 2231 young men, based on a recruitment rate of 15 per month, per NHS Trust site, using a phased recruitment strategy.

Process Evaluation and Trial Progression

The first 135 young men recruited and followed up for 6 months will form our internal pilot to assess trial implementation, participant responsiveness, intervention fidelity, and the acceptability of randomization and chlamydia screening for trial continuation. During the assessment, the following questions will be answered: “Can young men be recruited at a reasonable rate and to the numbers anticipated?” “Are young men willing to be randomized within the trial?” “Is chlamydia screening at T0 and T6 sufficiently acceptable and feasible to implement?” “Do young men remain in the study in sufficient numbers at 6-month follow-up?” “Are the intervention and study design sufficiently acceptable?” “Are site staff able to deliver the intervention with reasonable fidelity?”

To assess intervention implementation and engagement, participant access to and usage of e-HIS is recorded along with fidelity of ProHIS intervention delivery and completion of condom ratings. In-depth qualitative interviews with all site staff involved in the recruitment of internal pilot participants will also be conducted to explore acceptability of the research design and ease of trial delivery. Furthermore, at 6 months after randomization, internal pilot participants allocated to the ProHIS and e-HIS trial arms will be invited to participate in interviews to explore study acceptability, issues of contamination and protocol adherence, and intervention benefits. We expect that 20 interviews will be sufficient to reach theoretical saturation; however, if necessary, additional interviews will be undertaken with participants from subsequent recruitment phases.

Analysis

Analysis and presentation of data will be in accordance with the revised CONSORT 2010 statement [38]. The statistical analysis will be performed on available cases following intention-to-treat principles with due emphasis placed on confidence intervals for the between-arm comparisons. Baseline demographics (eg, age, ethnicity, deprivation, and sexual orientation) and self-reported outcome measure data (secondary process indicators) will be assessed for comparability between the arms using descriptive analyses.

The primary analysis will be undertaken using generalized linear modelling to compare the effectiveness of HIS-UK against usual care in reducing chlamydia test positivity at T6. The analysis will be repeated at T12 to examine longevity of intervention effect. Analyses will be extended to include the investigation of possible intervention moderators and mediators, the exploration of process measures (eg, number of condom ratings completed), and the identification of which young men most benefit from ProHIS and e-HIS (according to age, sexual orientation, ethnicity, and social deprivation). Similar comparative analyses using the secondary process indicators collected at T0-T12 will be undertaken using generalized linear mixed modelling to allow for the analysis of repeated measurements over time and comparison between the study arms. To meet our intention-to-treat principles analysis, withdrawals and protocol violators will be analyzed in their arms as randomized.

To assess the costs and benefits of HIS-UK (delivered via ProHIS and e-HIS) compared with usual care, both a within-trial analysis and a model-based economic analysis will be undertaken. The main within-trial economic analysis will assess cost-effectiveness based on incremental cost per quality adjusted life year gained at 6 months, with a secondary analysis of cost per case of chlamydia avoided at 6 months, reflecting the primary outcome of the trial; this analysis will then be repeated to measure cost-effectiveness over a 12-month period. Initially, the base case analysis will be framed in terms of a cost-consequence analysis for the 3 trial arms, and data will be reported in a disaggregated manner on the incremental cost and important consequences assessed in the trial.

If the trial shows that ProHIS or e-HIS are effective in reducing chlamydia positivity and other condom use health behavior outcomes, compared with usual condom distribution care, there are likely to be important cost implications for the health care sector, the wider public sector, and for society as a whole. If deemed necessary, a decision-analytic model will be used to extrapolate costs and outcomes beyond the end of the trial and synthesize data on costs and outcomes from a range of sources [39]. The evidence used in the model will be drawn from the trial and a comprehensive review of the literature on condom use and failure, prevalence of chlamydia and other STIs, transmission rates, and long-term outcomes. If data availability permits, a public sector and an NHS perspective will be adopted, in line with recommendations [40].

The results will be presented using cost-effectiveness acceptability curves to show the uncertainty surrounding the cost-effectiveness of the ProHIS and e-HIS interventions, for a range of thresholds for cost-effectiveness [41]. Both deterministic and probabilistic sensitivity analyses will be used to explore the inherent uncertainty around the estimates employed in the evaluation [39].

Ethics Approval

Ethics approval for the randomized controlled trial has been obtained from the University of Southampton Research Integrity and Governance Committee, and the Health Research Authority South Central Oxford B Committee (REC reference: 19/SC/0486).

Results

Funding was secured in February 2019, and recruitment was commenced in March 2020; however, due to the COVID-19 pandemic, recruitment was halted in April 2020. As a result,

the study was adapted to reduce clinical contact between recruitment site staff and participants (see "Post–COVID-19 Amendments"), and subsequently reopened to recruitment in July 2021, with a planned participant recruitment period of 30 months and a 12-month participant follow-up.

Discussion

Overview

The hypothesized main findings of this trial are that the HIS-UK intervention (delivered by either ProHIS or e-HIS) will reduce chlamydia test positivity among young men (16-25 years) by enhancing condom use experiences and improving correct and consistent condom use, as compared to usual condom distribution care. In addition, it is anticipated that the HIS-UK intervention, as compared to usual condom distribution care, will be cost-effective.

Strengths and Limitations

The strengths of this protocol include the use of a randomized controlled trial design, the targeted large sample, and the use of chlamydia biomarker testing. A limitation of the design is the restriction of participants to men aged 16-25 years. Future directions include adapting and evaluating the intervention among women and men of a broader age range.

Dissemination Plan

The results from this study will be presented at scientific conferences, published in peer-reviewed journals, and shared on social media. We will also share our findings with key stakeholders, including young men, clinicians, and commissioners of sexual health services.

Conclusions

This is the first randomized controlled trial evaluation of the HIS-UK intervention with young men. If the intervention is effective and cost-effective, this could have a positive impact on NHS services by reducing the incidence of STI rates and relieving pressure on staff time, financial costs, and other resources in the treatment of STIs. The intervention may also encourage sexual health services to adopt additional digital technologies and ultimately improve access to such services for young people, decreasing health inequalities engendered by fear of stigmatization.

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Disclaimer

No condom or lubricant brand is endorsed in any part of the study. The condoms and lubricants provided in the kits were selected based on both their availability (via the web or in retail outlets) and their features (size, shape, and material).

Conflicts of Interest

None declared.

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Abbreviations

CUE: condom use experience
e-HIS: HIS-UK delivered digitally
HIS-UK: home-based intervention strategy
NHS: National Health Service
ProHIS: HIS-UK delivered face-to-face
SF-12: 12-Item Short Form Health Survey
STI: sexually transmitted infection

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Protocol

Effectiveness of Artificial Intelligence–Assisted Decision-making to Improve Vulnerable Women's Participation in Cervical Cancer Screening in France: Protocol for a Cluster Randomized Controlled Trial (AppDate-You)

Farida Selmouni[1], PhD; Marine Guy[2], MPH, MD; Richard Muwonge[1], PhD; Abdelhak Nassiri[3], PhD; Eric Lucas[1], MSc; Partha Basu[1], MD, PhD; Catherine Sauvaget[1], MD, PhD

[1]Early Detection, Prevention & Infections Branch, International Agency for Research on Cancer, Lyon, France

[2]Regional Cancer Screening Coordinating Centre of Occitanie, Carcassonne, France

[3]Faculty of Law, Economics, Management and Economic and Social Administration, University of Western Brittany, Brest, France

Corresponding Author:
Farida Selmouni, PhD
Early Detection, Prevention & Infections Branch
International Agency for Research on Cancer
150, Cours Albert Thomas
Lyon, 69372
France
Phone: 33 0472738499
Email: selmounif@iarc.fr

Abstract

Background: The French organized population-based cervical cancer screening (CCS) program transitioned from a cytology-based to a human papillomavirus (HPV)–based screening strategy in August 2020. HPV testing is offered every 5 years, starting at the age of 30 years. In the new program, women are invited to undergo an HPV test at a gynecologist's, primary care physician's, or midwife's office, a private clinic or health center, family planning center, or hospital. HPV self-sampling (HPVss) was also made available as an additional approach. However, French studies reported that less than 20% of noncompliant women performed vaginal self-sampling when a kit was sent to their home. Women with lower income and educational levels participate less in CCS. Lack of information about the disease and the benefits of CCS were reported as one of the major barriers among noncompliant women. This barrier could be addressed by overcoming disparities in HPV- and cervical cancer–related knowledge and perceptions about CCS.

Objective: This study aimed to assess the effectiveness of a chatbot-based decision aid to improve women's participation in the HPVss detection-based CCS care pathway.

Methods: AppDate-You is a 2-arm cluster randomized controlled trial (cRCT) nested within the French organized CCS program. Eligible women are those aged 30-65 years who have not been screened for CC for more than 4 years and live in the disadvantaged clusters in the Occitanie Region, France. In total, 32 clusters will be allocated to the intervention and control arms, 16 in each arm (approximately 4000 women). Eligible women living in randomly selected disadvantaged clusters will be identified using the Regional Cancer Screening Coordinating Centre of Occitanie (CRCDC-OC) database. Women in the experimental group will receive screening reminder letters and HPVss kits, combined with access to a chatbot-based decision aid tailored to women with lower education attainment. Women in the control group will receive the reminder letters and HPVss kits (standard of care). The CRCDC-OC database will be used to check trial progress and assess the intervention's impact. The trial has 2 primary outcomes: (1) the proportion of screening participation within 12 months among women recalled for CCS and (2) the proportion of HPVss-positive women who are "well-managed" as stipulated in the French guidelines.

Results: To date, the AppDate-You study group is preparing and developing the chatbot-based decision aid (intervention). The cRCT will be conducted once the decision aid has been completed and validated. Recruitment of women is expected to begin in January 2023.

Conclusions: This study is the first to evaluate the impact of a chatbot-based decision aid to promote the CCS program and increase its performance. The study results will inform policy makers and health professionals as well as the research community.

Trial Registration: ClinicalTrials.gov NCT05286034; https://clinicaltrials.gov/ct2/show/NCT05286034
International Registered Report Identifier (IRRID): PRR1-10.2196/39288

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KEYWORDS

cervical cancer; screening; chatbot; decision aid; artificial intelligence; cluster randomized controlled trial

Introduction

Background

In France, there were an estimated 2920 new cervical cancer (CC) cases and 1117 related deaths in 2018, with marked geographical disparities within regions [1]. A decline in CC incidence and mortality rates was observed during the period of 1990 to 2018, although this was less pronounced in recent years [1]. The prognosis of CC is deteriorating in France, with a 5-year survival rate after diagnosis decreasing from 68% in 1989 to 1993 to 62% in 2005 to 2010 [2]. During the period of 2018 to 2020, the national triennial coverage rate was 59.2%, with a strong geographical disparity within French departments, ranging from 11.8% to 65% [3]. The national screening coverage rate appeared relatively stable since 2012 across the age groups and declined markedly in women older than 50 years, down to 44.2% in women aged 60 to 65 years [4].

The French organized population-based CC screening (CCS) program shifted from a cytology-based to a human papillomavirus (HPV)–based screening strategy in August 2020. HPV testing is offered every 5 years, starting at the age of 30 years. In the new program, women are invited to have the HPV test at a gynecologist's, primary care physician's, or midwife's office, a private clinic or health center, family planning center, or hospital. A reminder letter is sent to noncompliant women after 12 months from the date of the first screening invitation.

HPV self-sampling (HPVss) was also made available as an additional approach to recall noncompliant women 1 year after the initial invitation [5]. There is a strong body of evidence to support the usefulness of HPVss in increasing participation of hard-to-reach women in screening programs [6,7]. In France, 2 randomized controlled trials (RCTs) have been conducted to evaluate home-mailing of HPVss kits directly to noncompliant women in 2 regions [8,9]. Home-based HPVss testing was accepted among French women and increased participation in CCS compared with a recall letter: 18.3% versus 2.0% [8] and 22.5% versus 11.7% [9], respectively, among nonattendees. Some concerns remain regarding adherence to further follow-up among high-risk women with positive test results. The French studies reported substantial variation in compliance with follow-up among HPVss-positive women (41% vs 92%) [8,9]. These studies also found that less than 20% of noncompliant women performed vaginal self-sampling when an HPVss kit was sent to their home. Women are concerned about the self-test's effectiveness and are afraid of hurting themselves when collecting the sample [10].

In France, women older than 50 years, those with unfavorable socioeconomic status, those living in disadvantaged and in low-medical-density areas, those with long-term disease, and those covered by *complementary health insurance* are more likely to not participate in CCS [11]. Lack of information about CC and the benefits of CCS were reported as two of the major barriers among noncompliant women [12-14]. These barriers could be addressed by overcoming disparities in HPV- and CC-related knowledge and perceptions about CCS.

Studies showed that decision aids improve knowledge, decrease decisional conflict, and increase the proportion of individuals who are active in the decision-making process [15,16]. Decision aids must be carefully established, tested and validated by users, and meet their needs [17]. Standard information materials, even with simple text and design, are not an appropriate communication tool for individuals with low health literacy [18]. In contrast, animated educational videos were found to be the best way to communicate complex health information to such individuals [19]. Health literacy is defined as "[people's ability] to make judgements and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve their quality of life" [20]. Low health literacy is prevalent among people who are older, less educated, low-income, have chronic conditions, and do not speak the native language of the country where they live [21]. In France, the prevalence of low health literacy was estimated to be 51% (95% CI 34%-67%) [22].

One of the useful innovative tools being used to self-administer web-based health information is the chatbot. Chatbots, as artificial intelligence (AI) devices, are applications that provide information or services through interactions with users [23]. To our knowledge, no study has evaluated the usefulness of AI-based chatbot services to empower women and democratize the decision-making process about CCS. This study will be the first to develop and test a chatbot-based decision aid tailored to women with lower education attainment. Previous systematic reviews have shown that no RCTs have examined shared decision-making in CCS programs [16,24]. This paper describes the objectives and protocol of the cluster randomized trial (cRCT) using the Standard Protocol Items: Recommendations for Interventional Trials–Patient-Reported Outcomes (SPIRIT-PRO) guidelines.

Objectives and Endpoints

The primary objective of this AppDate-You study is to assess the effectiveness of a chatbot-based decision aid to improve women's participation in the HPVss detection–based CCS care pathway, in particular among noncompliant women living in disadvantaged areas in Occitanie Region, France.

The main secondary objectives are to evaluate the impact of the intervention on (1) the detection rate of cervical intraepithelial neoplasia grade 2+, (2) the intervals between the dates of the reminder letter and the HPVss test report and between the dates

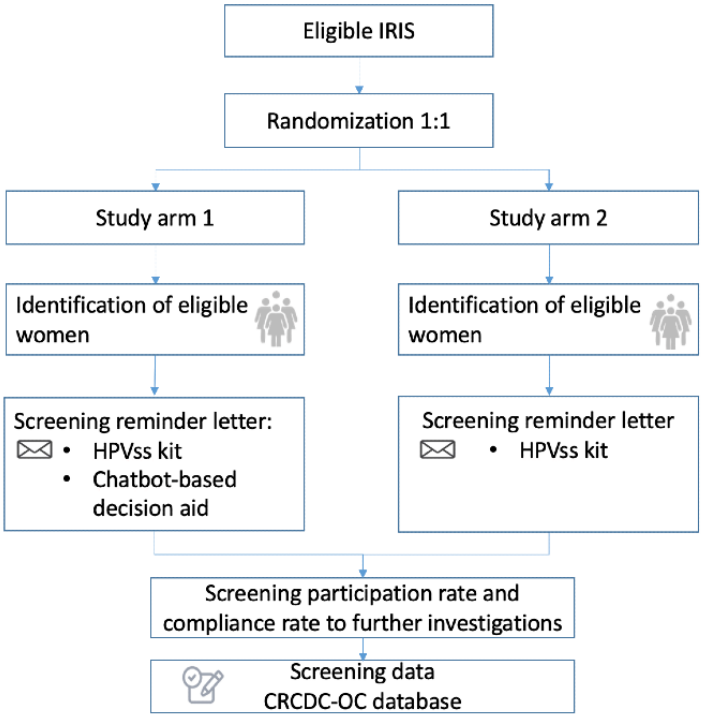
of sending a positive HPV test result and performing liquid-based cervical cytology (triage test), and (3) the efficiency (cost-effectiveness) of the intervention.

Methods

Study Design

A 2-arm cRCT will be conducted (Figure 1). A cluster is defined by aggregated units for statistical information (*Ilots Regroupés pour l'Information Statistique;* IRIS), corresponding to 2000 inhabitants per unit. Only IRIS classified as 4 or 5 (the most disadvantaged IRIS) in accordance with the French version of the European Deprivation Index will be included [25]. The study will be nested within the French CCS program in the Occitanie Region. Recruitment of women will start in January 2023 and end in December 2024, and HPVss-positive women will be followed-up for 12 months after the last participants are recruited.

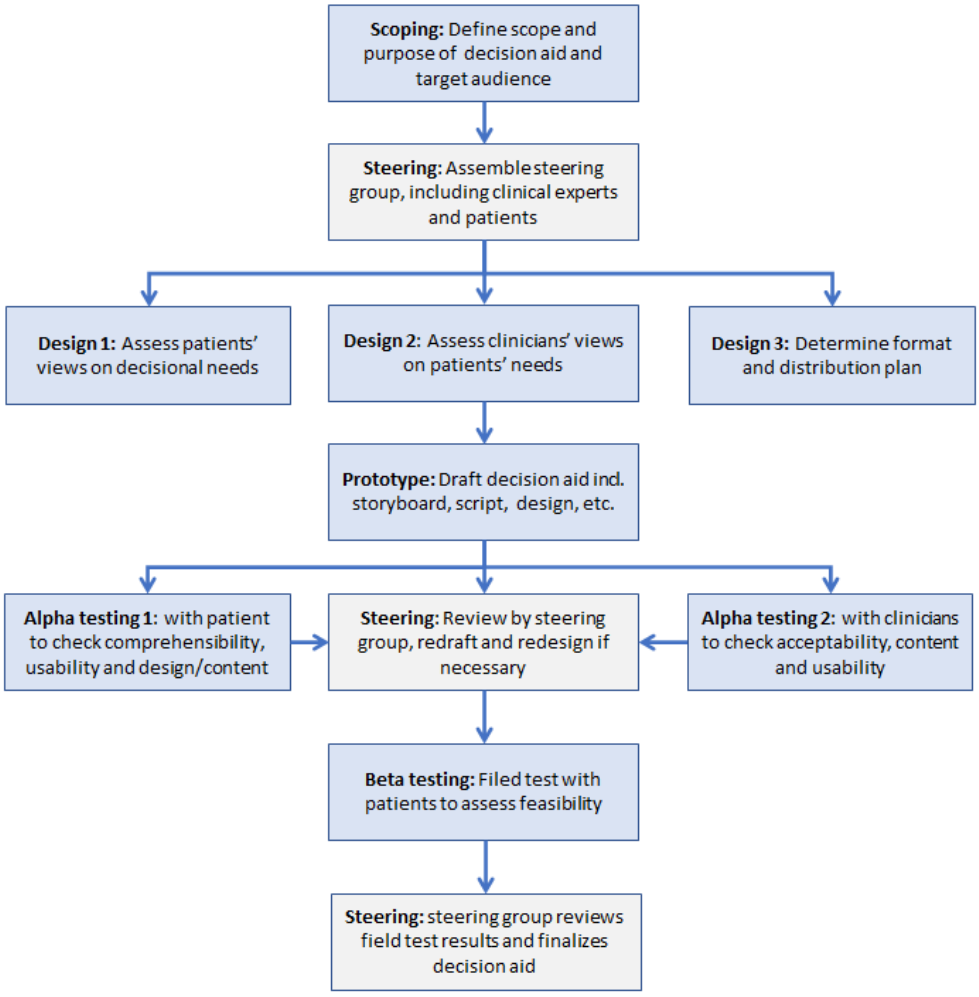
Figure 1. Flowchart of the study. CRCDC-OC: Regional Cancer Screening Coordinating Centre of Occitanie; HPVss: human papillomavirus self-sampling; IRIS: Ilots Regroupés pour l'Information Statistique.



Study Intervention

The chatbot-based decision aid will be developed using the validated Coulter framework on the basis of the International Patient Decision Aid Standards (IPDAS) [17]. This framework proposes 5 steps (Figure 2): (1) scoping and design, (2) development of a prototype, (3) "alpha" testing with women and clinicians in an iterative process, (4) "beta" testing in "real-life" conditions (field tests), and (5) production of a final version. The chatbot-based decision aid will be tailored to women with a lower education level and will be offered in several languages (the most spoken languages in the Occitanie region) and via several channels.

Figure 2. Model development process for decision aids (adapted from Coulter et al [17]).



Study Population

Eligible women are those aged 30-65 years who did not respond to an initial invitation letter to have an HPV test collected by a clinician, have not been screened for CC for more than 4 years, and live in the disadvantaged clusters in the Occitanie Region.

Women will be excluded from the study if they have undergone CC screening within the past 4 years, have had a hysterectomy, or have been diagnosed with and are receiving treatment for precancer or CC.

Sample Size

The sample size involved estimation of the number of clusters (IRIS) using a composite outcome, "well-managed" women, which is defined as those women who completed a valid HPVss test and were either advised of a negative result (in the case of HPVss-negative women) or completed the assessment (in the case of HPVss-positive women), and, where necessary, treatment pathway. The following assumptions were considered:

- Expected average cluster size of 250 eligible women; this is an estimate of the number of women in the target age range (30-65 years) within a cluster of 2000 people, based on the population pyramid of ages in the Occitanie Region.
- Expected proportion of overall well-managed women in the control group of 15%.
- Expected absolute increase of 10% in the proportion of overall well-managed women in the experimental group.
- Coefficient of variation taking into account the possibility of varying cluster sizes of 1.2 (arrived at because of the wide level of dispersion around the mean cluster size) [26].
- A 10% precision in the proportion of overall well-managed women, which would lead to a 0.029 intracluster correlation using a beta-binomial model [27].
- A power of 80% and a 5% 2-tailed significance level.

Under the aforementioned assumptions, the required number of clusters to randomize in each arm would be 10 (total: 20 clusters). However, if subgroup analyses are to be performed, stratifying on general population density, medical density of the department (high or low), and setting of the community (rural or urban), taking into consideration these α adjustments (α=.3125% [2.5%/8]) for each of the subgroup analyses in order to be able to remain with a 5% 2-tailed significance level for the overall effect, approximately 16 clusters in each arm (32 clusters in total) will be required for the subgroup analyses.

Randomization

A sampling frame of a list of disadvantaged clusters was obtained from Caen University, Caen, France. Clusters (IRIS) will be randomly assigned to the 2 randomization groups in a 1:1 ratio using computer-generated simple randomization. Eligible women living in the randomly selected disadvantaged

clusters will be identified using the Regional Cancer Screening Coordinating Centre of Occitanie (CRCDC-OC) database.

Study Procedures

Eligible women in both groups will receive screening reminder letters and HPVss kits. The HPVss kit will contain a self-adhesive barcode, an HPVss kit, instructions with illustrations on how to self-collect the vaginal samples, and a postage-paid, preaddressed return envelope. Women in the experimental group will receive an information letter explaining the nature of the research, its objective, and what participants will be required to do and how to access the chatbot-based decision aid.

Participants in both groups will be requested to either perform vaginal self-sampling at their home (with the collection kit provided) or have an HPV test with their gynecologist, primary care physician, or midwife. Those who choose HPVss will be encouraged to contact the CRCDC-OC via telephone or email in the event of any uncertainty.

HPV Test Analysis and Management of Results

Participating women in both groups will be asked to send the samples via regular mail to a centralized laboratory using the postage-paid envelope. The results will be communicated to the women, their primary care physician, and the CRCDC-OC generally within 2 weeks after the self-collected sample arrives at the centralized laboratory. Women with negative results will be advised to repeat CCS after 5 years. HPVss-positive women will be invited to consult their primary health physician, who will explain what a positive HPVss test result means and suggest further investigations in accordance with national guidelines [28].

HPVss-positive women will be referred for liquid-based cervical cytology triage:

- HPVss-positive women with a cytological diagnosis of atypical squamous cells of undetermined significance or worse will be referred for colposcopy.
- HPVss-positive women with a normal cytological diagnosis will be advised to undergo HPV testing 1 year later. If this triage HPV test, performed 1 year later, yields positive results, colposcopy should be performed; if this triage HPV test yields negative results, another HPV test should be offered 5 years later.

For women with an uninterpretable HPV test, a new HPVss collection kit will be sent to them. If the second HPV test result is also uninterpretable, the women will be advised by mail to have an HPV test with a health professional as soon as possible.

The CRCDC-OC will track the HPVss-positive women to investigate whether they receive follow-up procedures in accordance with national recommendations and will recall women or providers, if necessary.

Data Collection and Study Variables

The study data will be generated from the CRCDC-OC database. The source of the CRCDC-OC database is the French health insurance database (*Système National des Données de Santé*; SNDS). This database contains individualized and deidentified data on all medical expenditures and reimbursements. All medical care received in the public, private, or liberal sector is recorded in the SNDS. No additional personal or clinical information will be collected during this trial. Anonymized data for each individual participant will be received, stored, and handled at International Agency for Research on Cancer (IARC) using Research Electronic Data Capture, a secure, web-based software platform designed to support data capture for research studies [29,30]. All standard precautions will be taken to ensure the privacy and protection of personal and medical information. Only the principal investigators and coinvestigators as well as the data manager will have access to the data.

This database enables access to some data on women's characteristics (date of birth, place of residence, and type of health insurance), screening (HPV testing), and further investigations (cytology, colposcopy, biopsy, treatment of precancerous lesions, and surgery).

Real-time usage statistics generated by the chatbot platforms will be used to evaluate women's use of the chatbot. Chat volumes, response time to women's chat requests, the number of queries resolved, the main topics in women's requests, navigation flow, and women's satisfaction will be analyzed.

Primary Study Outcomes

The study has 2 primary outcomes: (1) the proportion of screening participation within 12 months among women recalled for CCS and (2) the proportion of HPVss-positive women who are "well-managed" as stipulated in the French guidelines. Both proportions will be compared between experimental and control groups, taking into account the stratification by age group, place of residence, and type of health insurance.

Secondary Study Outcomes

We will examine whether the intervention also improves the proportion of women providing valid vaginal samples and the proportion of women with invalid HPVss tests who repeat HPVss. We will also compare the detection rate of cervical intraepithelial neoplasia grade 2+ in the 2 groups. Median intervals between the date of the reminder letter and the date of the HPVss test report, and between the dates of sending a positive HPV test result and performing liquid-based cytology will be compared between groups, stratified by age group, place of residence, and health insurance type.

An evaluation of cost-effectiveness will also be performed, to first estimate the cost of the intervention and to calculate the incremental cost-effectiveness ratios as the mean difference in total costs between the intervention and control groups with the mean difference in effects, and expressed as both Euros and US dollars per percentage change in screening participation. Deterministic and probabilistic sensitivity analyses will also be conducted by varying key parameters that may affect the outcome and conclusions of the economic evaluation.

Women's use of the chatbot will also be assessed through usage and engagement statistics generated by chatbot platforms. We will estimate the average number of messages each participating woman exchanged with the chatbot, the average interaction time spent by each participant and a session-wise split of duration,

the average number of failed messages that the Chatbot failed to respond, the most frequently asked questions, and the language most often used to seek information, etc.

Statistical Analysis

The participants' categorical characteristics will be presented as proportions compared between the intervention and control groups using chi-square analysis. Continuous variables will be presented as median (interquartile range) values. Comparisons will be carried out using Kruskal-Wallis tests. The effect of the intervention on both the primary and secondary outcomes will be assessed using logistic regression models, adjusting for individual characteristics that are statistically significant in the univariate analysis and the cluster design. The effect estimates obtained from the regression analysis will be presented as odds ratios together with their 95% CIs. Just Another Gibbs Sampler software will also be used to model missing data in outcomes and/or explanatory variables [31].

Ethics Approval

The study protocol will be submitted to the French and the IARC ethics committees once the chatbot-based decision aid has been completed. No individual consent will be required; all participants will be informed of their rights not to participate or to object to the collection of their data. The design phase of the chatbot-based decision aid was approved by the IARC ethics committee (IEC 21-16).

Study Organization

The project will be coordinated by 2 committees. The steering committee (the AppDate-You Study Group) includes all scientific leaders and their collaborators of the 3 study teams: at the CRCDC-OC, the University of Western Brittany, and the IARC. This committee meets on a monthly basis to discuss all scientific and organizational aspects of the project and to decide on corrective measures to be taken, if necessary.

The scientific committee is composed of experts (an epidemiologist, a public health specialist, a gynecologist, and a sociologist), who are independent of the trial, and the scientific leaders of the 3 study teams. This committee meets once a year to make recommendations on the progress of the trial.

Results

To date, the AppDate-You study group is preparing and developing the chatbot-based decision aid (intervention). Once the decision aid has been completed and validated, we will conduct the cRCT as described above. Recruitment of women is expected to begin in January 2023. The results of the study will be the subject of a new academic publication.

Discussion

The HPVss test was recently introduced into the French organized CCS program for women who do not participate in regular screening. The goal of our intervention is to improve the effectiveness of the HPVss strategy among women living in deprived areas. If the proposed intervention is successful, the findings of this trial will inform policy makers and stakeholders to update local guidelines. The intervention would be easy to integrate into the current screening program and expand to other populations. Information tailored to audiences with low health literacy is also appropriate for people with high health literacy [19]. A chatbot-based decision aid solution can also be used in other screening or health programs.

There is vast interest in how to optimize the send/return ratio of HPVss kits. We expect our intervention tool to be accepted by women, with a large impact on women's participation in CCS. First, this is a validated framework based on a collaborative decision-making process among women, health professionals, health psychologists, decision-making experts, and the AppDate-You Study Group and a pilot study to ensure the feasibility and acceptability among the targeted women. Second, the COVID-19 pandemic has accelerated the adoption of digital uses; the French government and citizens turned toward digital technologies to respond to the health crisis and address a wide range of pandemic-related issues. According to the 2021 Digital Barometer, 94% of respondents in France use e-banking (+ 1 point from 2020), 93% have adopted e-administration (same as in 2020), 91% use e-commerce (+ 3 points), 87% use social networks (+2 points), and 83% use instant messaging (+ 1 point) [32]. Services using AI are up by 6 points and are used by 70% of French people [32].

However, our study has some limitations, including the fact that we are not able to guarantee that only women in the experimental group will use the chatbot-based decision aid; access to the chatbot will not require individual identification or codes. The chatbot will be accessible to everyone, which may bias the final results of our trial. This issue is common to all technology-based interventions, and it is not controllable. The AppDate-You Study Group decided not to evaluate some IPDAS effectiveness criteria, such as (1) "choice made" and (2) "decision-making process," because these criteria have been widely assessed in several trial situations, which have shown that a decision aid is effective in increasing knowledge, accurate risk perception, and value-based informed choice, and in reducing decisional conflict [16].

Chatbot communication methods are growing rapidly in the health care field. To date, few studies have evaluated the effect of these methods in health care. This study will help inform policy makers and health care professionals.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Disclaimer

Where authors are identified as personnel of the IARC/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the IARC/World Health Organization.

Authors' Contributions

FS, MG, RM, AN, and CS designed the study protocol. FS wrote the first draft of the manuscript. RM provided statistical input and guided the methodology. All authors reviewed and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 632 KB - resprot_v11i8e39288_app1.pdf]

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Abbreviations

CC: cervical cancer

CCS: cervical cancer screening
CRCDC-OC: Regional Cancer Screening Coordinating Centre of Occitanie
cRCT: cluster randomized controlled trial
HPV: human papillomavirus
HPVss: human papillomavirus self-sampling
IARC: International Agency for Research on Cancer
IPDAS: International Patient Decision Aid Standards
IRIS: Ilots Regroupés pour l'Information Statistique
SNDS: Système National des Données de Santé
SPIRIT-PRO: Standard Protocol Items: Recommendations for Interventional Trials–Patient-Reported Outcomes

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Protocol

Social Support as a Stress Buffer or Stress Amplifier and the Moderating Role of Implicit Motives: Protocol for a Randomized Study

Julia Schüler[1], PhD; Alisa Haufler[1], MSc; Beate Ditzen[2], PhD

[1]Department of Sport Science, Unversity of Konstanz, Constance, Germany

[2]Institute for Medical Psychology, Heidelberg, Germany

Corresponding Author:
Beate Ditzen, PhD
Institute for Medical Psychology
Bergheimer Str. 20
Heidelberg, 69115
Germany
Phone: 49 6221 568150
Email: beate.ditzen@uni-heidelberg.de

Abstract

Background: Previous research shows that providing social support in socioevaluative stress situations reduces participants' stress responses. This stress-buffer effect, however, does not hold for everybody, and some studies even found a stress-amplifying effect of social support. Motive disposition research suggests that social motives (affiliation and power) lead to differential and sometimes even opposing affective and physiological responses to interpersonal interaction processes. We here integrate both lines of research and hypothesize that participants with strong affiliation motives benefit, while participants with strong power motives do not benefit from social support in terms of psychobiological responses to a given stressor. Further, participants with strong affiliation and power motives are expected to respond to social support with the arousal of motive-specific affects and reproductive hormone responses (affiliation: progesterone; power: estradiol and testosterone). In addition, we test sex differences in the response to social support and in the strengths of social motives.

Objective: The main objective of this study is to test whether social motives and participants' sex moderate the effects of social support in stressful situations.

Methods: We aim to collect data from 308 participants recruited at our local university. Participants' social motives are assessed using a standardized measure in motive research (Picture Story Exercise). Then, the Trier Social Stress Test for Groups (TSST-G) is used to experimentally induce psychosocial stress. One group of participants receives social support from an associate of the experimenter, while the control group does not receive social support. Stress responses will be assessed by a modified version of the state anxiety scale of the State–Trait Anxiety Inventory and by physiological indicators of stress (cortisol and α-amylase from saliva samples) at 7 measurement points. Reproductive hormones will be analyzed in 4 of these 7 saliva samples. Heart rate and heart rate variability will be assessed continuously. We will additionally measure participants' performance in an interview (part of the TSST-G) using a self-developed categorization system.

Results: The Ethics Committee of the University of Constance approved the application to conduct the study on December 18, 2018. Furthermore, the study was retrospectively registered in the German Clinical Trials Register (DKRS; ID: DRKS00028503) on March 09, 2022. The start of the experiment was planned for the beginning of 2019, but was postponed to June 2021 due to COVID-19. Publication of the first results is planned for spring 2023.

Conclusions: Our theory-driven integration of social motives in social support research and the precise analysis of sex differences might disentangle inconsistent findings in TSST research. The more faceted view on individual differences has direct implications for applied contexts as it provides a framework for tailored conceptualizations of social support programs.

Trial Registration: German Clinical Trials Register DRKS00028503; https://tinyurl.com/5a87x4da

International Registered Report Identifier (IRRID): PRR1-10.2196/39509

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KEYWORDS

stress; Trier Social Stress Test; social support; social motives, cortisol, reproductive hormones

Introduction

Stress and Social Support

There is an extended body of research outlining that stress affects basically every physiological system [1,2] and significantly impairs subjective well-being [3,4]. Therefore, it is unsurprising that the World Health Organization anticipates stress-related illness to progress to the second leading cause of disease in the coming decades [5]. Hence, it is essential to better understand the complexity of the concept of stress to be able to develop effective interventions. In the last decades, a great deal of research has shown that social support, defined as "social interactions or relationships that provide individuals with actual assistance or with a feeling of attachment to a person or group that is perceived as loving or caring" [6], can improve health [7-10]. One of the leading explanations for this phenomenon is that social support has a stress-buffering effect [11,12] and can thus counteract the negative consequences of stress. For example, social support leads to lower mortality rates [13,14], and better recovery from surgery [15] and sport injuries [16]. Yet, interestingly social support does not work as a stress buffer for everyone [8]. We assume that social support is perceived differently by individuals and investigate social motives (affiliation and power motive) [17] as moderators. They influence the perception of interpersonal relationships and should therefore also explain responses to social support.

Implicit Motives

Implicit motives are preferences for certain kinds of incentives and disincentives, which modulate reward experiences [17-21]. Being relatively stable across time (such as personality traits), they drive, orient, and select behaviors for summaries [22]. Motive research has focused on the 3 domains of affiliation, power, and achievement motives, of which, we consider only social motives in our study.

Individuals with a strong affiliation motive derive pleasure from affiliative experiences [17,23]. They have the desire for warm and friendly interpersonal relations [24], aim to feel socially related, want to experience reciprocal care and concern for important others [17,25], and emotionally suffer from discord, rejection, and loneliness [17,25,26]. Situations in which these needs can be satisfied lead to an affiliation motive–specific affect, such as joy, and feeling socially related [27].

Individuals with a strong power motive have the desire to have an impact on others and influence others (in socially desirable and undesirable ways) in order to feel superior to others and gain or maintain reputation and prestige [28,29]. Simultaneously, they aim to avoid defeat, other's dominance, and feelings of inferiority [30]. In brief, they have "the capacity to derive pleasure from having physical, mental, or emotional impact on other individuals or groups of individuals and to experience the impact of others on themselves as aversive" [17]. The lack of opportunities in which others can be impacted or, even worse, situations signaling one's inferiority function as stressors and lead to a power motive–specific affect (eg, feeling inferior and experiencing limited control) and impaired well-being [31,32].

Social motives are also associated with specific hormones [33,34]. Being inferior, for example, in a contest situation, has been associated with a decrease in testosterone in men with strong power motives [35]. For high power–motivated women, motive frustration leads to a decrease in estradiol [35]. Arousal of the affiliation motive is accompanied by an increase in progesterone for both sexes [33,36,37]. Furthermore, social motives in relationship with stress have been associated with various parameters of health, including blood pressure and the immune system [20], medication use and somatic symptoms [38], or job burnout and physical symptoms [39]. In summary, previous research has confirmed that affiliation and power motives lead to differential emotional, behavioral, and physiological responses to social cues.

Social Support and Social Motives

Based on the evidence that both social support and social motives modulate the stress response, we aim to investigate to what extent the interplay of these 2 factors can contribute to further enlightenment of the stress-buffer effect. Social support situations are highly ambiguous, leaving wide room for interpretation about, for example, one's position in the social context, the intentions of the social support provider, and the quality of social relationships. By this, they are prototypes of social interaction processes, which are full of incentives or disincentives for social motives. They can, however, be perceived very differently by individuals with strong affiliation in contrast to power motives and therefore elicit different physiological and psychological responses. Thus, social support might signal a positive and warm relationship for individuals with a strong affiliation motive, but trigger feelings of weakness and inferiority in individuals with a strong power motive. In summary, we assume that social motives influence the perception of social support provided by others and function as a stress buffer in affiliation-motivated individuals and as a stress amplifier in power-motivated individuals.

Social Support, Sex, and Gender

Other moderators that are discussed to influence participants' responses to social support are sex and gender [8,40,41]. Women benefit stronger in terms of well-being from being socially supported than men [42,43], even though some studies found opposite effects [44]. Thus, the empirical evidence on whether and how women and men differ in their responses to social support is inconsistent.

Sex differences have also been found in social motive research. Since the arousal of the affiliation and power motives in a specific situation is accompanied by the release of female reproductive hormones (estradiol and progesterone) and a male reproductive hormone (testosterone), it is assumed that this sex specificity should also be reflected in corresponding motive differences. Women are expected to show higher scores in

affiliation motives, and men are assumed to have higher power motives. This was clearly empirically supported for the affiliation motive [45,46], whereas for the power motive, the result pattern is less clear [45,47]. These motives are assumed to correlate with a concept on a broader level of abstraction, that is, gender role self-concept (GRSC) [48]. The individual GRSC is defined as describing oneself with agentic traits like confident or assertive (masculine GRSC) versus with communal traits like empathic or cooperative (feminine GRSC). We assume that the inconsistent findings reported above may be due to shared variance among sex, GRSC, and motives. We aim to identify the specific influences of sex, GRSC, and social motives on the stress response to social support by considering them simultaneously and disentangling them in our statistical analyses.

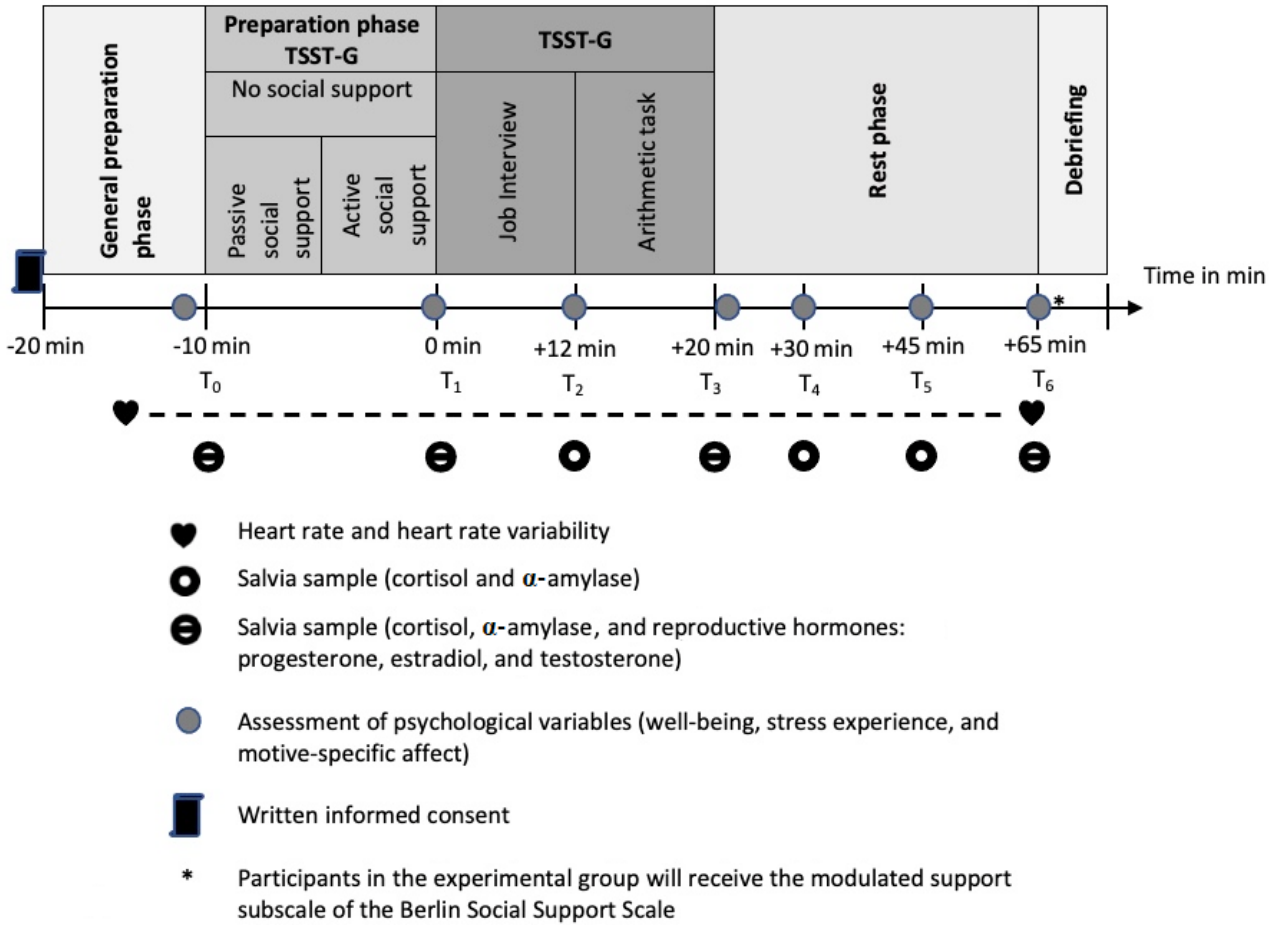
Planned Research

The main objective of this study is to test whether social motives and participants' sex moderate the effects of social support in stressful situations. We use the Trier Social Stress Test for Groups (TSST-G) [49] that is based on the Trier Social Stress Test (TSST) [50], which is an established stress-induction paradigm triggering strong psychobiological stress responses [51]. Schultheiss et al [52] found that the TSST elicited differently strong cortisol responses for individuals with weak and strong implicit achievement motives, which supports our assumption that the TSST might be a potentially suitable paradigm that reveals motive differences. Wiemers et al [53] concluded from their study that the TSST has a specific arousal effect for the implicit power motive.

This study varies from classic TSST studies in the following aspects. While TSST studies usually focus on the detection of the stress hormone cortisol [54,55], we add the analysis of reproductive hormones (progesterone, estradiol, and testosterone), which will allow us to examine the arousal of motives in social support situations. We will further extend the TSST paradigm by analyzing participants' responses in an interview (part of the TSST) to obtain an indicator for speech performance. While in the classical TSST paradigm, it is only announced that speech will be recorded (as an additional stressor), we here will actually record speech and apply a simple evaluation system to assess speech performance as a variable that we assume depends on stress.

Except for these variations, we will adhere to the procedure of the TSST-G [49]. As in previous studies analyzing social support [40,41,56], the experimental group will receive social support during the TSST preparation phase. The control group will also be exposed to stress but will not receive social support. To test the study hypotheses (see below), self-reports (well-being, perceived stress, and motive-specific affect) and biological parameters (heart rate, heart rate variability, cortisol, and reproductive hormones) will be collected (Figure 1).

Figure 1. Trier Social Stress Test for groups (TSST-G): Phases of the procedure.



Objectives

We will test the below hypotheses to investigate the role of social motives in the social support and stress relationship.

Hypothesis 1: Effect of Stress Induction Hypothesis

Participants in both groups (social support vs no social support) show an increase in stress responses comparable to that in previous studies. We expect a rise in the physiological parameter cortisol by at least 1.5 nmol/mL (Miller criterion) [57].

Hypothesis 2: Social Support × Social Motive Hypothesis

The affiliation motive moderates the effects of social support on stress responses. A higher affiliation motive of participants is associated with greater benefit from social support, that is, they will express lower psychobiological stress responses (better self-reported well-being, less perceived stress, lower heart rate, higher heart rate variability, and lower levels of cortisol and α-amylase). While the affiliation motive is expected to function as a stress buffer, the power motive is assumed to function as a stress amplifier. A higher power motive of participants is associated with greater negative impact from social support, that is, they will report lower well-being, more perceived stress, higher heart rate, lower heart rate variability, and higher levels of cortisol and α-amylase.

Hypothesis 3: Motive-Specific Arousal Hypothesis

Participants with strong affiliation and power motives respond to social support with arousal of self-reported motive-specific affect (ie, affiliation: joy and feeling socially related; power: feeling weak and inferior) and with an increase in motive-specific reproductive hormone responses (affiliation: progesterone; power: estradiol and testosterone).

Hypothesis 4: Sex Difference Hypothesis

Women and men are hypothesized to differ in their social motives, with higher affiliation and lower power motives in women than in men. Women and men will specifically respond to social support with relative increases in estradiol and progesterone in women and testosterone in men.

Hypothesis 5: Speech Performance Hypothesis

Participants who receive social support show better presentation performance in TSST interviews than participants in the no social support group. This relationship is moderated by social motives. Participants in the social support group perform better when the affiliation motive is high and perform worse when the power motive is high.

Exploratory Hypothesis: GRSC

On an exploratory level, we plan to investigate the association of self-reported GRSC with social motives and their moderating role on whether individuals of either sex benefit from social support.

Methods

Study Registration

This study was retrospectively registered in the German Clinical Trials Register (DKRS) on March 09, 2022, under the following number: DRKS00028503. The trial was not prospectively registered because COVID-19 restrictions led to uncertainty about whether, when, and under what circumstances (eg, wearing a FFP2 mask) data collection could take place.

Study Design

The study is based on a mixed within- and between-subject design. The within-subject factors are participants' stress responses (self-reports and biological markers) across the steps of the TSST procedure (Figure 1). The between-subject factors are experimental groups (social support vs no social support), social motives, and participants' sex. GRSC and other control variables will be assessed as controls and entered as covariates into the analysis models. Allocation will be based on a 1:1 ratio. There will be no cross-over into the experimental group.

The study will be conducted in the laboratory of sports psychology of the Department of Sport Science at the University of Konstanz, Germany. The analyses of hormones and α-amylase will be performed in the biochemical laboratory of the Institute for Medical Psychology in Heidelberg, Germany.

Ethics Approval

The study was approved by the Institutional Review Board of the University of Konstanz on December 18, 2018 (35/2018). Further, the participants will receive a study information sheet and give their informed consent in the screening online survey (Multimedia Appendix 1) before the laboratory session. If they fulfill the inclusion criteria, they will be invited to the laboratory session. Here, the participants will again read the study information sheet and sign the informed consent (Multimedia Appendix 2). Participants can discontinue the study at any time without giving any reason. They will still receive their payment.

To ensure confidentiality**,** personal data (email addresses) of potential and enrolled participants will be collected by the principal investigator and stored password-protected on the local university server. The information will not be shared.

Blinding

Participants and all experimenters involved in data collection and processing (eg, motive coders), with the only exception of social support providers, will be blinded to the intervention after assignment.

Sample Size and Recruitment

It is intended to recruit 154 participants (77 women). This sample size was calculated using a power analysis involving *G*Power 3.1* [58], with an additional 20% added to compensate for possible dropouts.

The recruitment will be done by flyer distribution in the University of Konstanz, as well as an entry in an online platform where experiments are offered by the departments of psychology and linguistics.

Eligibility Criteria

The following primary criteria must be fulfilled to participate in the study: (1) informed consent for all aspects of the study (agreement with video recording and hormone collection); (2)

age at least 18 years; and (3) ability to speak German as the native language.

Participants who meet the following exclusion criteria will be excluded from study participation: (1) previous participation in stress experiments, as well as psychology and sports students from the 5th semester and (2) presence of physical or mental illness, nicotine consumption, drug use, BMI of 30 or more, and regular use of medication (including hormonal contraception), as these could influence the physiological stress response [59].

Participant Adherence

Participants will receive €40 (about US $42) payment at the end of the laboratory session independent of whether or when participants decide to discontinue the study. To promote participant adherence with the appointment and study protocol, they will receive a reminder email after having filled in the web survey and 1 day before their laboratory appointment.

Procedure

Web Survey Prior to the Laboratory Session

The participants complete an online questionnaire (Limesurvey) at home. Here, the eligibility criteria are checked, the implicit motives are assessed by using the Picture Story Exercise (PSE) [60], and GRSCs [61], as well as other control variables, are measured. The exercise and sports activity questionnaire [62] will be administered to test a related but different research question (Multimedia Appendix 1). Participants, who are eligible for the study, will be invited to the laboratory session via email. Participants confirm their agreement that they will be contacted by email and learn that email addresses will be deleted after the appointment is made.

Laboratory Session

Figure 1 shows the schematic procedure of data collection. It starts with a general preparation phase, where the baseline measurements of physiological parameters (hormones), control variables, and psychological variables (self-reports about well-being, stress experience, and motive-specific affect) take place. In the preparation phase for the TSST-G, the participants prepare for the task. The participants in the experimental group receive social support during this phase, while the participants in the control group do not receive any social support. Finally, there will be a 45-minute rest period during which repeated physiological and psychological questionnaires will be completed. A detailed procedure is provided in Multimedia Appendix 3.

General Preparation Phase

In each laboratory session, 3 participants will arrive between 5:00 and 5:15 PM outside the laboratory and will be led individually to their own preparation room (so that they cannot contact each other). First, they will be asked to read the study information sheet again and then will provide their written consent (Multimedia Appendix 2). Afterwards, the participants will generate their participant code via paper and pencil format, which ensures that the saliva samples, as well as other collected data, can be stored anonymously. Then, they will complete a short day-screening questionnaire (Multimedia Appendix 4) on a computer, which will assess control variables (eg, sports, medication intake, smoking, and caffeine and alcohol consumption). Afterward, they will be asked to wear a pulse belt that contains a Polar H10 sensor (Polar Electro). When putting on the belt, the experimenter will leave the room. After that, the participants will provide an initial saliva sample at measurement time T0 (−11 min) and will complete the first test battery, including different questionnaires, on a computer (hereafter referred to as psychological questionnaires).

Preparation Phase of the TSST-G Without Social Support

For the preparation phase, each participant sits in a separate room. Here, they receive written instructions for the upcoming interview (Multimedia Appendix 5). After they have had 10 minutes of preparation time for this task, they give a saliva sample (T1, 0 min) and complete the psychological questionnaire again. Subsequently, the participants are individually led to their places in front of the panel.

Preparation Phase of the TSST-G With Social Support

The preparation phase is identical to the described scenario for the participants without social support, with the exception that the experimenter introduces a female associate as a student assistant who can assist the participants if needed. The female associate provides passive social support for the first 5 minutes, ostensibly working on the computer. In the second 5 minutes of the preparation phase, the associate gives active social support and also notes the reactions of the participants (Multimedia Appendix 6). At the end of the 10-minute preparation period, the associate asks the participants for a saliva sample (T1, 0 min) and tells the participants to complete the psychological questionnaire again. Then, rooms are changed. All other instructions are the same as in the group without social support.

TSST-G

Psychosocial Stress Induction

Our procedure is based on the TSST-G developed by Von Dawans et al [49]. Each participant is required to present his or her interview individually in front of the panel for 3 minutes at a time. During this time, the participant is interrupted in a standardized manner by the panel (Multimedia Appendix 7). After that, they give a saliva sample (T2, +12 min) and complete the psychological questionnaire. Subsequently, each participant has to perform the arithmetic task 3 times for 30 seconds. When this task is finished, they give another saliva sample (T3, +20 min). During this whole procedure, the participants are recorded with a microphone and a camera. The experimenter then leads the participants individually from the TSST-G test room to the respective preparation rooms. Here, they again fill in the psychological questionnaire.

Rest Phase

During the rest period, 3 additional saliva samples are collected (T4, +30 min; T5, +45 min; T6, +65 min). Participants who have received social support will complete a social support scale at T6 (+65 min) (Multimedia Appendix 8).

Debriefing

Finally, the experimenter leads all subjects to the TSST-G testing room and provides a debriefing about the aim of the study (Multimedia Appendix 9). Questions are answered as needed. The participants receive their payment and are dismissed.

Manipulation Check of Social Support

To check whether social support was received as such by the participants, a modified version of the received support subscale of the Berlin Social Support Scale [63] will be used (Multimedia Appendix 8; T6, +65 min). Item wording is adapted to the study context. Two items from the original scale are deleted because they refer to instrumental support, and the social support in this study rather refers to emotional and informal social support. The item "This student assistant was there for me when I needed her" is also counted as instrumental support according to Schulz and Schwarzer [63], but it can also be understood as emotional support and therefore remains included. Items are rated on a 4-point Likert scale ranging from 1 (not true) to 4 (exactly true). The original version of the received support scale has good internal consistency (α=.83). In addition, participants will be asked directly whether they received support from the student assistant and whether they found this support helpful.

Test Battery of Psychological Questionnaires

Participants are asked to complete the psychological questionnaire a total of 7 times (Figure 1).

Well-being will be captured via 6 items (short version A) from the Multidimensional Well-Being Questionnaire (MDBF) [64]. The items start with "Right now I feel…" and will be continued with 1 of the following adjectives: good, bad, alertness, fatigue, relaxed, and restlessness. The participants will be able to rate them on a 5-level scale labelled from *not at all* to *very*. A slightly modified version of the trait anxiety scale of the State-Trait Anxiety Inventory [65] will be used to assess the momentary anxiety of the participants. A total of 6 adapted items are included, which can be answered on a 5-point scale, as follows: "How big do you think your fear is at the moment?", "How much do you feel physically uncomfortable right now?", "How strong is your need to leave the situation?", "How tense is your feeling right now?", "How much are you in control of the situation?", and "How stressed do you feel?". To our knowledge, no standardized motive-specific affect questionnaire exists so far. We therefore created an adjective list that is theoretically derived from early work by McClelland [19] and added adjectives that have been used in more recent research [66] (see the self-determination theory [67]). Participants indicated for 7 items how they feel right now by using a 7-point response scale (1, *not at all* to 7, *very much*). The items are "socially related," "calm" (affiliation motive–specific affect; the item "relaxed" from the MDBF will also be used in the analysis for the affiliation motive), "strong," "excited," and "enthusiastic" (power motive), with "competent" and "self-determined" as additional items representing achievement and autonomy motive–specific affect, respectively (Multimedia Appendix 10). Construct validity of this motive-specific affect scale will be checked.

Social Motives

Implicit social motives are measured using the PSE [60], which is the most frequently used measure to assess implicit motives. Key validity criteria are met, interrater reliability is good, and retest reliability is satisfactory [34,60]. For further discussion, refer to a previous report [21]. The PSE will be part of the online questionnaire prior to the laboratory session (for validity of the computer version of the PSE) [68]. Participants will be instructed that they will see 6 different pictures, and for each of them, they should write a fictional story with a beginning, middle, and end. The pictures will be presented for 15 seconds, and then, a text box will appear, where they can type their story. Questions that help participants to organize their stories will be presented above the pictures (eg, "What is happening right now?" and "Who are the characters?"). For each story, the participants will have 4 minutes. After 3 minutes 30 seconds, a small reminder will appear asking them to finish the story. After the 4 minutes have elapsed, the next picture will appear. The 6 pictures "couple by the river," "nightclub scene," "sorrow," "beachcombers," "NewPic32," and "NewPic9" will be presented (Multimedia Appendix 1). As recommended previously [60], 2 experienced coders will score the stories for the power and affiliation motives according to Winter's scoring manual [69] (interrater reliability [intraclass correlation coefficient] is expected to be between 0.80 and 0.90). Disagreements between coders will be resolved by discussion [60]. Motive scores will be corrected by word count. For further details about test administration and scoring procedure, see a previous report [60].

All participants will complete a short German version of the Bem Sex Role Inventory to screen for GRSC [61].

Endocrine Measurements

Saliva samples will be collected for the recording of cortisol, α-amylase, and reproductive hormones. Approximately 10 mL of saliva will be dispensed through a straw into Salicaps (IBL International) (Multimedia Appendix 11). After the study, all saliva samples will be frozen and stored at −20°C. Hormone and enzyme levels will be analyzed at the stress biomarkers laboratory at the Institute of Medical Psychology, Heidelberg University Hospital.

Salivary Cortisol

The concentration of cortisol in saliva will be recorded in ng/mL. Seven saliva samples will be collected using Salicaps (IBL International) at measurement time points T0 (−11 min before the TSST-G), T1 (TSST-G onset), T2 (after the job interview), T3 (after the arithmetic task), and T4, T5, and T6 during the resting phase (+30 min, +45 min, and +65 min, respectively, after TSST-G onset). Cortisol will be determined with the Cortisol free in Saliva ELISA assay from Demeditec.

Salivary α-Amylase

We will record α-amylase in U/mL. The concentration is derived from the same 7 salvia samples as used for the cortisol analysis and will be determined by a kinetic colorimetric test. The reagents for this will be obtained from DiaSys Diagnosic Systems.

Reproductive Hormones

Reproductive hormones (testosterone, estradiol, and progesterone) will be recorded in pg/mL. Four saliva samples will be collected using Salicaps (IBL International) at the measurement time points T0 (−11 min before the TSST-G), T1 (TSST-G onset), T3 (after the arithmetic task), and T6 during rest (+65 min after TSST-G onset). Hormone concentrations will be determined by biochemical analysis in the laboratory. The following kits from IBL will be used for analysis: Testosterone Luminescence Immunoassay, 17 beta-Estradiol Saliva Luminescence Immunoassay, and Progesterone Luminescence Immunoassay.

Autonomic Nervous System

Heart rate and heart rate variability will be measured with a Polar H10 sensor (Polar Electro UK Ltd). The sensor is placed in a pulse belt that the participants will wear around their chest. With the help of a Polar station and an iPad, the participants' data are transmitted wirelessly and in real time.

Speech Performance

The participants will be videotaped while they complete the tasks (interview and arithmetic task) in front of the panel. The video sequences showing the recording of the interview will be coded for speech performance using a self-developed coding system. This system includes the following 3 quality criteria: the information content, the presentation style, and the perceived competence of the participants. The assessment of the information content is based on a checklist for the evaluation of a presentation according to Ascheron [70]. The content is scored on the following 5 items: "structure/organization," "comprehensibility of content," "flow," "information content," and "message." These items will be rated on a scale that ranges from 1 (*very good*) to 6 (*unsatisfactory*). A modified questionnaire of Ascheron [70] will be used to evaluate the presentation style. The 2 items intonation and English quality were left out because intonation overlaps with another item (emphasis) and English quality is irrelevant because the study will be conducted in German. The presentation style is rated on the basis of the following 5 items: "speed," "intelligibility," "emphasis," "body language," and "eye contact," whereby we added the latter item to complement the construct in more detail. The items will be scored using a 6-point scale (1, *very good* to 6, *unsatisfactory*). Since there is no suitable measurement tool for the assessment of perceived competence in the literature, we determined 5 items that should enable a differentiated evaluation of this construct. The following items will be scored on a 6-point scale: "technical language/vocabulary," "use of filler words," "use of everyday language," "interest," and "persuasiveness." Construct validity of this competence scale will be checked.

Data Management

The questionnaire data will be downloaded from Limesurvey and stored on the university server. The psychological questionnaire from T2, which will be collected by paper and pencil format, as well as heart rate and heart rate variability will be stored in an Excel table by the study experimenter directly after the study. The video file will also be saved directly after the experiment, on a laptop of the sport psychology laboratory and a back-up server. The saliva samples will be sent to the biochemical laboratory of the Institute for Medical Psychology in Heidelberg, Germany. To guarantee the accuracy of the analyses, 10% of the cortisol samples and 20% of the samples for reproductive hormones will be double assessed. The signed consent forms of the participants will be collected in the sport psychology laboratory in Constance. Only the experimenter will have access to the data, which will be stored for 10 years on a server of the University.

The participants will generate their own code that allows to merge the data of the web surveys with the data obtained in the laboratory.

Saliva samples will be stored in the biochemical laboratory at Heidelberg University Hospital for at least 2 years after completion of the study and will then be discarded.

Statistical Analysis

Statistical analysis will be performed using IBM SPSS Statistics, Version 28 (IBM Corp) for Windows (statistical analysis and graphs). We will perform an analysis of variance with repeated measures to determine if the TSST procedure results in significant increases in psychological and biological variables for all participants. We will calculate multiple linear regressions to examine interaction effects. In these regressions, we will first include the control variables, then the condition as a dummy variable, and finally the individual predictors and their interaction terms. To account for repeated measurements of the collected hormones, the area under the curve with respect to increase will be calculated and used as a dependent variable [71]. As an additional effort to ensure that participants with a delayed significant increase in their hormones will not be excluded, an adjusted increase value will be calculated, regardless of the time of measurement. This value will be obtained by subtracting the baseline value from the peak value. Multiple regressions will be calculated again with these adjusted values. Nonbiological dependent variables, such as those obtained from the psychological test battery, will be added as means. Only data from individuals who have fully completed the TSST protocol will be included in the final analyses. Missing data will be added by multiple imputation.

Explorative Statistical Analysis

There are exploratory analyses planned on the association of self-reported GRSCs with social motives and their moderating role in psychobiological responses to social support. No further subgroup analyses are planned.

Monitoring

Data Monitoring

In addition to the 2 principal investigators, who are in constant communication about data, no other data monitoring committee is required.

Description of Interim Analysis and Stopping Guidelines

No interim analysis or guidelines for study termination are provided. Data collection will cease when the target sample size is reached.

Harms

No adverse side effects have been reported with the TSST protocol. The experimenters will collect spontaneously reported adverse events and ask participants at the end of the experiment explicitly whether adverse events or unintended effects occurred.

Results

The Ethics Committee of the University of Constance approved the application to conduct the study on December 18, 2018. The start of the experiment was planned for the beginning of 2019 but was postponed to June 2021 due to COVID-19. The protocol version is dated May 22, 2022. Data collection will take place until the end of 2022. Publication of the initial results is planned for spring 2023.

Discussion

The aim of this study is to investigate whether social motives and participants' sex moderate the effect of social support in stressful situations. We expect that participants with a strong affiliation motive will benefit from social support in terms of reduced psychobiological stress responses when being critically evaluated by others. For those participants, social support is supposed to serve as a stress buffer. In contrast, social support is expected to act as a stress amplifier in participants with a high-power motive, resulting in higher psychobiological stress responses.

To elucidate the influence of implicit social motives on affect in specific situations, we will record participants' motive-specific affect. We postulate that participants with a high affiliation motive, will respond to social support with affiliation and an increase in progesterone. Participants with a high power motive will show feelings of inferiority and a decrease in testosterone or estradiol.

To explore the influence of implicit motives without bias, we also consider sex as a variable in our study. It is hypothesized that males exhibit a higher power motive and females exhibit a higher affiliation motive. This is expected to be reflected in motive-specific hormones.

Some studies have shown that social support has positive effects [72], while others have reported no, small, or adverse effects of social support [73,74]. With the introduction of implicit motives as moderator variables, as well as taking sex into account, we strive to explain why people react differently in same situations. Through this person-situation approach, we enable a more differentiated view on the effect of social support in stress situations. In summary, with this sophisticated view, we aim to provide a foundation that interventions could be designed in an individualized way and therefore only produce positive effects and no adverse effects.

A broad investigation with induced stress, standardized social support, and the assessment of implicit motives has not been performed in any study known to us. Furthermore, we will cover a large spectrum of methods with our planned study. In addition to self-reports (psychological test battery) and ratings by third parties (ratings of speech performance), we will additionally assess a variety of physiological parameters (hormones, heart rate, and heart rate variability). Therefore, this study lays a comprehensive foundation for further gainful research.

The lack of a control group receiving no stress induction (placebo TSST) could be considered a limitation of the study. However, since the TSST is an established procedure that reliably elicits stress, we believe that a control group can be avoided for pragmatic reasons [51]. In addition, the participants, as well as the research team, will wear FFP2 masks throughout the experiment owing to COVID-19. The effect of mask wearing on the TSST is difficult to assess and will need to be observed.

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Data Availability

The study protocol has been preregistered (Open Science Framework preregistration: registration DOI 10.17605/OSF.IO/984RW) [75]. Data and statistical codes will be published on Open Science Framework as they become available.

The data will still be accessible after publication by choosing publishing houses that support an open data policy. Furthermore, we will inform researchers about the openness of our data (eg, state repositories in publications and aim to publish in journals that use badges for open data) and explicitly invite members of our specific scientific disciplines to reuse the data (ie, in collaborations, at conferences, in talks, and for poster presentations).

Authors' Contributions

JS and BD are the principal investigators. They designed the study, and supervised the proposal and protocol development. AH contributed to the study design and wrote the first draft of the proposal. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Editorial Notice

This randomized study was only retrospectively registered, explained by authors as being related to uncertainty resulting from pandemic-related regulations about whether, when, and under what circumstances data collection could take place. The editor granted an exception from ICMJE rules mandating prospective registration of randomized trials, because the manuscript is a protocol for which recruitment has not yet begun. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness that may result, as retrospective registration does not prevent authors from changing their outcome measures retrospectively.

Multimedia Appendix 1
Screening online survey.
[DOCX File , 839 KB - resprot_v11i8e39509_app1.docx]

Multimedia Appendix 2
Study information sheet for the laboratory session.
[DOCX File , 24 KB - resprot_v11i8e39509_app2.docx]

Multimedia Appendix 3
Study protocol.
[DOCX File , 55 KB - resprot_v11i8e39509_app3.docx]

Multimedia Appendix 4
Daily screening questionnaire.
[DOCX File , 27 KB - resprot_v11i8e39509_app4.docx]

Multimedia Appendix 5
Instructions for participants.
[DOCX File , 15 KB - resprot_v11i8e39509_app5.docx]

Multimedia Appendix 6
Social support instructions for the associate.
[DOCX File , 20 KB - resprot_v11i8e39509_app6.docx]

Multimedia Appendix 7
Procedure for the panel.
[DOCX File , 37 KB - resprot_v11i8e39509_app7.docx]

Multimedia Appendix 8
Manipulation check for social support.
[DOCX File , 16 KB - resprot_v11i8e39509_app8.docx]

Multimedia Appendix 9
Debriefing form.
[DOCX File , 15 KB - resprot_v11i8e39509_app9.docx]

Multimedia Appendix 10
Test battery of psychological questionnaires.
[DOCX File , 48 KB - resprot_v11i8e39509_app10.docx]

Multimedia Appendix 11
Instructions for the collection and processing of saliva samples.
[DOCX File , 154 KB - resprot_v11i8e39509_app11.docx]

Multimedia Appendix 12

Peer-review report by the Deutsche Forschungsgemeinschaft (German Research Foundation).
[PDF File (Adobe PDF File), 476 KB - resprot_v11i8e39509_app12.pdf]

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Abbreviations

GRSC: Gender Role Self-Concept
MDBF: Multidimensional Well-Being Questionnaire
PSE: Picture Story Exercise
TSST: Trier Social Stress Test

TSST-G: Trier Social Stress Test for Groups

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Protocol

A Web-Based Intervention to Improve Health Literacy and Obesogenic Behaviors Among Adolescents: Protocol of a Randomized Pilot Feasibility Study for a Parallel Randomized Controlled Trial

Sasha A Fleary[1], PhD

Department of Community Health and Social Sciences, Graduate School of Public Health and Health Policy, City University of New York, New York, NY, United States

Corresponding Author:
Sasha A Fleary, PhD
Department of Community Health and Social Sciences
Graduate School of Public Health and Health Policy
City University of New York
55 W 125th St
New York, NY, 10027
United States
Phone: 1 6463640282
Email: sasha.fleary@sph.cuny.edu

Abstract

Background: Predictive theoretical models suggest that health knowledge works in conjunction with motivation and behavioral skills to influence adolescents' obesogenic behavior. However, most of the existing adolescent interventions target these variables in isolation. Furthermore, health literacy (HL), a precursor to health knowledge, is necessary for translating health knowledge into behavior and is negatively related to adolescents' obesity status. However, HL has not been included in obesity interventions targeting adolescents.

Objective: This study aims to pilot the feasibility of a 2-armed web-based obesity prevention intervention in school settings and assess the preliminary effectiveness of adding an HL module to an obesity prevention intervention for adolescents.

Methods: This web-based pilot feasibility study will take place in the Northeastern United States. Participants will be adolescents (aged 13-16 years) attending school, and recruitment will be conducted through flyers to parents and adolescents in participating classes or advisory groups at the school. The intervention includes 2 arms: an experimental arm that will receive an HL module and 3 obesity prevention modules and a comparison arm that will receive a vaping module and 3 obesity prevention modules. A blinded randomized procedure will be used to allocate classrooms and advisory groups to the experimental and comparison arms. The intervention will be fully web-based. Participants will complete measures of their HL and obesogenic behavior–related health knowledge, motivation, and behaviors at 3 time points (baseline, 1 month after the intervention, and 3 months after the intervention) via web-based surveys. The primary outcomes will be the measures of study feasibility (recruitment, retention, completion, and treatment fidelity rates). Secondary outcomes will be preliminary efficacy, as measured by logistic and linear regressions and calculation of effect sizes. Descriptive statistics will be calculated for all measures at each time point.

Results: This study was approved by the City University of New York Institutional Review Board in August 2020. As of June 2022, the web-based intervention design is complete and ready for use. Recruitment, data collection, and intervention implementation are scheduled to begin in September 2022. These results are expected to be published in 2023.

Conclusions: This study's feasibility findings will inform changes to the intervention content and randomized controlled trial design. The study's efficacy findings will inform the sample size for the full-scale randomized controlled trial and the preliminary utility of the intervention.

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KEYWORDS

health literacy; adolescent; obesity; prevention; diet; physical activity; web-based intervention; eHealth

Introduction

Background

Children and adolescents are increasingly experiencing obesity-related *chronic degenerative diseases*, which were once categorized as adult health problems [1]. For example, in the United States, there was a 30.5% increase in type 2 diabetes diagnoses in adolescents from 2001 to 2009 [2], and more recent data suggest a 7.1% annual increase in diagnoses [3]. A diagnosis of type 2 diabetes in childhood is related to the risk of kidney, nerve, and eye diseases and an increased risk of renal failure and other life-threatening and life-altering complications in young adulthood [4]. Similar to type 2 diabetes, other life-threatening adult chronic health issues such as cancer and heart disease are associated with obesity [5-7] and adolescent health behaviors [8]. Approximately 34% of adolescents in the United States are overweight or obese [9,10]. Furthermore, adolescents' obesity prevention health behaviors are low: approximately 42% and 41% eat <1 fruit and vegetable daily, respectively, and approximately 77% are physically active for <60 minutes per day [11]. The prevalence rates of fruit and vegetable consumption and sufficient physical activity (PA) are lower among adolescents with low family income [12] and those who identify as racial and ethnic minorities [13]. The prevalence rates of these behaviors must be improved to reduce current and future chronic disease risks in adolescents.

There are several obesity prevention interventions targeting determinants of obesogenic behaviors, including adolescents' social support and motivation [14-18], behavioral skills [15-18], attitudes [16,18], environment [15,19,20], and health knowledge [15,16]. However, their impacts on adolescents' obesogenic behaviors have been mixed. Furthermore, most of these interventions did not address all the aforementioned determinants in a single study design. Single determinant–focused interventions likely underestimate the role of individual-context interrelationships, the interrelatedness of the determinants, and the role of adolescent developmental attributes in health decision-making. Importantly, individuals' decision-making is complex as multiple determinants of health behaviors are either deliberately or unintentionally integrated during the decision-making process. Therefore, although adolescents may prefer or *lean in* on certain types of information and determinants, interventions targeting adolescents' obesity prevention behaviors should integrate multiple determinants, including knowledge and skills, and incorporate the impact of developmental characteristics and contextual influences on long-term change.

This intervention borrows elements from 3 existing interventions that address multiple determinants in a single design: New Moves [17,21], Go Girls! [16], and the Dutch Obesity Intervention in Teenagers (DOiT) [15]. The school-based New Moves intervention aimed to improve adolescents' diet- and PA-related knowledge, attitudes, beliefs, skills, and self-efficacy, as well as provide strategies for improving social support [17,21]. The community-based Go Girls! intervention aimed to improve knowledge, self-efficacy, social support, motivation, and behavioral skills for healthy eating and PA [16]. The school-based DOiT intervention aimed to increase adolescents' knowledge, awareness, behavioral skills, social support, habits, and self-efficacy regarding energy intake and output [15,22]. All 3 studies reported significant postintervention improvements in obesogenic-related behaviors.

These studies included activities that could be adapted for a web-based platform and provided a strong basis for our intervention. However, similar to other adolescent obesity prevention interventions, the New Moves, Go Girls!, and DOiT interventions do not include building adolescents' general skills for transferring knowledge into behavior (ie, health literacy [HL]). HL "entails people's knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and make decisions in everyday life concerning health care, disease prevention and health promotion to maintain or improve quality of life during the life course" [23]. In adults, HL is positively related to engagement in preventive health behaviors, the interpretation of health messages, and medical adherence [24-28]. Although HL is understudied in adolescents, existing research links HL to adolescents' health behaviors [29] and health decision-making [30,31]. We hypothesize that the inclusion of correlates of health decision-making in health behavior interventions during a critical transitional time to health decision-making independence for adolescents may significantly improve intervention outcomes. To the best of our knowledge, the direct impact of HL on adolescent health behavior change interventions has not yet been examined.

Objectives

The findings of this pilot study and future full-scale randomized controlled trial (RCT) will inform the inclusion of HL in health behavior interventions for adolescents and the inclusion of HL in the health education curriculum for adolescents. Furthermore, given its digital format, this intervention may easily be disseminated in schools as part of the adolescents' health curriculum. The main goal of this study is to develop and preliminarily evaluate a web-based obesity prevention intervention for adolescents with and without HL. This study distinguishes between HL and health knowledge; these 2 concepts tend to be inaccurately substituted in some research literature. However, HL is a precursor to health knowledge [32]; that is, HL is the skill needed to access, understand, and use health information for specific behaviors. Despite this, HL is understudied and rarely addressed in health behavior interventions. This study seeks to fill this gap. Aim 1 of this study is to modify and use successful components of existing obesity interventions in an interactive web-based platform with an added-on HL component. Aim 2 of this study is a 2-arm randomized clinical trial of the adapted web-based obesity prevention intervention for adolescents with and without an HL component. The purpose of this pilot RCT is to determine the feasibility and preliminary effectiveness of the intervention in

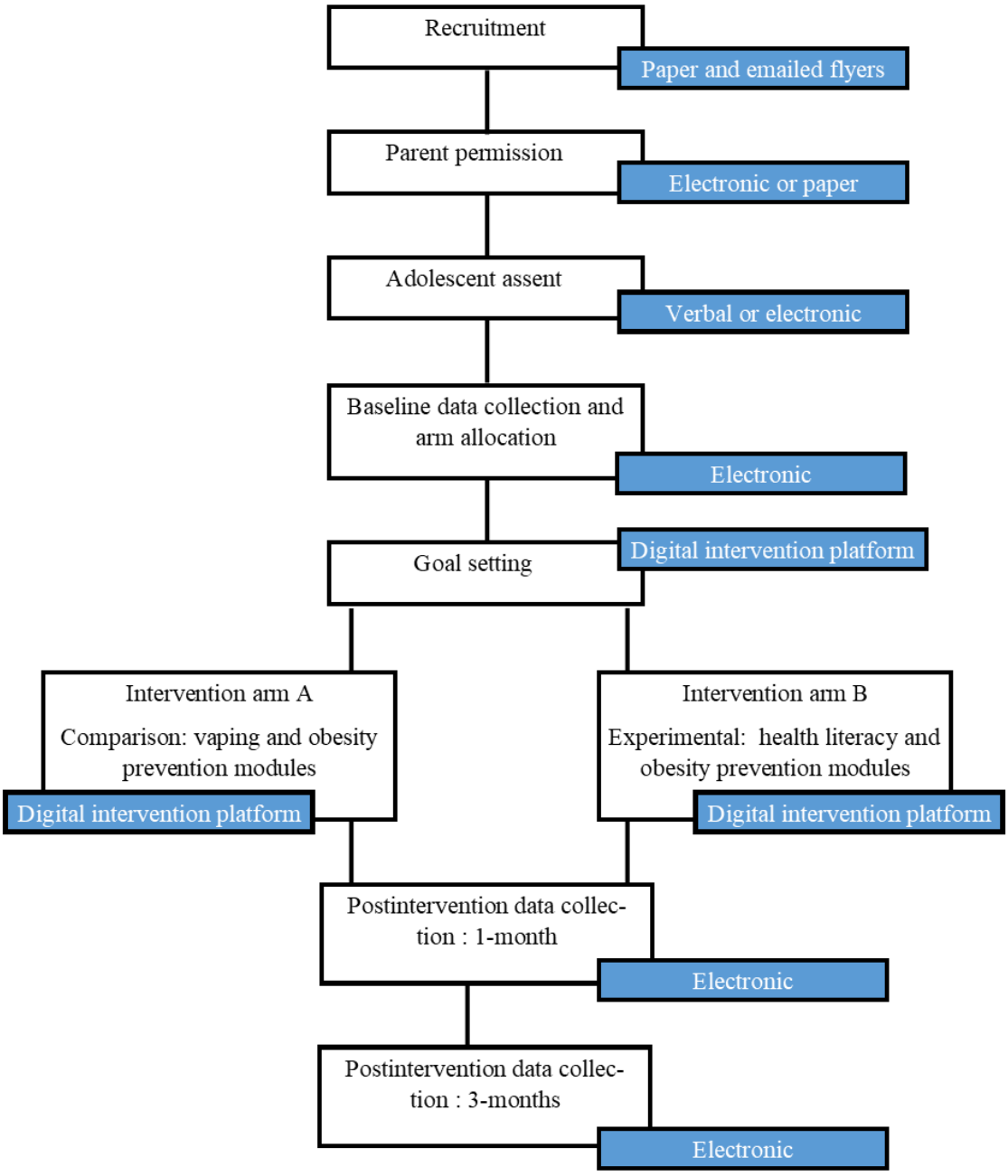
informing the full-scale RCT. Specifically, the primary objectives of this study are to (1) assess the acceptability of the intervention for adolescents; (2) determine the elements of the intervention with the highest adolescent engagement; and (3) determine the suitability and appropriateness of the intervention modality and implementation in school settings by examining the recruitment, retention, completion, and fidelity rates. The secondary objectives of this study are to measure the preliminary efficacy of the intervention to improve obesogenic behaviors and HL and collect data to calculate effect sizes and power analyses to inform the sample size needed for the full-scale RCT to determine whether adding an HL component to a web-based obesity prevention intervention improves adolescents' obesity prevention behaviors more than an obesity prevention intervention alone.

Methods

Trial Design

The trial design elements are reported to be consistent with the CONSORT (Consolidated Standards for Reporting Trials) guidance for pilot and feasibility studies (Multimedia Appendix 1) [33] and the CONSORT-EHEALTH (Consolidated Standards for Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth; Multimedia Appendix 2) [34]. This study is a parallel randomized controlled pilot trial and feasibility study with 1:1 classroom allocation to 2 study arms (experimental and comparison groups). Figure 1 shows the outline of the study flow.

Figure 1. Study procedures flowchart.



Participants

A total of 76 adolescents aged between 13 and 16 years attending high school in Boston, Massachusetts, United States, will be recruited for the study. The other inclusion criterion is parental permission to participate. Adolescents who are already participating in interventions related to healthy eating, PA, and obesity prevention or treatment or who have medical conditions that prevent them from engaging in PA or require adherence to extremely restricted diets (eg, ketogenic diet) will be excluded from the study. The proposed sample distribution for the study is at least 30 male and 30 female adolescents so that comparisons can be made across sexes, given the difference in obesogenic behaviors based on sex. In addition, 80% of the sample is expected to come from racial and ethnic minority groups, given that the study will be conducted in a multiethnic geographic location and school setting.

Recruitment and Consent

Responsive survey design methodology [35] will be used to ensure that the proposed sample is recruited. Specifically, we will monitor participant enrollment and establish timelines for changing or adding recruitment strategies to ensure that the proposed sample is recruited. In responsive survey design methodology, the least costly recruitment strategy is used first, and more expensive and time-consuming strategies are used to augment the inexpensive strategies to enroll hard-to-recruit participants. For the first phase of recruitment, school administrators will give study flyers to students and email them to parents of students in participating classes. The emailed flyers will include a Qualtrics link (Qualtrics) for parents to access the web-based parent permission form and a brief demographic survey. Parents will select *yes* or *no* to indicate whether they agree for their adolescent to participate in the study. The class or advisory group with the highest rate of returned parent forms (regardless of whether permission was granted or denied) will receive a class prize (eg, donation to the class field trip fund) at the end of the first 2 weeks of the recruitment period. The characteristics of the enrolled participants will be monitored to determine progress in recruiting the desired sample with regard to sex and racial and ethnic minority status. At the 2-week time point during phase 1 recruitment, the second phase of recruitment will be initiated in an attempt to achieve the desired sample. In phase 2, adolescents whose parents did not complete the permission form on the web will be given a study flyer with a QR code for parents to access the Qualtrics link. A paper permission form, demographic survey, and an empty envelope will also be attached to the flyer. Parents who complete the paper permission form will be asked to put it in the envelope, seal the envelope, and have their adolescents return the envelope to their teacher. At each phase of recruitment, teachers will also make announcements about the study in class, encouraging students to have their parents complete the permission forms. Recruitment will end 2 weeks after the initiation of phase 2 recruitment. The class with the highest increase in returned consent forms at the end of the second phase of recruitment will be incentivized with a class prize (eg, donations to their class trip and dance). The phase 1 recruitment strategy will be ongoing throughout the 4 weeks of recruitment as parents will be sent weekly reminder emails to complete the permission form and demographic survey. These procedures are consistent with several national studies (eg, the National Survey of Family Growth [36,37] and the National Survey of College Graduates [38]). Active monitoring of participant enrollment will occur throughout the 4 weeks of study recruitment and enrollment. To ensure that participation is voluntary and not coerced, incentives will be attached to the return of consent forms rather than study enrollment. All recruitment and consent materials will be available in English, Spanish, and Haitian Creole to accommodate Haitian Creole–speaking and Spanish-speaking parents with limited English language proficiency. Adolescent assent will be obtained on the web before data collection on the first page of the web-based survey. Adolescents who select *no* to assent will be exited out of the survey, and those who select *yes* will be able to see the survey. It should be noted that parental permission and adolescent assent are specific to the data collection related to the study. Adolescents who do not assent or obtain parental permission will still be required by their teachers to participate in the intervention as part of their class curriculum but will not complete surveys.

Intervention

Both study arms will receive 3 obesity prevention modules. However, the first study arm (ie, the comparison group) will also receive 1 module on vaping, whereas the second study arm (ie, the experimental group) will receive a module on HL. Obesity prevention modules will be administered after the vaping and HL modules. The intervention modules will be delivered using a web-based platform. The platform allows for a mix of didactic strategies, including informational videos, interactive practice activities and games, and self-assessments. Responses to assessments, activities, and games will be used to provide tailored feedback and reports. The intervention will be fully web based. Table 1 presents the objectives of the intervention modules, lesson objectives, and sample activities. It should be noted that all content was developed by the author and her team, and the content is hosted using the Dynamic e-Learning Platform, a web-based platform developed by the 3C Institute [39], which uses a mix of didactic instructions with self-assessments, demonstration videos, and interactive practice activities to apply learned skills.

Table 1. Intervention module and lesson objectives and sample activities[a].

Modules or lessons	Objectives	Activities
Introduction	N/A[b]	N/A
Goal planning	To guide adolescents as they make one eating and one physical activity goal that is specific, measurable, attainable, relevant, and time based	• Initial: assessment of adolescents' current dietary intake and physical activities; tailored suggestions for goals are provided based on adolescents' responses; adolescents then pick the goal they want to work on and are guided on making a plan for their goal through a series of how, when, where, and who questions with suggestions for responses • Other: check-in about progress on goals at the end of each module with tailored tips for getting back on track or increasing intensity of their goals based on their responses; tips correspond with the module (eg, tips after the motivation module focus on personal motivation and social support)
Getting the Skills Down module (HL[c]; experimental group only)	To improve adolescents' functional, interactive, critical, and media HL	N/A
Lesson 1: Reading Labels (functional HL)	To demonstrate how to read and use nutrition and medicine labels	• Didactic videos explaining the information on the labels with a focus on reading comprehension and numerical calculations, followed by practice exercises, including labels and scenarios in which adolescents would use labels
Lesson 2: Talking to Other People About Health (interactive HL)	To provide and reinforce skills for gathering health information from others and discussing health concerns with others, including friends, family, and health care providers	• Demonstration videos providing instructions and examples on how to talk to different people about health, followed by activities and scenarios to practice preparing for and navigating health conversations with parents, friends, providers, and other trusted adults
Lesson 3: Choosing Good Sources for Health Information (media HL)	To equip adolescents with skills to evaluate sources of information for reliability, accuracy, and intent and teach adolescents how to use multiple sources of information in health decision-making	• Didactic demonstration videos explaining how to identify and evaluate good sources of health information, followed by activities and scenarios where adolescents identify and evaluate good sources of information
Lesson 4: Using Health Information to Help Yourself and Others (critical HL)	To provide and reinforce skills for applying health information to improve personal and community health, educate adolescents about the role of social determinants of health in health decision-making, and provide suggestions on how to advocate for others	• Demonstration videos with illustrated scenarios showing different outcomes to different health decisions and didactic videos on how social determinants of health affect access to health resources and health decision-making and on advocacy; videos followed by activities evaluating the social environment for health, self-reflection to identify skills and passions, and how adolescents may want to use it to change their community
Getting the Truth module (vaping; comparison group only)	To improve adolescents' knowledge of the effects of vaping and provide strategies for preventing and seeking help when vaping is implicated	N/A
Lesson 1: Vaping Devices and Vaping	To explain what vaping is, how vapes work, and the effect of vaping on the body	• Demonstration videos on how vapes work and how it affects the body and people around the vaping person, followed by activities to reinforce knowledge about how vapes work and the consequences of vaping; quizzes to test knowledge about vaping administered before and after lessons
Lesson 2: Beliefs and Attitudes about Nicotine Products	To challenge common beliefs and attitudes about nicotine products and vaping specifically	• Demonstration videos showing the consequences of vaping and debunking common myths about vaping, followed by reflection questions about adolescents' beliefs about vaping and interactive activities where adolescents distinguish beliefs that may be myths vs facts

Modules or lessons	Objectives	Activities
Lesson 3: Refusing and Avoiding Vaping	To suggest strategies for refusing offers to vape and avoiding situations where friends vape	• Didactic videos demonstrating tips for refusing to vape and avoiding vaping, followed by activities and scenarios to practice conversations with friends to handle situations where vapes are present
Lesson 4: Recognizing Addiction and Getting Help	To provide tips on how to recognize when oneself or a peer is addicted to vaping and how to get help	• Didactic videos describing why and when some adolescents would want to receive help and where to receive help, followed by activities and scenarios where adolescents make decisions about receiving help
Getting the Facts Straight module	To improve adolescents' health knowledge about obesity prevention, healthy eating, physical activity, and sedentary behavior	N/A
Lesson 1: The Facts about Healthy Eating	To improve and reinforce adolescents' knowledge about what is required in a healthy diet and how to distinguish between healthy and unhealthy foods	• Didactic videos explaining healthy and unhealthy diets, followed by activities and scenarios around identifying and making healthy and unhealthy diet choices
Lesson 2: The Facts about Physical Activity	To inform adolescents about the recommendations for different types of physical activity and what is considered physical activity	• Didactic videos about the types of physical activity and the FITT[d] principle recommendations, followed by scenarios to practice different aspects of the FITT principles and guided exercises to help adolescents make a FITT plan for themselves
Lesson 3: Eating, Exercise, and Mood	To help adolescents recognize the connections between their eating, physical activity, and mood and provide proactive strategies to ensure that mood is not negatively affected by poor eating and activity choices	• Didactic videos describing the relationship between eating, physical activity, and stress, followed by activities on the effect of skipping meals and physical activity on mood and scenarios involving decision-making around scheduling meals and activities to avoid negative effects on mood
Getting the Mind Ready module	To improve adolescents' personal and social motivations for engaging in obesity prevention behaviors	N/A
Lesson 1: What Motivates You?	To encourage adolescents to think about what may motivate them to engage in healthy eating and physical activity and provide opportunities for self-reflection on what motivates adolescents	• Didactic videos describing motivation and providing examples of what motivates different adolescents and tips for getting motivated, followed by self-reflection activities and scenarios with adolescents needing the motivation to engage in healthy eating or physical activity
Lesson 2: Social Support	To describe how people in adolescents' lives can support their health goals and provide strategies for identifying and using sources of social support	• Didactic videos describing the types of social support and how adolescents may use these support to achieve their health goals, followed by reflection questions on the types of support adolescents already have and want and scenarios where adolescents practice navigating social support
Lesson 3: You Can Do This!	To provide adolescents with practical strategies for staying motivated	• Demonstration videos on setting small goals, finding goal partners, and self-efficacy, followed by scenarios to help characters set SMART[e] goals and identify goal partners and reflection questions to help participants identify their goal partner's needs and options
Get Going module	To address socioeconomic (and other) barriers to preventive health by reinforcing doable behavioral skills within the socioeconomic constraints experienced by adolescents	N/A

Modules or lessons	Objectives	Activities
Lesson 1: Setting Yourself Up to Make Healthy Choices	To provide adolescents with skills for making healthy eating and physical activity choices from the options available to them	• Demonstration videos demonstrating meal planning, grocery shopping, and identifying and using physical activity when one has limited resources, followed by activities to identify physical activity opportunities in different situations and settings and scenarios for healthy eating where adolescents have limited resources
Lesson 2: Using the 3 Rs to Make Healthy Choices	To explain how adolescents may use the 3 Rs (replace, reduce, and remove) when making decisions about healthy eating and physical activity	• Demonstration videos showing the 3 Rs in practice and providing tips for using the 3 Rs, followed by activities and scenarios to practice using the 3 Rs
Lesson 3: Practice Making Healthy Choices	To practice knowledge and skills learned throughout the 3 obesity modules in the intervention	• A game where the participant chooses an avatar (adolescent) and helps the avatar make healthy decisions from the time they wake up to the time they go to sleep; tailored feedback is provided after each decision

[a]Tailored feedback was provided based on adolescents' responses to the activities and questions throughout the intervention.

[b]N/A: not applicable.

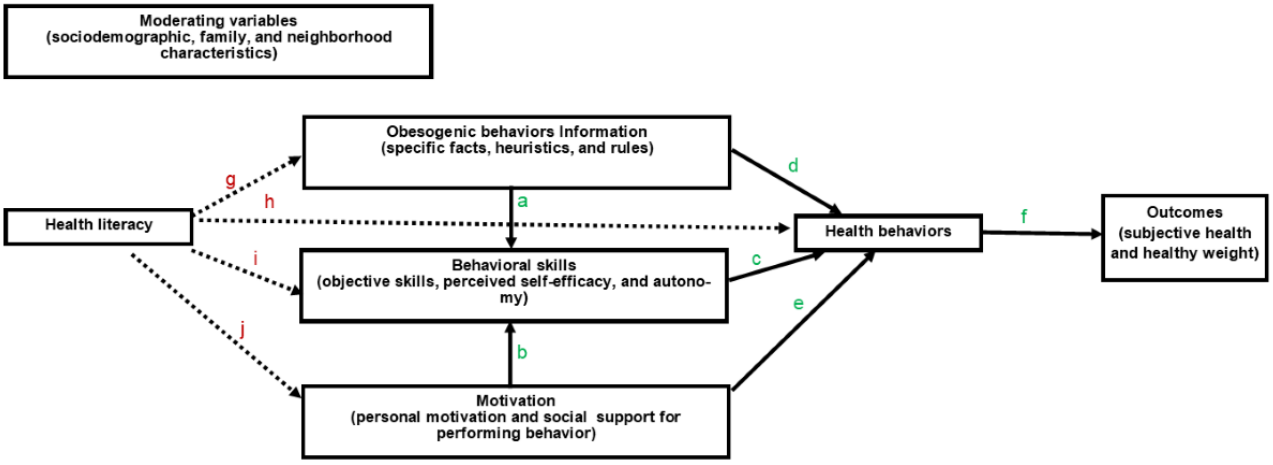
[c]HL: health literacy.

[d]FITT: frequency, intensity, type, and time.

[e]SMART: Specific, Measurable, Achievable, Relevant, and Time-bound.

This intervention is informed by the relational developmental systems framework, the Information-Motivation-Behavioral Skills (IMB) model, adolescents' inputs, and prior studies. The relational developmental systems framework, which is a developmental science framework, centers on the mutually influential relationships between individuals and contexts, as well as the plasticity of the relationships as the individual or context changes [40]. Research that applies a relational developmental systems framework seeks to answer *what important characteristics of individuals (eg, motivation, autonomy, health identity, health knowledge, and HL), among individuals of what status (eg, adolescents and low income), and in relation to what elements of the context (eg, family, peers, and neighborhood) are likely to be associated with what aspects of adaptive functioning (eg, healthy eating and PA)*. As such, this intervention is designed to account for and intervene in the mutually influential relationship of adolescents' individual and developmental characteristics, social determinants of health, health knowledge, and HL on health behaviors. The relational developmental systems framework is complementary to the more predictive IMB model [41]. The IMB model includes 3 critical determinants of the performance of health behaviors: health-related information (facts and beliefs), motivation (personal attitudes and social support), and behavioral skills (objective skills and confidence in performing the behavior). Information and motivation support behavioral skills that influence behavior (Figure 2, arrows *a*-*c*). However, information and motivation may directly affect behavior when only basic skills are required (Figure 2, arrows *d*-*e*). Health behaviors ultimately predict health outcomes (Figure 2, arrow *f*).

Figure 2. Information-Motivation-Behavioral Skills theoretical model.



The relational developmental systems framework was used to determine the variables that were explored in the IMB model. Given that the health-related information and behavioral skills constructs in the IMB model are specific to health behavior and that HL is a precursor to health knowledge [32] and likely independently influences motivation, behavioral skills, and

behavior, HL was included as a separate construct in the model (dashed lines in Figure 2). We expect HL to directly predict information, motivation, behavioral skills, and health behaviors (Figure 2, arrows *g-j*) and indirectly predict health behaviors through information (g→d and g→a→c), motivation (j→e and j→b→c), and behavioral skills (i→c). Therefore, improvements are expected in the experimental conditions for all variables in the model compared with the comparison group.

Regarding specific content, initial focus groups with adolescents informed the initial content of the HL modules, whereas prior obesity prevention intervention studies informed the content for the obesity prevention modules. In a preintervention development study by the author, adolescents participated in multiple focus groups where they described how they viewed HL, how they knew they were using HL, and what type of HL skills they felt they lacked [30,31]. Analyses of adolescents' responses resulted in the development of the IMB model for the use of HL in health decision-making in adolescents [30]. The conceptual underpinnings of the IMB model for the use of HL in health decision-making in adolescents and specific focus group findings were used to determine which key features of HL should be included in the intervention and how to present the content in a way that matches the context in which adolescents view themselves as engaging in HL. The obesity prevention modules were informed by the successful components of New Moves [17,21], Go Girls! [16], and DOiT [15].

Regarding acceptability and usability, adolescents participated in cognitive interviews while completing the HL and behavior skills modules. This was done before building out the other modules of the intervention. The feedback provided on the HL and behavior skills modules was used to revise the modules and was applied to the development of the remaining intervention modules.

For this feasibility study, all adolescents in the participating classes or advisory group will access the intervention on school computers during their homeroom or advisory periods. The intervention will be provided in lieu of class activities and will be solely web based. Specifically, teachers will only be involved in instructing adolescents to log into the web-based platform, and all other activities of the intervention will occur via the web-based platform. Adolescents will complete 1 lesson per homeroom or advisory period with 1 to 2 lessons per week, depending on their class schedule. The intervention website includes a *contact us* button so that students can report any concerns or comments. This will be closely monitored by research staff, who will work to resolve issues as quickly as possible.

Outcomes

Primary Feasibility Outcome Measures

According to Bowen et al [38], the assessment of study feasibility involves answering 3 main questions across 8 key areas of focus. Although Bowen et al [38] suggested asking whether it can work, does work, and will work, this feasibility study mostly focused on the first 2 questions (whether it can work and does work). The third question (whether it will work) is better aligned with the activities of a full-scale RCT. Textbox 1 provides a further explanation of the 8 areas of focus, as they relate to this study.

Textbox 1. Feasibility as applied to this study.

Acceptability: satisfaction, suitability, and attractiveness of the intervention

- Can it work?: In the prepilot activities, qualitative feedback on session components was solicited and used to modify the intervention for suitability and attractiveness.
- Does it work?: The pilot intervention will assess recruitment, completion, retention, and treatment fidelity rates as measures of satisfaction, suitability, and attractiveness of intervention.

Demand: likeliness of using the intervention

- Can it work?: In the prepilot activities, adolescents' risk and protective factors for obesogenic behaviors were considered in intervention development to ensure that the skills reinforced in the intervention would be generalizable across settings.
- Does it work?: The longitudinal study design will provide preliminary data on the retention of skills learned in the intervention. Web analytic data collected during the intervention (eg, time spent on modules and resources accessed through intervention) will determine the likeliness of using the intervention.

Implementation: successful delivery

- Can it work?: In the prepilot activities, participants were observed engaging with intervention content, and their comments were used to make content and stylistic changes to improve the utility and likelihood of prolonged engagement with the content.
- Does it work?: A pre-post follow-up design allows for the determination of the 3-month success rate of the intervention in changing obesity-related knowledge, motivation, and behavior. Participants' progress on goals will also be a marker of success.

Practicality: deliver intervention within confines of current resources

- Can it work?: Participants' usability observations and intervention evaluations will be used to assess feasibility, with participants serving as key informants.
- Does it work?: Postmodule evaluations will provide data to inform the next steps to improve the reach and effectiveness of the intervention (eg, need for tangible support such as fitness videos and fresh food boxes). Cost analyses will be conducted.

Expansion: expand to provide new service

- Can it work and does it work?: For future project goals and next steps, a randomized controlled trial with a representative sample powered to detect significant changes should be implemented. Future projects should also expand to include language and other cultural adaptations for specific groups (eg, Mexican, Haitian, and Dominican).

Limited efficacy: potential for success in a controlled environment

- Does it work?: The pilot design allows for assessing the potential for success in a controlled environment and calculation of effect size to develop larger efficacy trials.

Adaptation: implementation in new population

- Can it work and does it work?: For future project goals and next steps, the effectiveness of intervention in other settings (eg, libraries) need to be assessed, and feasibility and effectiveness in different populations after cultural and language modifications need to be evaluated.

Integration: successful integration into existing settings

- Can it work and does it work?: For future project goals and implications, the intervention should be integrated into schools and community organizations, and the sustainability in its current form must be monitored.

Secondary and Preliminary Efficacy Outcome Measures

Participants' demographics (eg, age, sex, gender, family income, race, ethnicity, and grades) and other characteristics (eg, home and neighborhood environment characteristics) will be collected at baseline. Secondary measures will be collected at each time point and will serve as measures of the preliminary efficacy of the intervention. Table 2 outlines the secondary measures used in this study.

Table 2. Secondary preliminary efficacy measures[a].

Measure	Topics assessed	Psychometric properties
Dietary screener questionnaire	Healthy and unhealthy food consumption	Good convergence with 24-hour dietary recalls [42]
National Youth Physical Activity and Nutrition Study	Healthy and unhealthy food consumption	Validity and reliability established [43,44]
Youth activity profile	Physical and sedentary activity	Cross-validated with objective measures of physical activity and resulted in similar group estimates acquired from objective measures [45]
Godin and Shephard Leisure-Time Physical Activity Questionnaire	Metabolic equivalents for leisure time physical activity	Validity and reliability established [46]
Newest vital signs	Functional health literacy	Cronbach α=.76; criterion validity *r*=0.59 [47]
Assessments of adolescent health literacy	Functional, interactive, and critical health literacy	Wright sample-independent reliability ≥0.80; good convergent and criterion validity [48]
Adolescent media health literacy scales	Media health literacy	Wright sample-independent reliability ≥0.80; good convergent and criterion validity [49]
Electronic Health Literacy	Digital health literacy	Cronbach α=.88 [50]
Canadian Assessment of Physical Literacy (modified for the study)	Physical activity knowledge	Validity and reliability established across multiple groups [51]
General Nutrition Questionnaire for Adults (modified for the study)	Healthy eating knowledge	Cronbach α≥.70; good construct validity [52]
Regulation of Eating Behaviors Scale (modified for the study)	Healthy eating attitudes	Cronbach α≥.79; good construct validity [53]
Psychosocial constructs for adolescent fruit and vegetables and dietary fat intake	Social motivation for healthy and unhealthy eating; diet-related self-efficacy	Cronbach α≥.61 [54]
Psychosocial constructs for adolescent physical activity and sedentary behavior	Social motivation for physical and sedentary activity; physical activity self-efficacy	Cronbach α≥.67 [55]

[a]All measures will be administered at baseline, posttest, and 3-month follow-up time points.

Data Collection

Data collection will be completed on the web using the Qualtrics survey platform. After a team member verbally explains the assent form, adolescents will be provided with a link where the first page will include the written assent form. After providing assent, adolescents will be routed to the survey. For the posttest and follow-up measures, adolescents will complete surveys 1 month and 3 months after the completion of the intervention. Similar to the baseline, data collection will be completed on the web using the Qualtrics survey platform.

Adolescents will be randomly selected to complete qualitative interviews at the end of the intervention to gather feedback on usability, acceptability, and suggestions for changes. All data collection will be performed while the adolescents are in school. Data files and other electronic study records will be stored in password-protected folders on a restricted-use server. Identifiable information will be kept separate from survey data; identifiable information will be deleted after the 3-month follow-up data collection is complete, and the data will be linked to the 2 other time points. Paper study materials will be scanned, and the scanned files will be stored in the same way as the electronic data. The paper study materials will be shredded after they are scanned.

Sample Size

The sample size was based on power calculations computed using the preliminary data. Preliminary data suggested that a sample of 60 participants (30 per group) would be sufficient. We plan to enroll and randomize 76 participants to allow a 20% dropout rate at the 3-month follow-up. The sample size is sufficient to calculate feasibility metrics and preliminary efficacy and inform future power calculations for a more complex full-scale RCT.

Randomization and Blinding

Sequence Generation

Classrooms and advisory groups will be randomly assigned to the experimental and comparison groups, with 2 classrooms and advisory groups per condition. Simple randomization will be performed using a random number computer program. Specifically, a blinded research team member who is not involved in providing assent and has no knowledge of the students in the classes and advisory groups will assign each classroom and advisory group a number from 1 to 4, and then, a computerized random number generator will be used to assign the classroom and advisory group to the conditions.

Allocation Concealment Mechanism

Randomization and intervention condition allocation will occur after the assent and baseline measure data collection. This information will be communicated to the teachers so that they

are aware of the content that the adolescents will receive. It is not possible to conceal allocation to adolescents as it will be obvious whether they received the HL or vaping modules.

Blinding

Participants will not be explicitly made aware of whether they are in the experimental or comparison group. However, it is not possible to *blind* them to their condition as the experimental condition is obvious.

Statistical Methods

Data Analysis

Regarding the metrics mentioned in Textbox 1, the recruitment rate will be assessed by calculating the percentage of adolescents enrolled in the study from the pool of adolescents approached for participation. The completion rate will be assessed by calculating the percentage of adolescents who complete the intervention from those who enroll. Retention rates will be assessed by calculating the percentage of participants who complete all elements of the study (intervention and data collection) compared with the number of participants who enroll. Treatment fidelity will be assessed using web analytics data gathered during the intervention. The median time spent on each intervention task will be calculated, and participants who spend <3 median absolute deviations below the median will be assumed to have not engaged with the content enough to be fully exposed to the treatment. Treatment fidelity percentages will be calculated based on users meeting a priori thresholds. On the basis of intervention research in adolescents [56-58], the conservative acceptable targets are as follows: recruitment=50%, completion=70%, retention=50%, and treatment fidelity=80%. Descriptive and content analyses will be conducted for quantitative and qualitative evaluation data, respectively.

Descriptive analyses will be calculated for all variables in Table 2. The 2 study groups will be compared in terms of baseline variables to assess whether a balance was achieved through randomization. Changes in continuous outcome variables from the pretest time point to 3 months will be compared between groups using linear regression, adjusted for sex and any potential confounders that are found to be unbalanced between groups at baseline. Binary outcome variables (outcome improved vs not improved) will be compared between groups using logistic regression, adjusted for sex and any potential confounders that are found to be unbalanced between groups at baseline. For each outcome, we will also analyze the time points together in the same model using linear and logistic mixed-effects models with random subject-specific intercepts and slopes. This will permit the analysis of all participants, including those who drop out. Mixed models can accommodate missingness at random.

Group differences in the change in metabolic equivalents and number of fruits and vegetables, as well as the SDs of the changes in each group, will be used to calculate the sample size for the full-scale RCT.

Power

This study is powered based on fruit and vegetable consumption and PA outcomes. Assuming 30 participants per group, an independent-sample *2*-sided *t* test, within-subject correlation of 0.5, and α=.025, there will be 80% power to detect a difference between groups on the change in the metabolic equivalents (PA) and fruit and vegetable consumption from the pretest time point to the 3-month follow-up of whether the true difference is 0.8 (PA) or 1.2 (fruits and vegetables) SDs or larger (ie, effect size 0.8). These calculations are based on preliminary data [59]. The data used in this study will be used to perform the power calculations.

Ethics Approval and Consent to Participate

All study procedures were approved by the City University of New York Institutional Review Board (2020-0575-PHHP) and will be conducted in accordance with the approved application. Data will only be used from participants with signed parent permission forms and who will assent to participate.

Results

The study has received institutional review board approval. Recruitment for the trial has not yet begun. Data collection is expected to begin in September 2022. The results are expected to be submitted for publication in an updated manuscript in June 2023. Feasibility and primary efficacy results will be reported according to the CONSORT guidelines [33] after the 3-month follow-up data are collected and analyzed.

Discussion

Principal Findings

Interventions to improve adolescents' health behaviors have yielded mixed results, and HL may be a key missing element in improving the efficacy and effectiveness of existing interventions. However, to the best of our knowledge, this is the first intervention study to test the utility of adding HL to health behavior interventions for adolescents. The findings of this study will inform the inclusion of HL as an intervention component, as well as the extent to which the principles of HL and adolescents' HL levels are considered in interventions designed for adolescents. Furthermore, the use of a digital platform (rather than in person) to implement the intervention is novel, and this study will provide evidence and preliminary data for using digital platforms for HL interventions. This is critical as interventions using digital platforms extend the reach and use of the intervention modules, as geography, personnel, and time constraints minimally affect implementation.

As an intervention similar to this one has not been conducted before, the range of feasibility constructs assessed in this pilot RCT will determine the optimal procedures for the full-scale RCT, as well as the dissemination of the intervention beyond the full-scale RCT. The information gathered from the feasibility constructs will also inform how other similar research questions are addressed in similar settings. For example, a digital intervention on adolescent substance use prevention and HL may use a similar methodology. Obtaining objective fidelity measures provides useful data on what might work in the intervention format beyond the subjective evaluation tools.

Limitations

A strength of this pilot and feasibility study is the inclusion of outcome measures to facilitate power calculations for a full-scale RCT. However, the small sample size means that preliminary efficacy is mostly useful for calculating RCT sample needs rather than making strong inferences about the utility of the intervention. Another limitation of this study is the use of schools. Schools are an isolated portion of the adolescent population as they exclude adolescents who may be homeschooled or out of school for other reasons. These excluded adolescents may have different HL, health behavior change needs, and access to resources; therefore, the efficacy and effectiveness of the intervention for these adolescents cannot be determined from this study. Furthermore, blinding could not be implemented. This may affect the results as adolescents in different conditions may discuss and compare what they are doing in their conditions, and this can lead to information seeking and knowledge acquisition, which conflates the findings.

Conclusions

This study is the first step toward addressing the HL needs of adolescents within the context of health behavior interventions. The findings of this study could inform the design and content of future health behavior interventions designed for adolescents.

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Data Availability

Data sharing is not applicable to this paper, as no data sets will be generated or analyzed during the study.

Authors' Contributions

This study was designed by SAF, and all manuscript drafts and revisions were completed by SAF.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards for Reporting Trials) 2010 extension for pilot and feasibility trials checklist.
[PDF File (Adobe PDF File), 241 KB - resprot_v11i8e40191_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH (Consolidated Standards for Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1304 KB - resprot_v11i8e40191_app2.pdf]

Multimedia Appendix 3
Peer review by the Center for Scientific Review Special Emphasis Panel - Small Grants for New Investigators to Promote Diversity in Health-Related Research (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 124 KB - resprot_v11i8e40191_app3.pdf]

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Abbreviations

CONSORT: Consolidated Standards for Reporting Trials
CONSORT-EHEALTH: Consolidated Standards for Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DOiT: Dutch Obesity Intervention in Teenagers
HL: health literacy
IMB: Information-Motivation-Behavioral Skills
PA: physical activity
RCT: randomized controlled trial

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Protocol

Evaluation of the SUCCESS Health Literacy App for Australian Adults With Chronic Kidney Disease: Protocol for a Pragmatic Randomized Controlled Trial

Jennifer Isautier[1], BExSci, MNutrDiet; Angela C Webster[2,3,4], PhD; Kelly Lambert[5,6], PhD; Heather L Shepherd[7,8], PhD; Kirsten McCaffery[1], PhD; Kamal Sud[9,10], MD, PhD; Jinman Kim[11], PhD; Na Liu[12], PhD; Nicole De La Mata[2], PhD; Shahreen Raihana[1], PhD; Patrick J Kelly[2], PhD; Danielle M Muscat[1], PhD; SUCCESS Study Group[13]

[1]Sydney Health Literacy Lab, Sydney School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

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

[3]National Health and Medical Research Council Clinical Trials Centre, The University of Sydney, Sydney, Australia

[4]Westmead Applied Research Centre, Westmead Hospital, Westmead, Australia

[5]School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, Australia

[6]Illawarra Health and Medical Research Institute, Wollongong, Australia

[7]Centre for Medical Psychology and Evidence-based Decision-making, School of Psychology, Faculty of Science, The University of Sydney, Sydney, Australia

[8]Susan Wakil School of Nursing, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

[9]Nepean Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

[10]Department of Renal Medicine, Nepean Hospital, Sydney, Australia

[11]School of Computer Science, The University of Sydney, Sydney, Australia

[12]The University of Sydney Business School, The University of Sydney, Darlington, Australia

[13]See Acknowledgments

Corresponding Author:
Danielle M Muscat, PhD
Sydney Health Literacy Lab, Sydney School of Public Health
Faculty of Medicine and Health
The University of Sydney
127A Edward Ford Building
Sydney, 2006
Australia
Phone: 61 93517819
Email: danielle.muscat@sydney.edu.au

Abstract

Background: We developed a smartphone app—the SUCCESS (Supporting Culturally and Linguistically Diverse CKD Patients to Engage in Shared Decision-Making Successfully) app—to support Australian adults with kidney failure undertaking dialysis to actively participate in self-management and decision-making. The content of the SUCCESS app was informed by a theoretical model of health literacy that recognizes the importance of reducing the complexity of health information as well as providing skills necessary to access, understand, and act on this information.

Objective: The purpose of this study is to investigate the efficacy of the SUCCESS app intervention.

Methods: We designed a multicenter pragmatic randomized controlled trial to compare the SUCCESS app plus usual care (intervention) to usual care alone (control). A total of 384 participants receiving in-center or home-based hemodialysis or peritoneal dialysis will be recruited from six local health districts in the Greater Sydney region, New South Wales, Australia. To avoid intervention contamination, a pragmatic randomization approach will be used for participants undergoing in-center dialysis, in which randomization will be based on the days they receive hemodialysis and by center (ie, Monday, Wednesday, and Friday or Tuesday, Thursday, and Saturday). Participants undergoing home-based dialysis will be individually randomized centrally using simple randomization and two stratification factors: language spoken at home and research site. Consenting participants will be invited to use the SUCCESS app for 12 months. The primary endpoints, which will be assessed after 3, 6, and 12 months of app usage, are health literacy skills, evaluated using the Health Literacy Questionnaire; decision self-efficacy, evaluated using the

Decision Self-Efficacy Scale; and rates of unscheduled health encounters. Secondary outcomes include patient-reported outcomes (ie, quality of life, evaluated with the 5-level EQ-5D; knowledge; confidence; health behavior; and self-management) and clinical outcomes (ie, symptom burden, evaluated with the Palliative care Outcome Scale–Renal; nutritional status, evaluated with the Patient-Generated Subjective Global Assessment; and intradialytic weight gain). App engagement will be determined via app analytics. All analyses will be undertaken using an intention-to-treat approach comparing the intervention and usual care arms.

Results: The study has been approved by Nepean Blue Mountains Human Research Ethics Committee (2020/ETH00910) and recruitment has begun at nine sites. We expect to finalize data collection by 2023 and publish the manuscript by 2024.

Conclusions: Enhancing health literacy skills for patients undergoing hemodialysis is an important endeavor, given the association between poor health literacy and poor health outcomes, especially among culturally diverse groups. The findings from this trial will be published in peer-reviewed journals and disseminated at conferences, and updates will be shared with partners, including participating local health districts, Kidney Health Australia, and consumers. The SUCCESS app will continue to be available to all participants following trial completion.

Trial Registration: Australia New Zealand Clinical Trials Registry (ANZCTR) ACTRN12621000235808; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380754&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/39909

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KEYWORDS

chronic kidney disease; health literacy; shared decision-making; eHealth; smartphone app

Introduction

Chronic kidney disease (CKD) affects up to 10% of the Australian population [1], with greater prevalence, higher mortality, and more rapid disease progression in culturally and linguistically diverse communities [2]. The long-term management of CKD is complex, requiring patient involvement both in decision-making and self-management. Effective self-management and health decision-making requires the ability to understand and use health information, a skill that is known as "health literacy" [3]. However, limited health literacy is common in CKD populations [4] and is independently associated with missed dialysis treatments, increased emergency department visits, increased mortality, and poorer quality of life [5,6]. This is further compounded by the fact that cognitive impairment is more prevalent in those undertaking dialysis compared to the general population, with deficits in attention, memory, and executive function [7]. These cognitive deficits may impact cognitive processing, speed, memory, and the ability to plan ahead and strategize—all necessary skills for participating in self-management and decision-making.

Interventions that focus on developing health literacy skills may have positive effects on shared decision-making and self-management for people living with chronic diseases [8]. In people with CKD, there is mounting evidence that health literacy interventions may increase kidney disease–related knowledge, improve self-care behaviors and self-efficacy, and decrease hospitalization rates and length of stay [9]. However, a recent systematic review highlighted that the quality of the evidence is low and that no studies have specifically targeted populations with low health literacy [9]. The authors concluded that future studies should use validated measures of health literacy and determine whether health literacy interventions redress inequity and, specifically, whether these interventions are more beneficial in those with low health literacy [9].

Health literacy interventions may take several forms, such as educational methods varying from formal classes, home visits, and study circles, through to multimedia and eHealth or online interventions [9,10]. eHealth interventions are potentially useful methods to deliver health literacy interventions. It is estimated that over 91% of Australians own a smartphone, and smartphones are used to access information more than any other devices [11]. Furthermore, smartphone interventions can reduce the cognitive burden placed on users by providing small unit-based learning called "microlearning," allowing users to return to the content at their own pace and in their own time. eHealth interventions have been shown in different settings to provide consumers access to relevant health information, enhance quality of care, and encourage behavior change [12]. Several CKD-related apps already exist; however, current evidence suggests that many CKD-related apps lack accurate, evidence-based information [13], and none are designed based on theoretical models to improve health literacy.

We recently developed a smartphone app—the SUCCESS (Supporting Culturally and Linguistically Diverse CKD Patients to Engage in Shared Decision-Making Successfully) app—to support Australian adults with kidney failure to actively participate in self-management and decision-making [14]. The SUCCESS app was developed with a multidisciplinary team that included researchers in various fields (ie, health literacy, shared decision-making, public health, epidemiology, and computer science), renal clinicians (ie, nephrologists, dietitians, physiotherapists, and social workers), and consumers living with kidney failure. Content was informed by a theoretical model of health literacy [15] that recognizes the importance of reducing the complexity of health information as well as supporting consumers to develop their skills and to access, understand, and act on this information. In this way, it adopts strategies to reduce the complexity of the content (ie, diet, fluids, medicine, physical activity, emotional well-being, and supportive care) and includes features to improve the health literacy skills of patients. The latter includes question prompt

lists and evidence-based volitional help sheets to support question-asking and behavioral change as well as animated skills training related to communication, shared decision-making, and critical appraisal of health information. Full details of the development and content of the app have been published elsewhere [14].

The purpose of this randomized controlled trial (RCT) is to investigate the efficacy of the SUCCESS app intervention for adults receiving in-center hemodialysis, home-based hemodialysis, or peritoneal dialysis, including those from culturally and linguistically diverse backgrounds and with lower health literacy. Our objectives are to assess the impact of the SUCCESS app on the primary outcomes, including health literacy skills, decision self-efficacy, and rates of unscheduled health encounters, and on the secondary outcomes, including knowledge, confidence, quality of life, symptom burden, and nutritional status.

Methods

Overview

The study methods have been informed by a feasibility study of the intervention [16]. This protocol is reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines and the CONSORT (Consolidated Standards of Reporting Trials) guidelines [17]. The trial was registered on the Australia New Zealand Clinical Trials Registry (ACTRN12621000235808).

Design

The SUCCESS trial is a 12-month multicenter pragmatic RCT with a 1:1 allocation to two groups: SUCCESS app plus usual care versus usual care alone.

Intervention

Intervention Development

The SUCCESS app was designed using strategies to reduce the complexity of the content as well as to include features to improve the health literacy skills of patients. The app embeds informational content relevant to living with kidney failure covering diet, fluids, medicine, physical activity, emotional well-being, and supportive care [14]. A four-step process was used to simplify written content, including calculating readability statistics, applying the Patient Education Materials Assessment Tool [18], supplementing written information with video and audio content, and incorporating microlearning and interactive quizzes.

The app also includes features to improve the communicative and critical health literacy skills of patients across four domains: skills to (1) access, (2) understand, (3) appraise, and (4) use health information to make health decisions and be involved in self-management. This is achieved through the inclusion of question prompt lists, volitional help sheets, and animated skills training in communication, shared decision-making, and critical appraisal of online information (Textbox 1). The SUCCESS app is designed for use on both iOS and Android platforms.

Textbox 1. Features of the SUCCESS app.

Question prompt lists

- Question prompt lists are prepared lists of questions that are designed to enable patients to identify questions they wish to ask the health care professional.
- Question prompt lists are embedded within the content areas of the SUCCESS (Supporting Culturally and Linguistically Diverse CKD Patients to Engage in Shared Decision-Making Successfully) app (eg, there is a question prompt list related to taking medications).
- Users are able to choose from a predefined list or write their own questions, which are saved in the app dashboard for use in upcoming health care consultations.

Volitional help sheets

- A volitional help sheet is a tool designed to enable the construction of effective implementation intentions in which participants are asked to link in memory temptations (ie, difficult situations that result in urges to engage in a specific behavior) with processes of change (ie, means by which behavior is changed or sustained).
- Volitional help sheets are embedded within each content area of the SUCCESS app. For example, participants can create a volitional help sheet to make a plan to drink less fluids. Plans are saved in the app dashboard for future use.

Videos

- Animated videos are available to build skills in the following areas:
  - Health care communication (eg, “Talking to your health care team”)
  - Shared decision-making (eg, “Making decisions”)
  - Critical appraisal of online information (eg, “Can I trust this health information?”).

Quizzes

- Content-specific quizzes are embedded into the app to encourage feedback and learning through the use of targeted questions separated by levels of difficulty.
- Users receive feedback and further information about the content of the quiz based on their understanding.

Public and Patient Involvement

A key strength of the development of the SUCCESS app was the combined effort of clinicians, health literacy experts, and consumers in the app development process. One consumer and a representative of Kidney Health Australia, the largest consumer advocacy organization for people with kidney disease, were part of the development team and provided valuable feedback regarding app content and usability. Further to this, the app was iteratively improved based on consumer feedback during the development the feasibility testing phases leading up to this trial. As part of this trial, we will continue to seek further feedback from participants on the SUCCESS app and make improvements, if required, after completion of the trial.

Study Setting

This study will be conducted across six local health districts charged with delivery of health care within the public sector in the Greater Sydney region—Sydney, Northern Sydney, Western Sydney, South Western Sydney, Nepean Blue Mountains, and Illawarra Shoalhaven—including six university teaching hospitals and six community dialysis centers. The Greater Sydney region includes 4,823,991 people (64.5% of the New South Wales population; 20% of the Australian population), of which 38% speak a language other than English at home [19]. The research sites were purposively selected to include broad geographical coverage across Sydney as well as socioeconomic and cultural diversity.

Study Population

The target population for this study are adults aged 18 years or over who are receiving dialysis, including those receiving in-center hemodialysis, either in the hospital or community hemodialysis centers; home hemodialysis; and peritoneal dialysis. Only participants who have the ability to speak English sufficiently well to provide informed consent will be recruited. We intend to translate and culturally adapt the app into other languages to further expand the diversity of future app users. Participants lacking the cognitive capacity to consent as determined by the nursing staff will be excluded.

Recruitment

Eligible participants will be identified by their health care providers and approached by the research team either in person during dialysis sessions or clinic visits or via telephone, email, or a letter of invitation; at this time, they will be provided with information about the study. Participants will be entered into the study after written consent is obtained on paper or via REDCap (Research Electronic Data Capture) and after eligibility criteria are met.

Randomization

Overview

Participants will be randomly allocated to either the SUCCESS app plus usual care (intervention) or usual care alone (control). Participants who are randomized to the intervention will be invited to use the SUCCESS app for a maximum of 12 months. Participants will be instructed to engage with the app *ad libitum* and will also receive monthly reminders to use the app via push notifications.

We will not randomize all participants individually due to the risk of intervention contamination, where the intervention is experienced by control group members as well as those allocated to the intervention group. This is possible because participants in the control and intervention arms may undergo dialysis in the same room three times each week for several hours. Instead, a two-tier pragmatic approach will be used to randomize participants depending on whether they are undergoing dialysis at home or receiving dialysis at the in-center (ie, satellite) dialysis units. Our planned approach will minimize contamination and allow for within-center comparisons.

Dialysis at In-Center Units

It is standard practice for patients on hemodialysis at the in-center units to receive dialysis treatment three times a week. Patients receiving in-center dialysis always attend on the same days: either Mondays, Wednesdays, and Fridays or Tuesdays, Thursdays, and Saturdays. Therefore, a pragmatic approach will be used at each center by randomizing patients according to their pattern of attendance. Depending on the center, all participants attending Monday, Wednesday, and Friday will be assigned to the same study intervention group, and those attending Tuesday, Thursday, and Saturday will be assigned to the alternate study intervention group.

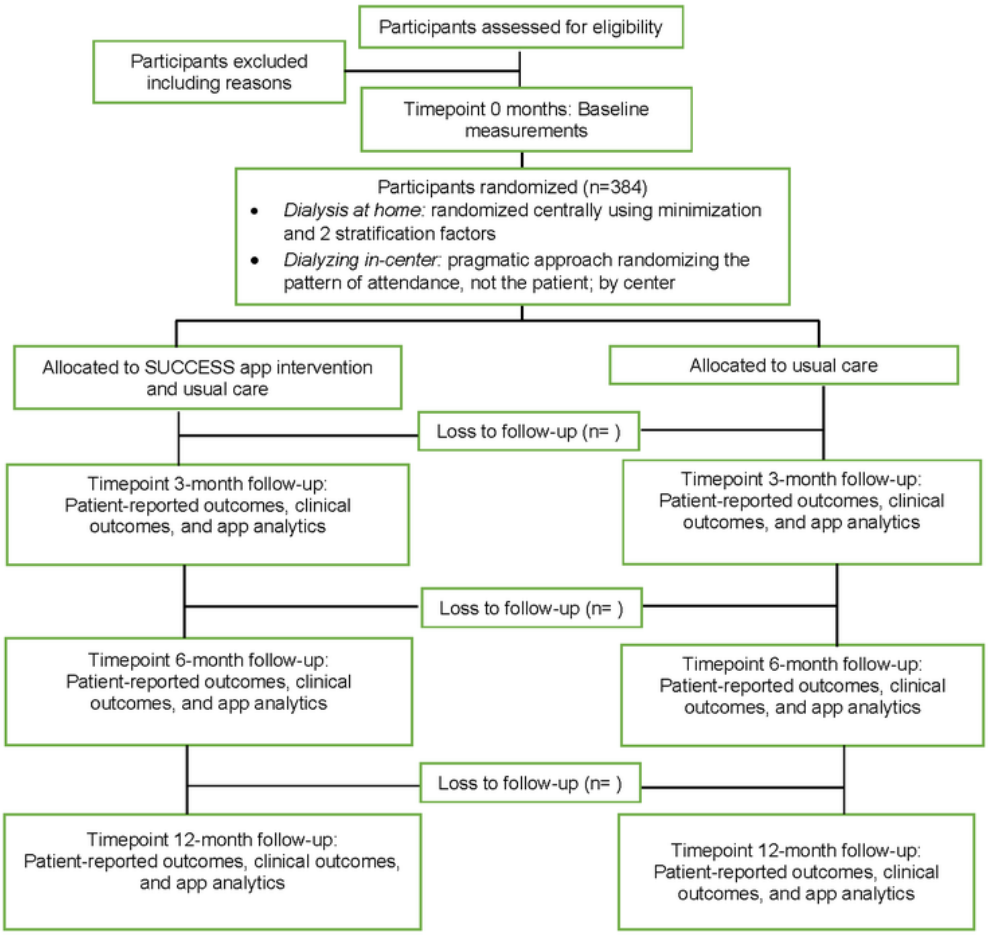
Dialysis at Home

Participants will be randomized individually using minimization and two stratification factors: the language spoken at home and the research site. An interactive voice response system will be used for randomization; this allows for research staff to call a third party—the National Health Medical Research Council Clinical Trials Centre—which allocates the randomization order.

Timeline

The study timeline will include four data collection timepoints: baseline and 3-month, 6-month, and 12-month follow-ups (Figure 1).

Figure 1. Study flow and timeline. SUCCESS: Supporting Culturally and Linguistically Diverse CKD Patients to Engage in Shared Decision-Making Successfully.



Study Outcomes

Once informed consent is obtained, baseline measures will be collected, including demographics, dialysis history, cognition level, and health and digital literacy status (Table 1 [20-30]). Our primary outcomes are health literacy, shared decision-making, and rates of unscheduled health encounters; these will be assessed at 3, 6, and 12 months of app usage (Table 1). Secondary outcomes include patient-reported outcomes and clinical outcomes; these will also be assessed at 3, 6, and 12 months of app usage (Table 1).

Table 1. Measurements collected throughout the trial.

Measure and description	Timepoint (month)			
	0	3	6	12
Baseline measurements				
Demographics: age, gender, country of birth, language spoken at home, Aboriginal and Torres Strait Islander status, and highest education attained.	✓[a]			
Dialysis history: mode of dialysis (hemodialysis or peritoneal dialysis), location of treatment (home or in-center), dialysis schedule (frequency of dialysis per week), and dialysis vintage (years on dialysis).	✓			
Cognition impairment: the MoCA[b] is a screening tool developed to assist clinicians in the detection of cognitive impairment [20]. It measures a person's orientation in time and space, short-term memory, abstract reasoning, attention, and many other aspects of cognitive ability. The MoCA tool was chosen as it is a more sensitive tool for detecting mild cognitive impairment compared to the MMSE[c] [21]. The MoCA returns a cognitive ability score ranging from 0 to 30, where a score of ≤26 suggests cognitive impairment [20].	✓			
Health literacy, self-report: the brief health literacy screener is a single-item screener to identify people with inadequate levels of functional health literacy in clinical settings [22,23]. The item asks, "How confident are you filling out medical forms by yourself?"; the item is rated on a 5-point response scale ranging from "not at all" to "extremely." The threshold for inadequate health literacy is "somewhat" or less.	✓			
Health literacy, performance-based: a brief comprehension test based on instructions similar to those found on a packet of aspirin bought over the counter [24]. Participants are asked to read a fictitious medicine label and respond to four questions, such as "What is the maximum number of days you may take this medicine?" and "List one condition for which you might take the tablet." The task was developed according to a conceptual framework that defines literacy as an ability to fulfill goal-directed tasks, in this case, in a health context. Health literacy is categorized as high (maximum score), medium (one error), or low (more than one error).	✓			
Digital literacy: the assessment of digital literacy was adapted from a validated instrument, the MACL[d], a 7-point Likert scale consisting of statements about attitudes toward computers [25]. For the purpose of this study, the questions were modified to reflect the context of smartphone usage, such as "I can switch on and off a mobile phone." Participants' mobile phone locus of control was assessed to understand how well they believe that they have control over the outcomes of events of their smartphone usage [25].	✓			
Primary outcomes: patient-reported outcomes				
Health literacy skills: the HLQ[e], a multidimensional tool that measures health literacy across nine distinct conceptual domains, will be used. The median reliability of the HLQ domains is 0.88, with a range from 0.77 to 0.90 [26]. For the purpose of this study, we have selected three to domains to explore: • Domain 2: have sufficient information to manage my health • Domain 6: ability to actively engage with health care providers • Domain 9: understand health information well enough to know what to do. Domain 2 assesses the strength of a participant's agreement with the statement on a 4-point ordinal scale, ranging from 1 ("strongly disagree") to 4 ("strongly agree"); domains 6 and 9 assess a participant's perceived ease in task completion on a 5-point ordinal scale, ranging from 1 ("always difficult") to 5 ("very easy").	✓	✓	✓	✓
Decision self-efficacy: the Decision Self-Efficacy Scale [23] measures self-confidence or belief in one's ability to make decisions, including participation in shared decision-making. This item consists of 11 questions where participants rate their confidence engaging in decision-making behaviors, such as "Getting the facts about the medication choices available." Items are rated on a 5-point ordinal scale ranging from 1 ("not at all confident") to 5 ("very confident").	✓	✓	✓	✓
Rates of unscheduled health encounters: this includes unexpected hospital and emergency visits and unscheduled dialysis events in the past 3 months as reported by participants; this is also verified by extracting this information from electronic medical records.		✓	✓	✓
Secondary outcomes: patient-reported outcomes				
Quality of life: the EQ-5D-5L[f] is a standardized instrument used to measure health-related quality of life in a wide range of health conditions and treatment settings [27].	✓	✓	✓	✓
Knowledge: an 8-item curriculum-based measure was purpose designed to assess knowledge about four key topics of dialysis self-management covered in the SUCCESS[g] app: (1) diet, (2) fluids, (3) medicines, and (4) physical activity. Questions (two per topic) were based on key learnings from the app, with points scored for correct answers (0 = incorrect, 1 = correct).	✓	✓	✓	✓
Health behavior**:** a theory-informed 11-item behavior questionnaire was adapted from previous literature [28] and matched to the content of the SUCCESS app. Participants are asked to respond "yes" or "no" to engaging in behaviors over the past week, such as "Checking the nutrition label when eating packaged food" (0 = no, 1 = yes).	✓	✓	✓	✓

Measure and description	Timepoint (month)			
	0	3	6	12
Confidence: an 11-item confidence measure was purpose designed based on the health behavior questionnaire above, including questions such as "How confident do you feel reading and understanding food labels?" Items are rated on a 5-point ordinal scale ranging from 1 ("not at all confident") to 5 ("extremely confident").	✓	✓	✓	✓
Self-management: two questions were designed to assess patient knowledge and adherence to phosphate binder medication prescription, as an indicator of self-management.	✓	✓	✓	✓
Secondary outcomes: clinical outcomes				
Changes in symptom burden: the POS[h] is a widely used and validated instrument used in clinical care and research. The POS-Renal is a short measure (11 questions) that collects information on the most common symptoms that renal patients experience [29].	✓	✓	✓	✓
Nutritional status: the PG-SGA[i] is a standard nutritional assessment tool measuring clinical indices (ie, weight, intake, symptoms, functional status, disease state, metabolic stress, and nutritional physical examination) in a range of chronic conditions [30]. The PG-SGA enables the patient and professional to quickly and easily assess and monitor the risk for malnutrition and to evaluate effects of interventions.	✓	✓	✓	✓
Interdialytic weight gain: this is a measure of weight gained between two consecutive dialysis sessions. The measure gives an indication of whether patients are adhering to fluid restrictions and is recorded at each dialysis session; the monthly average is easily calculated for each patient.	✓	✓	✓	✓
Key performance indicators: typical key performance indicators for dialysis will be linked and extracted from the Australian and New Zealand Dialysis and Transplant registry. This will include demographics, ethnicity, anthropometry, comorbidities, course of treatment, and survival rates.	✓	✓	✓	✓
App analytics—the following information will be extracted using Google Analytics: • How many people have registered or logged in? • How often do people log in? At what times? How does this relate to their dialysis times? • How long do people stay logged in? • Time between visits • Number of times people access app features (eg, quizzes and videos) • Number of visits to each page and subpage.	✓	✓	✓	✓

[a]A checkmark indicates that the measure will be performed at the indicated timepoint.

[b]MoCA: Montreal Cognitive Assessment.

[c]MMSE: Mini–Mental State Examination.

[d]MACL: Multicomponent Assessment of Computer Literacy.

[e]HLQ: Health Literacy Questionnaire.

[f]EQ-5D-5L: 5-level EQ-5D.

[g]SUCCESS: Supporting Culturally and Linguistically Diverse CKD Patients to Engage in Shared Decision-Making Successfully.

[h]POS: Palliative care Outcome Scale.

[i]PG-SGA: Patient-Generated Subjective Global Assessment.

Data Collection and Management

Quantitative data will be either collected using paper copies or captured electronically via REDCap, a web-based tool to capture data for clinical research and to create databases and projects. Baseline data will be collected in person, and follow-up data will be collected either in person or electronically based on patient preference and depending on COVID-19 restrictions at the time of data collection.

After enrollment, a unique identifier will be assigned to each study participant. Personal information about participants will be kept separate from the main data set and will not be shared. All data will be stored on password-protected REDCap databases. Spreadsheets and data analysis derived from this data will be stored in the University of Sydney Research Data Store only, and will not be downloaded to individually owned computers.

Qualitative Substudy

Qualitative data will be collected from participants at 3, 6, and 12 months. Semistructured interviews will be conducted by research staff trained in qualitative methods, in order to explore the experiences and perspectives of individual participants regarding usage of the app. The perspectives of users on the applicability of content and their ability to build capacity, become motivated, and identify opportunities to improve the management of their CKD will also be sought. Additional feedback from research participants on the content and design of the app will be discussed.

Participants for qualitative interviews will be purposively selected from those already enrolled to capture a range of demographic characteristics, including those with lower health literacy and from culturally and linguistically diverse backgrounds. Interviews will be conducted face-to-face during participants' scheduled dialysis sessions or virtually via

approved videoconferencing software. Participants dialyzing at home may complete interviews over the phone or virtually or can arrange a time to meet the interviewer at the dialysis clinic, depending on the COVID-19 restrictions at the time. All participants will have provided consent to participate in the interviews at the beginning of the study. Verbal consent will be confirmed for the interview, and the audio recording will be obtained at the start of the interview. The semistructured interviews are expected to last between 20 and 60 minutes and will be audio recorded.

Data Analysis

Overview

Analysis of data will occur using an intention-to-treat approach and will compare the intervention and usual care arms. For continuous and binary outcomes, linear and logistic regression models will be used, respectively, with study arm as a covariate. All models will also be adjusted for center using a random effect, and the type of patient (ie, receiving home-based or in-center care) will be adjusted for using a covariate.

Qualitative data will be analyzed using the Framework approach to thematic analysis [31]. Framework analysis is a matrix-based approach with columns depicting themes and rows listing the cases, enabling the relationship between themes and cases to be explored. The first step involves familiarization with the data, where one or two researchers will review the transcript and, using an inductive approach, they will then develop a list of emerging topics and salient themes. These initial impressions will form the basis of the coding framework. Then, additional researchers will independently read a subset of transcripts and review the framework, which will further be revised with continuous discussion if needed. One researcher will then code all the interviews into the final framework, of which a random subset (10%) will be double coded by an additional researcher to ensure rigor. Similarities or differences will be discussed and reassessed. Microsoft Excel will be used to summarize the themes and supporting quotes from each transcript in the framework. Prominent themes arising from the framework will be identified and discussed in-depth with the research team.

Missing Data

We will use best practice to decide when imputation is necessary for missing data, except for the outcome data, considering the percentage of missing data and plausibility of the “missing at random” assumption [32]. Where there is a large proportion of missing data, we will consider using a complete case or pairwise deletion approach. We will also perform sensitivity analyses to evaluate the robustness of our results. For outcome data, we will not use imputation methods and will only exclude participants who do not have baseline data and at least one follow-up outcome measure.

Sample Size

Our sample size has been calculated based on the primary outcome of the three Health Literacy Questionnaire (HLQ) domains. We assumed a minimal clinically important difference of 0.25 units in any one of the three HLQ domains. A sample size of 384 participants would result in greater than 90% power to detect a 0.25-unit change in an HLQ domain between the two arms, assuming an SD of 0.60, and at least 80% power, assuming an SD of 0.75. These SD values are based on published literature and equate to a standardized difference of 0.42 and 0.33, respectively; a standardized difference of 0.5 is considered a medium effect [33,34]. Our power calculation is based on conducting our analyses using 2-sided tests, a 5% significance level, and assuming 20% loss to follow-up (eg, due to death or kidney transplant).

For qualitative interviews, a maximum total sample size of 40 participants is planned. Interviews will continue until data saturation or until the maximum total sample size is reached.

Safety and Monitoring

The research staff team will meet fortnightly with the trial coordinator, project lead, or both to discuss recruitment and ensure that the rights, safety, and well-being of the participants enrolled in the trial are protected. At these meetings, the trial coordinator will verify that study activities and documentation are compliant with the study protocol. The trial coordinator and the research assistants will report any issues to the site-specific principal investigator as they arise. Furthermore, the trial coordinator and research staff team will meet regularly with the site-specific principal investigators and the University of Sydney investigators to report on the trial progress. If a participant is found to experience distress during data collection, the research assistants will have resources available for participants to be referred to the Beyond Blue Support Line, Lifeline, or back to their treating clinicians should they require it.

Accounting for Extenuating Circumstances

As per the CONSERVE (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances) 2021 statement [35], we have outlined our plan if the SUCCESS trial is interrupted due to COVID-19 restrictions (Textbox 2).

Textbox 2. Approach to deal with interruptions due to COVID-19 restrictions.

Extenuating circumstances

During the COVID-19 pandemic, there have been several occasions when the Australian government has announced lockdowns to reduce the risk of COVID-19 transmission within the community. During these lockdowns, research activities have been put on hold to reduce the risk of COVID-19 exposure to both participants and health professionals. Unfortunately, it is difficult to predict when these lockdowns may occur.

Impact

COVID-19 lockdowns may result in a slower recruitment rate and higher rate of participants lost to follow-up due to the inability of research staff to collect data at dialysis centers. Missing data may also arise directly or indirectly due to COVID-19. Procedures for missing data have already been specified in the protocol.

Mitigating strategies

Although face-to-face is the preferred approach for data collection for this trial, ethical approval has also been obtained to conduct the trial electronically or virtually. In this case scenario, the blind version of the Montreal Cognitive Assessment will be used, and the Patient-Generated Subjective Global Assessment will be collected at a later timepoint. Therefore, to reduce the interruptions due to COVID-19 lockdowns, the trial will be conducted electronically or virtually.

Ethics Approval

Ethical approval for this study was granted by the Nepean Blue Mountain Local Health District Ethical Committee as well as the local research governance offices at each of the participating sites (2020/ETH00910).

Results

Recruitment has begun at nine sites. We expect to finalize data collection by 2023 and publish the manuscript by 2024.The results from the RCT will be submitted for publication to an international peer-reviewed journal, regardless of the findings. In addition, the findings will be disseminated at conferences, and updates will be shared with partners, including participating local health districts, NSW Health, Kidney Health Australia, and consumers. The SUCCESS app will continue to be available to all participants undertaking the trial, after the trial has ended. In addition, the SUCCESS app will also be publicly available on the Apple App Store and Google Play for anyone to download.

Discussion

This pragmatic RCT, which will be implemented within a real-world setting, aims to determine the effectiveness of a complex health intervention—the SUCCESS app—to improve patient-reported psychosocial and clinical outcomes. Results from previous research by our group suggest that our recruitment strategy will lead to a diverse population, including people from culturally and linguistically diverse backgrounds [16,36] and those with varying levels of cognition and health literacy [37]. In this way, the trial seeks to address limitations of health literacy research conducted to date.

A key strength of this study is that the SUCCESS app is designed to develop transferable skills in health literacy and shared decision-making in a group of patients who have complex needs. That the app has not yet been translated into other languages limits the selection of participants into the trial and the generalizability of findings, and COVID-19 lockdowns across Sydney continue to impact recruitment, data collection, and study timelines.

The management of CKD requires constant patient involvement based on very complex and often difficult-to-understand health advice. If the SUCCESS app is effective, these skills could be applied across multiple decision contexts, such as CKD stages III and IV and those under renal supportive care, and could extend to the management of comorbidities associated with kidney failure. This is a particular strength, given that the majority of patients with CKD have comorbidities, such as cardiac disease, cerebrovascular disease, diabetes, and lipid disorders.

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Data Availability

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

Conflicts of Interest

DMM is a Director of a Health Literacy consultancy company; Health Literacy Solutions Pty Ltd.

Multimedia Appendix 1

External peer review report from the New South Wales (NSW) Ministry of Health - Translational Research Grants Scheme (TRGS) - TRGS EOI Review Panel (Australia).
[PDF File (Adobe PDF File), 125 KB - resprot_v11i8e39909_app1.pdf]

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Abbreviations

CKD: chronic kidney disease
CONSERVE: CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances
CONSORT: Consolidated Standards of Reporting Trials
HLQ: Health Literacy Questionnaire
PG-SGA: Patient-Generated Subjective Global Assessment
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUCCESS: Supporting Culturally and Linguistically Diverse CKD Patients to Engage in Shared Decision-Making Successfully

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Protocol

Mesh-Tissue Integration of Platelet-Rich Plasma–Decellularized Amnion Scaffold–Polypropylene Mesh Sandwiches Implanted in the Vesicovaginal Spaces of Hypoestrogenic Rabbit Models: Protocol for a Randomized Controlled Trial

Alfa Putri Meutia[1,2*], MD; Budi Iman Santoso[1*], MD, PhD, MPH; Andon Hestiantoro[1*], MD, PhD, MPH; Puspita Eka Wuyung[3*], PhD; Joedo Prihartono[4*], MD, MPH; Arief Boediono[5*], DVM, PhD; Suskhan Djusad[1*], MD, PhD; Amir Fauzi[6*], MD, PhD; Pribakti Budinurdjaja[7*], MD, PhD

[1]Doctoral Program in Medical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia

[3]Department of Pathology Anatomy, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia

[4]Department of Community Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia

[5]Department of Anatomy, Physiology and Pharmacology, Institut Pertanian Bogor University, Bogor, Indonesia

[6]Division of Urogynecology and Reconstructive Surgery, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sriwijaya - Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[7]Division of Urogynecology and Reconstructive Surgery, Department of Obstetrics Obstetrics and Gynecology, Faculty of Medicine, Universitas Lambung Mangkurat - Ulin General Hospital, Kalimantan Selatan, Indonesia

[*]all authors contributed equally

Corresponding Author:
Alfa Putri Meutia, MD
Doctoral Program in Medical Sciences
Faculty of Medicine
Universitas Indonesia
l Salemba Raya No. 6, Kenari, Senen
Jakarta, 10430
Indonesia
Phone: 62 81398751983
Email: a.meutia.urogyne@gmail.com

Abstract

Background: Mesh-augmented surgery with polypropylene meshes (PPMs) is often used in urogynecology and pelvic reconstructive surgery. However, the various complications that arise from its integration process have resulted in a decrease in the number of mesh-augmented surgeries performed worldwide. An approach to improving mesh-tissue integration is coating PPMs with anti-inflammatory and wound-healing molecules, such as platelet-rich plasma (PRP), which is a component of biotechnologies that are capable of accelerating wound healing. Estrogen is also known to have a beneficial effect on wound remodeling; therefore, a hypoestrogenic status may have negative implications for wound healing. The mechanism of how PRP plays a role in wound remodeling, especially among individuals in a hypoestrogenic state, has not been fully described until now.

Objective: Our aim is to investigate the impact of applying PRP to PPMs in hypoestrogenic rabbit models.

Methods: Our study will be a randomized controlled trial involving hypoestrogenic rabbit models. Samples were categorized into either the PRP group or the PPM group (1:1 ratio), with a minimum sample size of 16 in each arm, via simple random sampling. All samples were put into a hypoestrogenic state via bilateral oophorectomy. After confirming a decrease in estradiol level, the meshes were implanted in the vesicovaginal space. The samples were euthanized on the 14th, 28th, or 90th day of the surgery. The mesh-tissue integration process will be analyzed based on inflammatory parameters (inflammatory infiltrate, interleukin-17, and interleukin-1B expression); angiogenesis (CD31 expression); and collagen deposition, which will be assessed by using Masson trichrome staining.

Results: Our study is in the protocol development stage. A preliminary study regarding its feasibility, including the feasibility of the preparation of hypoestrogenic rabbit models, mesh implantation in the rabbits' vesicovaginal spaces, the PRP and amnion scaffold, started in February 2022. The results of our study are expected to be available by the end of 2022.

Conclusions: Our randomized controlled trial is designed to provide high-quality evidence on the effect of applying a PRP-decellularized amnion scaffold to PPMs in the vesicovaginal spaces of hypoestrogenic rabbit models.

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KEYWORDS

pelvic organ prolapse; vaginal mesh; platelet-rich plasma

Introduction

There are various management strategies for stress urinary incontinence and pelvic organ prolapse (POP), including mesh-augmented surgery using polypropylene meshes (PPMs). Sacrocolpopexy is an excellent alternative to apical repair that provides satisfactory results, with a level of effectiveness of 76% to 96% and a recurrence rate of 7.4% [1]. Although mesh-augmented surgery has high effectiveness and low recurrence rates, mesh-related complications, such as vaginal discharge, infection, chronic pain, adhesion, and extrusion/erosion, can harm women's quality of life. These adverse results from the implant can be related to abnormalities in the wound healing process [2].

Wound healing is a physiological reaction to tissue injuries and involves the following three overlapping phases: hemostasis/inflammation, proliferation, and remodeling. The inflammatory phase begins with the process of hemostasis and chemotaxis. Then, proinflammatory cytokines activate neutrophils, thereby limiting further damage and removing cellular debris and bacteria. Angiogenesis, re-epithelization, collagen formation, and injury contraction occur in proliferation. Any disruption to these phases leads to excessive wound healing or chronic wound formation. Unfortunately, most patients with POP are in a menopausal state, implying that hypoestrogenic conditions may also contribute to poor wound healing. Moreover, implantations adjacent to vaginal tissue, which is known to have typical flora, may also further disrupt the wound healing process [3,4].

Platelet-rich plasma (PRP) is known as a platelet concentrate with a 3 to 5 times higher than average platelet count that is obtained through the centrifugation of a blood sample. The potential therapeutic effect of PRP is based on its ability to improve tissue regeneration by releasing growth factors present in platelet α-granules [5,6], Considering its effects on the hemostasis, proliferation, and remodeling phases of wound healing, PRP could be used as a coating agent for PPMs in urogynecology and pelvic reconstructive surgeries. However, animal studies have been suggested to better ascertain a host's response to PRP-coated implants, especially in hypoestrogenic conditions.

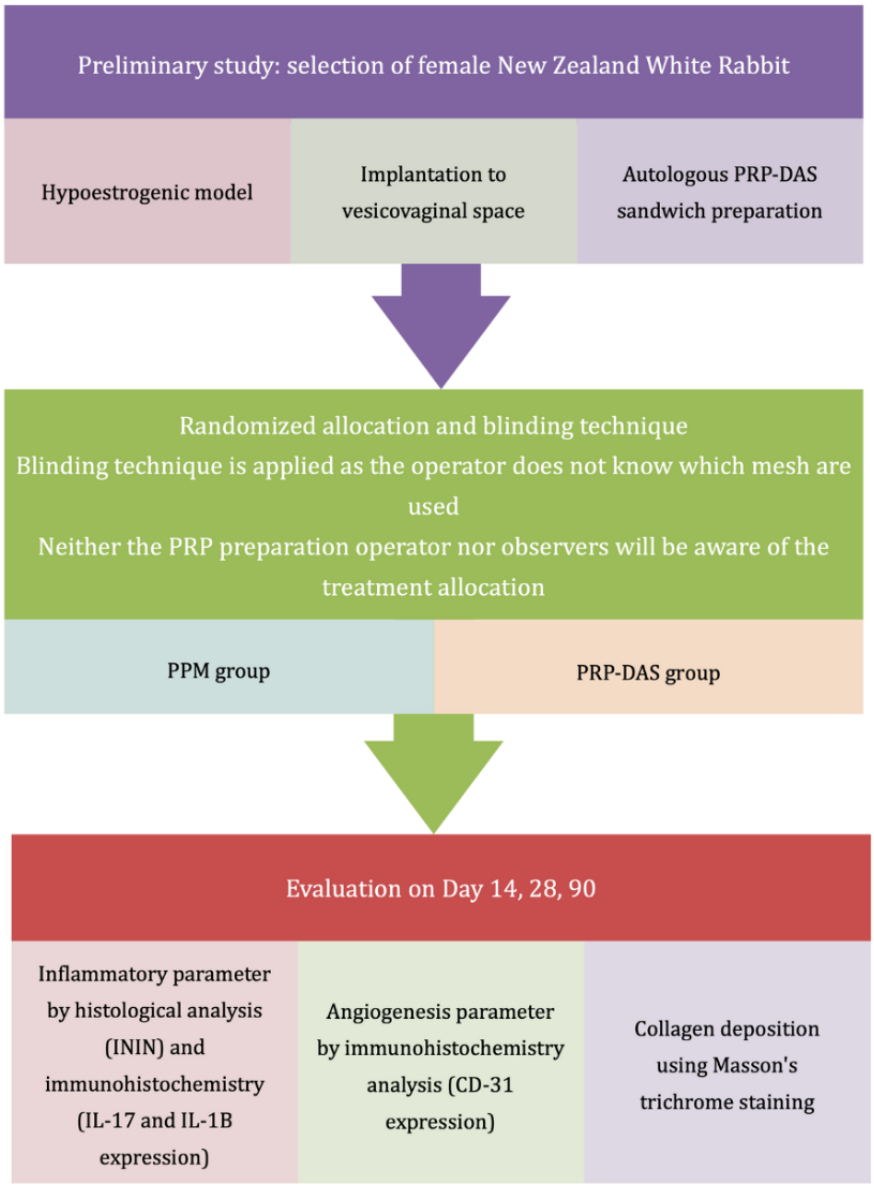
This protocol was designed to investigate the changes in the mesh-tissue integration of PRP-decellularized amnion scaffold (DAS)–PPM sandwiches implanted in the vesicovaginal spaces of hypoestrogenic rabbit models.

Methods

Study Design and Population

Our study is a randomized controlled animal trial that aims to investigate the changes in the mesh-tissue integration of PRP-DAS–PPM sandwiches implanted in the vesicovaginal spaces of hypoestrogenic rabbit models. The study plan for the proposed research is shown in Figure 1.

Figure 1. Study process flowchart. DAS: decellularized amnion scaffold; IL: interleukin; ININ: inflammatory infiltrate; PPM: polypropylene mesh; PRP: platelet-rich plasma.



Ethics Approval

The approval for the protocol of our study was granted by Animal Research Ethical Committee, Faculty of Veterinary Medicine, Institut Pertanian Bogor University, in September 2021 (ethical clearance number: 208 - 2021 IPB), and data collection commenced in February 2022. The protocol was prepared according to the ARRIVE (Animal Research Reporting In Vivo Experiments) 2013 checklist for reporting an animal study.

Hypoestrogenic Rabbit Model

A hypoestrogenic state was induced via bilateral oophorectomy. A 3-cm incision was made on the midline, and the identification of the uterus and mesovarium, followed by the ligation of ovaries using Vicryl 3.0 (Ethicon), was done. Estradiol levels before and after oophorectomy were measured via an enzyme-linked immunosorbent assay using the Estradiol Parameter Assay Kit (catalog number: KGE014; R&D systems). Blood samples were obtained from all rabbits by using a 23-gauge wing needle on the auricular vein and stored at room temperature for 30 minutes to allow for clotting. The samples were then centrifugated for 15 minutes at 1000 revolutions per minute. The serum was removed, pretreated, and assayed immediately. A hypoestrogenic state was confirmed when there was a ≥50% decrease in estradiol levels from baseline [7].

Vesicovaginal Mesh Implantation

The implantation of a PPM into the vesicovaginal wall was done by making a 3-cm incision on the midline of the lower abdominal wall, during which the bladder and uterus were identified. A further dissection was made toward the vesicovaginal space, and a 1×1-cm mesh was implanted on the anterior vaginal wall, as shown in Figure 2. A fixation suture using Prolene 3.0 (Ethicon) was made as a marker for tissue harvests in the future, as shown in Figure 3.

Figure 2. Image of the polypropylene mesh.

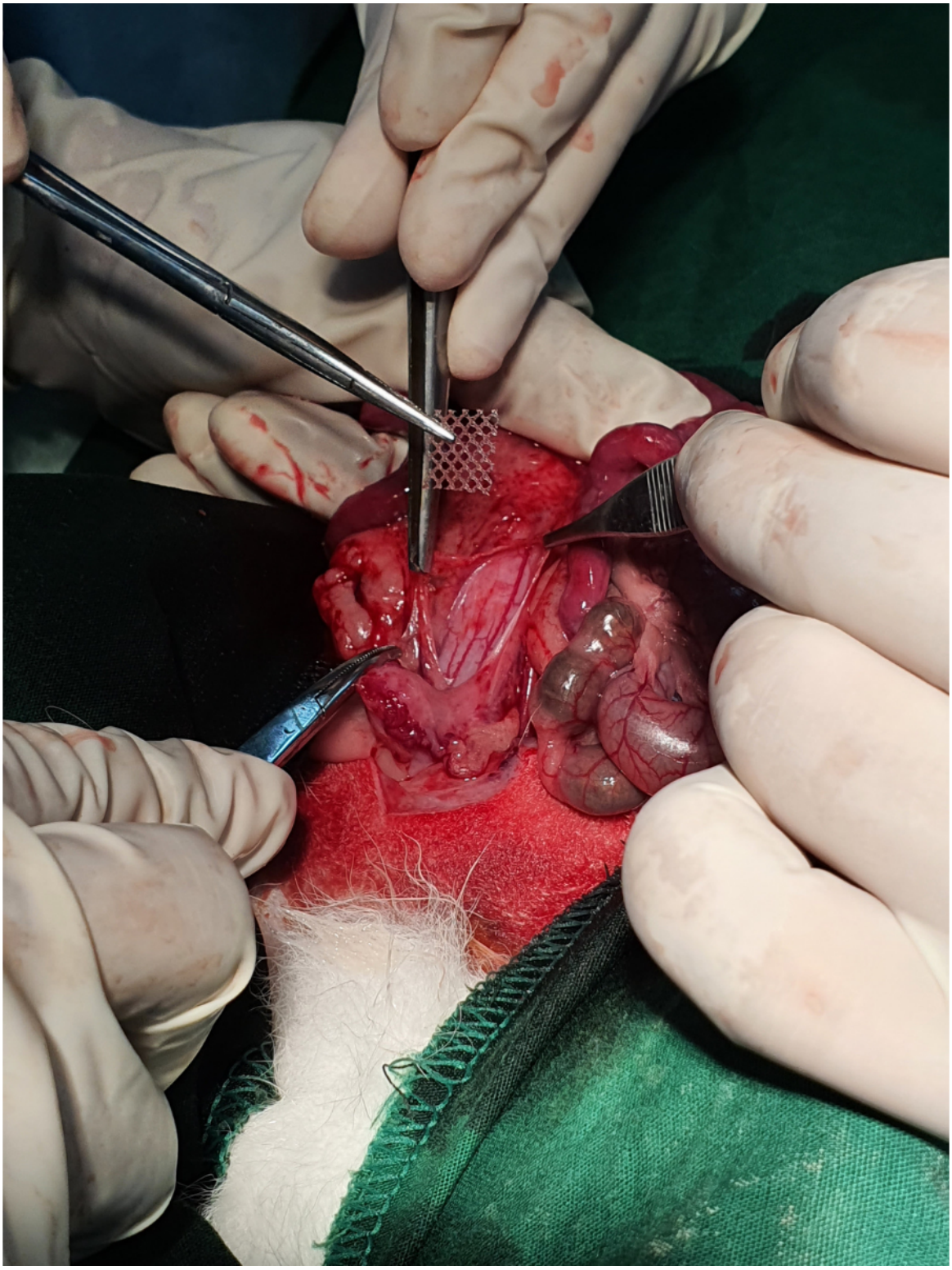
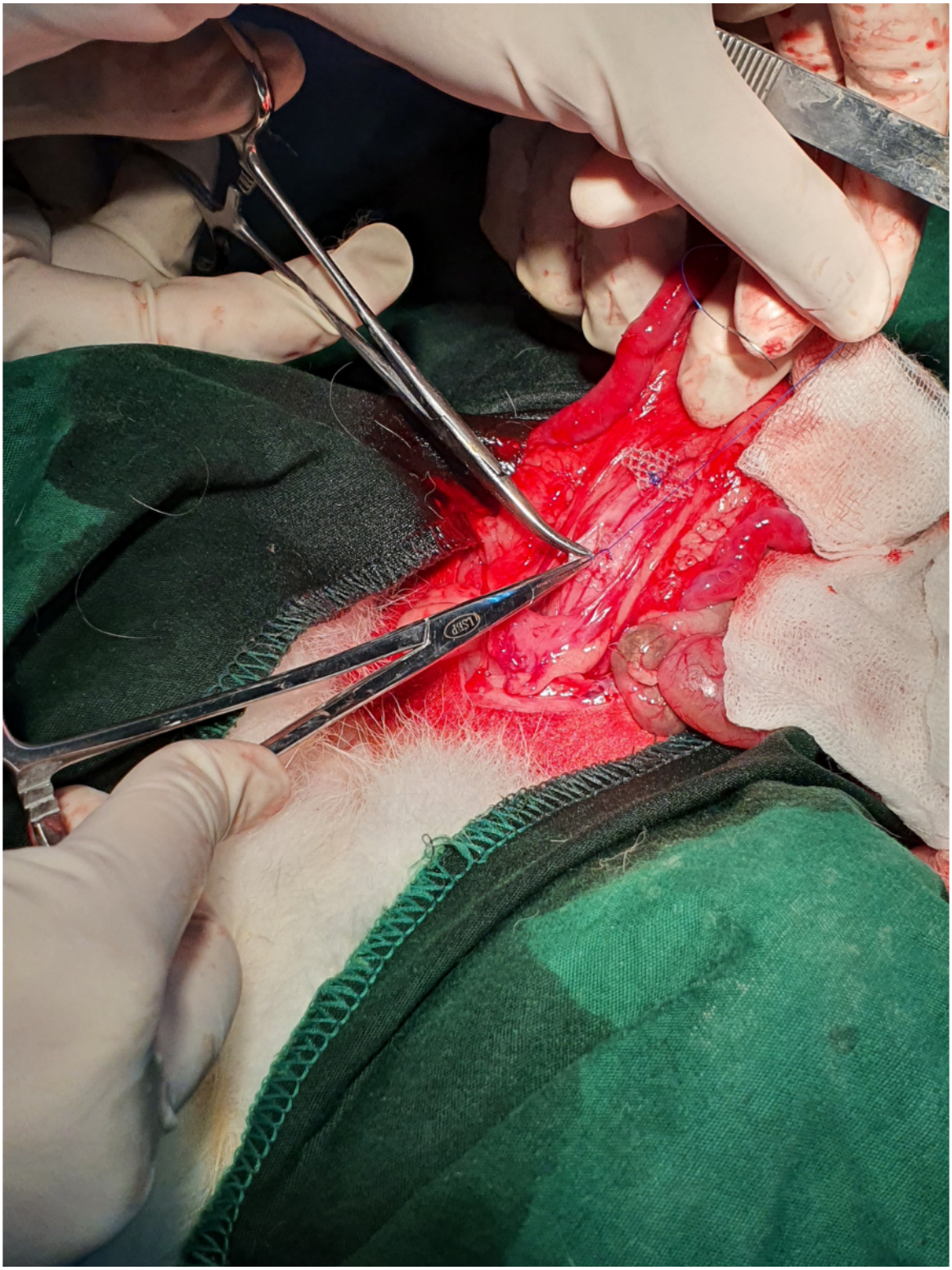


Figure 3. Application of the polypropylene mesh in the vesicovaginal space of a hypoestrogenic rabbit model.

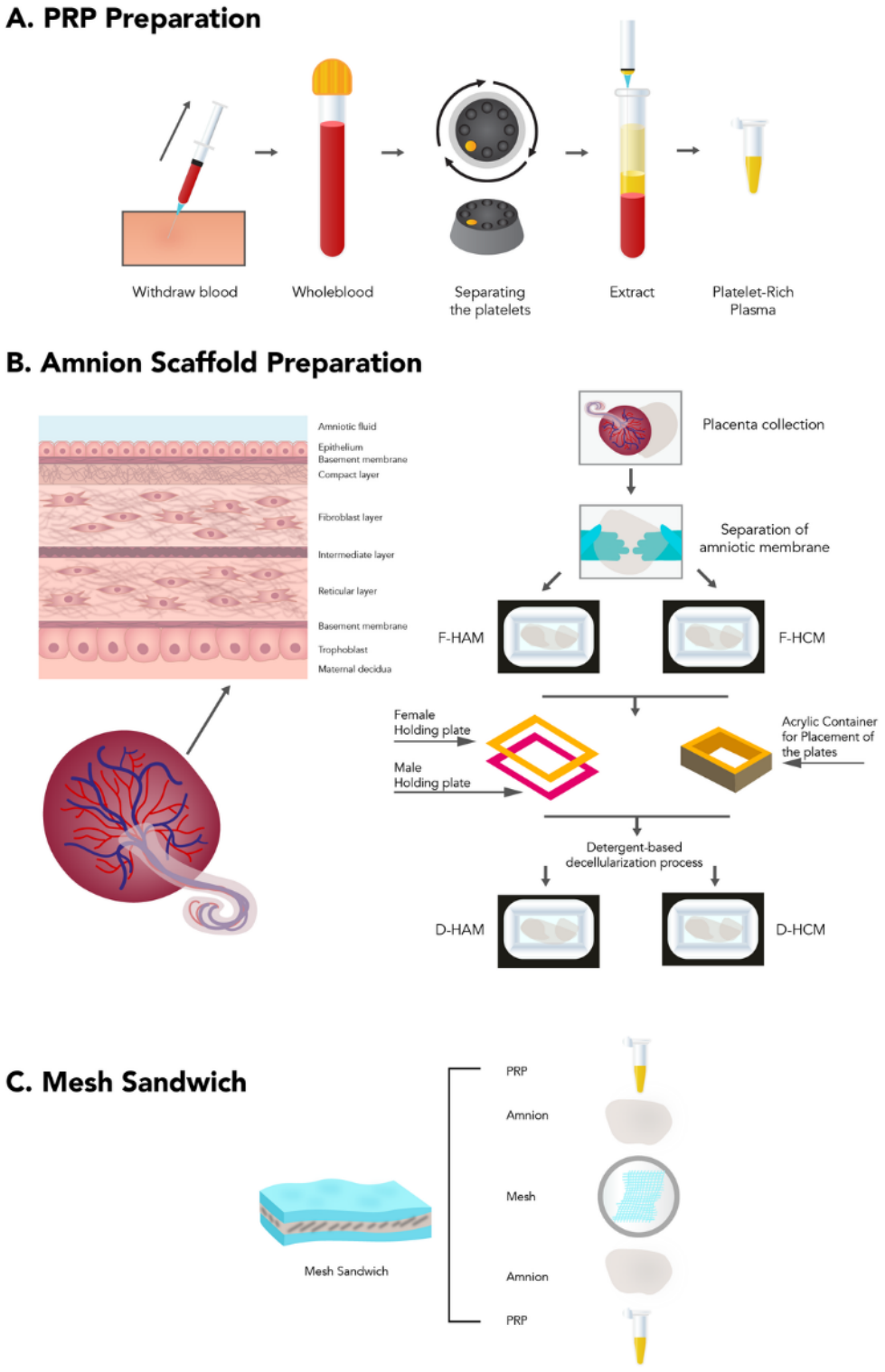


PRP-DAS–PPM Sandwich

Blood samples were taken from each subject by using a 23-gauge wing needle on the auricular vein. By using an autologous PRP preparation process that followed the standard protocol of our center, a platelet count was done before and after PRP preparation to ensure that the amount of platelets from each subject was standardized. A DAS was harvested from human placenta and collected in normal saline containing antibiotics (penicillin: 1000 IU/mL; streptomycin: 20 µg/mL, antifungal amphotericin B: 2.5 µg/mL). Under sterile conditions, the amnion will be separated from the chorion via blunt dissection under a laminar air hood. The separated amnion will be washed 2 to 3 times to remove all blood clots and blood. The amnion will be properly fixed on the cassettes of a bioreactor (19×14×0.3 cm). The amnion will be transferred to a 2% weight by volume sodium dodecyl sulphate solution, which will undergo gentle agitation on a shaker at 180 revolutions per

minute for 12 hours at room temperature. After 12 hours, the amnion will be transferred into deionized distilled water and stored in a deep freezer overnight. The amnion will be thawed on the next morning at room temperature, and this cycle will be repeated 8 to 10 times. The processes of decellularization will be checked at every fifth cycle via hematoxylin-eosin staining and 4,6-diamnionidino-2-phenylindol staining to confirm cell removal. A 1×1-cm mesh will be covered by a PRP-DAS on both sides, forming a sandwich configuration, as shown in Figure 4.

Figure 4. Proposed protocols for PRP-decellularized amnion scaffold–polypropylene mesh sandwich preparation. D-HAM: decellularized human amniotic membrane; D-HCM: decellularized human chorionic membrane; F-HAM: fresh human amniotic membrane. F-HCM: fresh human chorionic membrane; PRP: platelet-rich plasma.



Histologic and Immunohistochemical Analyses

Histologic Analysis

An inflammatory infiltrate analysis will be carried out histologically by using samples that will be placed in a container filled with 10% formaldehyde for 48 hours at 4 °C, transferred to a 70% alcohol solution, and fixed in 10% formalin. Then, the samples will be immersed in liquid paraffin to make a paraffin block. After a 30-minute incubation period, the paraffin blocks will be heated at 60 °C for 5 to 10 minutes; incubated twice in xylene for 5 minutes; and then rehydrated for 5 minutes once in 100% ethanol, once in 90% ethanol, once in 70% ethanol, and twice in deionized water. The samples will be stained via the hematoxylin-eosin staining method and observed using a microscope at a magnification of ×10 to ×40.

Collagen deposition will be assessed by using Masson trichrome staining.

Immunohistochemistry Analysis

Inflammation and angiogenesis will be analyzed using immunohistochemistry. We will use tissue samples that will be made into paraffin blocks by using the same method mentioned in the *Histologic Analysis* section. The endogenous peroxidase in the paraffin blocks will be inactivated with 3% H_2O_2 for 10 minutes at room temperature, blocked with 10% normal goat serum for 30 minutes at room temperature, and then incubated with primary antibodies overnight at 4 °C. Subsequently, the samples will be incubated with biotinylated secondary antibodies for 30 minutes at room temperature. Antigen-antibody binding will be assessed by using a detection system tool, and immunohistochemical staining will be performed by using diaminobenzidine. Objective calculations will be performed by calculating the immunoreactive area, which will be multiplied by the intensity to calculate optical density, using the imageJ tool (National Institutes of Health and the Laboratory for Optical and Computational Instrumentation).

To analyze inflammation, we will use monoclonal antibodies to interleukin (IL)-17 (Mybiosource) to detect IL-17 and IL-1B polyclonal antibodies (Bioss) to detect IL-1B. As for angiogenesis, we will use CD31 antibodies (WM59; Genetex) to detect CD31 levels in tissue samples.

Statistical Analysis

A statistical analysis will be accomplished for all clinical outcomes analyses. The data distribution will be tested by using the Kolmogorov-Smirnov test. SEs, 95% CIs, and *P* values will be reported. *P* values of ≤.05 will be considered significant for differences.

Results

Our study is at the protocol development stage, and as such, no results are available. The experimental procedures in this study will be done after a preliminary study for assessing its feasibility and ethical approval from Animal Research Ethical Committee, Faculty of Veterinary Medicine, Institut Pertanian Bogor University (approval number: 208-2021 IPB).

Discussion

Study Overview

Our study will investigate the impact of PRP-DAS application on mesh-tissue integration for the implantation of PPMs in rabbit models. We hypothesized that there would be a lower inflammatory response, higher levels of angiogenesis, and collagen deposition in hypoestrogenic rabbit models treated with a PRP-DAS.

The mesh-tissue integration process will be analyzed based on inflammatory parameters (inflammatory infiltrate, IL-17, and IL-1B expression), angiogenesis (CD31 expression), and collagen deposition (Masson trichrome staining). In the proposed study, we will attempt to develop a way to promote wound healing and mesh-tissue integration in mesh-augmented surgery for POP treatment.

PRP, as a source of concentrated growth factors, has been widely applied in the field of regenerative medicine. Several studies show the substantial clinical benefits of applying PRP in periodontal regenerative therapy, burn wound healing, and mesh-augmented surgery [8-12].

PRP Promotes Wound Healing

A study was done to investigate the effect of PRP on skin wound healing; a full-thickness skin defect model was used, and wound healing progress was analyzed at different time points after skin injury. The results showed that compared with the control group, wound closure in the PRP group was significantly accelerated, and the wounds were cleaner and exhibited much less exudation. These results were confirmed by several other studies [8-10].

PRP Decreases Wound Inflammatory Responses

A moderate inflammatory response is helpful to normal wound healing, though any disruption in this phase results in excessive wound healing or chronic wound formation. Several studies have shown decreases in inflammatory cell infiltration in PRP groups when compared with that in non-PRP groups [8-10].

PRP Promotes the Angiogenesis of Wound Tissue

Angiogenesis plays critical roles in effective wound healing. The results of several studies showed that the amount of neovascularization in wound tissue significantly increased in PRP groups when compared with that in control groups. These studies confirmed the positive impact of PRP on angiogenesis by measuring the expression of CD31, a marker for evaluating vascularization and angiogenesis, and vascular endothelial growth factor, a crucial growth factor for vascular endothelial cell division and angiogenesis in wound tissue. In these studies, CD31 and vascular endothelial factor levels increased, suggesting that PRP has a positive impact on angiogenesis [8-10].

PRP Promotes Wound Contraction and Collagen Arrangement

The expression and arrangement of collagen fibers in wounds determine the quality of tissue remodeling. In several studies, the evaluation of collagen deposition via the Masson trichromatic method showed a significant increase in collagen

deposition, which was accompanied by an ordered arrangement and uniform density, in PRP groups, suggesting that PRP could provide a favorable environment for further tissue remodeling [8-10].

Our study will identify the effect of a novel PRP-DAS–PPM sandwich on wound remodeling and tissue integration. The PRP will act as an anti-inflammatory and wound healing accelerator that will improve mesh-tissue integration through a nonconventional pathway. The results of our study will provide a better understanding on the underlying regulatory mechanism of PRP, especially among individuals in a hypoestrogenic state.

It is expected that there will be a lower inflammatory response, higher levels of angiogenesis, and collagen deposition in hypoestrogenic rabbit models treated with a PRP-DAS. The expected results are comparable to those of studies that were performed by Ávila et al [10] and Parizzi et al [6]. Ávila et al [10] showed that there was a significant difference in the number of inflammatory cells between the group with PRP and the group without PRP (P=.01) at 90 days, whereas Parizzi et al [6] showed that the group with PRP-coated meshes had a lower inflammatory infiltrate count at 30 days and exhibited increased collagen III deposition at 90 days.

The strengths of our study are the use of hypoestrogenic rabbit models and the use of the vesicovaginal space as the mesh implantation site. Similar studies used nonhypoestrogenic rabbit models and implanted meshes in the peritoneal space, which was sterile [10]. Therefore, previous studies did not describe the actual conditions for vaginally implanted meshes in menopausal women with normal vaginal flora (ie, the environment surrounding the mesh and how such an environment reduced a wound's healing potential). Our study will also be the first to perform PRP-DAS preparation. Further, a limitation of our study was the extensive training that each operator needed to undergo prior to performing the procedure.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report 1 by the Kementerian Riset Dan Teknologi (Ministry of Research and Technology) / Badan Riset Dan Inovasi Nasional (National Research and Innovation Agency) - Deputi Bidang Penguatan Riset Dan Pengembangan (Deputy for Strengthening Research and Development) (Jakarta, Indonesia).
[PDF File (Adobe PDF File), 180 KB - resprot_v11i8e37942_app1.pdf]

Multimedia Appendix 2
Peer-review report 2 by the Kementerian Riset Dan Teknologi (Ministry of Research and Technology) / Badan Riset Dan Inovasi Nasional (National Research and Innovation Agency) - Deputi Bidang Penguatan Riset Dan Pengembangan (Deputy for Strengthening Research and Development) (Jakarta, Indonesia).
[DOCX File , 680 KB - resprot_v11i8e37942_app2.docx]

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Abbreviations

ARRIVE: Animal Research Reporting In Vivo Experiments
DAS: decellularized amnion scaffold
IL: interleukin
POP: pelvic organ prolapse
PPM: polypropylene mesh
PRP: platelet-rich plasma

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Protocol

Oral Health Coaches at Well-Baby Clinics to Promote Oral Health in Preschool Children From the First Erupted Tooth: Protocol for a Multisite, Pragmatic Randomized Controlled Trial

Peggy C J M van Spreuwel[1,2], MSc; Katarina Jerković-Ćosić[1], PhD; Cor van Loveren[3], PhD; Geert J M G van der Heijden[2], PhD

[1]Research Group Innovation in Preventive Care, Hogeschool Utrecht University of Applied Science, Utrecht, Netherlands
[2]Oral Public Health Department, Academic Centre for Dentistry Amsterdam, University of Amsterdam and Vrije Universiteit, Amsterdam, Netherlands
[3]Academic Centre for Dentistry Amsterdam, University of Amsterdam and Vrije Universiteit, Amsterdam, Netherlands

Corresponding Author:
Peggy C J M van Spreuwel, MSc
Research Group Innovation in Preventive Care
Hogeschool Utrecht University of Applied Science
Heidelberglaan 7
Utrecht, 3584 CS
Netherlands
Phone: 31 654391441
Email: peggy.vanspreuwel@hu.nl

Abstract

Background: Early childhood caries is considered one of the most prevalent diseases in childhood, affecting almost half of preschool-age children globally. In the Netherlands, approximately one-third of children aged 5 years already have dental caries, and dental care providers experience problems reaching out to these children.

Objective: Within the proposed trial, we aim to test the hypothesis that, compared to children who receive usual care, children who receive the Toddler Oral Health Intervention as add-on care will have a reduced cumulative caries incidence and caries incidence density at the age of 48 months.

Methods: This pragmatic, 2-arm, individually randomized controlled trial is being conducted in the Netherlands and has been approved by the Medical Ethics Research Board of University Medical Center Utrecht. Parents with children aged 6 to 12 months attending 1 of the 9 selected well-baby clinics are invited to participate. Only healthy children (ie, not requiring any form of specialized health care) with parents that have sufficient command of the Dutch language and have no plans to move outside the well-baby clinic region are eligible. Both groups receive conventional oral health education in well-baby clinics during regular well-baby clinic visits between the ages of 6 to 48 months. After concealed random allocation of interventions, the intervention group also receives the Toddler Oral Health Intervention from an oral health coach. The Toddler Oral Health Intervention combines behavioral interventions of proven effectiveness in caries prevention. Data are collected at baseline, at 24 months, and at 48 months. The primary study endpoint is cumulative caries incidence for children aged 48 months, and will be analyzed according to the intention-to-treat principle. For children aged 48 months, the balance between costs and effects of the Toddler Oral Health Intervention will be evaluated, and for children aged 24 months, the effects of the Toddler Oral Health Intervention on behavioral determinants, alongside cumulative caries incidence, will be compared.

Results: The first parent-child dyads were enrolled in June 2017, and recruitment was finished in June 2019. We enrolled 402 parent-child dyads.

Conclusions: All follow-up interventions and data collection will be completed by the end of 2022, and the trial results are expected soon thereafter. Results will be shared at international conferences and via peer-reviewed publication.

Trial Registration: Netherlands Trial Register NL8737; https://trialsearch.who.int/Trial2.aspx?TrialID=NL8737

International Registered Report Identifier (IRRID): DERR1-10.2196/39683

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KEYWORDS

randomized clinical trial; dental caries; early childhood caries; oral health promotion; behavior change; motivational interviewing; dental public health; child health care; health inequality; prevention

Introduction

Dental caries (or tooth decay) represents a major public health problem affecting almost half of preschool-age children worldwide [1]. Early childhood caries (ECC) may have severe consequences on daily functioning and socialization in young children [2,3]. While dental caries is highly preventable with twice-daily toothbrushing using fluoridated toothpaste and limited sugar intake between main meals, compliance with these measures still requires much perseverance and endurance from parents. Noncompliance is often related to a lack of awareness among parents about their role in preventing ECC, a persistent belief that primary teeth are not important for oral health in later life, power struggles with the child, and tiredness of parents and their children [4-6]. As with many behavior-related diseases, dental caries shows marked socioeconomic disparities in all age groups [7,8].

Life-course epidemiology has highlighted that early childhood is critical for developing good oral health [9,10]. Positive oral hygiene behaviors and skills should be introduced early in the child's life, and parents need to acquire the knowledge to develop proper oral hygiene behaviors and skills [10]. This knowledge about the importance of caries prevention in early childhood contributes to the recommendation to have an early dental visit before the age of 1 year [11]. However, while in the Netherlands parents' compulsory health care insurance fully covers oral health care for their children up to the age of 18 years, oral health care professionals experience difficulties reaching children below 5 years of age, particularly those with lower socioeconomic backgrounds. As a result, less than half of Dutch children have visited an oral health professional at the age of 4 years, and dentin caries is present in about one-third of Dutch children aged 5 years [12,13]. At the same time, more than 90% of all newborns, including children from low socioeconomic backgrounds, visit well-baby clinics (WBCs) for preventive health care and vaccinations at regular intervals up to the age of 4 years [14]. Therefore, WBCs provide a unique window of opportunity for early oral health promotion.

Nevertheless, due to lack of time, medical and nursing staff at WBCs pay little attention to oral health promotion and timely referral to oral health professionals, prioritizing other child health issues over oral health promotion [15]. The second problem is that even when children visit an oral health professional on time, there is a lack of evidence-based interventions to provide appropriate preventive oral care starting from the first tooth [16]. Therefore, there is a double challenge in preventing poor oral health in early childhood. First, to reach young children with their parents in a timely fashion, and second, to develop and provide effective preventive oral health care and oral health promotion to address behavioral risk factors for poor oral health.

The Toddler Oral Health Intervention (TOHI; *Gezonde Peutermonden* in Dutch) has been developed to address these challenges by providing proven, effective early interventions. Firstly, in the TOHI, an oral health coach (OHC) is assigned by a dental clinic to participating WBCs in the same neighborhood. For children aged 6 to 12 months up to 48 months attending WBCs, the TOHI combines the regular WBC appointments with an appointment with the OHC. In doing so, the TOHI follows the example of the nationwide Scottish Childsmile program [17,18]. This program has successfully reached very young children and their parents through WBCs. Secondly, the OHC works according to the Non-Operative Caries Treatment And Prevention (NOCTP) approach, which has been reported to result in a 40% reduction in caries incidence in Dutch schoolchildren [19]. Thirdly, the OHC will use motivational interviewing (MI). While MI was initially developed as a behavioral technique for treating substance abuse [20], it has been shown to be effective in contributing to the prevention of ECC. MI has led to a reduction in caries incidence ranging from 16% to 26% and a 30% to 55% reduction in the number of decayed teeth [21-24]. Finally, the Health Action Process Approach (HAPA) [25], a theoretical framework to explain, predict, and modify health behaviors, provides tools to focus on the underlying determinants of behavior. By understanding the stages of behavioral change and focusing the intervention on the associated determinants, the impact of NOCTP and MI can be increased. The importance of determinants that underpin motivational and self-regulatory processes and help translate intention into behavior in oral health care, such as attitudes, self-efficacy, planning, and action control, has been demonstrated in previous research [26-29]. As the TOHI combines different existing components of health care and works on different organizational levels, it can be considered a complex intervention following the definition of the Medical Research Council (MRC) [30].

This paper describes a detailed research protocol to assess the effectiveness of the TOHI as an addition to usual WBC care, compared to usual WBC care only, in children aged up to 48 months. We hypothesize that the TOHI as an addition to usual care will reduce cumulative caries incidence at the age of 48 months (ie, the primary outcome measure), the sum of the number of decayed, missing, and filled surfaces and teeth (dmfs/dmft), the caries incidence density (person-time at risk to the first cavity), the presence of dental plaque, and the consequences of untreated caries (ie, secondary oral health outcome measures). We will study and report on (1) the oral health outcomes, (2) the behavioral outcomes, and (3) the balance between costs and effects of the TOHI.

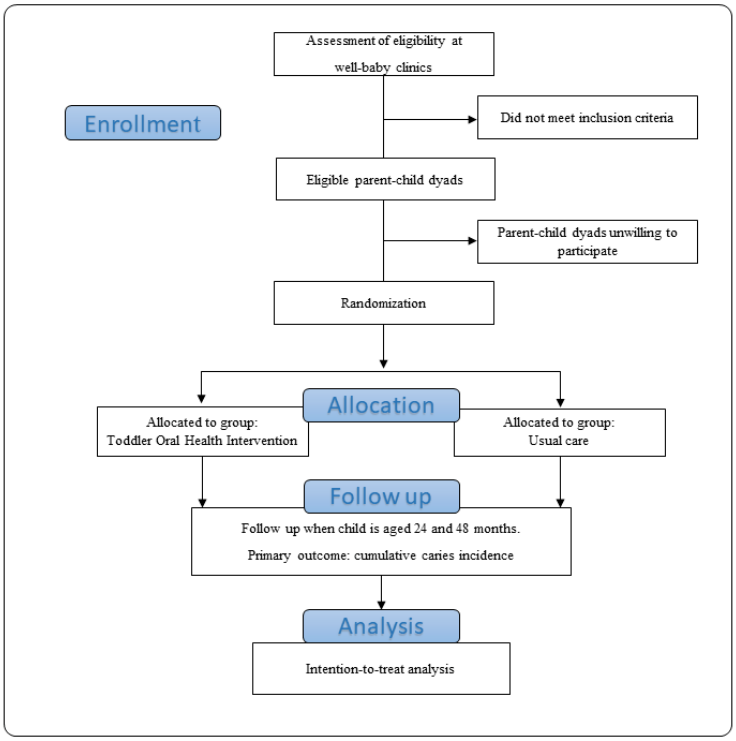
Methods

Trial Design and Setting

This protocol describes a pragmatic, 2-arm, individually randomized controlled trial (RCT) conducted in the Netherlands. The study population was recruited at 9 WBCs in urban and suburban regions with a population of predominantly low to

middle socioeconomic position (SEP). Figure 1 shows a flow chart of the study's overall design. This paper has been prepared following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines [31] and the Template for Intervention Description and Replication (TIDieR) [32].

Figure 1. Outline of the randomized controlled trial.



Ethical Considerations

Prior to study initiation, the research protocol was submitted to the Medical Ethics Committee of the University Medical Centre Utrecht for review and approval. The committee provided ethics clearance (NL60021.041.17; file number 17-133/D) and stated that the research complied with the applicable rules and requirements of the Medical Research Involving Human Subjects Act (Dutch abbreviation: WMO) and with the ethics code for the conduct of research as set out in the national Code of Conduct for Scientific Integrity in the Netherlands [33]. Participation was voluntary, and participants could withdraw at any moment with no consequences. Participants signed an informed consent form before enrollment. The trial is registered in the Netherlands Trial Register (NL8737).

Participants and Eligibility Criteria

This study includes parent-child dyads with children aged 6 to 12 months. The study excludes dyads with (1) children in need of specialized health care for a physical, mental, or medical condition; (2) parents with insufficient knowledge of Dutch; and (3) parents who expected to move outside the region of the WBC within the duration of the study. In the case of twins, only 1 child is enrolled in the study.

Sample Size Calculation

Previous studies show that the average number of caries lesions in Dutch children at the age of 5 years is 4.5 (SD 4.5) [12]. This information was used for study size estimation using G*power 3 [34]. This showed that the intervention group needed at least 149 participants to demonstrate a reduction in cumulative caries incidence of at least 30% with a statistically significant Mann-Whitney *U* test allowing for statistical power (1-β) of .8 and a 2-sided α of .05 as a threshold for statistical significance. With an anticipated 30% loss to follow up, the aim was to include at least 200 participants per group.

Intervention Randomization

With a 1:1 ratio, participating parent-child dyads were individually allocated to the intervention or control group. This allocation of the TOHI as an add-on to usual care was stratified for each WBC (9 in total) and educational level of the mother (classed as low, medium, or high) as an indicator of SEP. A computerized random sequence generator [35] with a block size of 4 to ensure equally filled strata in each group was used to allocate the intervention status to predefined unique ID numbers. Accordingly, an intervention allocation file was prepared, including intervention codes with blocked series of ranked unique participant IDs for the strata.

Informed Consent and Concealment of Intervention Allocation

Research nurses who were not involved in the intervention allocation determined the eligibility of parent-child dyads attending the selected WBCs. First, all eligible dyads received verbal and written information about what participation in the study entailed. Then, the parents or persons with parental legal authority signed the informed consent form to confirm voluntary participation. Upon receipt of this form, the principal investigator assigned a unique patient ID based on the WBC and education level of the mother. The corresponding intervention status was retrieved from the prepared allocation

files of an independent data administrator. Next, the principal investigator contacted the parents to inform them about the allocated intervention and to ensure that they understood all the information about their participation.

Blinding to the Nature of the Intervention

The research staff involved in clinical assessments are kept blinded to the nature of the allocated treatment. Due to the nature of the intervention, blinding of participating parent-child dyads has not been possible. To maintain the blinding of outcome assessors, parents are repeatedly instructed not to talk about the intervention they received with the assessors. The success of the blinding of the outcome assessors is tested by asking them the following question: "To which group is this child assigned according to your opinion?" Possible answers are as follows: "Control group: I know for sure," "Intervention group: I know for sure," "Control group: I think so," "Intervention group: I think so," and "I do not know" [36,37].

Intervention Development

The MRC guidance on developing and evaluating complex clinical health care interventions was utilized in development and evaluation of the TOHI [30]. Prior to this study, the feasibility of the TOHI was investigated in a small-scale feasibility study and evaluated through semistructured interviews with stakeholders, including oral health professionals, OHCs, youth health care professionals, and parents. The resulting findings were instrumental in the study design and were used to refine the TOHI and adapt it to participating WBCs in the trial. Textbox 1 presents the conceptual framework for the TOHI. A full description of the TOHI, following TIDieR reporting guidelines [32], is available in Multimedia Appendix 1. The different components of the TOHI are described below.

Textbox 1. Conceptual framework of the Toddler Oral Health Intervention.

Components of the Toddler Oral Health Intervention

- Using well-baby clinics to reach parents with newborn children
- Using the Non-Operative Caries Treatment And Prevention Method for individual risk assessment and preventive oral care
- Using motivational interviewing as the main tool to elicit internal motivation for desired behavior
- Using the Health Action Process Approach behavioral theory to guide the intervention based on underlying determinants of behavior

Expected mediators and secondary outcomes

- Increased self-efficacy
- Increased outcome expectancies
- Increased risk perception
- Intention forming for favorable oral health behavior; oral health coaches will explore barriers to and facilitators of favorable oral health behavior and focus on action planning and coping planning for favorable oral health behavior
- Action and maintenance of favorable behavior; if necessary, oral health coaches will work on recovery self-efficacy

Oral health behaviors

- Twice-daily toothbrushing with fluoride toothpaste
- Improved dietary habits with respect to oral health (eg, limiting sugar intake and the use of bottle-feeding, and drinking water more often)

Primary oral health outcome

- Reduced cumulative caries incidence

Interventions

In both the intervention and the control group, all dyads received or are receiving preventive child health care at the WBCs, which are regulated under the Public Health Act 2008. When a baby is registered in a municipality in the Netherlands, parents receive an invitation from the nearest WBC for a series of at least 13 appointments between birth and the age of 4 years. The goals of this preventive health care program are to monitor growth and development, detect health and social problems (or risk factors) at an early stage, screen for metabolic conditions and hearing in the newborn, deliver the national vaccination program, and provide advice and information on health [14]. According to the Public Health Act, this advice includes brief oral health promotion, such as the use of fluoridated toothpaste (at 500 ppm-750 ppm) and the advice to visit an oral health professional within the first year of life (Dutch Public Health Act, Article 6, paragraph 1, Dutch Public Health Decree). Dyads enrolled in the intervention group receive the TOHI in addition to this preventive health care program. Dyads enrolled in the control group receive only the usual care that all children receive at all WBCs in the Netherlands.

The TOHI builds on four components: (1) visiting an OHC at a WBC, (2) training OHCs to work accord to the NOCTP method, (3) using MI, and (4) using HAPA. The general understanding underlying the TOHI is that caries is a localized process and to a large extent can be prevented by brushing the teeth with fluoride toothpaste and lowering the frequency of sugar intake. With this understanding in mind, the OHC aims

to create awareness among parents that through establishing adequate oral health behavior, they can effectively contribute to preventing caries in their children. The standardized protocol of the NOCTP method contributes to a uniform and transparent approach for OHCs and parents [19]. The method assigns 1 point based on parental cooperation and motivation, measured by the child's oral hygiene and whether they follow the key oral health messages of the Ivory Cross national guidelines [38], and 1 point for active or incipient caries or lesions (Table 1). MI is used in the TOHI to elicit parents' internal motivation and explore barriers and facilitators for desired oral health behavior. Finally, HAPA is a hybrid behavioral model that explicitly outlines 2 different phases of health behavior change: a motivational, intention-forming phase and a volitional phase in which translation of intention into action takes place [25]. Guided by HAPA, the OHCs focus on motivational and self-regulatory processes, such as self-efficacy, planning, and action control, which have been shown to be mediators in translating intentions into behaviors [29]. The OHC combines the NOCTP protocol with an intervention guided by HAPA and MI skills to determine which aspects of behavior need to be addressed for a tailored intervention.

Table 1. Criteria for caries risk assessment, recall interval, and intervention.

Caries risk score	Risk	Intervention	Interval
0	Low	Periodic oral examination	Combined with scheduled well-baby clinic appointment within 6 to 12 months
1 (without active caries lesions)	Average	Shortened interval for periodic oral examination and exploration of barriers to and facilitators of self-care agreements	Combined with scheduled well-baby clinic appointment within 3 to 6 months or extra appointment when indicated
1 or 2 (with active caries lesions)	High	Shortened interval for periodic oral examination and exploration of barriers to and facilitators of self-care agreements; if necessary, referral to a dental office for fluoridation or treatment of caries lesions or incipient caries lesions	Combined with scheduled well-baby clinic appointment within 1 to 3 months or extra appointment when indicated

Procedures of the TOHI

Face-to-face, 10-to-20-minute appointments with an OHC were combined with the child health care appointments at the WBC at the ages of 6 or 8, 11, 15, 18, 24, 36, and 42 months. Every appointment with the OHC started with an assessment of the child's caries risk, following the NOCTP protocol. Subsequently, the OHC adjusted the oral health promotion to this risk by targeting the mediating determinants according to the HAPA, depending on the parents' health behavior phase. When the intention was formed, self-care agreements were made in the volitional phase that focused on planning and action control to translate intentions into behaviors. Additionally, ambivalent feelings and barriers or facilitators to self-care agreements were explored using MI to stimulate intrinsic motivation and reinforce parents in existing positive behavior. According to the NOCTP protocol, when an increased caries risk was detected, the OHC could decide to schedule an additional appointment. If incipient caries lesions were detected, parents were educated on how to clean the caries lesion, and the use of fluoride toothpaste was again emphasized. When dental treatment for caries was deemed necessary, the OHC referred the participants to a dental clinic.

Materials Used for the TOHI

A penlight and disposable materials (eg, cotton rolls to dry elements, dental mirrors, and wooden toothpicks to detect dental plaque on elements) were used for oral assessments by the OHC. In addition, the OHC used predefined paper patient records to ensure efficient and uniform reporting. These paper records contained age-related oral health topics to discuss, a caries risk assessment according to the NOCTP protocol, and an assessment of the parents' oral health behavioral stage. The final caries risk and behavioral stage guided the OHC to follow-up actions, such as which mediating determinants from the HAPA should be addressed with the intervention (Multimedia Appendix 2). Parents in the intervention group received a specially developed TOHI booklet at baseline. This booklet was developed for 2 reasons. First, it contained oral health reports for each appointment with the OHC, which effectively communicated the child's caries risk to the parents. These reports also covered agreed self-care actions to reduce caries risk. Together with the parents, the OHC examined and recorded the barriers to self-care actions and the mediating determinants of self-efficacy, action planning, and coping planning in these reports (Multimedia Appendix 3). Finally, the booklet covered essential oral health information and provided tips and tricks that the OHC could refer to.

Oral Health Coaches and Training

Eligible OHCs for this study had a background in dentistry (they were dentists, dental hygienists, or dental assistants). They were prevention-minded, trained (or willing to be trained) in the NOCTP method, had good social communication skills, and had experience in pediatric dentistry. In addition, all OHCs received training in the TOHI delivered by a certified MI trainer and the principal investigator, who are both experienced in training oral health professionals and students in NOCTP, HAPA, and MI. A pediatric dietitian provided extra training on infant and toddler nutrition related to oral health. The first training session took place before the study started. Subsequently, training continued every 3 to 4 months for the duration of the study. During this training, the focus was on recognizing stages of health behavior, using HAPA, and developing advanced MI skills, such as recognizing and managing behavioral resistance and detecting ambivalence. Learning these skills takes time and is an ongoing process. Therefore, the training consisted of presenting practical

examples of (successfully resolved) complex cases provided by the OHCs, role-playing, and peer feedback. In addition, the MI trainer provided individual feedback via self-recorded audio fragments that were uploaded by the OHCs. These audio fragments were assessed biannually with the Motivational Interviewing Treatment Integrity (MITI) [39] system by an independent MI expert. The results of the intervention fidelity will be analyzed and prepared for an original process evaluation article alongside the article reporting the results of the effectiveness study.

Design of Data Collection

The outcome measures and additional data were collected with online questionnaires at baseline and with online questionnaires and clinical examinations when the children reached the ages of 24 and 48 months. Table 2 provides an overview of measurements and timepoints.

Table 2. Measurements and timepoints.

Timepoint	Study period			
	–T1[a]	T0[b]	T1[c]	T2[d]
Enrollment				
Eligibility screening	✓[e]			
Informed consent	✓			
Allocation	✓			
Interventions				
Toddler Oral Health Intervention performed at ages 6-8, 11, 14-15, 18, 24, 30, and 36 months		✓	✓	✓
Care as usual		✓	✓	✓
Primary outcome				
Clinical assessment of cumulative caries incidence with Merged International Caries Detection and Assessment System [40]				✓
Secondary outcomes				
Clinical assessment of average number of decayed, missing, and filled surfaces and teeth with Merged International Caries Detection and Assessment System			✓	✓
Clinical assessment of person time at risk for first cavity with Merged International Caries Detection and Assessment System and incidence density			✓	✓
Clinical assessment of consequences of untreated dental caries with the PUFA (visible pulpal involvement, ulceration caused by dislocated tooth fragments, fistula, and abscess) index			✓	✓
Clinical assessment of presence of dental plaque with Simplified Oral Hygiene Index, 6-surface method [41]			✓	✓
Online questionnaire assessment of oral health behavior with self-developed items		✓	✓	✓
Online questionnaire assessment of psychosocial constructs of the Health Action Process Approach items (action self-efficacy, risk perception, outcome expectancies, intention, action planning, coping planning, and action control), adapted from Gholami and Schwarzer (2014) [42]		✓	✓	✓
Online questionnaire assessment of oral health–related quality of life with the Early Childhood Oral Health Related Quality of Life [43] scale			✓	✓
Online questionnaire assessment of child cooperativeness at oral examinations with the Frankl behavior scale [44]			✓	✓
Compliance, fidelity, and cost outcome measures				
Total care delivered by oral health coach, assessed by frequency and time in minutes as reported by the oral health coach			✓	✓
Reasons for and number of visits to a dental clinic (other than Toddler Oral Health Intervention), assessed by parent interviews				✓
Oral health coach mastery of motivational interviewing competencies, assessed by applying Motivational Interviewing Treatment Integrity codes to audio recordings [39]		✓	✓	✓

[a]–T1: screening and allocation.

[b]T0: baseline.

[c]T1: follow-up at age 24 months.

[d]T2: follow-up at age 48 months.

[e]✓: measurement or action performed at this time point.

Training of Outcome Assessors

The clinical outcome measures were collected by trained and calibrated dentists or dental hygienists in an assessor-blinded manner. The assessors were experienced in the use of the International Caries Detection and Assessment System (ICDAS) codes [40] for teaching or research purposes. Therefore, the training consisted of the online International Caries Classification and Management System (ICCMS) core e-learning [45] system and an online interrater reliability test developed for this study. This test presented 20 expertly verified high-quality pictures with different merged ICDAS scores in random order. If necessary for calibration, additional norming meetings were organized to maintain the performance of the assessors for the duration of the study.

Outcome Assessments

At 24 and 48 months, a knee-to-knee examination (Figure 2) is completed with the assistance of the parents or caregivers. The selected tooth surfaces are scanned from the incisal to the gingival edge with a toothpick to determine the presence of dental plaque. Next, the child's teeth are cleaned and dried with cotton rolls or gauze to enable an adequate view of the tooth surfaces and systematic examination of each tooth for the presence of caries or incipient caries. Findings are recorded in an online case record form developed for this study by an assistant. If no assistant is available, an audio recording is used so that the assessor can work efficiently and speak their findings aloud, preventing recall bias in later reporting. In cases with findings such as dentine caries, caries-related inflammation, and eruption failure of the primary teeth, parents receive a letter with the advice to visit a dentist and the reasons for doing so. If necessary, the OHC provides a list of nearby dentists. After dental treatment, children in the intervention group return for follow up with the OHC.

Figure 2. Knee-to-knee position for oral examination.

Primary Outcome

The cumulative caries incidence at the age of 48 months will be assessed by merged ICDAS [40] scores. These merged scores differentiate teeth as being sound or having initial, moderate, or severe caries.

Secondary Outcomes

The average dmfs/dmft number and the caries incidence density (person-time at risk to the first cavity) will be calculated from the merged ICDAS scores. Consequences of untreated dental caries will be measured using the PUFA (visible pulpal involvement, ulceration caused by dislocated tooth fragments, fistula, and abscess) Index [46]. The presence of dental plaque will be determined with the 6-surface method of the Simplified Oral Hygiene Index [41]. Child cooperativeness during the outcome assessments will be documented by clinical assessors using the modified Frankl behavior scale [44].

Behavioral change over time will be assessed based on self-reported oral health behavior and psychosocial constructs from the HAPA, measured with online questionnaires at baseline, age 24 months, and age 48 months. The early childhood oral health–related quality of life will be measured using the Early Childhood Oral Health Impact Scale [43].

Demographics and Patient Characteristics

The demographic characteristics include the children's age, sex, family composition, mother's highest educational attainment according to the International Standard Classification of Education [47], and health literacy measured with the 16-item European Health Literacy Survey Questionnaire (HLS-EU-Q16) [48].

Design of Data Analyses

All analyses of the effectiveness of the TOHI will make use of the intention-to-treat principle. To prevent biased principal data analysis, concealment will be maintained during data analysis. The blinding of the study comparison will be broken only after the completion of data analysis for the evaluation of outcomes for children at the age of 48 months. After data cleaning and prior to data analysis, the amount and patterns of missing data will be explored. Sensitivity analysis will be used to explore the impact of missing data. The 3 following scenarios will be assumed: stability over time (last value carried forward or backwards to replace missing value), best case (largest positive change score observed to replace missing value), and worst case (largest negative change score observed to replace missing value).

The intervention effects for the cumulative caries incidence at 48 months and the average dmfs/dmft will be compared as the risk difference (additive scale), numbers needed to treat, and the relative risk (multiplicative scale), all with the 95% CI. Effects for subgroups (ie, WBC, education level of the mother, and health literacy) will be evaluated with interaction terms in a multivariate regression analysis. To determine incidence density and person-time at risk, the median and mean between-group differences in caries incidence (or the person-time to first caries lesion) will be based on a Kaplan-Meier analysis and incidence differences and ratios. In addition, when applicable, Cox proportional hazard regression analysis will be applied to explore relations with independent variables. Between-group differences at the age of 24 months will be assessed for the secondary outcomes, notably changes in the behavioral determinants (defined according to the HAPA), plaque, and self-reported oral health behavior, using linear regression analysis. Results from all analyses will be presented with the 95% CI. For all analyses, the SEP stratum will be used as the primary covariable, while sociodemographic characteristics for which a baseline difference is observed will be used as secondary covariables. Such postrandomization differences between groups will be explored using descriptive statistics. A difference of 20% for discrete variables, a full standard deviation (pooled) for normally distributed data, and a quartile for nonnormally distributed data will be used as thresholds for similarity.

Cost-Effectiveness

Measurement and Inventory of Costs

The *Dutch Manual for Costing Studies in Health Care* will guide the identification of costs [49]. Cost prices will be calculated individually, which means that the frequency and reason for visits to the dental clinic will be requested for both groups. Based on this information, a cost price can be calculated. For the intervention group, the cost for the add-on TOHI will be based on the reported time that the OHC spent at each appointment.

Cost-Effectiveness Analysis

If the TOHI is shown to be superior as an additional treatment to usual care in the analysis of the principal outcome (using the imputed data set), we will analyze the balance between the effect and cost of the TOHI. We will then report the results of a cost-effectiveness analysis and a cost-utility analysis. Incremental cost-effectiveness ratios will be calculated by dividing the difference in total costs between conditions by the difference in average effect size. Because we will calculate costs over 48 months, correction for inflation will be considered. Bias-corrected and accelerated bootstrapping with 5000 replications will be used to calculate the 95% CI around the mean difference in total costs between the treatment groups. Bootstrapping will also be used to estimate the uncertainty surrounding the incremental cost-effective ratio, which will be graphically presented on cost-effectiveness planes. Results from the economic evaluation will be reported in line with the Consolidated Health Economic Evaluation Reporting Standards Statement [50].

Results

The first parent-child dyads were enrolled in June 2017, and recruitment finished in June 2019. In total, 402 dyads have been randomized. Interventions and data collection for all of these dyads will be completed by the end of 2022. Therefore, final results are expected in the first half of 2023.

Discussion

This paper describes the study protocol for a multisite, pragmatic RCT that will examine the effectiveness of an innovative approach in preventing ECC in Dutch preschool-age children. The literature on prevention strategies for ECC assumes that interventions initiated during pregnancy or in the first year of life have a good chance of success [9,51,52]. However, there is currently no consensus on targeting preschool-age children from the first year of life and effectively offering preventive care from first tooth eruption [16,53]. As a result, there is a gap in the current provision of preventive oral care, and knowledge is lacking among the target group and health professionals [15,54]. Furthermore, our study population is at risk of caries at an age at which oral health care is shown to be of low priority for many, even though health insurance fully covers it [8]. Therefore, the TOHI study has been welcomed by oral health professionals and public health care workers. With this pragmatic multicenter study, we aim to contribute to the current evidence base on preventive oral health care, particularly the effects of ECC preventive interventions in preschool children, and inform current practices and standards for dental care and youth health care.

Before initiating our TOHI study, 5 RCTs with similar objectives and populations in a public health setting had been published [21,55-59]. Since then, the results of another 8 RCTs have been published (as of February 2021) [21,51,52,60-65].

Comparing our study with these previous studies reveals similarities and differences. Most of these studies concerned oral health outcomes and the organization of care similar to ours to ensure early access to oral health promotion or dental care; most studies focused on target groups from the lower social classes. All studies started within the first year of the child's life (or during pregnancy) and had caries incidence or cumulative caries incidence as the principal outcome measure. Interventions included repeated oral health messaging, handing out pamphlets or oral hygiene products, and providing maternal counselling using MI and anticipatory guidance, sometimes combined with professional fluoride applications. Only 1 of the published studies described a tailored intervention where counselling was based on an individual caries risk approach, such as was used in the TOHI [58]. To our knowledge, none of the published studies assigned oral health professionals as OHCs to WBCs to provide preventive care combined with the regular WBC visits. While some studies included nonrandomized comparisons or even used historical control groups, others used clustered randomization. The study sizes ranged from 187 to 1441. Follow up for study endpoints in the published studies ranged from 12 to 48 months, with some continuing to observe the children until school age. None of these studies continued the intervention after the age of 42 months.

When interpreting the results of this study, the strengths and weaknesses of the study design and conduct must be taken into account. First, a strength is that the TOHI is based on strategies that have proven to be successful in previous studies. We have interviewed parents, oral health professionals, and public health workers on their needs and priorities for promoting the oral health of preschool children. Representatives of these groups have contributed to the study design phase and regularly convened during the conduct of the study. The intervention principles have been translated into a standardized, structured approach with practical instructions for oral health coaches and parents, which has been tested in a small-scale feasibility study. Nevertheless, combining oral health promotion by OHCs at WBCs requires organizational changes in the provision of public and oral health care and commitment from parents.

Second, our study methods endeavored to prevent bias wherever possible by publishing the study design and transparently reporting the methods and procedures used for the determination of statistically appropriate sample size, the randomized, stratified, and concealed intervention allocation, and for blinding of study staff involved in collecting study data and analyzing study outcomes. However, our study was designed for real-life practice and required compromises. In particular, decisions about trade-offs between the optimum research design and the practicalities of delivering health care in the real world were challenging [66]. While the usual-care control condition (the current nationwide, municipal Public Health Service protocol at WBCs) was assumed to include recommendations and advice on oral health, a previous study has shown that little can be expected from this [15]. Therefore, the TOHI was studied as a pragmatic RCT and delivered as an add-on to usual care. A placebo for the TOHI to blind participants to the allocated add-on intervention was not feasible. Hence, information bias cannot be ruled out as influencing the study results because of the pragmatic study design.

Third, it is generally known that RCTs usually include participants with a higher level of education or greater motivation and interest. In anticipation of this, WBCs were selected after consultation with the municipalities to represent neighborhoods with a predominantly low-SEP population. In addition, during participant recruitment, much attention was paid to translating the patient information required by the medical ethics committee, being physically present at the WBCs, designing banners and flyers with accessible information, and providing information by telephone to those interested.

Finally, this study had a relatively long follow-up time compared to most other studies on this topic. Therefore, to ensure sufficient statistical power to detect clinical relevance and statistical significance for the principal endpoint, a 30% dropout rate was taken into account when estimating the initial sample size before the start of the intervention.

Dissemination and implementation of our TOHI approach are planned on different levels and in various directions. The dissemination plans include activities both scientific and practical, and therefore include activities such as publication of the results of the RCT in scientific journals and presentations at conferences, as well as activities in support of national oral health policy and practice. For the dissemination of knowledge to practice, distinctions can be made between dissemination plans on the micro, meso, and macro levels. Activities at the micro level include training courses, education and post–initial education, and online or offline workshops to update oral health professionals with knowledge about preventive oral care from first tooth eruption and provide practical tools. At the meso level, the project group investigated what was needed for sustainable implementation of the TOHI; this will be translated into ready-to-use implementation plans for the practices. At the macro level, the knowledge and results will be shared with local and national politicians, policymakers, and health insurers to examine how oral care for the very youngest individuals can be organized differently and how this should be financed. Finally, it should be noted that we have created a practice network in which, in terms of implementation and maintenance of change of practice, establishing ownership of the TOHI is our main goal.

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Authors' Contributions

PCJMvS, KJC, GJMGvdH, and CvL contributed to the idea and concept of the study. PCJMvS, KJC, GJMGvdH, and CvL contributed to the design, methodology, and protocol of the study. PCJMvS, KJC, GJMGvdH, and CvL contributed to the acquisition of study funding. PCJMvS contributed to preparing the draft of the manuscript. KJC, GJMGvdH, and CvL contributed to critical revision of the manuscript draft. KJC, GJMGvdH, and CvL contributed to the final approval for publication of the manuscript. KJC, GJMGvdH, and CvL contributed to supervision of study conduct. PCJMvS, KJC, GJMGvdH, and CvL contributed as guarantors of study integrity.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intervention description of the Toddler Oral Health Intervention following TIDier.
[DOCX File , 29 KB - resprot_v11i8e39683_app1.docx]

Multimedia Appendix 2
Example of patientrecord.
[PDF File (Adobe PDF File), 112 KB - resprot_v11i8e39683_app2.pdf]

Multimedia Appendix 3
Example of oral health report.
[PDF File (Adobe PDF File), 894 KB - resprot_v11i8e39683_app3.pdf]

Multimedia Appendix 4
Peer-reviewer report 1 from the Taskforce for Applied Research SIA (The Netherlands).
[PDF File (Adobe PDF File), 535 KB - resprot_v11i8e39683_app4.pdf]

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Abbreviations

dmfs/dmft: decayed, missing, and filled surfaces and teeth
ECC: early childhood caries
HAPA: Health Action Process Approach
HLS-EU-Q16: 16-item European Health Literacy Survey Questionnaire
ICDAS: International Caries Detection and Assessment System
MI: motivational interviewing
MRC: Medical Research Council
NOCTP: Non-Operative Caries Treatment And Prevention
OHC: oral health coach
PUFA: visible pulpal involvement, ulceration caused by dislocated tooth fragments, fistula, and abscess
RCT: randomized controlled trial
SEP: socioeconomic position
TIDieR: Template for Intervention Description and Replication
TOHI: Toddler Oral Health Intervention
WBC: well-baby clinic

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Protocol

Learners' Perspectives of Professionalism: Protocol for a Mixed Methods Systematic Review

Nagina Khan[1,2], BHSc, PhD; Walther van Mook[3,4,5], MD, PhD; Subodh Dave[6,7,8], MMed; Sohyun Ha[1], BSc; Joshua Sagisi[1], BSc, MMSc; Nicole Davi[1], BA; Chantel Aftab[1], BA, MPH; Sucheta Tiwari[9], MSc, MD; Marie Hickman[6], BA; Wolfgang Gilliar[1], DO

[1]Department of Osteopathic Medicine, Touro University Nevada, Henderson, NV, United States

[2]Association of University Teachers of Psychiatry, London, United Kingdom

[3]Department of Intensive Care Medicine, Maastricht University Medical Centre, Maastricht, Netherlands

[4]School of Health Professions Education, Faculty of Health, Medicine, and Life Sciences, Maastricht University, Maastricht, Netherlands

[5]Maastricht UMC+ Academy, Maastricht, Netherlands

[6]Department of Osteopathic Medicine, Derbyshire Healthcare NHS Foundation Trust, Derbyshire, United Kingdom

[7]Department of Osteopathic Medicine, University of Bolton, Bolton, United Kingdom

[8]Royal College of Psychiatrists, London, United Kingdom

[9]East London NHS Foundation Trust, London, United Kingdom

Corresponding Author:
Nagina Khan, BHSc, PhD
Department of Osteopathic Medicine
Touro University Nevada
874 American Pacific Drive
Henderson, NV, 89014
United States
Phone: 1 702 777 3975
Email: nkhan786can@gmail.com

Abstract

Background: Professionalism has come to be associated with competence in medical education, with the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values, and reflection in daily practice for the benefit of the individual and community being served. Recent studies indicate students should have the opportunity to observe the application of knowledge and skills by their mentors to improve patient health and safety. A noticeable detail that needs implementation into the curriculum is the inclusion of student perspectives. This review will explore students' understanding and experience of professionalism in undergraduate medical education (UME).

Objective: This paper presents the protocol for a review that aims to develop an integrated synthesis of qualitative and quantitative studies resulting in recommendations for medical school curricula to incorporate the learners' perspectives in teaching professionalism in UME.

Methods: We will take an integrated approach to synthesis. Data will be extracted from the included studies, and quantitative data will be "qualitized." PubMed (Medline), Embase, PsycInfo, and ERIC (Education Resources Information Center) will be searched for studies published in English from 2010 to 2021. Studies will be screened and critically appraised for methodological quality using the Mixed Methods Appraisal Tool by 2 researchers, with disagreements resolved by a third researcher. Qualitative, quantitative, and mixed methods studies will be considered. Our population of interest is undergraduate medical students; hence, studies on medical residents and graduate medical students will be excluded. We will consider studies that explore how concepts of professionalism are understood, experienced, and taught in undergraduate medicine and on how medical students understand and develop the identified constructs of professionalism.

Results: This study is in the screening phase; therefore, no results are available at this time. However, we had initiated the searches, screening, and are currently in the critical appraisal stage. We will commence preparation to clean and convert the data for coding in July 2022, and analysis will be ongoing from the end of July 2022 until submission for publication in November 2022.

Conclusions: This research will contribute to the student perspectives on professionalism in medical education literature. The findings will aid in the creation of a checklist to guide the development of a curriculum on professionalism in UME.

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KEYWORDS

professionalism; undergraduate medical education; medical school; medical education; medical curriculum; teaching methods; teaching; medical students; student; undergraduate; convergent integrated synthesis; integrated synthesis; curriculum; recommendation; learner; perspective; review

Introduction

Background

Professionalism has become an important topic in medical education with growing recognition of the importance of medical students and doctors in developing excellence in professionalism [1]. The Association of American Medical Colleges states that physicians must be altruistic, knowledgeable, skillful, and dutiful [2]. Among the 6 general competencies listed by the Accreditation Council for Graduate Medical Education are "interpersonal and communication skills that result in effective information exchange and teaming with patients, their families, other health professionals" and "professionalism, as manifested through a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population" [3,4]. Competence in these areas not only necessitates that training programs support the development of competence but also that they evaluate students' professionalism. The American Board of Internal Medicine certification program contains issues associated with ethics and professionalism [5]. These efforts accentuate the importance of training and assessing professionalism [6]. Professionalism remains a recognized core competency of doctors [7], implying that the classification and definition of professionalism are also subjected to contextual and temporal changes [8]. Professionalism is an important aspect of training and health systems; however, integration into teaching varies, from formal teaching to learning through nonintegrated methods such as the hidden curriculum. Two elements, namely context (environment) and learners' perspectives, have shown to be important in undergraduate medical education (UME) because students training to be physicians need to develop a sense of consistency that contributes context specificity as well as resilience to working in complex, rapidly changing environments. The shifting debate in medical education emphasizes that education remains learner centered and should be guided by learner needs [9].

The perspective of learners is underrepresented in the literature, with few studies focusing on learners. In recent years, a number of investigations have presented evidence on how certain types of medical education, such as longitudinal integrated clerkships [1-3], can support professionalism and patient-centered approaches. However, there is still insufficient evidence as to how, why, and in what circumstances learners' perspectives and engagement with professionalism are valuable. These data are central if we are to improve medical education for the development of professional physicians [4]. Learners, as active participants in their education, may provide unique insights into not only the intervention but also the context in which the learning occurs (context-environment) [10]. Therefore, we contend that identifying and integrating approaches from learners' perspectives is important for supporting their understanding of working in complex environments. This gap could prove fundamental to the engagement of students with professionalism and for them to shift from simply enacting key competencies to embedding them in real environments through their own thought processes as learners to increase satisfaction in their work, career, and professional competence in ways they find acceptable and easy to understand.

Consequently, the aim of our work is to explore undergraduate medical students' views toward professionalism education and to identify the barriers to and facilitators of integration in the undergraduate medical curriculum.

Objective

The objective of this review is to develop an integrated synthesis of qualitative and quantitative research to derive recommendations for UME relevant to incorporating learners' perspectives in the current teaching of professionalism in the curriculum. Specifically, we aim to:

- Identify learners' perceptions of the potential barriers to or facilitators of professionalism;
- Identify learners' experience with the most useful methods that are used to teach professionalism;
- Determine future priorities for the curriculum, considering the strengths and limitations of the complexity of individual cases and the changing health care environment.

Methods

Inclusion Criteria

Population

We will include studies on undergraduate medical students, and we will exclude studies on medical residents and graduate medical students.

Phenomena of Interest

We will explore studies on learners' perspectives, attitudes, understanding, and experiences of professionalism in UME.

Context

We will consider studies that explore the concepts of professionalism and medical students' understanding of and experiences with it, including a focus on the teaching methods

that allow experiential learning and context. The settings will include community practices, hospitals, and academic settings.

Types of Studies

This review will consider qualitative, quantitative, and mixed methods studies.

Qualitative studies will include designs such as primary qualitative studies, underpinned with ethnography, phenomenology, and grounded theory; ethnographic interviews; narrative studies; and program evaluations. Unpublished studies will not be included.

Quantitative studies will be included if they are program evaluations.

Studies published in English (for easy access and ease of interpretation) and published from 2010 to 2021 will be included. Since contemporary health systems are changing, we will focus on current perceptions as related to student understandings and not the historical beginnings of professionalism.

Study Design

The integrative review method (Textbox 1) was selected for this study to include a broad range of empirical studies (both qualitative and quantitative) [11-13]. This research design is appropriate as the research question is focused on the why and the how, as well as examining a contemporary phenomenon. This method is appropriate for our study because the integrative review reexamines, critiques, and synthesizes findings from separate but related research to develop new frameworks or perspectives about a specific phenomenon or topic [14]. An integrative review addresses a new or emerging topic as opposed to mature topics and provides an initial model rather than recreating previous models [12,14,15]. This method will be carried out via the following steps (also see Table 1):

- Create a search strategy with the specialist medical librarian;
- Search databases and remove duplicates from the retrieved articles using Mendeley Reference Manager (Mendeley Ltd);
- Screen the articles according to the inclusion and exclusion criteria using Rayyan software (Rayyan) [16];
- Conduct a critical appraisal using the Mixed Methods Appraisal Tool (MMAT) [17];
- Integrate both quantitative and qualitative data to focus on the same research question;
- Transform the data into a similar format (eg, “quantitized” or “qualitized” [18]);
- Comb narratively and present a narrative analysis of the findings.

Overall, the findings will elicit learners’ perspectives of professionalism and their experience of the most useful methods used during teaching.

Textbox 1. A summary of methodological approaches for convergent integrated mixed methods systematic reviews [13].

Review design: Convergent integrated
Description: Involves data transformation that allows reviewers to combine quantitative and qualitative data
What is involved in the integration? Direct assimilation
Methods for integration: Content analysis, vote counting, thematic synthesis

Table 1. Outline of a mixed methods study.

Study component	Description
Qualitative	• Construct a search strategy, retrieve articles, remove duplicates, and screen according to the inclusion criteria • Critically appraise the articles included, code the data, and convert the data for analysis • Analysis of data
Quantitative	• Construct a search strategy, retrieve articles, remove duplicates, and screen according to the inclusion criteria • Critically appraise the articles included, code the data, and convert the data for analysis • Analysis of data
Mixed analysis	• Qualitative data: identify themes • Quantitative data: qualitize and identify themes • Combine identified themes, draft a list of guidelines from the findings, and finalize the document and disseminate

Information Sources

The databases searched include PubMed, Embase, PsycInfo, and ERIC (Education Resources Information Center).

Search Strategy

The search strategy was created to retrieve both published and unpublished studies using the Peer Review of Electronic Search Strategies 2015 guideline [19]. An initial limited search of Embase, PubMed, PsycInfo, and ERIC was undertaken to identify articles on the topic. The keywords contained in the titles and abstracts of relevant articles, as well as the index terms used to describe the articles, were applied to develop a full search strategy for the 4 databases mentioned above (Multimedia Appendix 1) [20]. The search strategy, including all identified keywords and index terms, was adapted for each included information source.

Study Selection

Following the search, all identified citations were collated and uploaded into Mendeley and duplicates were removed. The citations were exported to a systematic review software (Rayyan QCRI [16]). Titles and abstracts were then screened by 2 independent reviewers for assessment against the inclusion criteria for the review. In instances where reviewers did not agree, a third reviewer adjudicated on whether the article should be retrieved. At present, the full text of the selected citations has been assessed for inclusion by the reviewers. A third reviewer was asked to adjudicate if there is disagreement between the reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria were recorded and reported in the systematic review. The included articles will then be critically appraised using the MMAT [17]. The results of the search will be reported in full in the final systematic review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [21,22].

Data Extraction

Data will be extracted from qualitative studies included in the review by 2 independent reviewers using customized Microsoft Word tables (Microsoft Corp) for recording and extracting data (see Tables S1 and S2 in Multimedia Appendix 2). The data extracted will include specific details about the population, context, culture, geographical location, study methods and findings, themes, and the phenomena of interest relevant to the review objective. Findings will be extracted and assigned a level of credibility. Any disagreements that arise between the reviewers will be resolved through discussion or with input from a third reviewer.

Data Analysis

For qualitative and quantitative data to be integrated, data needs to be transformed either by converting qualitative data into quantitative data (ie, quantitizing) or by converting quantitative data into qualitative data (ie, qualitizing). This stage will be carried out by the 2 researchers qualified in qualitative research methods and verified by a third researcher. We will:

- Qualitize quantitative data;
- Extract the data and convert them into themes, categories, typologies, or narratives [18];
- Use thematic analysis [23,24] since it can be widely used across a range of epistemologies and research questions [25] (this technique can be used to distinguish, analyze, structure, explain, and describe themes found in a data set [26]).

Ethical Considerations

This study does not involve the use of animal or patient data, or recruitment of human subjects. Consequently, the research conducted as part of this study presents minimal risk and fits one of the exempt review categories as defined by institutional review board regulations at Touro University Nevada.

Results

This study is in the critical appraisal stage; therefore, no results are obtainable. At the writing stage of this protocol, we had initiated the searches for the review, which included search strategy development, removal of duplicate articles, and screening.

We received no external funding for this study.

Discussion

Complex Concepts

In this study, we will use mixed methods to generate a checklist of items for consideration in the process of developing a curriculum on professionalism for medical students. An integrative review design was selected for this study to allow for the use of both qualitative data and quantitative findings [27].

We anticipate most of the concepts of professionalism to be perceived as complex by learners. As the purpose of this study is to develop a checklist for guidance in generating a curriculum on professionalism, our key insights will be used to bring student understandings of professionalism into the formal teaching of this subject to improve the learning and training of physicians, to positively impact patient outcomes, and to reduce errors and risk.

We will investigate and focus on the understanding gained from using mixed methods to explore our study objectives. We contend that this combined focus on quantitative and qualitative data used collectively provides a rich understanding of professionalism teaching and would help create innovative academic curricula that contribute to teaching complex elements of professionalism.

We believe this will support our students in identifying early on not only with the profession but taking it one step further to also identify with the environments that they will likely be involved in when assessing, meeting, and treating patients. Additionally, our research aims to identify learners' perceptions of actual or potential barriers to or facilitators of professionalism in those environments. Further research exploring such concepts and processes could be developed. Our international research team is committed to structuring contextual knowledge about professionalism, developing links that will exist longitudinally, and attempting to continually teach current findings on the topic of professionalism.

Strengths and Limitations

The strength of this study includes the use of both quantitative and qualitative methods. Furthermore, the research team is made of medical students and medical educators who have been involved in this project from the beginning. The guidance checklist will be coproduced with input from medical students. The study is limited in that we will not have the added benefit of accessing any raw data (including transcriptions, reflective notes, and author insights about the context of the studies included) [28].

Conclusion

We aim to create a checklist to guide the development of a curriculum on professionalism. This checklist will directly incorporate insights from student learners and will have detailed justifications and rationale for a curriculum on professionalism. Our study will potentially have implications for learning, teaching, and future assessment of professionalism in medical education, health systems, and educational policies.

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Authors' Contributions

NK and WG were involved in study conception and design. NK, WvM, WG, and SD drafted the manuscript. MH performed the literature searches. All authors revised the manuscript critically for intellectual content and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 16 KB - resprot_v11i8e37473_app1.docx]

Multimedia Appendix 2
Data extraction tables.
[DOCX File , 16 KB - resprot_v11i8e37473_app2.docx]

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Abbreviations

ERIC: Education Resources Information Center
MMAT: Mixed Methods Appraisal Tool
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UME: undergraduate medical education

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Protocol

Micronutrient Supplementation for Pregnant and Lactating Women to Improve Maternal and Infant Nutritional Status in Low- and Middle-Income Countries: Protocol for a Systematic Review and Meta-analysis

Sachin Shinde[1], MA, MPA, PhD; Dongqing Wang[1], PhD; Mashavu H Yussuf[2], PhD; Mary Mwanyika-Sando[2], MD, MPH; Said Aboud[3], PhD; Wafaie W Fawzi[1], MD, MPH, PhD

[1]T H Chan School of Public Health, Harvard University, Boston, MA, United States

[2]Africa Academy for Public Health, Dar es Salaam, United Republic of Tanzania

[3]Department of Microbiology and Immunology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania

Corresponding Author:
Sachin Shinde, MA, MPA, PhD
T H Chan School of Public Health
Harvard University
90 Smith Street
Boston, MA, 02115
United States
Phone: 1 617 435 1445
Email: sshinde@hsph.harvard.edu

Abstract

Background: Two billion people in low- and middle-income countries (LMICs) are deficient in key nutrients. Nutritional deficiencies worsen during pregnancy, causing adverse outcomes for the mother and the fetus, with consequences after pregnancy. These effects may be mitigated by providing micronutrient supplementation to women during pregnancy and lactation. However, the effects of micronutrient supplementation on the nutritional status of pregnant and lactating women and that of their infants remain largely unclear in LMICs.

Objective: The purpose of this systematic review and meta-analysis is to determine the effects of single, double, or multiple micronutrient supplements during pregnancy or lactation on maternal and infant nutritional status in LMICs.

Methods: Randomized controlled trials of single, double, or combinations of micronutrients assessing effects on the maternal (serum, plasma, and breastmilk) and infant (serum and plasma) nutritional status will be included. MEDLINE (through PubMed), EMBASE, CENTRAL (through Cochrane Library), and the World Health Organization (WHO) library database will be used to identify relevant published studies, starting from the inception of each database until February 28, 2022. The Cochrane Risk of Bias Tool will be used to assess the risk of bias in the included studies. The selection of studies, data extraction, and risk of bias assessment will be carried out independently by 2 reviewers. A narrative summary will be provided of all the included studies. Meta-analyses will be performed whenever possible, and the heterogeneity of effects will be evaluated using I^2, subgroup analyses, and metaregression. The certainty of the evidence for each outcome will be assessed using the GRADE (Grading of Recommendation, Assessment, Development, and Evaluation) approach.

Results: We will conduct meta-analyses using Stata software (version 16, StataCorp) and present both a narrative and systematic summary of all studies included in this review in text and table form. For continuous outcomes, effect estimates will be expressed as mean differences and standardized mean differences, while for binary outcomes, they will be expressed as risk ratios, rate ratios, hazards ratios, or odds ratios, all with 95% CIs and comparing the intervention group with the control group. When studies for an outcome are adequately consistent with respect to intervention, comparator, and definition of the outcome, a random-effects, inverse variance-weighted meta-analysis will be conducted. We will provide a narrative synthesis for outcomes with insufficient data or extreme heterogeneity.

Conclusions: This review will provide evidence upon which to base policy and programming for women in LMICs to supplement micronutrients in pregnancy and lactation. Detailed results disaggregated by variables such as maternal age, sex of infant, duration,

and dose of intervention may also help policy makers, researchers, practitioners, and government agencies to adopt more effective maternal and child health policies and programs in LMICs. The review will also identify any gaps in the existing evidence.

Trial Registration: PROSPERO CRD42022308715; https://tinyurl.com/y33cxekr.

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antenatal care; multiple micronutrient supplementation; pregnant and lactating women; systematic review and meta-analysis; review; meta-analysis; meta-analyses; low- and middle-income countries; LMIC; low income; middle income; women's health; pregnant; pregnancy; natal; maternal; maternity; infant; baby; babies; lactation; lactating; breastfeed; nutrition; vitamin; nutrient; supplement

Introduction

Background

Micronutrient deficiency is defined as an insufficient intake of vitamins and minerals required in small amounts by the body for good health, growth, and development [1]. Often referred to as hidden hunger, micronutrient deficiency, undernutrition, and overweight and obesity make up the triple burden of malnutrition. Worldwide, there are around 2 billion people who do not receive adequate micronutrients [2,3]. Women of reproductive age (15-49 years old) in low- and middle-income countries (LMICs) often have concurrent deficiencies of multiple micronutrients due to inadequate dietary intake and limited choices in fruits, vegetables, animal proteins, and fortified foods [1]. Micronutrient deficiencies can also be caused by infections and chronic diseases that directly interfere with nutrient absorption [4]. The World Health Organization (WHO) contends that micronutrients are important for maternal and child health because they help the body produce hormones, enzymes, and other substances essential for normal growth, development, and functionality [1]. In pregnancy and lactation, however, the burden and severity of micronutrient deficiencies are worsened by the increased demand, leading to potentially adverse effects on both the mother and her newborn [5]. Moreover, repeated pregnancies and short interpregnancy intervals may also affect maternal micronutrient status [6]. As a result, multiple micronutrient deficiencies are common among pregnant women, particularly in LMICs [7].

Anemia affects half a billion women worldwide or about 29% of nonpregnant women and 38% of pregnant women, mostly in South Asia and Central and West Africa, while maternal vitamin A deficiency affects approximately 15% of pregnant women [8]. It is well-established that iron-deficiency anemia in the reproductive age, especially during pregnancy, can lead to adverse maternal and newborn outcomes, including an increased risk of maternal mortality, perinatal mortality, and low birth weight [9]. Deficiencies in other micronutrients, such as vitamins A, B-complex, C, D, and E, are also common in LMICs, resulting in poor pregnancy outcomes, fetal growth retardation, and maternal and child health problems [9-13]. For example, folate deficiency is undoubtedly associated with neural tube defects [14], and low vitamin D levels during pregnancy may contribute to preeclampsia, small-for-gestational age, and perinatal mortality [15]. Malnutrition of the mother can also impact her offspring's long-term outcomes, such as growth, neurodevelopment, cognition, and cardiovascular, pulmonary, and immune function [7]. Therefore, unaddressed micronutrient deficiencies may threaten the survival and well-being of women and their newborns and put subsequent generations at risk of malnutrition due to intergenerational transfer [4].

Micronutrient malnutrition among women can be reduced by diet diversification, large-scale and targeted fortification, biofortification of staple crops, and micronutrient supplements [16]. Multivitamins and mineral supplements are commonly consumed during pregnancy in high-income countries, but this practice is less common in LMICs. Currently, there is a move toward multiple micronutrient supplementation in pregnant women to reduce adverse pregnancy outcomes in these parts of the world. To address the issue of multiple and concurrent micronutrient deficiencies, the United Nations Children's Fund, United Nations University, and the WHO developed a multiple micronutrient (MMN) tablet called UNIMMAP (United Nations International Multiple Micronutrient Antenatal Preparation). The MMN tablet provides the daily recommended intakes of vitamins A (800 µg), B1 (1.4 mg), B2 (1.4 mg), B6 (1.9 mg), B12 (2.6 µg), C (70 mg), D (200 IU), E (10 mg), niacin (18 mg), folic acid (400 µg), copper (2 mg), selenium (65 µg), and iodine (150 µg) with 30 mg of iron and 15 mg of zinc for pregnant women. [17] However, the WHO does not yet universally recommend multiple micronutrient supplements for pregnant women over the current practice of prenatal supplementation with iron and folate, except in the context of rigorous research [18,19].

Most of the recent studies and reviews on maternal and infant nutrition and pregnancy outcomes have approached the issue by investigating either a single micronutrient or multiple micronutrients [9,10,14-16,20,21]. In many of these reviews, data from studies conducted in LMICs are included. However, significant heterogeneity in results has been reported, and it is unclear whether micronutrient supplementation has comparatively greater benefits in any particular settings or subgroups. Furthermore, while there is ample evidence of the benefits of maternal micronutrient supplementation on pregnancy outcomes [22], few studies have examined the effect of these supplements on micronutrient status among women and children. Many of the systematic reviews are several years old [16,20,21] and thus highlight the need for an updated synthesis of evidence based on more recently completed trials. Therefore, a synthesis of evidence on micronutrient supplementation during pregnancy and lactation, which focuses

on vitamins and their effect on maternal and infant nutrition status in LMICs, will provide the basis for future research and discussions of policy implications.

Specific Aims

The review will summarize the available evidence on single, double, or multiple micronutrient supplements in LMICs. We aim to achieve the following objectives through this review: (1) to assess the effects of single, double, and multiple micronutrient supplements among pregnant or lactating women on maternal (plasma, serum, and breast milk) and infant nutritional status (plasma, and serum) in LMICs; (2) to understand the effect modifiers (such as micronutrient supplement dose and duration) that might alter the impact of micronutrient supplements on maternal and infant status; and (3) to identify subgroups of women and infants who might experience greater effects from micronutrient supplements and identify the sources of heterogeneity across studies.

Methods

Data Sources, Search Terms, and Search Strategy

We will search MEDLINE (through PubMed), EMBASE, CENTRAL (through Cochrane Library), and the WHO library database and conduct a manual search of bibliographies to identify potentially relevant published studies using a combination of medical subject headings (MeSH) and text words denoting micronutrient supplements and maternal and infant micronutrient status. We will search all databases for eligible studies starting with the launch of each database until February 28, 2022. We will also examine cross-references and bibliographies of the included studies to identify additional sources of information. This search will be supplemented by reviewing ClinicalTrials.gov and organizational websites such as the International Initiative for Impact Evaluations, WHO, World Bank, United Nations Children's Fund, and the United Nations Population Fund. When possible, reports written in languages other than English will be translated by colleagues who are native speakers of those languages. Studies that cannot be adequately translated will not be considered.

We will use the PICO (participant, intervention, control, and outcomes) model (Table 1) to guide our search strategy, but we will not be restricted by the outcome to maintain a broad search. The search will use indexing terms, including MeSH terms, keywords, and free text words. First, a broad search strategy will be performed in PubMed without time restrictions; for example, type of study (randomized controlled trial) AND intervention (single, double, or multiple micronutrient supplements) AND population (pregnant and lactating women) AND setting (low- and middle-income countries). We will confirm the sensitivity of the search strategy by identifying several sentinel articles. The PubMed strategy provided in Multimedia Appendix 1 will be adapted to suit other databases. We will document the following details for each search: databases searched, date of search, search strategy (ie, subject headings and keywords, including whether terms are expanded or truncated and how they are combined), filters used, and the number of records retrieved. Additionally, a source will be provided for each publication identified through manual search (ie, name of the journal, website, conference proceedings, etc).

Table 1. Eligibility criteria for the systematic review and meta-analysis in PICO (participant, intervention, control, and outcomes) format.

Population	Pregnant or lactating women of any age and parity, living in a low or middle - income country
Intervention	• Single, double, and multiple vitamin supplementation (including micronutrient powders, tablets, syrups, and lipid-based micronutrient supplements)
Control	• Author-defined (placebo, only iron supplement, only iron and folic acid supplement, or no care)
Outcomes	• Micronutrient deficiencies
Maternal outcomes	• Vitamin A serum/plasma/breastmilk retinol • Vitamin B1 serum/plasma thiamine • Vitamin B2 serum/plasma riboflavin (flavoenzymes flavin mononucleotide and flavin adenine dinucleotide) • Vitamin B3 serum/plasma (niacin and metabolite) • Vitamin B5 serum/plasma pantothenic acid • Vitamin B6 serum/plasma/breastmilk pyridoxal phosphate • Vitamin B7 serum/plasma biotin • Vitamin B9 folic acid or folate serum/plasma/breastmilk • Vitamin B12 serum/plasma cobalamin • Vitamin C plasma/serum/breastmilk • Vitamin D serum/plasma (25-hydroxyvitamin D) • Vitamin D breast milk (D3) • Vitamin E serum/plasma/breastmilk tocopherol • Vitamin K serum/plasma/breastmilk
Newborn outcomes	• Vitamin A serum/plasma retinol • Vitamin B1 serum/plasma thiamine • Vitamin B2 serum/plasma riboflavin (flavoenzymes, flavin mononucleotide, and flavin adenine dinucleotide) • Vitamin B3 serum/plasma (niacin and metabolite) • Vitamin B5 serum/plasma pantothenic acid • Vitamin B6 serum/plasma pyridoxal phosphate • Vitamin B7 serum/plasma biotin • Vitamin B9 folic acid or folate serum/plasma • Vitamin B12 serum/plasma cobalamin • Vitamin C plasma/serum/breastmilk • Vitamin D serum/plasma (25-hydroxyvitamin D) • Vitamin E serum/plasma tocopherol • Vitamin K serum/plasma

Eligibility

The inclusion and exclusion criteria for this study are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Only randomized controlled trials (RCTs) will be included. Participants may be randomly assigned, individually or in clusters, to intervention and comparison groups. Crossover designs will be eligible for inclusion.
- Studies involving healthy pregnant or lactating women of any age and parity.
- Studies conducted in low- and middle-income countries, as defined by the World Bank in the 2021 [23].
- Studies of single (vitamins A, B-complex, C, D, E, or K), double, or multiple vitamin supplementation (containing at least three micronutrients) in the form of tablets, drops, syrup, or powder for pregnant or lactating women. We will also include trials of multiple micronutrient supplements that contain folate (vitamin B) with iron supplements (mineral). There will be no restrictions regarding the duration of exposure to the intervention, the provider of the intervention, and the frequency of the intervention (eg, daily or intermittent supplementation).
- Studies that examined the impact of lipid-based micronutrient supplements. We will, however, analyze the studies focusing on lipid-based micronutrient supplements separately, as these provide additional calories and nutrients that might have independent effects on outcomes of interest.
- Studies including a control group that received only iron, only iron and folic acid supplement, placebo, or no care
- Studies assessing the maternal and infant micronutrient status as the outcomes using biochemical tests.Table 1 provides the details on maternal and infant outcome definitions. International units will be used for all maternal and infant outcomes.
- Published articles as well as ongoing studies that have preliminary findings available.
- We will not place any restrictions on the study year, language, sample size, or duration of the intervention.

Exclusion criteria

- Quasi-experiment trials and nonrandomized controlled studies.
- Studies without a proper comparator intervention arm (eg, uncontrolled before-after studies).
- Observational studies such as cohort, case-control, and cross-sectional designs.
- Editorials, commentaries, opinions, and review articles. However, we will use review articles to identify additional original articles.
- Studies focused on populations with specific conditions (eg, populations with chronic or genetic diseases such as HIV, tuberculosis, or metabolic disorders).
- Studies that examined the impact of fortified food supplements.
- Studies focusing only on pregnancy outcomes such as low birth weight, preterm birth, small for gestational age birth, perinatal death, stillbirth, and neonatal death, or maternal and infant status of minerals, and those that do not report on nutritional status.

Data Management

Records retrieved from electronic databases will be stored in EndNote X9 (Clarivate Analytics). Additionally, the records will be imported into Covidence (Veritas Health Innovation), an internet-based program that facilitates the streamlined management of systematic reviews. Duplicates will be detected and removed first by EndNote and then by Covidence.

Study Selection

Studies for the title and abstract screening and full-text screening will be managed using Covidence. First, 2 reviewers (authors SS and MHY) will independently assess all the search results (ie, titles and abstracts) based on the inclusion and exclusion criteria to eliminate irrelevant studies. Then, the full-text screening will be conducted in duplicate according to the same inclusion/exclusion criteria. If there is a difference of opinion between the 2 reviewers, it will be resolved in discussion or by a third reviewer (author DW), if necessary. The inter-rater agreement will be measured by computing the raw percentage of agreement and Cohen κ coefficient. Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [24], a study flow diagram will be maintained stating the specific reasons for exclusion. Journal titles and authors' names will not be concealed from reviewers.

Data Extraction

The data of studies included in the review will be independently extracted and entered by the 2 reviewers. A data extraction form will be developed and then pilot-tested on 5 randomly selected studies. We will extract the following information: title, authors (first author and corresponding author), contact information of the corresponding author, journal (or source for unpublished reports), calendar year of publication, calendar year of intervention, country, source of funding, study design, sample size (for cluster RCTs, number of clusters for each group, and number of participants in each group), sample characteristics (eg, age, sex, socioeconomic status), intervention (including timing, duration, dosage, nutritional content, and cointerventions), measure of adherence, comparator/control, outcomes assessed, and main findings with point estimates and measures of variance (standard errors, 95% CIs, or *P* values). We will compile multiple reports from a single study, as there may be additional results in several reports. For missing information or inconsistent results across reports of a single study, we will contact the corresponding author via email for more accurate results or additional information. We will attempt

to contact the author a maximum of 2 times. If we cannot resolve the data issue after this, we will analyze the available data and discuss the possible impact of the missing data.

Quality Assessment

Two independent reviewers will conduct the risk of bias assessment. We will resolve any uncertainties or disagreements by discussion or by bringing in a third reviewer if necessary. In each included RCT, we will assess the risk of bias for each outcome reported instead of performing an analysis of the whole study. We will use the second version of the Cochrane Risk of Bias tool, known as RoB II, for RCTs [25]. This tool considers the following 5 domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results. Each domain will be judged as having a "low risk of bias," "high risk of bias," or "some concerns." An RCT will be considered as having a low risk of bias if its risk is low across the domains; high risk of bias if its risk is high in at least 1 of its domains, or some concerns for 3 or more domains that lower confidence in the results. We will consider an RCT to have some concerns if it raises some concerns in at least 1 domain but is does not have a high risk of bias for any domain. If necessary, we will contact the authors of the reports to obtain more information. A summary of our assessment of bias risk will be compiled into a table in which each judgment, along with the justification, will be outlined. We will also analyze the overall strength of the evidence for each outcome using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) tool [26].

Data Synthesis

A narrative and systematic summary of all the studies included in this review will be presented in the text as well as a table. We will treat micronutrient supplementation as a dichotomous exposure (intervention versus control). In the case of an intervention study with more than 2 arms, each arm will be treated separately. Effect estimates for continuous outcomes will be expressed as mean differences (MDs) and standardized mean differences (SMDs) with 95% CIs comparing the intervention group with the control group. Using the same format for each outcome (eg, means and standard deviations for continuous data), we will convert scales so that an increase/decrease always indicates improvements or deteriorations of an indicator. In cases where the data reported by included studies are not usable (ie, cannot be pooled with other data), we will contact the corresponding author for access to data or revised statistics. If we are unable to contact the corresponding author, or the data is unavailable, we will retain the study as eligible but restrict further analysis. Data on continuous outcomes will be presented as either an MD if outcomes have been measured on the same scale or an SMD if outcomes have been measured on different scales with 95% CIs. Changes in baseline scores and final measurements will be eligible for pooling if the scales and measurements are similar. Due to the differences in measurement reliability, we will not combine final values and change scores as SMDs. The standard deviation of the change will also be reported when combining measures of treatment effect with SMDs.

Effect estimates for binary outcomes will be expressed as risk ratios, rate ratios, hazard ratios, or odds ratios, all with 95% CIs and comparing the intervention group with the control group. Different studies may define deficiency of the same vitamin using different cutoffs. In the primary analyses, we will follow the cutoffs chosen by the authors to define the deficiency, while in the sensitivity analyses, we will restrict to only those studies that used well-established cutoffs. Our data extraction for RCTs will be based on intent-to-treat analyses.

We will conduct a random-effects, inverse variance-weighted meta-analysis for an outcome if studies for that outcome are sufficiently consistent in terms of intervention, comparator, and outcome definition. Since the effect of micronutrient supplementation is expected to be heterogeneous across dose, duration, and populations, the random-effects method will be used. The generic inverse-variance approach will be used for both binary and continuous outcomes to adjust study weights according to the variance of the effect estimate. We will interpret overall effect estimates that have an associated *P* value less than 0.05 as statistically significant but will also comment on those effects where the upper and lower CIs have just crossed the line of no effect. The GRADE tool [26] will be used to assess the quality of the evidence for the outcomes for which the meta-analysis is to be conducted. Meta-analyses will be conducted only when there are data for a minimum 2 studies per the outcome of interest. Sensitivity analyses will be conducted to determine whether the removal of studies with a high risk of bias significantly influences findings.

We will assess effect heterogeneity by computing the I^2 statistic, which represents the percentage of the total variation in the effect estimates that is due to true heterogeneity rather than chance. An I^2 statistic over 50% will be considered substantial heterogeneity. We will assess the sources of heterogeneity by conducting subgroup analyses. Subgroup analyses for outcomes will be conducted when 2 or more studies are available per subgroup of interest. The following prespecified subgroups will be considered: pregnancy versus lactation status of women, maternal age, type/formulation of micronutrient supplement (single, double, or multiple micronutrients), duration of intervention, dosage of the micronutrient supplements, presence of cointerventions (by itself or combined with complementary interventions), baseline nutritional status in mothers, sex of infant, country or geographic region, and risk of bias (low, high, or some concerns). To further explain heterogeneity, we will perform a metaregression using the predictors mentioned above.

We will use contour-enhanced funnel plots to detect publication bias if there are 10 or more studies available for an outcome. Publication bias is unlikely if data forms a symmetric inverted funnel shape around the mean effect estimate. In addition, we will perform the Egger test to determine funnel plot asymmetry [27].

For outcomes with insufficient data or extreme heterogeneity that cannot be assessed in subgroup analyses or metaregression,

we will provide a narrative synthesis without a meta-analysis. Statistical analyses will be conducted using Stata software (version 16, StataCorp).

Registration and Reporting

This systematic review and meta-analysis protocol has been registered on the PROSPERO database (registration number CRD42022308715). In the event of protocol amendments, the date of each amendment will be accompanied by a description of each change and the rationale on PROSPERO. In preparing this protocol, we followed the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols) checklist, [24], which is contained in Multimedia Appendix 2. Our systematic review will be reported following the Cochrane Handbook for Systematic Reviews of Interventions [28] as well as the PRISMA guidelines [24].

Ethics Approval

Ethics approval was not required for this systematic review and meta-analysis because we are only examining secondary data already available in scientific databases.

Results

As of June 30, 2022, we have run and imported the searches into all selected databases. In total, we have extracted and screened the 23,702 searches for titles and abstracts. We plan to complete the data extraction and analysis for selected studies and write the report by December 2022.

Discussion

Summary

In this planned review and meta-analysis, we will assess the evidence available on the impact of maternal multiple micronutrient supplements on infant and maternal nutrition. By synthesizing evidence regarding potential effect modifiers that could alter the effectiveness of micronutrient supplements on maternal and infant status, the findings from this study will fill important knowledge gaps and provide directions for future research and policies.

Appropriate care and adequate prenatal preparation and nutrition are important factors that affect the nutritional status and outcome of pregnancy for mothers, children, families, and society. Nutritional deficiency during pregnancy and lactation may have adverse effects on the mother, the child, and future generations. The prevalence of concurrent deficiencies of multiple micronutrients among pregnant women and young children is well documented, particularly in LMICs [5-8]. Micronutrient supplementation, either alone or in combination, has shown to be effective in improving maternal, birth, and child outcomes. For example, the 2019 Cochrane review of 17 trials found that multiple micronutrient supplementation with iron and folic acid after 20 weeks of pregnancy reduced preterm births and small-for-gestational-age births in underweight women, decreased small for-gestational-age births in normal-weight and normal-stature women, and reduced perinatal mortality when supplementation was initiated after 20 weeks of gestation [20]. However, there are still significant gaps in the evidence regarding the optimal dose of iron (30 versus 60 mg) and the timing and duration of multiple micronutrient supplements for maximum positive effects, as well as the extent and potential benefits of multiple micronutrients beyond anemia and pregnancy outcomes [29].

The WHO-recommended dose of iron ranges from 30 mg to 60 mg, although most prenatal programs have used a daily dose of 60 mg [18,19]. In contrast, the lower dose of 30 mg iron is included in the UNIMMAP preparation (together with 14 other micronutrients) [17], as the absorption of iron is expected to be enhanced due to vitamins C, A, and B2. There is growing scientific consensus that multiple micronutrient supplements containing iron and folic acid are superior to iron and folic acid supplementation alone. Recent data from an individual patient data meta-analysis of 17 RCTs including over 100,000 women living in LMICs found that multiple micronutrient supplementation in pregnancy reduced the risk of low birth weight, preterm birth, and being born small for gestational age [22,30]. Yet, a sensitivity analysis of 11 of these 17 trials showed that multiple micronutrient supplements containing low dose iron (≤30 mg) were associated with higher stillbirth and neonatal mortality than iron-folic acid alone with 60 mg iron [22,30]. Furthermore, in a meta-analysis of randomized trials of prenatal iron use, a dose-response analysis showed a linear decrease in maternal anemia with higher doses of iron, up to 66 mg per day. The meta-analysis also found an association between higher doses of iron with a linear increase in birth weight and a decrease in the risk of low birth weight [9].

Accordingly, WHO recommendations call for research on the use of multiple micronutrient supplementation over iron and folic acid supplementation alone for pregnant women in low-resource settings [18,19]. Moreover, the Micronutrient Forum recommends multimicronutrient supplementation as “context specific-research,” including the use of micronutrient supplements in the context of prenatal care services informed by implementation research as well as continuing clinical research as part of a global agenda to inform future WHO guidelines as they are revised and updated [31,32]. While current evidence from multiple micronutrients supplementation trials suggest the immediate benefit for pregnancy outcomes [16,18-20,22], future studies are warranted to examine the appropriate dose of multiple micronutrient supplementation and identify high-risk groups and regions where the effectiveness of prevention is likely to be the highest and thus may offer the greatest public health return on investment.

Multimicronutrient supplements can lower maternal morbidity and mortality by directly treating a pregnancy-related illness or by indirectly reducing complications during delivery when compared to iron and folic acid supplementation alone. However, the effectiveness of micronutrient supplementation programs has frequently been measured by the outcomes of pregnancy (eg, preterm birth, low birth weight, and perinatal mortality), and evidence regarding the effects of micronutrient supplementation on maternal and infant nutritional status is limited and inconsistent. In fact, in some cases, micronutrient deficiency was persistent even after multiple micronutrient supplementation. For instance, in a double-blind RCT in Nepal, zinc or zinc combined with other vitamins and minerals had no

additional benefit, compared with iron plus folic acid, for improving iron status or anemia among pregnant women [33]. There have also been reports of persistent micronutrient deficiency in Bangladesh despite prenatal supplementation with multiple micronutrients promoting pregnancy-related benefits [34,35]. A clustered-randomized trial assessed the efficacy of a daily multiple micronutrient supplement with 15 nutrients, each provided approximately 1 recommended daily allowance (RDA). Compared with iron and folic acid supplement, vitamins B12, A, and D, and zinc status indicators were 3.7% to 13.7% higher, and ferritin, γ-tocopherol, and thyroglobulin indicators were 8.7% to 16.6% lower for the multiple micronutrient group compared with the iron and folic acid supplement group, with a 15% to 38% lower prevalence of deficiencies of vitamins B12, A, and D and zinc (P<.05 for all) [35]. Consequently, evaluating the effectiveness of multimicronutrient supplements and their dose in improving the nutritional status of both mothers and infants can help inform future formulations.

Currently, there is only limited evidence available on the dosing of multiple micronutrient supplements. A double-blind, randomized controlled trial assessed the effects of prenatal multiple micronutrient supplementation with 1 or 2 RDA, compared with the conventional iron and folic acid supplementation, on birth weight and perinatal mortality in urban Guinea-Bissau. A dose-response effect was observed with a 53-gm increase in birth weight after administration of 1 RDA of the micronutrients and 95 gm after 2 RDA, and no differences were observed in perinatal mortality between the study groups [36]. In addition, there is mixed evidence on the effect of multimicronutrient supplements with varying dosages in HIV-infected pregnant women. For example, a 2 × 2 factorial design trial of vitamin A (30 mg β-carotene plus 5000 IU preformed vitamin A) and multivitamins (20 mg B1, 20 mg B2, 25 mg B6, 100 mg niacin, 50 µg B12, 500 mg C, 30 mg E, and 0.8 mg folic acid) in Tanzania showed that the provision of multivitamin supplements decreased the risk of fetal death, low birth weight, preterm birth, and small size for gestational age, whereas vitamin A supplementation did not [37]. There are studies in progress assessing the scaling up of multimicronutrient supplements, as the UNIMMAP formulation in Bangladesh, Madagascar, Burkina Faso, and Tanzania that might show substantial benefits in terms of mortality reduction and poor birth outcome, by shifting from iron folic acid supplementation to multimicronutrient supplement in prenatal care programs [29].

In addition, vitamin B12 deficiency has been linked to poor fetal growth and development and heightened chronic disease risks [7]. Among Indian women with an approximately 50% prevalence of B12 deficiency, prenatal 50 µg vitamin B12 supplements, nearly 20 times the dose in the UNIMMAP multiple micronutrient supplements, prevented a decline in vitamin B12 from early to late pregnancy [38]. In a blinded, placebo-controlled trial among Bangladeshi women randomized to receive 250 µg/day B12 (ie, 96-100-fold higher than RDA) or placebo throughout pregnancy and the 3-month postpartum period along with 60 mg iron and 400 µg folate, the maternal status of plasma vitamin B12 and colostrum and breast milk B12 was substantially improved by 250 µg/day supplements throughout pregnancy and lactation. In addition, infants born to supplemented mothers had improved vitamin B12 status (ie, higher plasma B12 and lower plasma homocysteine and methylmalonic acid concentrations) [39]. However, a randomized, double-blind, placebo-controlled trial assessing the effect of a multivitamin supplement on perinatal outcomes in Dar es Salaam, Tanzania, found that multivitamin supplements containing 50 µg of vitamin B12 produced a nonstatistically significant decline in the odds of having inadequate vitamin B12 in breast milk [40].

Consequently, there is a need to systematically synthesize the evidence to decide which micronutrients are of greatest concern in LMICs, the criteria for prophylactic single nutrient or multiple micronutrient supplementation, and the outcomes to be measured. We anticipate that the findings of this review will help advance the recommendations for scaling up multiple micronutrient supplementation during pregnancy [17,18,41]. Disaggregated results by other variables, such as maternal age, sex of infant, duration of intervention, and dose of intervention, may also aid policy makers, researchers, practitioners, and governmental and nongovernmental agencies in supporting better maternal and child health programs and policies in LMICs.

Limitations

Our study has a couple of limitations. First, the data from this review will be gathered exclusively from published studies, excluding data from unpublished studies and or literature that has not been peer-reviewed (eg, reports). Although it has been suggested that researchers should aim to include unpublished studies in meta-analyses and systematic reviews, including these studies can in itself introduce bias [28]. It is likely that the unpublished studies that are located are not representative of all unpublished studies. In some cases, the identification of unpublished studies may be dependent on the willingness of investigators to provide data. This could depend again on the results of the study, with more favorable results being provided more readily [28]. Additionally, unpublished studies may have a lower methodological quality than published studies. Second, we will only collect data from RCTs, as we believe databases from LMICs contain enough randomized trials to answer the question of interest. Moreover, we will not include nonRCTs because their potential biases are likely to be greater when compared with RCTs. The nonrandomized studies of interventions also differ in their ability to estimate causal effects.

Acknowledgments

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Data Availability

All data that will be generated and analyzed during this study will be included in the published article or its supplementary information files. We will submit our findings for peer-reviewed publication and present them at relevant conferences.

Authors' Contributions

SS is the guarantor. SS, DW, and WWF developed the research questions and methodology. All authors contributed to developing the search strategy, the risk of bias assessment strategy, and the data extraction form. SS drafted the manuscript. All authors read, provided feedback on, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed search strategy.
[DOCX File , 16 KB - resprot_v11i8e40134_app1.docx]

Multimedia Appendix 2
PRISMA-*P* 2015 Checklist.
[DOCX File , 20 KB - resprot_v11i8e40134_app2.docx]

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Abbreviations

GRADE: Grading of Recommendation, Assessment, Development, and Evaluation
LMIC: low- and middle-income country
MD: mean difference
MeSH: medical subject heading
MMN: multiple micronutrient
PICO: participant, intervention, control, and outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols
RCT: randomized controlled trial
RDA: recommended daily allowance
SMD: standardized mean difference
UNIMMAP: United Nations International Multiple Micronutrient Antenatal Preparation
WHO: World Health Organization

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Protocol

Development and Implementation of an Interprofessional Digital Platform to Increase Therapeutic Adherence: Protocol for a Mixed Design Study

Carole Anglade[1], MPO, PhD; Mylaine Breton[2], MBA, PhD; Frederic Simard[3]; Terry Fitzpatrick[3]; Meighen Fitzpatrick[3]; Geneviève Bruneau[4], DMV, MD; Isabelle Gaboury[1], MSc, PhD

[1]Department of Family Medicine and Emergency Medicine, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Longueuil, QC, Canada

[2]Faculty of Medicine and Health Sciences, Department of Community Health, University of Sherbrooke, Longueuil, QC, Canada

[3]MedHelper Inc, Pointe-Claire, QC, Canada

[4]GMF-U de Saint-Jean-sur-Richelieu, Saint-Jean-sur-Richelieu, QC, Canada

Corresponding Author:
Carole Anglade, MPO, PhD
Department of Family Medicine and Emergency Medicine
Faculty of Medicine and Health Sciences
Université de Sherbrooke
Campus de Longueuil C P 200
150, Place Charles Le Moyne
Longueuil, QC, J4K 0A8
Canada
Phone: 1 514 343 7645 ext 7921
Email: carole.anglade@usherbrooke.ca

Abstract

Background: Adherence to care plans is a major issue in health care systems. Improved adherence has several potential benefits such as ensuring treatment effectiveness and control of chronic diseases. There is currently a lack of tools to maximize treatment adherence in an integrated manner, that is, covering multiple aspects of patients' health continuously throughout their medical care. To ensure better adherence, such tools must meet the needs of patients with chronic conditions as well as those of health care professionals. Acknowledging the health issues associated with nonadherence to treatment, an industry-research-clinical partnership aims to adapt a digital platform—facilitating patient-health care professional interactions—to improve therapeutic adherence in patients with chronic illnesses. The platform allows for exchanges between patients and health care professionals to facilitate the timing of medication use or chronic disease management and maximize patient adherence.

Objective: This study aims to (1) identify the needs of patients living with a chronic condition and their health professionals concerning their interactions regarding treatment; (2) codevelop an adaptation of an interactive patient-professional platform that meets the needs identified; and (3) then test the platform and document its effects and acceptability in a clinical setting.

Methods: The study will use a creative design thinking process based on the needs expressed by users (patients and health professionals) concerning treatment adherence for chronic diseases (eg, diabetes, asthma, high blood pressure, depression and anxiety, chronic obstructive pulmonary disease). A mixed method evaluation research design will be used to develop and evaluate the platform. Qualitative data will be used to assess user needs and acceptability of the platform, and quantitative data will provide the necessary insights to document its effects.

Results: Technological development of the platform has been completed. Recruitment for the first part of Phase 1 started in May 2022. The results of this project to codevelop an interprofessional digital platform to increase therapeutic adherence will be relevant to clinicians and managers seeking contemporary solutions that support patient adherence to treatment for chronic diseases. These results will enable optimal use of the platform and identify areas for improvement in interactive patient-health care professional apps.

Conclusions: The adoption of an interactive digital platform to facilitate effective exchanges between patients and health care professionals in primary care settings could improve adherence to treatment. The platform tested in this project takes a first step

in this direction by ensuring that the technological product is developed according to the needs of patients as well as the health professionals who are likely to use it.

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KEYWORDS

adherence; disease management; primary health care; electronic platform; chronic disease; design thinking; acceptability

Introduction

Background

Adherence to care plans is a major issue in health care systems. According to the World Health Organization, adherence to long-term therapies for chronic illnesses in developed countries is 50%, and rates in developing countries are even lower [1]. In Canada, fewer than 51% of patients follow their prescribed treatment regimen for many chronic diseases, affecting a large portion of a population that requires strict adherence to minimize the risk of health deterioration or comorbidities [2]. Nonadherence not only leads to preventable worsening of disease [3] but also generates additional costs for the health care system and for employers due to absenteeism [4,5]. Although the responsibility for adherence has traditionally been attributed solely to patients, it is now acknowledged that some of the responsibility is shared by the professionals delivering care, with patient-professional interactions having a significant impact [6]. Therefore, adherence to medical treatment must be analyzed from a communication perspective taking into account how patients and health professionals interact and exchange health information.

Exponential growth in the number of various apps available to consumers has directly influenced the health information environment. As early as 2012, 19% of smartphone owners in the United States had previously used a health app, a usage rate that is only increasing as the population becomes more accustomed to the daily use of technology. The popularization of smartphones is changing the way users record, store, and exchange their health information and has a direct effect on patients, including improving self-management of their condition [7]. The connectivity and interactivity of health apps must be further developed to support treatment adherence in such a way that the effort required of the users to obtain or manage their health information is minimized.

Concerns have been reported about the fact that technologies are not yet designed to support data collaboration between patients and health professionals [8]. In connected health, which refers to a health care system connected with smart medical devices, communication gaps hinder progress toward higher quality health care and improvements remain to be seen [9], although projects on connected health are rapidly emerging worldwide, particularly in North America [10]. To identify needs and plan solutions, the perspective of patients has proven to be particularly relevant and valuable [11]. It is, therefore, critical to properly evaluate the user experience when developing and implementing apps to facilitate interactions between health care professionals and patients. Among the methodological approaches identified to assess users' needs in emerging projects on connected health, design thinking has been recognized for innovative and often technological aspects that meet health care requirements [12].

Design Thinking

Design thinking comes from the design industry and is a method designers use to "match people's needs with what is technologically feasible and what a viable business strategy can convert into customer value and market opportunity" [13]. According to this approach, for an innovation to be successful, it should meet 3 challenges: answer the needs of users, be technically feasible, and be economically viable [14]. The design process is always confronted with the importance of the user experience: if a product does not please users, it will not be used. In this approach, a key to success is using the designer's sensibilities; otherwise the first step—understanding the needs of future users—cannot be achieved. The designer must then rely on integrative thinking to find solutions that respond to both the needs identified and their context. During the implementation phase, potential solutions are tested using an iterative process until they are considered satisfactory. Thus, while the approach does come from the field of technological design, design thinking is characterized by a human-centered approach to problem solving [15]. It also allows for the involvement of participants with no design experience but whose expertise is necessary (such as professionals or patients) to achieve a product that corresponds to their needs through simple and engaging activities [16].

This creative process also aims to stimulate critical discussions through practical methods to bring about structural change in any type of organization [17]. In their recent review, Altman et al [18] identified 24 health care studies that used design thinking, a large majority of which were successful in achieving their objectives. Moreover, all 4 studies that compared interventions showed greater satisfaction, usability, and effectiveness using a design thinking approach than using a traditional approach [18].

Adaptation of an Interactive Patient-Professional Platform

Acknowledging the health issues associated with nonadherence to treatment, a health technology start-up first developed an app for patient medication adherence without any patient-health care professional connectivity or interaction features. As more end users started using the app to manage their medications, the team observed that patients who used the app at the request of a health care professional (physician or pharmacist) demonstrated a higher level of engagement and adherence to their care plan. The team concluded that a web-based app

designed to enable health care professionals to easily create and transfer digital care plans to patients would be an effective approach from an operational perspective for professionals and from an engagement perspective for patients. As a result, they developed a digital platform offering a patient-health care professional interaction model that seamlessly links the development, sharing, and monitoring of care plans. The platform provides postdiagnostic support to patients taking medication or following a care plan. This innovative digital health solution combines unprecedented connectivity to clinical services with a web-mobile digital platform for execution. The platform is offered as a SaaS solution and consists of 3 fully integrated components that close the loop of the entire care plan journey: (1) The web platform allows professionals or individuals to create a care plan that can consist of medications, health data measurements, and other therapies. Custom care plan activities can also be created to meet the needs of the most complex care plans. (2) Individuals can quickly activate their account and access their care plan via the mobile app. Reminders and alarms are predefined in advance by the health care professional and ready for execution by the patient. (3) Once the care plan has been accepted, patients are given access to a suite of tools to execute and report on their care plan. Some key features include push notification reminders, persistent alarms, access to medication leaflets and images, notes, a dashboard, and a report with adherence results. The report can be securely shared with a health care professional via a code so the professional can view results using the web platform.

Objectives

This research project aims to:

- identify the needs of patients living with a chronic condition and their health professionals concerning their interactions about treatment;
- codevelop an adaptation of an interactive patient-professional platform meeting the needs identified; and
- test the platform and document its effects and acceptability in a clinical setting.

Methods

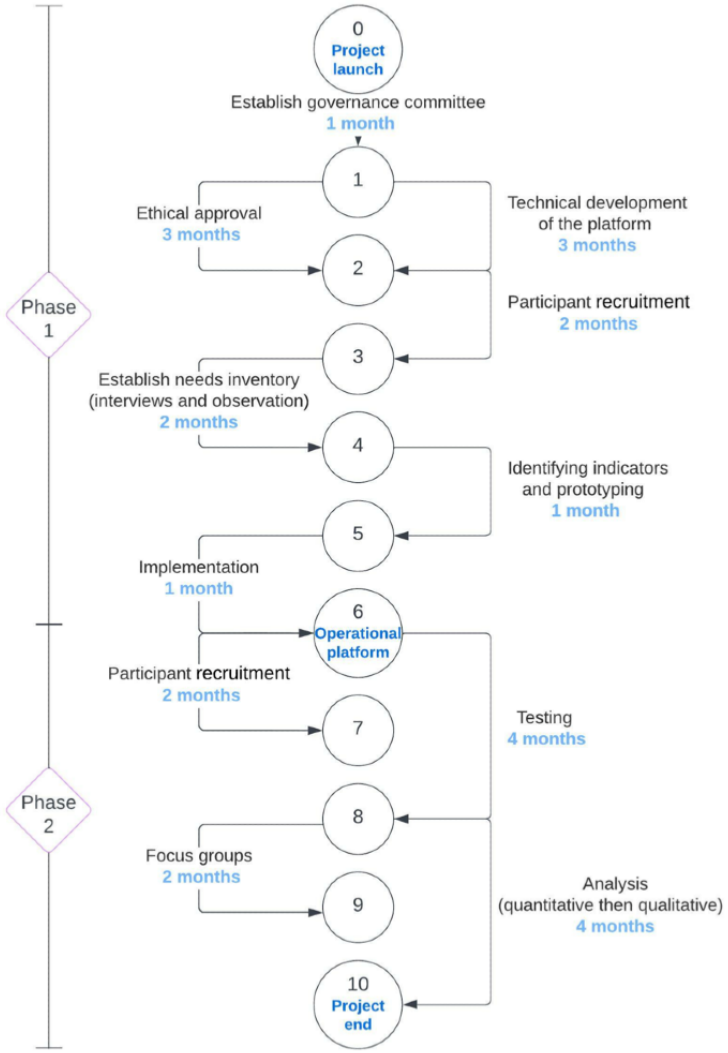
Study Design

The project will follow a multimethod evaluative design focused on the needs expressed by users (patients and health professionals) and is divided into 2 phases. The first phase includes a design thinking approach and consists of cyclic phases to understand user needs, identify solutions, and integrate them into a prototype. The second phase will use a pre-post design with qualitative and quantitative data analysis to document optimal use of the platform. The project will develop and test the platform in collaboration with a teaching family medicine group in Quebec that includes a broad representation of primary care practitioners.

Procedure

Figure 1 presents the events and their dependencies of the 2 project phases.

Figure 1. PERT diagram of the duration and tasks of the project.



Phase 1: Needs Assessment and Platform Development

Recruitment

The teaching family medicine group where recruitment will take place welcomes various learners: family medicine residents, medical externs, and trainees from different professions. The main missions of this clinic are providing care to the population, contributing to the training of health professionals in an interdisciplinary environment, and participating in research and teaching activities.

For this phase, we aim to recruit at least five professionals (a combination of family physicians, nurse practitioners or registered nurses, and pharmacists) and five patients from the clinic. The recruitment of health professionals will be done on a voluntary basis via email invitations that will be sent by the research team. Patients will be recruited based on a purposive sampling approach [19] guided by the recruited health professionals, who will be better able to determine the relevant pathologies to be included. Inclusion criteria for patients will include adults who speak English or French and have a chronic illness such as diabetes, chronic obstructive pulmonary disease, depression/anxiety disorders, high blood pressure, or asthma. Patients who do not have a technological tool compatible with the platform (ie, smartphone) will be excluded. Upon patient approval, the research process (including obtaining informed consent) will be explained to the patient by the research team.

Data Collection

To develop usable technological supports or apps, it is essential to determine the needs of users [20]. To collect the maximum number of relevant needs from participants, 2 data collection methods will be used in an effort to triangulate findings [21]. The explicit needs of patients and health care professionals will be collected through semistructured individual interviews [22]. Textbox 1 presents an excerpt of the patient interview guide.

Textbox 1. An excerpt of the patient interview guide.

Thank you for agreeing to participate in this research project. You have been invited to participate in this interview because you have one or more chronic conditions.

What is your primary chronic illness?

1. How do you manage your (*name of disease*) on a daily basis?
2. Who are the health professionals you communicate with in relation to your (*name of disease*)?
3. What do you talk about with (*professional X*)? – *for each professional*
4. How are your exchanges with (*professional X*) going? – *for each professional*
   - Who initiates the exchanges? You or (*professional X*)?
   - In what way? During a visit, by phone, by email...
   - How do you document the tracking of your (name of disease) to share with (*professional X*)?

These interviews will be used to develop a journey map of the platform's users. Journey mapping originated in the marketing and service fields [23] and was initially used to help visualize, in detail, a particular organizational process or service, but is increasingly being used in health services [24]. They are especially useful to explore the experience of customers, users, or patients as they navigate a physical or virtual environment. In this project, the findings of the interviews will be used to draw a journey map diagram (see example in Figure 2), providing a holistic view of the patient experience.

Figure 2. Example of a journey map.

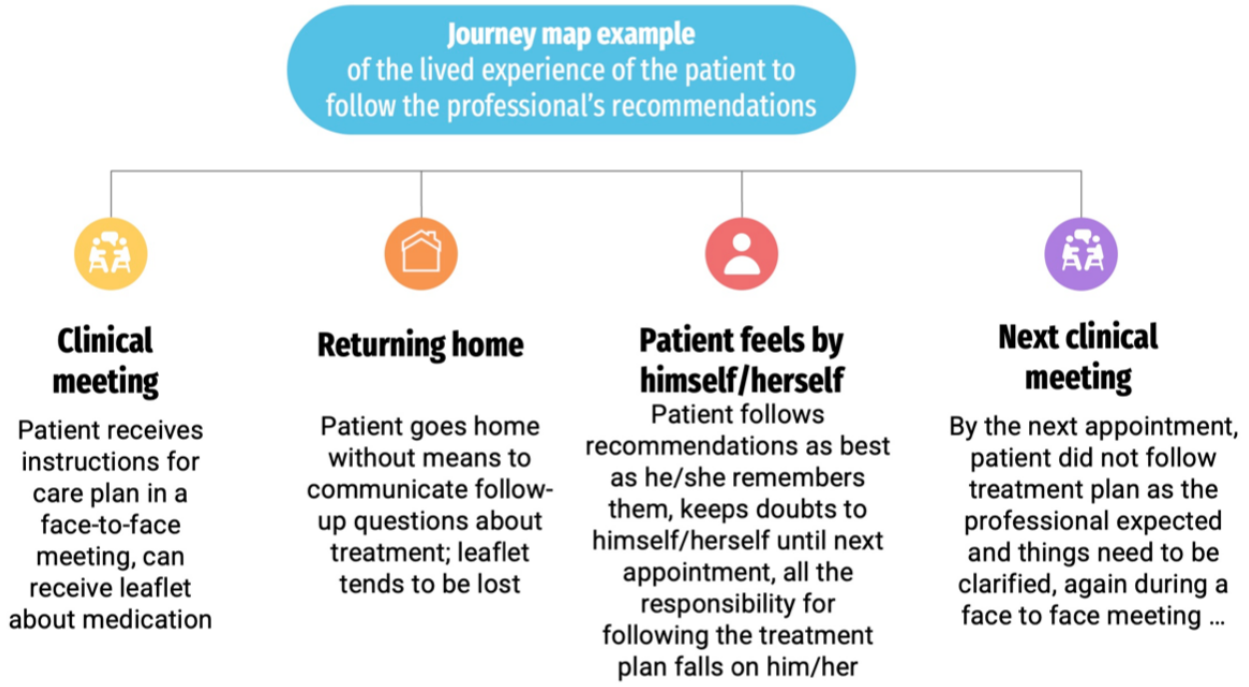


Figure 2 presents an example of a simple journey map focused on exchanges between patients and their health professionals and the lived experience of patients as they follow the professional's recommendations. The journey map produced in Phase 1 will include the key elements that the qualitative analysis will highlight from the data.

Next, 4-6 observations will be made of interactions between health professionals and patients during consultations for chronic disease follow-up to highlight the latent needs of these populations [20]. Latent needs are those that participants are not aware of but that can be identified by external observation of a situation. Priority will be given to interactions with different health professionals and patients with various chronic conditions. During observations, notes will be taken by a member of the research team and will include a description of the interaction between the patient and health professional, whether it takes place in person, by phone, or by text. The description will focus on the content of the exchanges as well as their modalities. These qualitative methods (interviewing and observation) will allow for observations of all aspects of the user's objectives, needs, and preferences without relying on indirect deductions from quantitative measurements [25].

Analysis Strategy

Verbatim interview and observation notes will be subjected to thematic content analysis [26]. Explicit and latent needs will be used as themes for analysis. Explicit needs will be the focus of interview analyses, whereas latent needs will be the focus of observation analyses. For example, if during the observation of an interaction between a patient and physician, the patient reports that he/she did not take the blood pressure as often as the physician requested because he/she lost the paper on which the information was written, the latent need would be for the platform to offer an option for clinical recommendations to be coupled with a recall alarm. First, a member of the research team will familiarize themselves with the data by (re)reading all transcripts and notes. This will offer insights about the similarities and differences between participants' experiences. We will then apply the following coding actions: (1) making codes, (2) organizing codes, and (3) combining patterns through an iterative process [27]. This analysis will allow for an inventory of user needs.

Both explicit and latent needs will then be translated into prototype specifications, which will be associated with metrics or indicators. For example, if a patient reports a desire to ask his/her health professional questions between clinical meetings, a prototype of the platform will be made with the specification that both the patient and the professional can initiate an exchange through the platform and that these initiations will be counted. The research team will collect these indicators for each iteration of the platform to assess the implementation of changes made through the prototyping process. Possible indicators include the following: rate of adherence to treatment as prescribed, measured as the percentage of events in the care plan that are completed by the patient versus the total number of events in the care plan; patient retention rates on the platform, which will be measured by the number of visits to the platform by patients per week; and satisfaction levels and acceptability of health care professionals and patients.

Based on the identified needs and the journey map, the development team (professionals, patients, and the research team) will reflect on the various prototypes using design thinking techniques in an iterative fashion, which implies redesigning on the basis of successive user testing [28]. During design thinking meetings (2 or 3), sketch modeling (in 2D or 3D) will be used to create a model that conveys how the participants imagine the platform. The material needed for these meetings consists, for example, of paper and pen, tape, cardboard, scissors. The research team will participate in these meetings by contributing elements based on analyses of interviews and observations. Together, the group will confirm the specifications for the prototype, which will then be implemented into the platform and discussed in an iterative manner at 1 or 2 more meetings. These iterations will focus on the user experience of professionals and patients. The technical team will be responsible for implementing the prototypes.

The development team will stop the iterative process of improving the platform, according to predefined rules [29], and proceed to Phase 2 as soon as the final prototype has been implemented as an operational version of the platform.

Phase 2: Pre-Post Trial of Platform Use

The second phase consists of an evaluation of the platform at the primary health care clinic. The acceptability and feasibility of the platform will be tested.

Recruitment

Recruitment will take place at the same clinic as in Phase 1. An email will be sent by the research team to health professionals at the participating clinic (n=23) inviting them to join the digital platform. As in Phase 1, patients will be invited by health professionals to participate in the study based on predefined criteria (eg, chronic condition, instructions required, biometric data to be collected) according to a purposeful sampling approach [19]. The same selection criteria as described in Phase 1 will be applied in Phase 2, unless the former has indicated a need to adjust these criteria. A total of 50 patients will be recruited, as well as 5-10 health professionals (physicians, resident physicians, registered and clinical nurses, pharmacists). Upon obtaining informed consent from both patients and professionals, the study steps will be explained by the research team. An automated email will then be sent by the professional to each patient via the web portal with the steps to follow to download the platform and access the information and instructions related to the care plan.

Data Collection

In Phase 2, the recruited patients and health professionals will use the interprofessional digital platform for 6 months. During this time, the indicators decided on in Phase 1 will be quantified by extracting data collected from the platform and the electronic medical record (EMR) of each participating patient. These data will form the quantitative database for Phase 2.

In addition, 2-3 focus groups of patient users and 1-2 focus groups of professional users will be held at the end of the testing period to provide feedback and recommendations on the platform. Users will be selected to form a convenience sample based on their level of use of the platform (low, moderate, and intensive) [30]. Recruitment for the focus groups will cease when theoretical saturation is achieved, meaning that no new codes will emerge from the analysis [31].

Analysis Strategy

Pre-post analyses using Student *t* tests for paired data will be performed using SPSS software (IBM, Inc.). McNemar tests will be used for dichotomous and categorical indicators.

Verbatim transcripts of group interviews will be analyzed according to a thematic content analysis [12] similar to that used in Phase 1. Quantitative data will inform on treatment adherence and patient-health care professional communication related to establishing adherence. Qualitative data will provide insights into how to promote adherence through the platform by capturing what is important to both patients and professionals when managing patients' health conditions. This mixed methods design will allow for the data collected to form a coherent whole in order to improve the platform.

Ethics Approval

The protocol presented in this manuscript, as well as the informed consent forms and semistructured interview guides,

was reviewed and approved by the Research Ethics Committee of the Integrated Health and Social Services Centre of Montérégie-Centre (an administrative region of Quebec; study ID 2022-677) on December 7, 2021.

Data Availability

Data sharing is not applicable to this article as no complete data sets were generated or analyzed at this stage of the study.

Results

Technological development of the platform has been completed. Recruitment for the first part of Phase 1 started in May 2022. As shown in the Program Evaluation Review Technique (PERT) diagram, completion of both phases of the project should be achieved within 14 months, around July 2023. Study results will be available in Fall 2023. The COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist [32] will be used to ensure transparent reporting of the characteristics of the findings.

Discussion

Anticipated Main Findings

This engaging digital platform aims to provide a new tool for health care professionals involved in managing chronic diseases. The platform will enable patient-health care professional exchanges that will facilitate chronic disease management, including the timing of medication use. During follow-ups, professionals will be able to obtain patient data in a secure manner and modify treatments or treatment plans as needed. The results of this project will be relevant to clinicians and managers seeking contemporary solutions to support patient adherence to treatment. These results will enable optimal use of the platform and identify avenues for improvement in the use of interactive patient-health care professional apps. As part of this applied research project, new functionalities will be deployed by participating health care professionals via the web portal. These new functionalities will be accessible for use in actual consultation situations via the existing web browser, distinct and separate from the operational tools currently used by professionals, such as the EMR. Efforts will be made to facilitate integration of the new functionalities into the EMR, thereby reducing required computer use and simplifying the process, once evaluation of the platform is completed and following the recommendations made in the final report. Integration of the web portal into the EMR is a critical success factor for broader rollout.

The adaptation of the platform based on the identified needs of patients living with a chronic condition and their health professionals will be acceptable to both professionals and patients.

Comparison With Previous Work

Although the impact of mobile technologies for chronic disease management may have appeared inconsistent at first [33], as the technology was adapted and improved, it became clear that mobile health can truly support better management of chronic diseases. Studies focused on diabetes first demonstrated positive physiological and behavioral outcomes with mobile health technologies [34-37]. In 2018, a systematic review by Lee et al [38] confirmed that mobile health can also support effective behavior intervention strategies for the management of other chronic diseases, such as cancer, fibromyalgia, spina bifida, or cardiovascular diseases. One of the factors identified as enhancing self-management in patients with chronic conditions in mobile health approaches was improved communication between patients and health care providers, which is one of the key features of the platform developed in this project.

Patient Health Benefits

It has been shown that adherence to treatment decreases rapidly and proportionally as the number of activities included in a care plan increases [39]. Unfortunately, this is a typical situation in chronic diseases, where adherence is less than 50% when the prescribed treatments include 4 or more events per day, significantly increasing the risk of patients' health status gradually deteriorating [40]. The emergence of chronicity affects the physical and mental well-being of patients and family caregivers. By focusing on adherence, the digital platform aims to help patients and health care professionals stabilize health status and avoid the development of chronic conditions and comorbidities. Better adherence to care plans can also improve employee productivity and reduce absenteeism, an issue that has significant economic repercussions for employers [4].

Clinical Benefits

This project will allow for experimentation with a digital platform promoting patient empowerment and the individualization of care and allow for an unprecedented level of patient-health care professional interactions as well as access to guidance and other information shared by health care professionals (medications, nonmedicated therapies, biometric data). Data collected by the patient, such as medication use, adherence rates, notes, and side effects, will be accessible to health professionals via the web portal. This research project aims to demonstrate that the higher level of patient empowerment expected or to be achieved through this interactive and integrated (web and mobile) digital platform will improve adherence to prescribed care plans.

Benefits for Health Care Professionals

Information quality gains are expected for health care professionals when users of the digital platform return to the clinic. Professionals will be able to access a web portal interface specifically designed to view patient care and biometric data in real time using a secure code generated by the patient via the digital platform. This new approach will allow physicians and nurses to view medications, other care plan elements, biometric measures, and patient adherence rates in less than a minute via a standardized web interface. Direct productivity gains are also expected for professionals relative to the traditional approach, which is based on verbal exchanges with patients.

Operational Benefits

The study will also test new ways of performing traditionally manual tasks that can now be done via the new platform, such as distributing notes and patient instructions. This new way of communicating treatment-related information will not only

allow the patient to obtain instructions effortlessly via the digital platform, but also, as a bonus, eliminate the risk of instructions being misplaced. Therefore, this project plans to observe the impact of the platform on patient follow-up on information provided and potential lightening of the task load of health professionals, a factor that may promote their adoption of the platform. In addition, the project will allow us to observe, from an intrinsic perspective, impacts for professionals, a nonnegligible notion in a context that is sometimes difficult for human resources (particularly during the pandemic, when patient-health care professional interactions were constantly adapting).

Strengths and Limitations

As shown by Ahmed et al [41], there are now multiple technological options aimed at improving adherence to treatment, at least medication adherence. However, the lack of studies that included health care professionals during app development is concerning. In their review, only 57 of the 420 free apps identified were developed with the involvement of health care professionals. One of the strengths of our study is the inclusion of both patients and health professionals, from exploration of their needs at the beginning, to their active participation during elaboration of the prototype, to testing of the platform in their practices. Furthermore, the efforts that will be made to allow communication between the platform and the EMR will be a significant benefit over other existing apps. As a feasibility research study, this project does not involve a control group nor does it have an effective sample size. However, our aim is not to demonstrate a generalizable effect of the platform on the management of chronic diseases but intends to create a tailored and relevant tool to be implemented in an authentic clinical setting.

Conclusions

This research project will explore in-depth the use of an adapted interprofessional digital platform to maximize treatment adherence in an authentic clinical environment. By creating a model of patient-primary health care professional interactions, this platform will ease the process of developing, sharing, and monitoring care. The adoption of an interactive digital platform to facilitate effective exchanges between patients and health care professionals in primary care settings could improve adherence to treatment. The platform tested in this project takes a first step in this direction by ensuring that the technological product is developed according to the needs of patients as well as the health professionals who are likely to use it.

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Conflicts of Interest

Although 2 of the authors are Chief of Product & Strategy and Chief Executive Officer at MedHelper Inc., which created the platform studied, no author expects to gain financially by the publication of this paper. The creators of the platform did not interfere in any way with the methodological decisions, data collection, or scientific analysis of this project.

Multimedia Appendix 1
Results of the 4th Call for projects of the Fonds de Soutien à l'innovation en Santé et Services Services (FSISSS).
[PDF File (Adobe PDF File), 149 KB - resprot_v11i8e34463_app1.pdf]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
EMR: electronic medical record
PERT: Program Evaluation Review Technique

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Protocol

Codevelopment of Implementation Interventions to Support Parent-Led Care for Pain in Infants: Protocol for a Qualitative Descriptive Study

Britney Benoit[1], PhD; Christine Cassidy[2], PhD; Jacqueline van Wijlen[1], BScN, MN; Quinn Correll[1], BScN; Marsha Campbell-Yeo[2], PhD; Sionnach Hendra[1], MSc; Ruth Martin-Misener[2], PhD; Jennifer MacDougall[3], BScN; Ashley Cameron[3], BScN

[1]Rankin School of Nursing, St Francis Xavier University, Antigonish, NS, Canada

[2]School of Nursing, Dalhousie University, Halifax, NS, Canada

[3]Nova Scotia Health, Antigonish, NS, Canada

Corresponding Author:
Britney Benoit, PhD
Rankin School of Nursing
St Francis Xavier University
2321 Notre Dame Avenue
Antigonish, NS, B2G 2W5
Canada
Phone: 1 9028671396
Email: bbenoit@stfx.ca

Abstract

Background: Untreated pain in infants is associated with adverse health outcomes. Despite strong evidence for accessible, effective, and low-cost parent-led pain-relieving interventions such as breastfeeding or chestfeeding and skin-to-skin contact, these interventions are not routinely used.

Objective: The objective of this study is to support the implementation of parent-led pain interventions by identifying barriers to and facilitators of parent-led, evidence-informed pain care in infants during acute procedures. In addition, this study aims to develop theory-informed, contextually relevant implementation interventions for supporting the use of parent-led pain care for infants in hospital and community contexts.

Methods: This study will consist of 2 phases that follow a systematic, theoretically informed approach guided by the Theoretical Domains Framework and Behavior Change Wheel. In phase 1, we will use a qualitative descriptive design to explore barriers and facilitators to using parent-led pain care in infants from the perspectives of hospital and community-based clinicians, clinical leaders, and families. In phase 2, we will use the Behavior Change Wheel to design tailored implementation interventions that have evidence for effectively addressing identified barriers in collaboration with an advisory committee of administrative, clinical, and family leaders.

Results: Ethics approval for this study was obtained in December 2020. As of May 2022, a total of 15 participants have been enrolled in phase 1. The results from all phases will be reported in 2023.

Conclusions: Following the completion of this study, we will have co-designed theoretically informed implementation interventions that can be pilot-tested and experimentally applied. The findings will be used to implement parent-led interventions that improve patient safety and health outcomes for diverse families.

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KEYWORDS

breastfeeding; chestfeeding; skin-to-skin contact; infant pain; implementation; qualitative

Introduction

Gender-neutral Infant Feeding Language

We are conscious of perpetuating oppressive and harmful discourses that do not reflect all childbearing families cared for in our health system and communities [1-3]. Therefore, we used inclusive gender-neutral language whenever possible throughout this protocol. This includes the use of terms such as *breastfeeding* or *chestfeeding* to better reflect diverse lactation experiences [3].

Incidence and Outcomes of Acute Pain Exposure in Infants

All infants experience pain as part of routine care, both in hospitals and in the community. For example, all infants undergo a routine intramuscular injection of vitamin K to prevent bleeding [4] and a heel lance procedure to collect blood for metabolic testing and routine serum bilirubin screening [5] in the first hours of life. Repeated heel lancing is required in infants diagnosed with common clinical concerns such as hyperbilirubinemia [5] or hypoglycemia [6]. Children in Canada additionally undergo multiple necessary intramuscular injections for immunization, with the majority occurring between 2 and 18 months of age [7]. Studies examining the effects of untreated pain in infants have linked this exposure to adverse cardiorespiratory, hormonal, and neurodevelopmental effects [8-18]. In preterm infants, pain is associated with increased stress and inflammatory hormone release, which impede growth and tissue repair [8,9]. The motor, cognitive, and behavioral effects of untreated pain in preterm infants include poor growth of the body and head [15], reduced visual perceptual abilities [16], poorer language outcomes [17], and greater internalizing behaviors (anxiety and depression symptoms) [10,18] throughout childhood. In full-term infants, structural and functional alterations in both the peripheral and central nervous systems have been linked to both short- and long-term alterations in pain processing, most notably, increased sensitivity to pain during later procedures [11-14,19].

Parent-Led Pain Care in Infants: Breastfeeding or Chestfeeding and Parent-Infant Skin-to-Skin Contact

In light of these adverse consequences of infant pain, intensive scientific efforts have been undertaken to determine effective pain-reducing treatments. Although pharmacological agents such as opioids and topical anesthetics [20,21] have been studied, there is limited evidence for their safety and pain-reducing efficacy for the routine acute painful procedures that infants commonly undergo. In contrast, parent-led interventions are low-cost and have strong evidence of pain-reducing efficacy and safety [22-24]. In our most recent systematic reviews of breastfeeding [22] and parent-infant skin-to-skin contact [24] as interventions for procedural pain, we found that these interventions have the strongest evidence for reducing pain associated with acute tissue-breaking procedures.

Barriers to Parent-Led Pain Management in Infants

Overview

Most of the evidence describing pain management practices in infants is in the neonatal intensive care unit (NICU) environment. Although both nurses and parents report positive perceptions regarding the pain-reducing effectiveness of breastfeeding and skin-to-skin contact for infants [25,26], uptake and sustained implementation of these interventions in clinical practice has been limited [25,27], with less than half of the infants receiving any form of pain-relieving treatment during tissue-breaking procedures [27]. Common reasons for not using these interventions include lack of knowledge, stress and anxiety, gatekeeping and parent exclusion, and challenges associated with the physical environment [25].

Lack of Knowledge

Lack of knowledge about pain management in infants has been identified as a barrier to evidence-informed pain care [28-30]. Parents reported feeling apprehensive about participating in pain relief methods as they were not informed of pain in infants and nonpharmacological pain management approaches, including skin-to-skin contact and breastfeeding [24]. Parents reported that resources such as educational pamphlets, videos, workshops, or active counseling as educative initiatives for parent-led pain management in infants would be useful to enhance their awareness of the importance and use of parent-led pain-reducing strategies [28,31,32]. Health care providers, including nurses and physicians, may lack the communication skills needed to effectively relay information about pain in infants to families under their care [33]. A study found that educational pamphlets were used but only as part of the patient's discharge package [32]. Parents who lacked knowledge regarding parent-led pain management interventions in infants stated that to be appropriately educated, the health care team needed to improve on how and when information was given to them [25].

Stress and Anxiety

Stress and anxiety are also barriers to parental involvement in pain management in infants [28,29]. Parents who lack knowledge of pain relief interventions have been found to feel anxious and uncertain about their ability to provide pain relief [29]. Multiple studies have shown that parents in particular found it stressful to be present during painful procedures, either because of their own phobia and fear of needles or because it was emotionally very difficult to watch their infant in pain [28-30].

Gatekeeping and Parental Exclusion

The attitudes and behaviors of health care providers influence the abilities of parents to participate in parent-led pain management in infants [30]. Health care providers have reported feeling responsible for pain management, acting in a gatekeeper role by deciding *who* provides pain relief measures and *how* they are provided [28-30]. Health care providers may exclude parents from participating in painful procedures, because they underestimate the abilities of the parents or feel as though they are protecting the parents from fear or anxiety [28]. Some studies have shown that staff members excluded parents from being

involved in pain relief during painful procedures, because their presence was seen as an additional stressor to the health care provider [29,31].

Physical Environment

Studies in this area have been conducted in NICU settings. The physical environment of the NICU acts as a barrier to parent-led pain management in infants [28,29]. Parents may struggle to find their role as caregivers in restrictive medicalized environments [28]. Technology and equipment, including incubators, act as barriers that limit the ability of parents to participate in pain relief measures [29]. The NICU has been described as lacking physical space for parents to be present [28] and has policies that prevent them from being present during reports or medical rounds, thus restricting access to their baby [29].

Facilitators of Parent-Led Pain Management in Infants

Three facilitators have been identified to support parent-led pain management in infants in the literature, including motivation of parents to participate, the physical environment, and access to information.

Motivation to Participate

The main facilitator of parent-led pain management in infants identified is the motivation of parents to be active participants in pain relief strategies and their eagerness to be educated on the subject [28-30,34]. Parents of infants in the NICU found that seeing their infant in pain increased their desire to be involved in their care and pain reduction [29]. Health care providers who showed a positive attitude toward parental involvement in pain management in infants and who empowered parental education, influenced the motivation of parents to participate in strategies of parent-led pain management in infants [28,29,31]. Parents were more likely to be involved in pain management in infants when they wanted knowledge about pain in infants and felt responsible for the well-being of their infant [28].

Physical Environment

Although studies have identified the physical environment as a barrier to parent-led pain management in infants, some studies have shown that it is also a facilitator. Parents felt more comfortable participating in pain relief strategies when the physical environment was *family-friendly* [28]. Parents also stated that private rooms and kangaroo care chairs promoted participation [29].

Accessibility to Information and Clear Communication

Access to educational tools and information, as well as open communication between parents and staff about pain management in infants has been reported to promote parent participation [28,34]. Parents who had access to educational tools, such as pamphlets or videos, felt more prepared to participate in parent-led pain management [29]. A study suggested multiple ways of disseminating this information, including during birthing or parenting classes, in hospitals or physician' offices, and in waiting rooms [34]. Parents were also more likely to participate in parent-led pain management, if the information used to educate them was obtained from a credible source [34]. Family-centered care approaches, in which health care providers partnered with parents on pain management in infants, promoted parental participation [31]. Health care providers who communicated appropriate timing and tasks for parent-led pain management enabled parents to be open to participating in pain relief [29].

Rationale for This Study and Study Objectives

Overall, the literature highlights numerous barriers, facilitators, and opportunities to support parent-led pain care in infants, with a focus on NICU settings. However, limited research has been conducted that aims to better support the uptake of these best-practice interventions for infants cared for outside neonatal units, particularly in community settings. Most infants undergo routine painful procedures as part of healthy infant care delivered by postpartum clinical services, primary care providers, and community public health offices. Therefore, to promote positive outcomes, health care safety, and access to best-practice pain care, it is imperative that strategies that support the sustained implementation of parent-led pain care in infants be identified in diverse hospital and community care environments.

Furthermore, parent-led pain care may be hindered by ineffective implementation strategies in the local context. Successful implementation of evidence-informed practices relies on a comprehensive understanding of the barriers and facilitators to change and tailoring implementation interventions to the local context [35]. The use of theory can assist in identifying potential behavioral determinants that influence implementation. Subsequently, implementation interventions can be tailored to specific behavioral determinants and as a result, will likely bring about change [36]. To date, a theoretically informed approach to identifying behavioral determinants and developing tailored implementation interventions has not been described in the literature. To address this gap, the aims of this study are to (1) identify barriers to and facilitators of parent-led evidence-informed pain care in infants (ie, breastfeeding or chestfeeding and skin-to-skin contact) during routine acute procedures and (2) develop theory-informed, contextually relevant implementation interventions to support the use of evidence-informed pain care in infants in community- and hospital-care contexts.

Methods

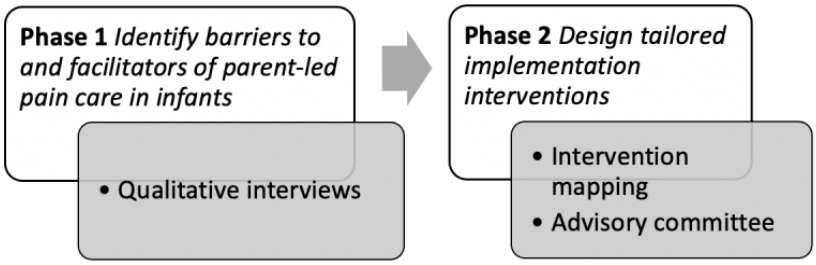
Theoretical Framework

This study will consist of 2 phases (Figure 1) that follow a systematic, theoretically informed approach guided by the Theoretical Domains Framework (TDF) [36,37] and the Behavior Change Wheel (BCW) [38] to understand the barriers and facilitators and to design tailored implementation interventions.

The TDF is an integrated framework that provides a robust guide for implementation studies [36-39]. It has been previously used to identify barriers to and facilitators of evidence use in different health care contexts [36,40]. In addition, it has also been used to identify empirically tested implementation strategies to support evidence use [38]. The BCW is a systematic

intervention design guide that pairs with the TDF to design tailored implementation interventions [38]. We use theory to guide this qualitative implementation study as it supports comprehensive identification of barriers to and facilitators of behavior change as well as development of complex and evidence-informed interventions to target barriers and enablers identified by participants [38]. A description of the phases of this study have been provided in the subsequent sections.

Figure 1. Study phases.



Phase 1: Identify Barriers to and Facilitators of Parent-Led Pain Care in Infants

In phase 1, we will use a qualitative descriptive design [41], using one-on-one interviews to explore the barriers to and facilitators of using parent-led pain care during acute procedures.

Setting and Sample

Our setting includes regional hospitals and community-based contexts that provide perinatal and infant care in northeastern Nova Scotia, Canada. To obtain diverse perspectives, we will use stratified purposive sampling [36,42] of hospital and community-based health care providers (eg, acute care nurses, public health nurses, family practice nurses, acute and primary care physicians or nurse practitioners, midwives, obstetricians, and laboratory technicians), clinical leaders (eg, lactation consultants), administrators and policy makers (eg, program managers), and families who have used hospital or community perinatal services in northeastern Nova Scotia in the last 12 months. Face-to-face, semistructured, in-person interviews with each consenting participant will be conducted. We will aim to recruit approximately 20 to 30 [36,42,43] participants to obtain in-depth data related to the implementation of parent-led pain care. The large sample size was selected based on the heterogeneity of the target sample. To ensure that we have adequate representation and achieve data saturation across diverse health systems and experiences of parent participants, we will use qualitative sampling criteria [44] (which include evaluation of data variations, contraindications, and clarity) to determine if additional targeted recruitment of specific participant groups and exploration of specific experiences is needed to achieve depth and richness in the data. To recruit health system participants, a recruitment email containing study details and an invitation to participate in the study will be circulated through key research team partners and networks. For parent participants, electronic recruitment posters will be circulated via social media, and hard copy recruitment posters will be distributed through hospital and community antenatal care contexts across the province. We will strategically and purposively sample participants who identify as members of equity-seeking groups with diverse intersections of identity, represented across sex, gender, ethnicity, socioeconomic status, immigration or migration status, sexual orientation, ability status, and geography.

Data Collection

The TDF domains [36,37] were used to develop the semistructured interview questionnaires (Textboxes 1 and 2) and guide the analysis of participant interviews. The study interview guides were piloted with a parent partner and a health care provider partner to ensure the appropriateness and adequacy of the interview questions and the feasibility of completing the interview questions within a 60- to 90-minute time frame. Minor revisions to both interview guides were made based on partner feedback. One-on-one semistructured interviews are completed with each consenting participant.

Textbox 1. Study interview guide (family participants).

Knowledge

- Have you or others you know used breast/chestfeeding and/or skin-to-skin contact to manage your babies' pain? Tell me a little bit about that experience/what you know about using breast/chestfeeding or skin-to-skin contact to manage your baby's pain.
- How do/did you find information about using breast/chestfeeding or skin-to-skin contact for managing your baby's pain?

Skill

- What knowledge or supports do you use to breastfeed or provide skin-to-skin contact to your baby during pain? Is there additional knowledge or support that you need to breastfeed or provide skin-to-skin contact to your baby during pain?

Intentions and goals

- How important do you feel it is for your baby to be breast/cheastfed or be in held skin-to-skin contact during pain?

Beliefs about consequences

- Are there any benefits to using breast/chestfeeding or skin-to-skin contact to manage your baby's pain? Are there any negatives to using breast/chestfeeding or skin-to-skin contact to manage your baby's pain?

Environmental context and resources

- What factors influence you to use skin-to-skin contact or breast/chestfeeding to manage your baby's pain? (Prompt(s): stressors, resources, barriers, or facilitators)

Beliefs about capabilities

- How confident do you feel in your ability to breastfeed or provide skin-to-skin contact to manage your baby's pain? (Prompt: Is there anything that would make you more confident?)
- Are there challenges related to breast/chestfeeding or providing skin-to-skin contact for your baby when they are in pain? (Prompt(s): Is there anything that would make using breast/chestfeeding/skin-to-skin contact for your baby during pain easier?)

Social influences

- Do your family/friends influence your decision to use breast/chestfeeding or skin-to-skin contact to manage your baby's pain? (Prompt(s): If yes, how would they influence your decision? To what extent do they influence your decision?)

Emotion

- Do emotions, both positive or negative, influence your decision to use skin-to-skin contact or breast/chestfeeding for your baby's pain management? (Prompt(s): fear of consequences of using/not using skin-to-skin contact or breast/chestfeeding, anxiety, or stress).

Conclusion

- Are there any other key things related to using breast/chestfeeding or skin-to-skin contact to manage your baby's pain that were not discussed today that you think are important to talk about?

Textbox 2. Study interview guide (health care provider and administrator participants).

Knowledge

- Have you or others you know used breast/chestfeeding and/or skin-to-skin contact to manage infant pain? Tell me a little bit about that experience/what you know about using breast/chestfeeding or skin-to-skin contact to manage infant pain.
- How do/did you find information about using breast/chestfeeding or skin-to-skin contact to manage infant pain?

Skill

- What knowledge, resources, or skills do you use to support breast/chestfeeding and/or skin-to-skin contact to manage infant pain? Is there additional knowledge, resources, or skills that you need to support breast/chestfeeding and/or skin-to-skin contact to manage newborn pain?

Intentions and goals

- How important do you think it is for infants to have breast/chestfeeding or be held in skin-to-skin contact for pain management during procedures? If important, what actions have you taken toward using these strategies for pain management?

Beliefs about consequences

- Are there any benefits to using breast/chestfeeding or skin-to-skin contact to manage infant pain? Are there any negatives or harms to using breast/chestfeeding or skin-to-skin contact to manage infant pain?

Environmental context and resources

- What factors influence your decision or ability to use skin-to-skin contact or breast/chestfeeding for pain management in infants? (Prompt(s): stressors, resources, organizational culture, barriers, or facilitators).

Beliefs about capabilities

- How confident do you feel in your ability to support breast/chestfeeding or skin-to-skin contact to manage infant pain? (Prompt: Is there anything that would make you more confident?)
- Are there challenges related to supporting breast/chestfeeding or skin-to-skin contact for infants during painful procedures? (Prompt(s): Is there anything that would make supporting breast/chestfeeding/skin-to-skin contact for infants during pain easier?)

Social/professional role identity

- Do you feel like you have a responsibility to use pain management strategies for infants? Why or why not?
- Have you or others you know acted as a leader to support breast/chestfeeding and/or skin-to-skin contact for pain management in infants? (Prompt: If yes, what does that leadership look like in your organization and/or experience?)

Social influences

- How do your colleagues influence your decision to support breast/chestfeeding or skin-to-skin contact to manage pain in infants? (Prompt(s): To what extent do they influence your decision?)

Reinforcement

- Are there any incentives for you to support skin-to-skin contact or breast/chestfeeding for pain management in infants?

Emotion

- Do emotions influence your decision to support skin-to-skin contact or breast/chestfeeding for pain management in infants? (Prompt(s): fear of consequences of using/not using skin-to-skin contact or breast/chestfeeding, anxiety, stress, or burnout)

Conclusion

- Are there any other key things related to supporting breast/chestfeeding or skin-to-skin contact to manage infant pain that were not discussed today that you think are important to talk about?

Data Analysis

The transcriptions of audio-recorded interviews will undergo inductive-deductive qualitative content analysis [45-47] using NVivo (QSR International) qualitative data analysis software [48]. We will specifically use an intersectionality tool developed for use alongside the TDF [49] to support sex- and gender-based+ analysis. This tool includes intersectionality prompts for each of the 14 TDF domains to be used in participant interviews and data analysis to draw out information on the influences of social factors and structures of power on the implementation of parent-led pain care in infants [49]. First, 2 reviewers (BB and at least one other author) will deductively categorize [46,47] participant responses in the interview data into the 14 TDF domains [37]. Second, principles of inductive qualitative content analysis [46,47] will be used to generate

categories and subcategories of salient barriers and facilitators related to the implementation of parent-led pain care within each of the relevant TDF domain categories [46]. To do this, participant responses will be read multiple times to identify the main points being addressed in relation to the TDF domains. Responses will be read line by line to generate codes, and these codes will be synthesized into higher level categories of barriers and enablers relevant to each of the TDF domains. Strategies to ensure trustworthiness in qualitative research [50,51] and implementation studies [52] will be used. Such approaches include clearly documenting and reporting the analysis process [45,52] and the culture, context, and selection and characteristics of the included participants [42,45,50,52]. Research participants will also be asked to provide feedback on the findings of the analysis (during the advisory committee meetings in phase 2) to ensure that they accurately represent experiences [45,50,51].

It is anticipated that the data from this diverse group of clinicians, clinical leaders, administrators, policy makers, and parents will highlight key behavioral determinants for interventions to support the use of parent-led pain care in infants which are in practice in hospitals and in the community.

Phase 2: Develop Theory-Informed, Contextually Relevant Implementation Interventions

Overview

Phase 2 of this study will build on the findings of phase 1 to develop theoretically robust, empirically tested implementation interventions aimed at supporting the identified facilitators and overcoming the barriers to the use of parent-led pain care in infants. These interventions will be tested in subsequent studies. To do this, we will use the BCW [38], a systematic guide that pairs with the TDF to design tailored implementation interventions. We will implement a 2-step approach to the intervention design.

Phase 2(a): Mapping of Implementation Interventions

First, our research team will review the findings from phase 1 interviews alongside the BCW. The BCW provides 9 intervention functions (eg, education and environmental restructuring) that provide evidence for effectively changing behaviors in each TDF domain. We will map the relevant barriers and facilitators identified by participants within each of the TDF domains onto the intervention functions. Next, the BCW will be further used to map the intervention functions onto key "active ingredient" intervention components to create tailored interventions that target the identified barriers and facilitators in participant interviews.

Phase 2(b): Advisory Committee

Next, we will hold two 3-hour meetings with an advisory committee of several key administrative, clinical, and parent stakeholders who participated in phase 1 interviews to critically review the findings from phase 1 and the implementation interventions identified in phase 2(a). We will strategically invite committee members to ensure diverse and intersecting representation based on sex, gender, ethnicity, socioeconomic status, immigration or migration status, sexual orientation, ability status, and geography, ensuring a minimum of 2 parent stakeholders.

First, the research team will present the advisory committee the findings from phases 1 and 2(a) as a foundation for the refinement of implementation strategies. Second, a facilitator will lead the advisory committee to critically review the findings from phase 1 and the implementation interventions identified in phase 2(a) using the affordability, practicability, effectiveness and cost-effectiveness, acceptability, safety, and equity intervention criteria [38]. All discussion details will be documented by the study research assistant, consistent with the intervention development guidelines [52]. Strategies will be used to encourage authentic engagement and participation from all members of the advisory committee [53]. Such strategies will include using targeted questions for specific participant groups (ie, clinical stakeholders and parent stakeholders) to ensure feedback is obtained from all participants. In addition, small breakout groups will be used to facilitate targeted discussions, and participants will be encouraged to share verbal or written individual feedback or notes after the meeting has ended, if they are more comfortable doing so [53]. This discussion will help identify intervention feasibility and options for intervention delivery in different care environments and provide an opportunity to identify and refine details of optimal intervention implementation (eg, content, settings, recipients, providers, intensity, duration, and fidelity).

Following the completion of phase 2, we will have co-designed theoretically informed implementation interventions that have evidence for effectively supporting evidence implementation. These implementation interventions can subsequently be pilot-tested and experimentally applied in future studies to support the use of parent-led pain care for infants in both hospital and community contexts.

Patient Engagement

Supporting the use of parent-led pain management strategies for infants has been identified as a clinical priority by parents in our previous work [26,54], and they will be engaged across the phases of this study. Following recommendations for patient and caregiver engagement from the Canadian Institutes of Health Research Strategy for Patient Oriented Research Patient Engagement Framework [55] and Health Quality Ontario [56], we have a dedicated parent partner as a member of our research team who is and will be engaged throughout the entire research process to ensure that parent or family perspectives and voice are well represented. Parents will be interviewed to identify their perspectives on barriers to and facilitators of using parent-led pain care in infants and will be regularly consulted to provide feedback on interpretation of the interview data throughout the data analysis. In addition, we will engage parents as members of our advisory committee. Parents will be supported to actively contribute to discussion regarding the adaptation and application of interventions to support the use of parent-led pain care in infants. Parent participants will be compensated for their contribution to study interviews and advisory committee work based on a parent partner compensation policy detailed by Solutions for Kids in Pain, a Canadian knowledge mobilization network [57]. Across all

phases of this work, we will specifically engage families with diverse perspectives to provide a rich understanding of the complex ways in which equity, diversity, and inclusion influence the use of parent-led pain care in infants. It is anticipated that by engaging parents in this study, we will build relationships with parents who can be engaged as partners in subsequent research projects.

Research Team

Our collaborative research team consists of clinicians, scientists, and administrators supporting service delivery to infants cared for in the community and acute care settings in northeastern Nova Scotia. Our team has expertise in pain assessment and management in infants, breast(chest)feeding promotion and support, parental interventions for pain in infants, maternal-child health, knowledge translation, implementation science, and acute and primary care. Our team includes a parent partner, and we have buy-in from key clinical and administrative collaborators in participating public health and hospital units.

Ethics Approval

Ethics approval for this study was obtained from the Nova Scotia Health Research Ethics Board in December 2020 (#1026212).

Results

As of May 2022, we have enrolled 15 participants in phase 1 of this study.

Discussion

Overview

Supporting the use of parent-led pain care in infants is essential for positive parent and infant health outcomes. This study will follow a systematic and theoretically informed approach to comprehensively map the barriers to and facilitators of parent-led pain care in infants in diverse hospital- and community-based practice contexts. These identified barriers and facilitators will inform the development of co-designed, theoretically informed implementation interventions tailored to a variety of clinical practice settings. The results of this study will expand on previous literature describing barriers to and facilitators of parent-integrated pain care [28] by specifically developing implementation interventions to support parental participation. Following the completion of this study, the identified implementation interventions will be pilot-tested and experimentally evaluated in subsequent research to understand their impact on parent integration in pain management in infants.

Strengths

A strength of this study is that it is guided by implementation science theory to support the development of tailored implementation interventions. The TDF [36,37] and BCW [38] have been previously used to comprehensively map barriers to and facilitators of evidence use in health care [36,40] and develop implementation strategies to support evidence use [38]. The recruitment of a diverse sample of health care providers and parents will enhance the relevance of the findings. Inclusion of a parent partner and clinical stakeholders on the research team, as well as completion of advisory committee meetings to review and revise implementation interventions, will ensure that parent and clinician perspectives and voice are well represented. Given the strong theoretical foundation, the diverse sample, and purposive inclusion of stakeholder voice in this work, we anticipate that the developed implementation interventions will be successful in supporting parent-led pain care in infants in subsequent research.

Limitations and Anticipated Challenges

The recruitment and retention of diverse and representative participants is a potential challenge that could impose limitations on this research. To proactively minimize this risk, we have specific support with participant recruitment through members of our research team (which includes health systems partners, a parent partner, and support from the Solutions for Kids in Pain, a Canadian knowledge mobilization network). We will provide all participants a gift card as an honorarium for taking part in the study interviews, and parent partners will be compensated for participation in the study advisory committee [56]. In addition, participants may experience additional or shifting workload demands and commitments as part of the response of the health and social system to the COVID-19 pandemic. As such, we have dedicated long time blocks in the work plan of our study to conduct study procedures and account for competing priorities.

Conclusions

This protocol represents a theoretically informed and evidence-based approach to comprehensively understanding the barriers to and facilitators of parent-led pain care in infants and design implementation interventions to support best-practice pain care for infants. The successful integration of parents in pain care is crucial to support patient safety and positive health outcomes for diverse infants and families.

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Authors' Contributions

BB will take responsibility for overseeing all aspects of this study, including its progress and timely completion. JM and AC will provide expertise related to clinical practice environments and support participant recruitment, the contextualization of findings, and dissemination. BB will oversee and complete data collection. BB will lead data analysis with support from CC, JvW, SH, and QC. MC-Y and RM-M will provide mentorship in all aspects of this study. All authors contributed to manuscript development and read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BCW: Behavior Change Wheel
NICU: neonatal intensive care unit
TDF: Theoretical Domains Framework

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Protocol

Passive Mobile Self-tracking of Mental Health by Veterans With Serious Mental Illness: Protocol for a User-Centered Design and Prospective Cohort Study

Alexander S Young[1,2], MSHS, MD; Abigail Choi[1], BS; Shay Cannedy[2], PhD; Lauren Hoffmann[2], MA; Lionel Levine[3], MS; Li-Jung Liang[4], PhD; Melissa Medich[2], PhD; Rebecca Oberman[5], MSW, MPH; Tanya T Olmos-Ochoa[5], MPH, PhD

[1]Semel Institute for Neuroscience & Human Behavior, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, United States

[2]Veterans Integrated Service Network-22 Mental Illness Research, Education and Clinical Center, Greater Los Angeles Veterans Healthcare System, Department of Veterans Affairs, Los Angeles, CA, United States

[3]Henry Samueli School of Engineering and Applied Science, University of California, Los Angeles, Los Angeles, CA, United States

[4]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, United States

[5]Center for the Study of Healthcare Innovation, Implementation & Policy, Greater Los Angeles Veterans Healthcare Center, Department of Veterans Affairs, Los Angeles, CA, United States

Corresponding Author:
Alexander S Young, MSHS, MD
Semel Institute for Neuroscience & Human Behavior
Department of Psychiatry and Biobehavioral Sciences
University of California, Los Angeles
300 UCLA Medical Plaza
Los Angeles, CA, 90095
United States
Phone: 1 310 794 7219
Email: ayoung@ucla.edu

Abstract

Background: Serious mental illnesses (SMI) are common, disabling, and challenging to treat, requiring years of monitoring and treatment adjustments. Stress or reduced medication adherence can lead to rapid worsening of symptoms and behaviors. Illness exacerbations and relapses generally occur with little or no clinician awareness in real time, leaving limited opportunity to modify treatments. Previous research suggests that passive mobile sensing may be beneficial for individuals with SMI by helping them monitor mental health status and behaviors, and quickly detect worsening mental health for prompt assessment and intervention. However, there is too little research on its feasibility and acceptability and the extent to which passive data can predict changes in behaviors or symptoms.

Objective: The aim of this research is to study the feasibility, acceptability, and safety of passive mobile sensing for tracking behaviors and symptoms of patients in treatment for SMI, as well as developing analytics that use passive data to predict changes in behaviors and symptoms.

Methods: A mobile app monitors and transmits passive mobile sensor and phone utilization data, which is used to track activity, sociability, and sleep in patients with SMI. The study consists of a user-centered design phase and a mobile sensing phase. In the design phase, focus groups, interviews, and usability testing inform further app development. In the mobile sensing phase, passive mobile sensing occurs with participants engaging in weekly assessments for 9 months. Three- and nine-month interviews study the perceptions of passive mobile sensing and ease of app use. Clinician interviews before and after the mobile sensing phase study the usefulness and feasibility of app utilization in clinical care. Predictive analytic models are built, trained, and selected, and make use of machine learning methods. Models use sensor and phone utilization data to predict behavioral changes and symptoms.

Results: The study started in October 2020. It has received institutional review board approval. The user-centered design phase, consisting of focus groups, usability testing, and preintervention clinician interviews, was completed in June 2021. Recruitment and enrollment for the mobile sensing phase began in October 2021.

Conclusions: Findings may inform the development of passive sensing apps and self-tracking in patients with SMI, and integration into care to improve assessment, treatment, and patient outcomes.

Trial Registration: ClinicalTrials.gov NCT05023252; https://clinicaltrials.gov/ct2/show/NCT05023252

International Registered Report Identifier (IRRID): DERR1-10.2196/39010

(JMIR Res Protoc 2022;11(8):e39010) doi:10.2196/39010

KEYWORDS

serious mental illness; mobile health; mental health; passive sensing; health informatics; behavior; sensor; self-tracking; predict; assessment

Introduction

Background

Serious mental illnesses (SMI), such as schizophrenia and bipolar disorder, are disabling and intrusive disorders that can impact educational attainment, work productivity, social functioning, and life expectancy [1]. Psychosocial and psychopharmacological interventions can improve symptoms and health, employment, and education [2]. For individuals with schizophrenia, maintenance antipsychotic treatment is the primary approach for treatment; however, on average, 42% of patients with schizophrenia have been found to be nonadherent to medication treatment, often resulting in worse symptomatology [3,4]. Worsening symptoms can lead to decreased social interaction and make patients less likely to seek help [5,6]. Thus, patient symptoms can worsen or relapse while presenting limited opportunities for mental health clinician awareness, and little opportunity to intervene.

Although warning signs for symptom exacerbation or relapse differ among individuals, they are often consistent within an individual over time. Exacerbations start as mild and increase as symptoms worsen, with 75% of families reporting observable changes between 2-4 weeks before relapse [7]. A study found that the interval between worsening symptoms and relapse was at least one week in 50% of patients [8]. Given a window of opportunity to intervene, interventions were developed and tested to prevent relapse or hospitalization through intermittent drug techniques; however, these interventions showed modest to no effectiveness when implemented [4]. There was noted difficulty getting individuals to reliably self-monitor and report their warning signs early enough for medication changes to prevent relapse, suggesting a need for additional patient support and more reliable monitoring.

Mobile apps and passive mobile sensing technologies could be an approach to help people with SMI self-monitor [9]. Passive mobile sensing can use sensor and phone data from mobile devices to detect health-related behaviors (eg, exercise, social interaction, sleep), which may allow one to detect changes in symptoms and functioning across various behavioral domains like activity, sociability, and sleep [10,11]. These associations have been found in patients with SMI. For example, behavioral indicators for psychiatric symptoms of mood and anxiety disorders monitored through mobile sensing were found to predict clinically assessed symptoms of depression and posttraumatic stress disorder [12]. In patients with bipolar disorder, depressive and manic symptoms were associated with changes in activity and phone communication, while other studies found activity and location to be correlated with mood states [13-16]. In patients with schizophrenia, self-reported stress, depression, and psychotic experiences were also associated with mobile sensor data related to sleep, activity, and communication, signaling the potential for developing predictive models from passive mobile sensing data to aid in identifying changes in symptoms and functioning [17].

Approximately 75% of individuals in treatment for SMI report being willing to participate in digital interventions for stress, health, and mental health [18]. Additionally, patients with SMI find computerized self-assessments acceptable provided they have a clinical application and can help prevent serious adverse events for themselves or others. In a previous study of patients with schizophrenia, passive mobile sensing was found feasible when participation was voluntary [19]. This suggests at least a degree of acceptability among patients with SMI to use passive mobile sensing for managing SMI symptomatology.

Although a few previous mobile sensing studies have centered on individuals with SMI, very few have focused on US veterans—a population with unique physical and mental health needs that may also benefit from this technology. Approximately 4% of veterans have SMI and an estimated 44% of veterans with SMI have moderately severe or severe symptoms [20]. According to a review of health care utilization by veterans, it was found that veterans with SMI were the highest users of inpatient services, with 22% and 41% of patients requiring hospitalization or an emergency department visit, respectively [21]. There are significant effects on patients with SMI and their families associated with worsening symptoms that can lead to diminishing quality of life and medical health. Relative to patients with other mental illnesses, patients with SMI had the greatest percentage of deaths during a 1-year follow-up period [21]. The human costs associated with relapse in patients with SMI are significant, and there is a need to address the difficulty with getting patients to reliably self-monitor and promptly report their warning signs.

A 2014 Veterans Affairs study found that 60% of 249 patients with SMI had a smartphone, with 64% of smartphone users also using apps on their phones [22,23]. Veterans with SMI used similar smartphone functions as the general population and typically kept their phones with them most or all of the time, suggesting that passive mobile sensing may be feasible for this population [22]. Additionally, as time is required for the detection of worsening symptoms and intervention, the period between warning signs and potential relapse is noteworthy.

Veterans with SMI on average experienced early warning signs of worsening symptoms 208 days prior to relapse, similar to patients in the general population with SMI [24]. Considering smartphone usage and period of time prior to relapse, passive mobile sensing may be a viable means for patients with SMI to improve outcomes through the development of self-monitoring tools that can help detect or predict worsening symptoms, allowing for earlier assessment, intervention, and improved outcomes.

Research Aims and Objectives

This study aims to determine the feasibility, safety, and acceptability of passive mobile sensing in patients in treatment for SMI, and to develop and study predictive analytic models to identify associations between symptoms and behavioral domains measured.

The objectives are as follows:

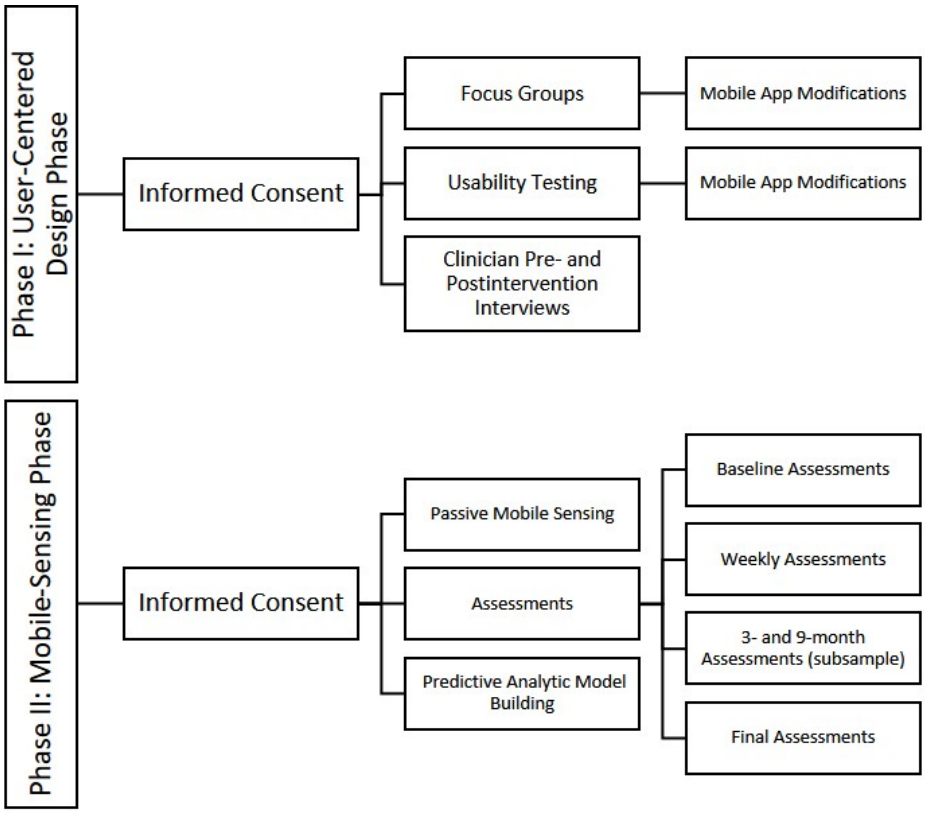
1. Using focus groups and usability testing, conduct user-centered design of passive mobile sensing with self-tracking of activities, sociability, and sleep
2. Study the feasibility, acceptability, and safety of passive mobile sensing of mental health with feedback of mental health status to participants
3. Use mobile sensor and phone utilization data to develop individualized estimates of sociability, activities, and sleep as measured through weekly interviews
4. Study the predictive value of using data on sociability, activities, and sleep to identify worsening of psychiatric symptoms

Methods

Study Design

The study consists of two phases: a user-centered design phase and a mobile sensing clinical trial phase (Figure 1). The study uses a passive mobile sensing app that displays data gathered in the form of interactive patient dashboards. The user-centered design phase (Phase I) focuses on usability of and perceptions regarding the app. The mobile sensing phase (Phase II) studies the safety, feasibility, and acceptability of passive mobile sensing, and uses data to develop predictive models for behavioral domains associated with SMI symptoms.

Figure 1. Study phases: user-centered design and mobile-sensing phase.



Eligibility and Screening

All participants are recruited from the VA Greater Los Angeles Healthcare System (GLA VA), with clinicians included if they are providing care for veterans with SMI. The following inclusion criteria are used: (1) clinical diagnosis of SMI, defined as schizophrenia, schizoaffective disorder, or bipolar disorder, (2) risk for symptoms based on having had, during the past year, psychiatric hospitalization, psychiatric emergency care, lived at a crisis program, or more than 6 outpatient visits, and (3) ownership of a phone running Android OS with a data plan. The following exclusion criteria are used: (1) under the age of 18 years and (2) has a conservator/legally authorized representative.

Study Site and Recruitment of Study Participants

A list of potentially eligible participants was identified using Veterans Affairs data systems. In addition, flyers were posted

at clinics and announcements were made at group meetings to invite participation. Individuals interested in participating had a phone screening verifying diagnosis, age, and last treatment. After confirming potential eligibility, prospective participants were scheduled for an in-person or virtual screening visit at which further information was provided and eligibility assessments were re-verified. Additionally, individuals were asked if they own a smartphone running Android OS with a data plan. If an individual was eligible, full informed consent was obtained, and they were enrolled.

Ethics Approval

The study has been approved by the Institutional Review Board of the GLA VA (project number IIR 19-392).

Phase I: User-Centered Design

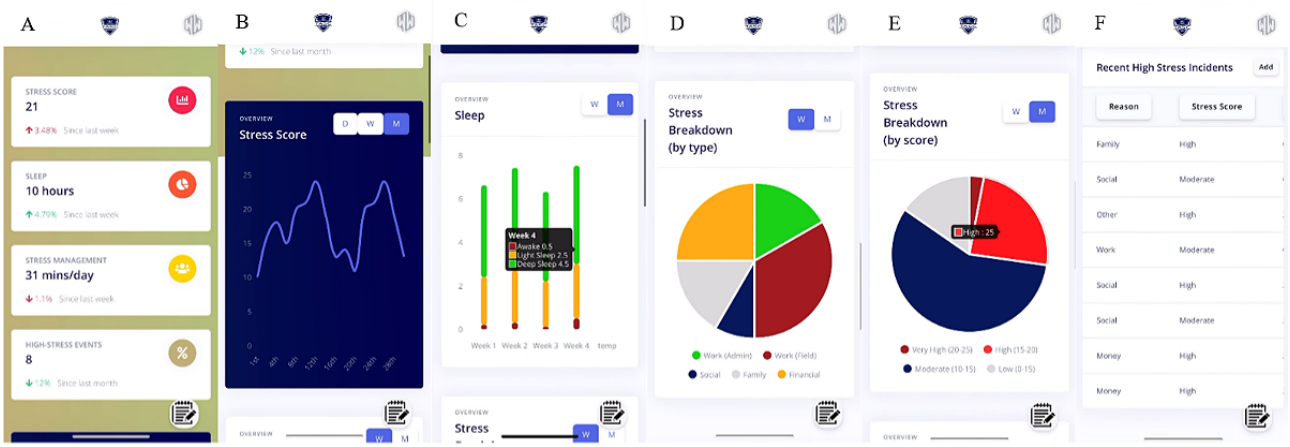
Data Collection

To study the feasibility, acceptability, and safety of passive sensing and self-tracking, the Technology Acceptance Model was used [25]. Components of the Technology Acceptance Model include perceived usefulness, ease of use, attitudes, self-efficacy, norms, facilitating conditions, and behavioral intent. Three focus groups and usability testing were conducted to receive feedback regarding the app and new dashboards. The interactive dashboards for activities, sleep, and sociability display scores by type and intensity, as well as over time (Figure 2A-Figure 2F, Multimedia Appendix 1). Focus groups were co-led by a qualitative methods expert and investigator, with each group containing six veterans. Participants of focus groups were asked questions regarding perceived usefulness, ease of use, attitudes, self-efficacy, norms, facilitating conditions, and behavioral intent. Focus groups aimed to elucidate the acceptance and usability of the dashboards and the app overall.

Modifications were made in response to focus group feedback and usability trials. Usability trials were conducted by a qualitative methods expert and research assistant with 8 veterans meeting inclusion criteria. Veterans participated individually and were asked to complete specific tasks on the app (eg, find the sleep dashboard). They were asked about downloading and opening the app, reviewing dashboards, closing the app, and managing the app. They were asked to express their thoughts as they navigated the app, and RAs noted what the participants said and did. Both focus groups and usability testing lasted approximately 45 minutes.

Before and after the trial phase, semistructured interviews were conducted with clinicians who provide treatment to patients with SMI at the GLA VA. Preintervention interviews with clinicians assessed the acceptability of mobile sensing, its usefulness as a tool to improve clinical assessment and care, and recommendations for improvement. Post–sensing phase interviews will assess how to engage patients, and reflect on findings, implementation issues, and resources needed for sustainability and incorporation into routine practice.

Figure 2. Mobile self-tracking app dashboard prototype examples. (A) Overview of behaviors. (B) Interactive score calculated over time. (C) Chart breaking down behavioral details over time. (D) Chart breaking down behaviors into categories. (E) Chart breaking down scores over a week or month on the scale of low, moderate, high, and very high. (F) Notes on recent incidents and their severity. Higher-resolution version of this figure is available in Multimedia Appendix 1.



App Development and Maintenance

Modifications to the app are rolled out in response to information security requirements, operating system updates, characteristics of phone devices, and needed changes for data acquisition or transmission. Qualitative data collected during user-centered design, as well as data from the mobile self-tracking phase, are used to guide modifications. Some modifications may require a new download of the app, which can be done using phone-based software or during weekly research assessment calls.

Phase II: Mobile Sensing

Following consent and enrollment, participants underwent a baseline assessment. This consisted of an interview regarding demographics, symptoms, functioning, treatment utilization, mobile phone usage, housing status, substance abuse, and cognitive deficits (Table 1). Additionally, throughout the sensing phase of the study, weekly assessments were conducted by phone with participants to assess their sleep, sociability, activities, symptoms, and safety. The rate of serious adverse events during participation will be monitored.

Table 1. Overview of data collection instruments and schedule of assessments for passive mobile sensing phase.

Measure	Data collected and measuring instrument	Visit administered
Sociodemographic data	• Gender, ethnicity, race, marriage, work and school history, service history	Baseline, final
Psychiatric illness history	• The World Health Organization Disability Assessment Schedule (WHODAS 2.0) [26] • Perceived Stress Scale (PSS-4)	Baseline, final
Substance use	• DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure-Adult[a]	Baseline, final
Cognition	• Digit Symbol Coding Test (DSCT)	Baseline, final
Occupation, social, symptom-related, and overall functioning	• Mental Illness Research, Education, and Clinical Center Global Assessment of Functioning (MIRECC GAF) [27]	Baseline, final
Medication possession ratio	• Pharmacy data 12 months prebaseline [28]	Baseline, final
Health care utilization	• Service Use and Resources Form (SURF) [29]	Baseline, final
Housing stability	• Residential Time-Line Follow-Back [30]	Baseline, weekly, final
Psychopathology	• Brief Psychiatric Rating Scale (BPRS)[b] [31]	Baseline, weekly, final
Sociability	• Abbreviated Lubben Social Network Scale [32] • Objective Frequency of Social Contact scale [33,34]	Baseline, weekly, final
Activity, routines, habits	• International Physical Activity Questionnaire [35] • Social Functioning Scale (SFS)[c] [36]	Baseline, weekly, final
Sleep	• Pittsburgh Sleep Quality Index (PSQI)[d] [37] • Insomnia Severity Index (ISI)[e] [38]	Baseline, weekly, final

[a]Substance-use items only.

[b]Positive Symptoms Factor (psychosis), Activation Factor (mania), Affect Factor (depression) [39,40].

[c]Independence Performance and Prosocial Domain.

[d]Components 1, 2, 3, and 6.

[e]Insomnia Problem Items.

At the baseline assessment visit, the app was downloaded onto the participant's phone and activated. Every time the app is activated on a device, an individualized ID is generated by the server. Following activation, the app runs in the background and collects data passively without further action from the user. The server generates an automated report daily that includes the IDs of participants who have not recently transmitted any data, and research staff contact participants to investigate and troubleshoot.

The app collects passive behavioral data in three domains that have been previously shown to be measurable with these data: activities, sleep, and sociability (Figure 3). The app uses the AWARE application programming interface (API) that manages the querying and data packaging, transmission, and storage. The input data are drawn from phone utilization, sensors, software on Android phones that process sensor data, and Google APIs (Table 2). The Google Fused Location API and Google Activity Recognition API are used for postprocessing of sensor data. Although most recent phones contain most or all of these data sources, some older phones may lack certain sensors; the app uses all available sensor data.

The data collected from the app are encrypted and cached locally on the device, and transmitted to the platform's remote server when Wi-Fi is available. If Wi-Fi is not available, data are cached locally until a connection is established. Data are transmitted through an encrypted channel to a web application on a server where it is stored in a secure, encrypted format. Following confirmation of successful transmission, data are deleted from the phone.

A random subsample of participants was selected to partake in 3- and 9-month evaluation assessments, which are semistructured interviews that are recorded and transcribed until data saturation is achieved. Interviews assess for acceptability of passive sensing, usefulness, ease of use, attitudes, and behavioral intention toward use. Participants also provide additional feedback regarding the app. There is a 9-month follow-up and final visit for all participants, in which measures from baseline are readministered.

Figure 3. Passive mobile sensing and utilization data and behavioral domains.

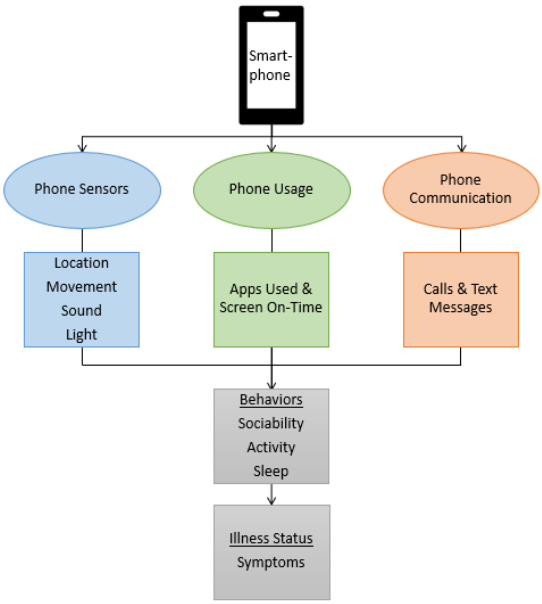


Table 2. Mobile sensing data for modeling of behavioral domains.

Behavioral domain	Input data from phone	Model output classifiers
Activities		
• Physical activity intensity and duration vs sedentary • Organized activities: number and duration outside the individual's residence • Regular structured activities throughout each day (location and duration)	• Accelerometer sensor • Linear accelerometer Android software • Gyroscope sensor • Rotational vector Android software • Step counter Android software • Significant motion Android software • Activity Recognition Google API[a] • Fused Location Google API (uses GPS and Wi-Fi)	• Short International Physical Activity Questionnaire (4 items) [35] • Independence, Performance and Prosocial domains of the Social Functioning Scale (15 items) [36]
Sleep		
• Total sleep duration • Uninterrupted sleep • Regular daily sleep and wake times	• Ambient light sensor • Ambient sound sensor • Significant motion Android software • Fused Location Google API (uses GPS and Wi-Fi) • Phone unlock, screen interactions, and on-time duration • Log of phone calls placed • Log of messages sent • Apps opened • App duration of use	• Pittsburgh Sleep Quality Index Components 1, 2, 3, 6 (5 items) [37] • Insomnia Problem items from the Insomnia Severity Index (3 items) [38]
Sociability		
• Communication in person or in a public social environment • Communication with a diverse set of individuals • Communication with repeated partners	• Log of phone calls placed with phone numbers • Log of phone calls received with phone numbers • Log of messages sent with phone numbers • Log of messages received with phone numbers • Social media apps opened • Social media apps (keystrokes and duration used) • Messaging or email apps opened • Messaging or email apps (keystrokes and duration used) • Ambient sound sensor • Activity Recognition Google API used Location Google API (uses GPS and Wi-Fi)	• Abbreviated Lubben Social Network Scale (6 items) [32] • Objective Frequency of Social Contact scale (6 items) [34]

[a]API: application programming interface.

Data Management and Security

During informed consent, participants are informed about how the system works; how data are collected, transmitted, and stored; and who has access to the data. The mobile app communicates with a secure server where sensor data are housed. Data are encrypted when at rest on the mobile device, in transit to the server, and on the server.

Data Analysis Plan

Feasibility, Acceptability, and Safety

Qualitative interviews are professionally transcribed and analyzed deductively for major subthemes of usefulness, ease of use, attitudes and behavioral intention toward use, acceptability, strengths and weaknesses, barriers and facilitators of use, safety, and recommendations about revisions and implementation efforts. Results inform adjustments of the app and modifications of methods for enrollment and maintenance of participation.

Data obtained from the mobile self-tracking phase's quantitative baseline patient characteristics will be studied using multivariate analyses to determine potential associations with the themes of feasibility, acceptability, and safety of passive sensing. Qualitative data from the 3-month and 9-month interviews will be used to evaluate these themes.

Feasibility is characterized by studying the extent to which potential subjects enroll, maintain involvement, and complete study assessments. Acceptability is characterized by counting the number of days participants use mobile sensing and dashboards, as well as by analyzing data from semistructured interviews. Safety is measured using the rate of serious adverse events. Additionally, important medical events may also be considered a severe adverse event if jeopardizing the participant or requiring a medical or surgical intervention.

Building Predictive Models

Mobile phone sensor and utilization data are used to develop individualized estimates of sociability, activity, and sleep that will also be measured through weekly interview. Data gathered by the app provide detailed patient data over the follow-up period. Real-time data streams construct behavioral measures of interest. As data are collected at vastly different frequencies and durations with different noise and error rates, a 2-step modeling approach is used. Step 1 preprocesses sensing data to derive features capturing events of interest. Step 2 builds prediction models using machine learning techniques to estimate correlations between sensor and phone utilization data, and behavioral assessments and symptoms.

During the data preprocessing step (Step 1), sensor and utilization data are captured at varying frequencies for different domains and summarized using activity profiles (over a day or a week). Daily or weekly activity profiles are constructed based on the amount of time that the individual spends at an activity level (eg, above a threshold) or engaged in an activity at a given day or week.

In Step 2 (prediction model development), various machine learning algorithms are used to build, train, and select prediction models for each of the patient's behavioral assessment domains. Model development occurs in three stages: unsupervised learning to reduce dimensionality (Stage 1), supervised learning to build candidate models (Stage 2), and cross-validation to estimate out-of-sample performance of the prediction model and select the best models (Stage 3). Models developed through supervised machine learning methods are evaluated in the out-of-sample predictive performance using leave-one-out cross-validation.

Results

The study started in October 2020. The patient focus groups, usability trials, and clinician interviews enrolled 17 veterans, 8 veterans, and 16 clinicians, respectively. Data collection for the user-centered design phase was completed in June 2021. Recruitment for the mobile tracking phase started in October 2021 with the goal of recruiting 125 patients. This study is expected to conclude in July 2023.

Discussion

Overview

This study will determine the feasibility and acceptability of passive mobile sensing, and estimate the extent to which behavioral data predicts behaviors and psychiatric symptoms in patients with SMI. We anticipate that passive mobile sensing will be feasible and acceptable in most patients with SMI. We hypothesize that passive mobile data will be associated with behaviors and psychiatric symptoms, and that these associations will vary among individuals.

Passive mobile sensing could be an innovative method to improve self-monitoring of behaviors associated with worsening symptoms of SMI. There is increasing support for the validity of behavioral indicators for mobile sensing platforms as predictive of psychiatric symptoms [12,41]. Additionally, the feasibility and acceptability of passive mobile sensing in patients with SMI has been explored with encouraging results [41,42].

Potential Limitations

Some challenges are expected in recruitment, enrollment, and retention in the patient population. To overcome these difficulties, strategies like monitoring and tracking patient flow, fair and appropriate compensation, and flexible assessment scheduling are used. Due to the COVID-19 pandemic, it has been difficult to conduct in-person screening visits; consequently, the study is adopting virtual screening, consents, and assessments to recruit and enroll participants.

Additionally, as the data are collected from smartphones, we expect missing data points. Various approaches will be considered to adjust for missing data when creating activity profiles. One such approach is the similarity assumption that the proportion of time that a participant spends at a given activity level during observed times is like that during unobserved times, which is similar to the missing at random assumption in longitudinal data analysis. Another approach is to use the planned machine learning approaches to evaluate missing data patterns.

Conclusion

If found to be feasible, acceptable, and safe, passive mobile sensing can become a clinical tool for patients with SMI, allowing access to dashboards of activity, sociability, and sleep that can be used as a tool for monitoring symptoms and behaviors. The adoption of such apps may also be viable and its integration into clinical care may further improve clinical outcomes for patients with SMI. The findings of this study hope to guide the development of passive sensing and modeling that could dynamically assess mental health and identify the risk for worsening illness. It hopes to eventually guide the development of a platform that is acceptable and desirable to patients, helping patients and their clinicians to monitor their clinical status, identify the risk for relapse, and allow for early intervention.

Acknowledgments

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Data Availability

Mobile sensor data collected during this project contain information that is sensitive. These data are also difficult to deidentify to a level that ensures that data cannot be reidentified in the future. As a result, data will not be available in public repositories and access to data is restricted.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Higher resolution version of Figure 2. Mobile self-tracking app dashboard prototype examples. (A) Overview of behaviors. (B) Interactive score calculated over time. (C) Chart breaking down behavioral details over time. (D) Chart breaking down behaviors into categories. (E) Chart breaking down scores over a week or month on the scale of low, moderate, high, and very high. (F) Notes on recent incidents and their severity.

[PNG File , 411 KB - resprot_v11i8e39010_app1.png]

Multimedia Appendix 2

Peer-reviewer report from the HSR-4 Mental and Behavioral Health - Health Services Research Parent IRG - Office of Research & Development.

[PDF File (Adobe PDF File), 134 KB - resprot_v11i8e39010_app2.pdf]

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Abbreviations

API: application programming interface
GLA VA: VA Greater Los Angeles Healthcare System
SMI: serious mental illness

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Protocol

Transdiagnostic Psychopathology in a Help-Seeking Population of an Early Recognition Center for Mental Disorders: Protocol for an Experience Sampling Study

Marlene Rosen[1*], PhD; Linda T Betz[1*], MSc; Christian Montag[2], Prof Dr; Christopher Kannen[2], MSc; Joseph Kambeitz[1], MD, Prof Dr

[1]Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany
[2]Institute of Psychology and Education, Ulm University, Ulm, Germany
[*]these authors contributed equally

Corresponding Author:
Marlene Rosen, PhD
Department of Psychiatry and Psychotherapy
Faculty of Medicine and University Hospital of Cologne
University of Cologne
Kerpener Straße 62
Cologne, 50937
Germany
Phone: 49 221 478 87166
Email: marlene.rosen@uk-koeln.de

Abstract

Background: Prevention in psychiatry provides a promising way to address the burden of mental illness. However, established approaches focus on specific diagnoses and do not address the heterogeneity and manifold potential outcomes of help-seeking populations that present at early recognition services. Conceptualizing the psychopathology manifested in help-seeking populations from a network perspective of interacting symptoms allows transdiagnostic investigations beyond binary disease categories. Furthermore, modern technologies such as smartphones facilitate the application of the Experience Sampling Method (ESM).

Objective: This study is a combination of ESM with network analyses to provide valid insights beyond the established assessment instruments in a help-seeking population.

Methods: We will examine 75 individuals (aged 18-40 years) of the help-seeking population of the Cologne early recognition center. For a maximally naturalistic sample, only minimal exclusion criteria will be applied. We will collect data for 14 days using a mobile app to assess 10 transdiagnostic symptoms (ie, depressive, anxious, and psychotic symptoms) as well as distress level 5 times a day. With these data, we will generate average group-level symptom networks and personalized symptom networks using a 2-step multilevel vector autoregressive model. Additionally, we will explore associations between symptom networks and sociodemographic, risk, and resilience factors, as well as psychosocial functioning.

Results: The protocol was designed in February 2020 and approved by the Ethics Committee of the University Hospital Cologne in October 2020. The protocol was reviewed and funded by the Köln Fortune program in September 2020. Data collection began in November 2020 and was completed in November 2021. Of the 258 participants who were screened, 93 (36%) fulfilled the inclusion criteria and were willing to participate in the study. Of these 93 participants, 86 (92%) completed the study. The first results are expected to be published in 2022.

Conclusions: This study will provide insights about the feasibility and utility of the ESM in a help-seeking population of an early recognition center. Providing the first explorative phenotyping of transdiagnostic psychopathology in this population, our study will contribute to the innovation of early recognition in psychiatry. The results will help pave the way for prevention and targeted early intervention in a broader patient group, and thus, enable greater intended effects in alleviating the burden of psychiatric disorders.

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KEYWORDS

help-seeking population; phenotyping; ecological momentary assessment; symptom networks; transdiagnositc psychiatry; prevention; early intervention; psychiatry; mental health

Introduction

Background

Prevention and early intervention in psychiatry provide promising ways to address the immense burden of mental illness [1-3]. The currently established prevention approach implemented in early recognition services focuses on risk syndromes developed for predicting specific diagnoses (eg, psychosis [4,5]). However, the majority of help-seeking patients who present at early recognition services are not covered by these specific risk syndromes, as they do not fulfill the respective criteria that indicate the increased risk that qualifies them for targeted intervention [4,6]. Thus, in a sizable proportion of this population, early recognition centers for mental disorders currently miss out on a critical potential for preventive efforts. In fact, help-seeking populations present with a mixture of various symptoms [7] such as depressive, anxious, and psychotic symptoms. Depressive and anxiety symptoms have proven to be among the main reasons why individuals seek help [8,9], whereas psychotic symptoms are of interest as they are the most burdensome for the affected individuals as well as for the health care system, despite their low prevalence [10]. These symptoms are shared across different diagnoses [11-13], as well as different disorder states such as risk-syndrome, subthreshold, and full-threshold disorders [11]. Similarly, growing evidence demonstrates that distress is a mediating and triggering factor for psychopathology at large [12-16]. Taken together, help-seeking populations are much more heterogeneous than previously assumed and may develop manifold potential outcomes [17] or show other unfavorable outcomes such as persisting deficits in psychosocial functioning [18].

Thus, there is a growing call for a broader, transdiagnostic approach for prevention in psychiatry [19-22]. Although there is important data on the psychopathology of patients presenting to early recognition centers (eg, [6,8,23,24]), their interpretation is limited by the typically purely cross-sectional, retrospective, and diagnosis-specific character of the assessments. However, symptoms fluctuate over time [25-27], and important insights are missed when neglecting this dynamic component of psychopathology in help-seeking populations. Moreover, as outlined above, conventional assessments are often considered in isolation rather than in concert, neglecting the transdiagnostic, intertwined nature of psychopathology in help-seeking populations. Collectively, these observations underline the necessity to use novel methods to enrich traditional self- and observer-based reports to understand the psychopathology in help-seeking populations.

One novel method consists of integrating 2 distinct innovative ideas that have emerged in the field of psychopathology in recent years [28]. The first idea consists of intensive longitudinal measurements of symptoms and other relevant variables via the Experience Sampling Method (ESM), which has become increasingly feasible and accepted in recent years, especially with the advance of mobile technology such as smartphones [29,30]. ESM provides valid insights into psychopathology as it occurs in daily life by assessing the targeted phenomena repeatedly during the course of the day within a specific time period. ESM increases ecological validity compared to retrospective reporting, reduces biases resulting from false memory or aggregation processes of experience over a longer time period, and allows the collection of data at the within-person level [31].

The second idea is the network approach mainly put forward by Borsboom et al [32-34] (recent overview [35]), in which psychopathology is conceived as a dynamic system of connected, interacting, and maintaining symptoms and other clinically relevant variables [32,36]. In line with a clinician's perspective, symptoms are assumed to co-occur because of functional relations between them rather than due the common dependence on an underlying disorder entity [33,35,36]. With its inherently transdiagnostic outlook [34,37], the network approach is well suited for conceptualizing the psychopathology of help-seeking populations, where the patterns and strength of symptom expression is typically highly heterogeneous.

The integration of network analyses with ESM data enables rich insights beyond those obtained by established assessment instruments. Specifically, the intensive time-series data that result from ESM can be used to model symptom networks that offer a promising gateway into understanding the dynamics of psychopathology on the group and individual levels [38]. On the group level, dynamic symptom networks allow us to exploratively map out the potential average causal relations among individual symptoms in the same measurement window and across measurement windows. Personalized symptom networks are of special interest, as they allow the conceptualization of psychopathology as a set of person-specific dynamic processes [36,39]. By revealing the symptoms and processes most relevant to each individual, these approaches hold the potential to personalize interventions [36,40].

Due to these properties, many interesting studies have been published proving the potential of longitudinal symptom network models in advancing the psychopathological understanding of specific psychiatric conditions [41,42]. However, insights into the dynamic structure of psychopathology of a heterogeneous help-seeking population of a psychiatric early recognition center—the interactions of a broad, transdiagnostic set of symptoms, as well as the associations with risk and resilience factors and psychosocial functioning—are still lacking so far.

Thus, with this proposed study, we aim to provide the first explorative, transdiagnostic phenotyping through the combination of ESM with network analyses. This will be the one of the first studies aimed at phenotyping the transdiagnostic help-seeking population of an early recognition center for mental disorders by applying ESM.

Findings from this innovative approach integrated with those derived from established assessments represent a promising way to address a larger proportion of the help-seeking population as compared to current diagnosis-specific strategies aimed at preventing the burden of psychiatric disorders. Moreover, the results will have their core value in generating hypotheses regarding central dynamic psychopathological processes. These provide a basis for follow-up work dedicated to informing preventive interventions by testing experimentally whether the interventions on particular symptoms or processes lead to changes consistent with the estimated network model [43].

Aim

The PhenoNetz study aims to explore the transdiagnostic phenotyping of a help-seeking population of an early recognition center for mental disorders using innovative, intensive longitudinal data collection via a smartphone app. A better understanding of the relevant psychopathology in this population is of great relevance given the lack of adequate interventions [44]. Combining ESM with network analyses allows for unique insights into the as yet underresearched early transdiagnostic psychopathological processes in the help-seeking population of an early recognition center of mental disorders, as well as to explore their association with risk, resilience, and psychosocial functioning.

Methods

Setting and Participants

In total, 100 participants will be recruited from the help-seeking population presenting at the early recognition center of mental disorders at the University Hospital of Cologne (Früherkennungs- und Therapiezentrum; FETZ) [45], with an expected dropout rate of 25% leading to a total of 75 participants in the final sample. Dropouts include the participants that withdraw from the study, are no longer reachable, or terminate the study without a sufficient number of ESM measurements (for details, see the data analysis section). The FETZ offers specialist diagnostics for the early recognition of mental disorders, with a focus on severe mental illness, in particular psychotic disorders. However, the first contact is independent of this focus and accessible for all people aged 18-40 years that have noticed any changes in their experience and behavior. Most patients find out about the FETZ through internet research or are referred by health care practitioners.

For a naturalistic characterization of the help-seeking population presenting at the FETZ using ESM, we will not impose specific inclusion criteria for participation in the PhenoNetz study. Similarly, to ensure the validity of the obtained data, only a small part of the help-seeking participants will be excluded based on the following criteria:

- acute suicidal thoughts
- IQ ≤ 70
- aged >40 years
- known previous illness of the central nervous system, as well as untreated, unstable somatic illnesses with known effects on the central nervous system (eg, untreated hypothyroidism)
- insufficient knowledge of the German language

Procedure and Materials

All patients presenting at the FETZ not fulfilling any of the listed exclusion criteria will be addressed either directly at the FETZ or via telephone or email (given permission to contact was obtained by the clinical personnel at the FETZ) and informed about the background, goal, design, risks, benefits, and data security aspects of the study. Any open questions the participants might have will be answered directly by one of the primary investigators (MR and LTB). All willing participants will provide written informed consent prior to their participation in the study. All participants will be compensated with €40 (US $42.08) for their participation. Participants can withdraw from the study at any time without negative consequences.

Figure 1 illustrates the study design. During the baseline assessment, data on sociodemographics, medication, substance use, psychopathology including psychosocial functioning, as well as risk and resilience factors will be assessed through both observer- and self-ratings (Table 1). All data will be collected via the Research Electronic Data Capture (REDCap) software [46]. In the baseline assessment, the mobile app used for ESM data collection in the study, *insightsApp* [47] (Figure 2a), will be installed on the personal smartphones of the participants. As the *insightsApp* only runs on Android devices, participants with personal smartphones using other operating systems (eg, iOS) will be provided with a study smartphone for the study period. Participants will be encouraged to complete as many surveys as possible without substantial inconvenience or compromising their personal safety (eg, disrupting sleep or while driving). Compensation for participation will not depend on the number of completed assessments.

Figure 1. Study design of the PhenoNetz study. Participants included will undergo baseline assessment with self- and observer-ratings, followed by a 14-day ESM data collection period. In the subsequent follow-up assessment, selected self- and observer-ratings will be collected again. If desired, the participants will receive personalized feedback on their ESM data after the 2 weeks of ESM data collection, such that the feedback does not interfere with ESM data collection. ESM: Experience Sampling Method.

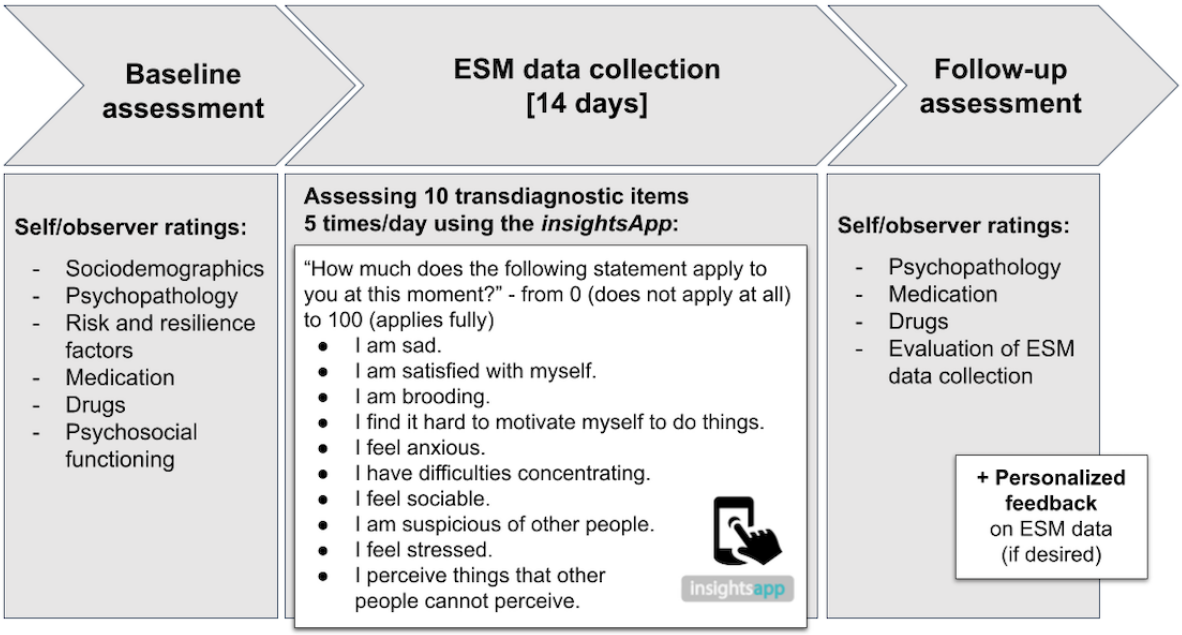

Figure 2. Layout of the *insightsApp*. (a) Main menu; (b) In-app reminder; (c) Visual analogue scale for answering transdiagnostic items.

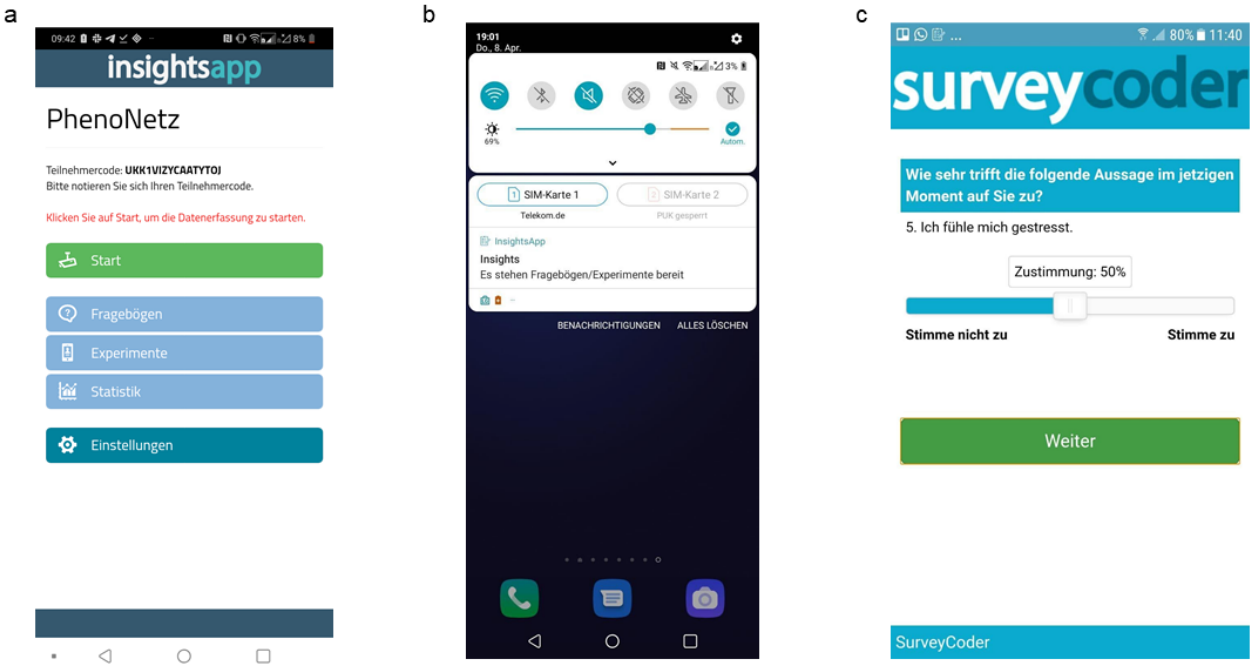

Table 1. Constructs with scales assessed at the baseline and follow-up assessments (before and after the Experience Sampling Method [ESM] period, respectively) of the PhenoNetz study.

Construct	Questionnaire	Self- vs observer -rating	Baseline assessment	Follow-up assessment
Sociodemographics	Self-designed questionnaire assessing gender, age, primary language, nationality, current living or housing conditions, highest level of education, highest vocational degree, current employment/professional activity, marital status/partnership, number of siblings, highest level of education of primary caregivers, highest vocational degree of primary caregivers	Observer-rating	✓	
Psychopathology				
Diagnostic classification	Structured Clinical Interview for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) [48]	Observer-rating	✓	
Current substance use	Analogous to the Personalized Prognostic Tools for Early Psychosis Management study [49]	Observer-rating	✓	✓
Current medication	Analogous to the Personalized Prognostic Tools for Early Psychosis Management study [49]	Observer-rating	✓	✓
Depression	Beck Depression Inventory [50]	Self-rating	✓	✓
Anxiety	State and Trait Anxiety Inventory [51]	Self-rating	✓	✓
Social phobia	Social Phobia Inventory [52]	Self-rating	✓	✓
Psychotic symptoms	Community Assessment of Psychic Experience [53]	Self-rating	✓	✓
Quality of life	World Health Organization Quality of Life Questionnaire [54]	Self-rating	✓	✓
Risk and resilience				
Childhood trauma	Childhood Trauma Questionnaire [55]	Self-rating	✓	
Bullying	Bullying Scale [56]	Self-rating	✓	
Resilience	Resilience Scale for Adults [57]	Self-rating	✓	
Coping	Coping Inventory for Stressful Situations [58]	Self-rating	✓	
Personality	NEO-Five Factor Inventory [59]	Self-rating	✓	
Attachment	Attachment Style Questionnaire [60]	Self-rating	✓	
Expressed emotion	Level of Expressed Emotion Scale [61]	Self-rating	✓	
Social support	Multidimensional Scale of Perceived Social Support [62]	Self-rating	✓	
Introspection	Self-Reflection and Insight Scale [63,64]	Self-rating	✓	✓
Self-efficacy	Self-Efficacy Scale [65]	Self-rating	✓	
Psychosocial functioning	Global Functioning Social and Role Scales [66]	Observer-rating	✓	
Experience with ESM period	Adapted from Frumkin et al [67]	Self-rating		✓

Using ESM, potentially relevant transdiagnostic (subthreshold) symptoms such as sadness, anxiety, psychotic experiences, and stress will be recorded (Textbox 1). The items are based on previous studies and questionnaires, given the lack of standardized ESM assessment in clinical populations [43,68]. In-app reminders will be sent out 5 times a day at fixed time points: 9:30 AM, 12:30 PM, 3:30 PM, 6:30 PM, and 9:30 PM, for a duration of 14 days (Figure 2b). Fixed sampling schemes are common in network applications to ESM data [43,67,69-71], given that they lead to equidistant measurements, an important assumption of 2-step multilevel vector autoregressive (mlVAR) modeling [38]. In psychiatric populations, fixed sampling schemes have also been associated with increased compliance [72]. In each survey, participants will be asked how much they endorse a certain feeling or behavior at the time of filling out the survey: “Wie sehr trifft die folgende Aussage im jetzigen Moment auf Sie zu?” (How much does the following statement apply to you at this moment?). Responses will be given on a visual analogue scale (as a percentage) from 0=“trifft überhaupt nicht zu” (does not apply at all) to 100=“trifft voll und ganz zu” (applies fully), with a slider that can be moved in 1-unit increments (Figure 2c). Participants will be asked to fill in the

items as soon as possible after receiving the in-app reminder, but no later than 60 minutes afterwards, following prior research (eg, [43,73,74]). Filling in the items takes about 1-1.5 minutes in total. Similar ESM protocols were deemed acceptable for clinical populations in prior studies [31,67,75]. The *insightsApp* will be used only for the regular, active collection of transdiagnostic symptoms by means of the described self-report questions. No personal information (such as name and phone number, etc.) or passive data are accessed, stored, or transferred by the *insightsApp*. To maximize the number of completed surveys for each participant, the participants will be contacted at least once during the assessment period to assess instruction adherence, identify any concerns associated with the method, and help the participants with any problems in completing the ESM questionnaire.

Textbox 1. Experience Sampling Method (ESM) items assessed in the PhenoNetz study (along with the English translation).

1. Ich bin traurig (I am sad).
2. Ich nehme Dinge wahr, die andere Menschen nicht wahrnehmen können (I perceive things that other people cannot perceive).
3. Ich habe Schwierigkeiten, mich zu konzentrieren (I have difficulties concentrating).
4. Ich bin kontaktfreudig (I feel sociable).
5. Ich fühle mich gestresst (I feel stressed).
6. Ich bin zufrieden mit mir (I am satisfied with myself).
7. Ich fühle mich ängstlich (I feel anxious).
8. Es fällt mir schwer, mich zu Dingen zu motivieren (I find it hard to motivate myself to do things).
9. Ich bin misstrauisch gegenüber anderen Menschen (I am suspicious of other people).
10. Ich grüble (I am brooding).

In the follow-up assessment conducted after the 14 days of ESM data collection, information on psychopathology, medication, and substance use will be assessed again, referring to the 14 days during which ESM data were collected (Table 1). In addition, experiences and strain associated with the ESM data collection will be assessed via a questionnaire translated and adjusted from a previous study conducted in clinical participants [67] (Table S1 in Multimedia Appendix 1). If desired, participants will be provided with a personalized feedback report on their ESM data.

Data Security

Using a smartphone app installed on the personal smartphone of the participants for data assessment requires particular attention to data security (a broader discussion on ethical concerns regarding digital phenotyping procedures in the psychological and psychiatric sciences have been previously described [76,77]). Therefore, subjects must provide additional consent to allow data to be collected within the app and grant the necessary permissions to the app on the smartphones (such as being notified by the app about available surveys). The ESM data collected by the *insightsApp* are pseudonymized (16-digit alphanumeric codes) and sent directly to a server hosted and maintained by a professional web hosting service after each survey. Answers to the surveys are only stored temporarily locally on the smartphones and deleted once they are transmitted to the server. To secure the data transfer from the smartphone to the server, the connection between the *insightsApp* and the backend software on the server is encrypted by the use of a Secure Sockets Layer certificate.

Safety

Given that this study is observational, there are no direct risks associated with participation. Previous studies have demonstrated good acceptance of ESM protocols similar to the one implemented in this study. Even if participants become more aware of their symptoms due to high-frequency data collection, this does not have a negative effect in terms of worsening symptoms [31,67,78]. Participants can terminate the ESM data collection at any time without giving reasons. Participants who are acutely suicidal or a danger to others will immediately be presented to the service physician for further assessment. Should this become apparent in a telephone call, participants will be reported to the responsible social psychiatric service.

Data Analytic Plan

All statistical analyses will be conducted in the R statistical software (R Foundation for Statistical Computing) [79]. Descriptive analysis of the sample will include mean, SD, median, and IQR as appropriate. The participants included in the analysis will be compared to those that dropped out of the study or were excluded due to too few available measurements (see sample size and the required number of ESM observations) via appropriate classes of permutation tests [80]. Changes in measures that were assessed twice, pre- and post-ESM (see Table 1), will be compared via linear mixed modeling. Prior to the analyses of ESM data, we will detrend the ESM data by fitting fixed-effects linear regression models to each ESM item, regressing out a linear trend on time (ie, general increases/decreases in items over time) and mean-center ESM items per person. We will then generate group-level and personalized networks via a 2-step mlVAR modeling approach as described in detail below. These analyses will allow us to examine symptom dynamics within multiple individuals (n>1; fixed effects) and for individual participants (n=1; random effects). Originally, we planned to estimate and analyze “truly” personalized networks solely based on data from individual participants (such as those that could be derived via a graphical

vector autoregressive model [28]). However, results from a simulation study [81], published as a preprint 1 month after our study commenced, suggest that our sampling scheme potentially lacks the power to detect a nonnegligible proportion of true edges in truly personalized networks, which is why we decided to refrain from this analytic approach.

2-Step mlVAR Model

We will use a mlVAR model, as implemented in the R package "mlVAR." In the mlVAR model, the average dynamical relationships on the group level are modeled as fixed effects, whereas regression coefficients are allowed to vary between patients as random effects.

First, we will estimate 3 group-level network structures including the 10 assessed symptoms, reflecting the average process of all participants (fixed effects): between-subject (an undirected partial correlation network between the means of participant's scores, capturing, in general, whether participants high on a given node are also high on other nodes during the 2-week course of the study), contemporaneous (an undirected partial correlation network showing how symptoms relate to each other in the same window of measurement, controlling for temporal relationships), and temporal (a directed network displaying symptoms predicting each other across an approximately 3-hour lag, while controlling for all other experiences in the model at the prior measurement). Centrality will be assessed using strength centrality (indicating the summed absolute edge strengths connected to a specific node) in the contemporaneous network, and in-strength (indicating the summed absolute strengths of all incoming edges) and out-strength (indicating the summed absolute strengths of all outgoing edges) in the temporal network will be assessed using the R package "qgraph" [82].

Second, we will generate 2 types of personalized networks for each participant based on estimated random effects of the mlVAR model: a contemporaneous network and a temporal network. These personalized networks are not truly idiographic, in the sense that they borrow information from other subjects [38,41]. However, in doing so, the mlVAR model can perform well in estimating personalized networks even if the number of ESM observations is comparatively low for a particular participant. Given that the mlVAR model does not perform participant-specific model selection, all estimated personalized networks will contain all edges [38].

We will use orthogonal estimation for contemporaneous and temporal effects. For the contemporaneous and temporal group-level networks, we will use the conservative "AND-rule" approach in retaining and plotting significant edges. A detailed description of methodological details has been described previously [38,41].

Specifically, we have planned the following analyses:

1. We will compute group longitudinal networks (between-person, contemporaneous, and temporal [28]) as described above.
2. We will identify symptom centrality and unique partial correlations among symptoms in the contemporaneous and temporal group-level networks. We hypothesize that on the group level, feeling stressed will be the most central symptom in the contemporaneous network and predict most other experiences in the temporal network, given that stress experience is frequently discussed as a transdiagnostic factor in psychopathological experiences [13-16]. For the temporal network, we have no a priori hypothesis with regard to the most central item.
3. We will evaluate the degree of association between risk factors (eg, childhood trauma) and network connectivity, assessed by the global strength of personalized networks (temporal and contemporaneous) in a linear modeling approach. Based on prior research and theoretical considerations [33,83,84], we hypothesize that risk factors will be associated with increased network connectivity. Similarly, we hypothesize that poorer psychosocial functioning will be associated with increased network connectivity.
4. We will explore how the strength of specific symptom-symptom connections in individual contemporaneous and temporal networks relates to the degree of presence of specific risk and resilience factors.

Sample Size and the Required Number of ESM Observations

Formal power analyses have not yet been worked out for group-level network models based on intensive longitudinal data. Power at the intraindividual level is a function of within-person variability; there should be sufficient variability such that the intraclass coefficient is not too close to 1, which should usually be the case when having a large number of assessments per person as in our study [85,86]. The performance of network estimation methods also depends on the unknown true network structure—the network equivalent of a true effect size in power analysis [41]. Supplementary materials from Epskamp et al [38] report simulation results for mlVAR models, showing that mlVAR models are excellent in recovering the fixed effect structures with a small amount of data, starting at 50 participants. With our targeted sample size of 75, which represents a realistic recruitment goal in the population of interest, we will surpass this threshold, leading to an adequately powered analysis for the estimation of a mlVAR model. Due to the methodological novelty of symptom networks based on intensive time-series data, there exist no guidelines on the number of ESM observations required [41]. More observations collected over a longer period of time improves the stability and validity of the results; however, this has to be balanced against the feasibility of the integration of the study into the daily lives of the participants. With 75 targeted observations collected over 14 days, our study is similar to the study designs of previous ESM projects conducted in psychiatric populations [67,70,73-75,87,88]. Following recommended guidelines [89] and prior studies [38,71], participants with fewer than one-third of the possible ESM observations (ie, 23) will be excluded from the network estimation.

Ethics Approval

Ethics approval was granted by the Ethics Committee of the University Hospital Cologne in October 2020 (reference number 20-1092).

Results

Study recruitment started on November 11, 2020, and was completed on November 10, 2021. Of the 258 participants who were screened, 93 (36%) fulfilled the inclusion criteria and were willing to participate in the study. Of these 93 participants, 86 (92%) completed the study. As of May 2022, data analysis is ongoing. The first results are expected to be published in 2022.

Discussion

Expected Findings

This study aims to extract an explorative phenotyping of the heterogenous help-seeking population of a psychiatric early recognition center. Applying ESM, we will attempt to depict transdiagnostic symptom networks and explore their association with protective and risk factors, as well as psychosocial functioning.

The diverse and transdiagnostic character of help-seeking populations [7] limits the potential of current, narrow concepts of prevention in psychiatry [17,19]. Our exploratory study might provide a first glimpse at the dynamics between transdiagnostic symptoms as well as the associations with outcome and preceding conditions independent of diagnostic categories. Such new insights might be more valuable for alternative preventive approaches targeting a broader patient group than currently established approaches [90]. The central transdiagnostic items and processes we will identify might represent anchor points for interventions [91], which might deviate from diagnosis-specific manuals only focusing on symptoms and processes covered by diagnostic criteria [92]. Furthermore, insights into potential etiological processes, identified by the association with risk and resilience factors as well as psychosocial functioning, might inform prevention strategies [44,92]. Dynamic models based on ESM data being more in line with the true nature of psychopathology instead of static models [25,27,92] might be more effective in the prediction of outcome. In particular, transdiagnostic symptomatology was not often depicted by ESM studies so far [72]. Hypotheses based on the findings of our explorative study might guide future research.

Strengths and Limitations

The atheoretical approach of our study facilitates truly innovative insights not biased or limited by established theories and structures. In addition, the choice for a naturalistic sample with only a limited set of inclusion and exclusion criteria is valuable for external validity.

However, there are several limitations in the design of our study that need to be considered. First, we acknowledge that the use of study smartphones may result in the underrepresentation of iPhone users in our study, as well as less valid data collection than if the participants can use their own smartphones.

The biggest challenge during the conceptualization of the study was the lack of officially validated ESM items. In general, as gold standards for the novel methodology of ESM are missing, researchers construct their own ESM items or refer to items used in previous studies [43,68,93]. Furthermore, most ESM studies focus on specific diagnoses (eg, major depressive disorder [72]). In a *transdiagnostic* ESM design, by contrast, it is difficult to cover the entire diversity of different disorders due to the further limited number of items per diagnosis-specific phenomenology. These difficulties underscore a recent call for valid and reliable scales suitable for investigating the short-term dynamics of emotions and state mental health problems [43].

Future Directions

ESM represents only one of the various powerful elements (eg, digital phenotyping [94,95]) used to gain insights into relevant variables collected in everyday life to improve prevention and targeted early intervention. Studying the digital footprints left by the human-smartphone interaction (eg, log-in frequency, the use of different apps, and calling behavior) can provide additional important insights into the psychopathological states in help-seeking individuals [96]. Exploring the potential of ESM as a self-monitoring intervention in help-seeking populations (similar to approaches in depressive disorder [26]) is another exciting avenue for future research.

Conclusion

In clinical science, intensive longitudinal assessments of symptoms in daily life are deservedly receiving more and more attention [36,40,41] that might result in enhanced patient benefit. By applying ESM and network analyses, our study intends to contribute a milestone toward innovation in understanding help-seeking populations in psychiatry, helping a greater proportion of this heterogeneous and crucial target group [40]. Subsequent impacts on early states and the progress of mental disorders might reduce the associated personal, familial, societal, clinical, and economic burden more effectively.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire to assess experiences and strain associated with the ESM data collection translated and adjusted from a previous study conducted in clinical participants. ESM: Experience Sampling Method.
[PDF File (Adobe PDF File), 99 KB - resprot_v11i8e35206_app1.pdf]

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Abbreviations

ESM: Experience Sampling Method
FETZ: Früherkennungs- und Therapiezentrum (the early recognition center of mental disorders at the University Hospital of Cologne)
mlVAR: multilevel vector autoregressive

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Protocol

Molecular Classification of Endometrial Carcinoma: Protocol for a Cohort Study

Inês Moreira[1*], MD; Carla Bartosch[2*], MD, PhD; Manuel Teixeira[3*], MD, PhD; Marta Ferreira[1*], MD

[1]Oncology Department, Instituto Português de Oncologia do Porto, Porto, Portugal

[2]Pathology Department, Instituto Português de Oncologia do Porto, Porto, Portugal

[3]Genetics Department, Instituto Português de Oncologia do Porto, Porto, Portugal

[*]all authors contributed equally

Corresponding Author:
Inês Moreira, MD
Oncology Department
Instituto Português de Oncologia do Porto
Rua Dr António Bernardino de Almeida
Porto, 4200-072
Portugal
Phone: 351 225084000
Email: ines.almeida.moreira@ipoporto.min-saude.pt

Abstract

Background: Endometrial carcinoma (EC) is the most common gynecologic malignancy in developed countries and the fourth most frequent in women worldwide. The cornerstone of treatment for EC is surgery. Clinicopathological features are currently used to help determine the individual risk of recurrence and the need for adjuvant treatment after surgery. Nonetheless, there is significant interobserver variability in assigning histologic subtype when using a morphological classification, revealing the need for a more unified approach. The Cancer Genome Atlas (TCGA) project identified 4 distinct prognostic EC subtypes based on genomic abnormalities. Surrogate assays including 3 immunohistochemical markers (p53, MSH6, and PMS2) and 1 molecular test (mutation analysis of the exonuclease domain of DNA polymerase epsilon; *POLE*) allowed the development and validation of a simplified molecular classifier that correlates with the TCGA classification, has prognostic value, and can easily be used in clinical practice. This molecular classification categorizes EC in 4 subtypes: *POLE* mutated, mismatch repair–deficient, p53 abnormal, and no specific molecular profile. Applying this classification in clinical practice will help tailor adjuvant treatment decisions.

Objective: The aim of this study is to retrospectively apply this novel molecular classification to a cohort of patients with EC treated in a comprehensive cancer center, to assess its applicability in clinical practice, to evaluate clinical outcomes by molecular subtypes, and to assess its prognostic value.

Methods: In this retrospective cohort study, patients with primary EC diagnosed during and after 2013 and treated or followed at our institution, after definite surgery, will be included. Demographic and clinicopathological data will be obtained from electronic health records and from pathology reports. Laboratory methods will include immunohistochemical study of p53 and mismatch repair proteins, as well as *POLE* mutational analysis by genetic sequencing. The primary end point is recurrence-free survival and secondary end points are disease-specific survival and overall survival. A descriptive analysis of variables will be carried out. Survival analysis will be performed using the Kaplan-Meier method and the groups will be compared using the log-rank test.

Results: This protocol was reviewed and approved by the Instituto Português de Oncologia do Porto, Portugal, ethics committee in October 2021; patient selection from our cancer registry began the same month. A total of 160 patients will be included. This work will present real-life results that will allow a better understanding of the Portuguese EC population and the distribution of the molecular subgroups throughout. We will use these results to understand the prognostic value of this classification in our population and its role in adjuvant therapy decisions. This study is anticipated to conclude in December 2022.

Conclusions: This study will provide important information regarding these women's outcomes according to this new molecular classification and will support its use when discussing a patient's need for adjuvant treatment.

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KEYWORDS

endometrial carcinoma; molecular classification; prognosis; POLE; mismatch repair; p53

Introduction

Background

Endometrial carcinoma (EC) is the most common gynecologic malignancy in developed countries and the fourth most frequent in women worldwide [1]. Incidence of EC has been increasing in the past several years, mainly due to an increase in obesity rates, which is one of the most important risk factors for this disease [2]. Other conditions associated with metabolic syndrome, including diabetes mellitus and polycystic ovary syndrome, and conditions involving excess estrogen exposure such as estrogen-producing tumors or tamoxifen use (which has antiestrogenic effects in the breast and proestrogenic effects in the uterus) are other known risk factors. Protective factors against EC include multiparity and oral contraceptive use [2]. Lynch syndrome, an inherited disorder caused by germline mutations in DNA mismatch repair genes, accounts for approximately 3% of all endometrial cancers [2]. Women with mutations in *MLH1*, *MSH2*, *MSH6*, or *PMS2* have up to a 40%-60% lifetime risk of developing both endometrial and colorectal cancers, as well as a 9%-12% lifetime risk of developing ovarian cancer [3].

The cornerstone of treatment for EC is surgery, consisting of a total hysterectomy and bilateral salpingo-oophorectomy [4]. Most patients with EC present with early-stage, low-grade disease that has a low risk of recurrence and can be managed by surgery alone. Clinicopathological features including age, International Federation of Gynaecology and Obstetrics (FIGO) stage [4], depth of myometrial invasion, tumor differentiation grade, histopathologic tumor type (endometrioid, serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed), and lymphovascular space invasion help determine the individual risk of recurrence and the need for adjuvant treatment after surgery [5]. A risk group classification to guide adjuvant therapy decisions was proposed by the European Society of Medical Oncology (ESMO) 2013 clinical practice guidelines and was updated at the ESMO 2016 consensus conference [6,7]. Nonetheless, there is significant interobserver variability in assigning histologic subtype when using this morphological classification, revealing the need for a more unified approach. Moreover, there are many unanswered questions regarding EC's optimal management, including which, if any, adjuvant therapies to administer.

The Cancer Genome Atlas (TCGA) endometrial collaborative project identified 4 distinct prognostic EC subtypes based on genomic abnormalities, raising the possibility of more precise tailoring of adjuvant therapy [8]. These 4 subgroups include DNA polymerase epsilon (*POLE*) ultra-mutated (with a very high mutation burden in the exonuclease domain of *POLE* that leads to its inactivation and failure in proofreading during DNA replication), microsatellite instability (MSI) hypermutated, copy-number low, and copy-number high. This molecular classification correlates with patient prognosis and may help to improve the identification of early-stage patients who may benefit from adjuvant therapy. However, these genomic methodologies, including genome sequencing, are expensive and can be complex, when obtaining DNA from frozen tissue.

In an effort to bring this molecular classification to routine clinical practice, a reproducible and cost-effective approach that correlated to the TCGA classification was proposed [9]. A simplified molecular classifier was developed, which identifies four molecular subtypes that are analogous to the four genomic subgroups described in TCGA:

1. Pathogenic mutations in the exonuclease domain of *POLE* (*POLE* mutated; *POLE*mut) corresponding to the POLE ultra-mutated phenotype
2. Mismatch repair–deficient (MMRd), with altered immunohistochemical expression of mismatch repair proteins (MMR), corresponding to the MSI hypermutated group
3. No specific molecular profile (NSMP), with preserved p53 and MMR immunohistochemical expression, corresponding to the copy-number low group, having a low mutational burden
4. p53 abnormal (p53abn), with aberrant p53 immunohistochemical expression, including complete loss and/or overexpression of p53, corresponding to the copy-number high group, with a high mutational burden

This classification is based on surrogate simple molecular assays used in clinical practice that could replicate the TCGA classification: MMR immunohistochemistry (IHC) assay (MLH1, MSH2, MSH6 and PMS2) to identify MMRd, genetic sequencing for *POLE* exonuclease domain mutations, and an IHC assay for p53 (wild type vs mutation-type expression; p53wt and p53abn, respectively). These tools can be used in standard formalin-fixed paraffin-embedded (FFPE) material.

Different working groups achieved replication of TCGA survival curves with statistical significance using this molecular classification. These results were further confirmed and validated in other patient cohorts, establishing this simple molecular classifier as a prognostic marker for progression-free and disease-specific survival [10,11]. Tumors with *POLE*mut (~10% of ECs) were mainly of the endometrioid type and had very favorable prognosis, and p53abn tumors (~11%) were associated with aggressive tumor characteristics and consisted mostly of high-grade serous ECs, with poor outcomes. MMRd tumors (28%) and NSMP tumors (~51%) were also mostly endometrioid ECs and had an intermediate prognosis.

The majority of EC can be classified into 1 of the 4 molecular subgroups. However, in a small subset of patients (3%-5%), molecular analysis will show more than one classifying alteration, also referred to as "multiple-classifier" EC [12,13]. The prognosis of these "multiple-classifier" ECs is still uncertain but available survival data demonstrated that *POLE*mut-p53abn EC shows clinical outcomes comparable to *POLE*-mutated EC

without abnormal p53 expression and that MMRd–p53abn shows clinical outcomes comparable to MMRd without abnormal p53 expression [13].

The prognostic value of the molecular classification shown in the previous studies was explored in a retrospective combined analysis of the PORTEC-1 and PORTEC-2 cohorts [14]. These authors concluded that molecular analysis was feasible in >96% of the patients and also reported an unfavorable prognosis for the p53abn group, an intermediate prognosis for the MSI and NSMP groups, and a favorable prognosis in the *POLE*-mutated group. This classification was further investigated in the high-risk patient cohort of the PORTEC-3 trial, and the impact of adjuvant treatment for each molecular subgroup was also evaluated [15]. In this cohort, molecular analysis was successful in 97% of patients; the authors concluded that the molecular classification has a strong prognostic value in high-risk EC (again showing an excellent outcome for *POLE*-mutated patients and a worse outcome for p53abn patients, with the MSI and NSMP groups having an intermediate outcome), and that patients with p53abn EC should be considered for adjuvant chemoradiotherapy, whereas for those with *POLE*-mutated ECs, de-escalation of adjuvant treatment should be considered. These two retrospective analyses further support the incorporation of this molecular classification in the risk stratification of patients with EC, as well as in future trials, with the aim of reducing both overtreatment and undertreatment. Moreover, applying this classification in clinical practice will led to personalized treatment approaches based on molecular risk groups and may help tailor immunotherapy in patients with EC [16].

The more recent European Society of Gynaecological Society/European SocieTy for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) guidelines of 2021 for the management of patients with EC recommend using the molecular classification in all ECs, especially high-grade and/or high-risk tumors, and it should be integrated with traditional pathologic features to define prognostic risk groups [17].

To determine the optimal adjuvant treatment within each molecular subtype, this molecular-based classification should be incorporated in future clinical trials to improve outcomes for women with EC; for example, molecular-integrated classification is currently being investigated in the PORTEC-4a trial and in the RAINBO umbrella program (Refining Adjuvant treatment IN endometrial cancer Based On molecular profile) [18,19].

Objectives

The aim of this study is to analyze the distribution of the molecular subtypes in patients with EC treated at our cancer center (Instituto Português de Oncologia do Porto, Portugal; IPO-Porto) and their respective correlation with histopathological and patient characteristics, to assess its applicability in clinical practice, to compare molecular subtypes and ESMO risk groups, and to evaluate clinical outcomes by molecular subtype and assess the prognostic value of this molecular classification. We also aim to evaluate the behavior and clinical evolution of patients with tumors categorized as multiple-classifier, a subject where information is still scarce, in order to better understand their prognosis.

Methods

Study Design

This is a retrospective cohort study of patients with primary EC, diagnosed during and after 2013 and treated or followed at IPO-Porto, after definite surgery.

This study will be carried out by the Medical Oncology department of IPO-Porto, in collaboration with the Pathology and Genetics departments. The Medical Oncology department will be responsible for the selection of patients, gathering and analysis of data, and elaboration of the final report. Pathology will oversee the molecular analysis via IHC in tumor specimens. The investigation of *POLE*mut will be carried out by Genetics. All departments participated in the study design.

Participants and Cohort Identification

This study will include women aged ≥18 years with written informed consent, histological diagnosis of primary EC, definitive surgical staging performed, surgery specimen available at IPO-Porto (for molecular analysis), and availability of clinicopathological and outcome data.

Patients with the following characteristics will be excluded: concurrent cancer being treated at the same time as EC; any neoadjuvant treatment; and metastatic (stage FIGO IVB) and advanced disease (stage FIGO III – IVA with residual tumor).

Patients will be selected from the IPO-Porto cancer registry and from the diagnostic database of the Pathology department. We will start by selecting all women with an EC diagnosis during and after 2013, and evaluate each patient according to the inclusion and exclusion criteria. Afterward, this database will be sent to the Pathology department to check for tumor sample availability.

With a power of 80% and a maximum probability of type 1 error of 5%, the target sample size is estimated to be 160 patients. With this target sample size, we estimate that we will have sufficient power to find statistically significant differences in the study's primary and secondary end points.

Clinical and Laboratory Data Collection

Demographic and clinicopathological data will be obtained from electronic health records and from pathology reports. As for laboratory methods for p53 and MMR protein IHC study and *POLE* mutational analysis, data will be collected as described below.

p53 and MMR IHC

A representative FFPE tissue block will be selected for p53 and MMR protein IHC study. IHC assays will be performed on FFPE tissue sections using a Leica Bond-III automated staining instrument according to the manufacturer's instructions. The following antibodies, clones, titers, and vendors will be used: p53 (Clone D07, 1:200, Dako), MLH1 (Clone ES05, 1:150, Leica), MSH2 (Clone 25D12, 1:150, Leica), MSH6 (Clone PU29, 1:200, Leica), and PMS2 (Clone MOR4G, 1:50, Leica).

Immunostained slides will be evaluated by a pathologist using the following classification: p53 wild type expression (ie, multifocal expression); p53 mutation type/aberrant expression, which includes complete absence of expression, cytoplasmic expression, and overexpression; MMR-proficient tumors (ie, those with intact MMR protein expression); and MMR-deficient tumors (ie, those showing patterns of MMR expression that include complete loss, subclonal loss, or weak immunoexpression).

POLE Mutation Analysis

Tissue sections from selected FFPE tissue blocks will be used for tumor macrodissection and DNA extraction. Genomic DNA will be submitted to polymerase chain reaction amplification followed by Sanger sequencing, using primers for the exonuclease domain of the *POLE* (exons 9-14) gene. *POLE* variants will be described according to LRG_789t1 (NM_006231.4) and the Human Genome Variation Society guidelines [20].

The following information will be collected for posterior data analysis: patient-related variables (age, body mass index, Eastern Cooperative Oncology Group performance status at diagnosis, date of diagnosis); tumor-related variables (histological subtype, tumor grade, FIGO 2009 stage, lymphovascular space invasion, myometrial invasion, nodal status, ESMO clinical risk groups, pelvic or aortic lymphadenectomy, adjuvant treatment performed, type of adjuvant treatment, *POLE* exonuclear domain mutations, p53 IHC status, MMR IHC status, molecular subtype [*POLE*mut, MMRd, NSMP, p53abn, multiple-classifier]); outcome-related variables (recurrence of disease, location of metastasis, death, cause of death, status at last follow-up visit, date at last follow-up visit).

Study End Points

The primary end point of this study is recurrence-free survival, defined as the time from the date of surgery until recurrence of disease documented by the attending physician. Secondary end points are disease-specific survival, defined as the time from the date of surgery until death due to EC, and overall survival, defined as the time from the date of surgery until death from any cause.

Statistical Analysis

Descriptive analysis of variables will be carried out. Continuous variables will be presented using quantitative measures (median, median, quartiles, minimum and maximum values, and standard deviation). Categorical variables will be presented as frequencies and percentages. The Kolmogorov-Smirnov test will be used to verify the normality of the data.

Comparisons between groups will be performed, using Mann-Whitney and Kruskal-Wallis tests for continuous variables. Chi-square or Fisher exact tests will be used to evaluate the association between categorical variables, when appropriate. Survival analysis to assess the main outcomes over time will be performed using the Kaplan-Meier method and the groups will be compared using the log-rank test. Univariable and multivariable analysis with Cox regression models will be used to control the survival analysis according to relevant factors.

A P value <.05 will be considered significant. Statistical analysis will be conducted using the SPSS software (version 27; IBM Corp).

Data Availability and Collection

In October 2021, after ethics committee approval (see below), patient selection from the IPO-Porto cancer registry began. This information will then be sent to the Pathology department to verify tumor material availability. Afterward, the selection of patients' tumor samples will be completed and data collection and laboratory analysis will begin.

Ethics Approval

This protocol was reviewed and approved by the IPO-Porto ethics committee in October 2021 (CES IPO: 233/021). Informed consent will be collected. This study will be conducted according to the principles of the Helsinki Declaration [21]. All collected information will be processed anonymously and used solely for the purposes of this protocol.

Results

Laboratory analysis is scheduled to start after all inclusion data have been collected, and is expected to be concluded by October 2022. Final data analysis will proceed, with an aim to publish a peer-reviewed paper divulging results by the end of 2022.

This protocol will be submitted for grant applications to several entities that support clinical and translational research to obtain funding.

Discussion

Principal Findings

Molecular classification and its prognostic value were validated based on retrospective studies. Its prognostic value was further explored in a retrospective analysis of cohorts of patients from previous randomized trials that included patients with EC. These studies support the incorporation of this molecular classification in the risk stratification of patients with EC, as well as in future trials, with the aim of reducing both overtreatment and undertreatment. Based on these results, the ESGO/ESTRO/ESP guidelines published in January 2021 [17] recommended the use of this molecular classification in all ECs, especially high-grade and/or high-risk tumors, and that it should be integrated with traditional anatomopathological features to define prognostic risk groups. Prospective trials incorporating this molecular classification are currently in progress [18,19] and its application in clinical practice is only just starting.

Our study will present real-life results that will allow a better understanding of the Portuguese EC population and the distribution of the molecular subgroups in this population. We will use these results to understand the prognostic value of this classification in our population and its role in adjuvant therapy decisions. We anticipate that our findings will correlate to previously published studies [9-11]. However, these studies were conducted in North America and northern Europe, so

differences in the molecular profile of this southern European population might be expected.

Strengths

Information obtained from this study will help tailor adjuvant therapy in patients with EC according to molecular subgroups and introduce this molecular classification into our center's clinical practice. We now know from the studies that validated this molecular classification that, despite traditional clinicopathological features, patients with *POLE* mutations have an extremely good prognosis and therefore may not need adjuvant treatment (even if they have high-risk histological features that would make them candidates for adjuvant treatment according to current practice). On the other hand, patients with p53 abnormal IHC status are associated with worse prognosis, and so adjuvant therapy should be mandatory. Patients in the MMRd and NSMP subgroups have an intermediate prognosis and adjuvant therapy decisions should be individualized. Applying this molecular classification to the decision of whether to proceed with adjuvant treatment will help reduce undertreatment and overtreatment and therefore reduce patient morbidity related to treatment toxicities and health care–related costs.

Moreover, we hope to characterize clinicopathological and molecular features of multiple-classifier EC, which is an area of the literature where information is lacking, and understand the evolution and prognosis of these multiple-classifier tumors. We believe this study will provide clinically relevant data for the management of EC. This study will also enable the identification of potential Lynch syndrome patients, who warrant specific surveillance.

Limitations

Besides being a retrospective analysis, this study has some limitations. There is a possibility of having to exclude various patients if there are no tumor samples available, which might decrease follow-up time. Moreover, due to budget constraints, we will not be able to use next-generation sequencing, as previous groups have used, to determine the presence of *POLE* mutations, and we will be using Sanger sequencing instead. Although this might pose a challenge to correlating our findings with work already published, we will be able to evaluate how this method behaves for this particular purpose and perhaps establish Sanger sequencing as a more economical alternative to next-generation sequencing, despite it being more time-consuming.

Conclusions

Molecular classification provides prognostic information that impacts the management of patients with EC. However, its use in clinical practice is only just beginning and results from prospective trials are eagerly awaited. This study will provide important information regarding these women's outcomes according to this new molecular classification and will support its use when discussing a patient's need for adjuvant treatment. Ultimately, the use of this classification will reduce treatment-related morbidity and health care–related costs.

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Authors' Contributions

All authors contributed equally to all phases of the protocol design, as well as in the preparation and revision of this manuscript.

Conflicts of Interest

MF received honoraria for speaking and advisory board membership from AstraZeneca, MSD, and Roche, and had travel, accommodation, and meeting expenses paid for by AstraZeneca, MSD, Pfizer, and Roche. All other authors declare no conflicts of interest.

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Abbreviations

EC: endometrial carcinoma
ESGO: European Society of Gynaecological Society
ESMO: European Society of Medical Oncology
ESP: European Society of Pathology
ESTRO: European SocieTy for Radiotherapy and Oncology
FFPE: formalin-fixed paraffin-embedded
FIGO: International Federation of Gynaecology and Obstetrics
IHC: immunohistochemistry
IPO-Porto: Instituto Português de Oncologia do Porto, Portugal
MMR: mismatch repair proteins
MMRd: mismatch repair–deficient
MSI: microsatellite instability
NSMP: no specific molecular profile
p53abn: p53 abnormal
POLE: DNA polymerase epsilon

POLEmut: POLE mutated
RAINBO: Refining Adjuvant treatment IN endometrial cancer Based On molecular profile
TCGA: The Cancer Genome Atlas

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Protocol

Supporting Self-management and Quality of Life in Bipolar Disorder With the PolarUs App (Alpha): Protocol for a Mixed Methods Study

Erin E Michalak[1], PhD; Steven J Barnes[2], PhD; Emma Morton[1], PhD; Heather L O'Brien[3], MLIS, PhD; Greg Murray[4], PhD; Rachelle Hole[5], MSW, PhD; Denny Meyer[4], DBL

[1]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

[2]Department of Psychology, University of British Columbia, Vancouver, BC, Canada

[3]School of Information, University of British Columbia, Vancouver, BC, Canada

[4]Centre for Mental Health, Swinburne University of Technology, Melbourne, BC, Canada

[5]Canadian Institute for Inclusion and Citizenship, University of British Columbia, Kelowna, BC, Canada

Corresponding Author:
Erin E Michalak, PhD
Department of Psychiatry
University of British Columbia
420-5950 University Blvd
Vancouver, BC, V6T1Z3
Canada
Phone: 1 604 827 3393
Email: erin.michalak@ubc.ca

Abstract

Background: Quality of life (QoL) is increasingly being recognized as a key outcome of interventions for bipolar disorder (BD). Mobile phone apps can increase access to evidence-based self-management strategies and provide real-time support. However, although individuals with lived experiences desire support with monitoring and improving broader health domains, existing BD apps largely target mood symptoms only. Further, evidence from the broader mobile health (mHealth) literature has shown that the desires and goals of end users are not adequately considered during app development, and as a result, engagement with mental health apps is suboptimal. To capitalize on the potential of apps to optimize wellness in BD, there is a need for interventions developed in consultation with real-world users designed to support QoL self-monitoring and self-management.

Objective: This mixed methods pilot study was designed to evaluate the alpha version of the newly developed PolarUs app, developed to support QoL self-monitoring and self-management in people with BD. Co-designed using a community-based participatory research framework, the PolarUs app builds on the web-based adaptation of a BD-specific QoL self-assessment measure and integrates material from a web-based portal providing information on evidence-informed self-management strategies in BD. The primary objectives of this project were to evaluate PolarUs app feasibility (via behavioral use metrics), the impact of PolarUs (via the Brief Quality of Life in Bipolar Disorder scale, our primary outcome measure), and explore engagement with the PolarUs app (via quantitative and qualitative methods).

Methods: Participants will be residents of North America (N=150), aged >18 years, with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision diagnosis of BD type 1, BD type 2, or BD not otherwise specified as assessed by structured diagnostic interview. An embedded mixed methods research design will be adopted; qualitative interviews with a purposefully selected subsample (approximately, n=30) of participants will be conducted to explore in more depth feasibility, impact, and engagement with the PolarUs app over the 12-week study period.

Results: At the time of publication of this protocol, the development of the alpha version of the PolarUs app was complete. Participant enrollment has begun in June 2022. Data collection is expected to be completed by December 2022.

Conclusions: Beyond contributing knowledge on the feasibility and impact of a novel app to support QoL and self-management in BD, this study will also provide new insights related to engagement with mHealth apps. Furthermore, it will function as a case study of successful co-design between people with BD, health care providers, and BD researchers, providing a template for the

future use of community-based participatory research frameworks in mHealth intervention development. The results will be used to further refine the PolarUs app and inform the design of a larger clinical trial.

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KEYWORDS

eHealth; mobile health; mHealth; bipolar disorder; self-management; engagement; mobile phone

Introduction

Background

Bipolar disorder (BD) is characterized by episodes of pathologically depressed or elevated mood states, with a global estimated lifetime prevalence of 2.4% [1]. Although BD can be associated with significant distress, disability, and mortality [2], many individuals with BD report a good quality of life (QoL) [3,4]. Accordingly, optimal treatment of BD involves not only symptom management but also attention to QoL [5,6]. For example, there is only a small to moderate correlation between mood stability and QoL [7-10], indicating that interventions *specifically* targeting QoL are required.

QoL is a treatment outcome prioritized by people living with BD [11-13] and encompasses a broad range of constructs from symptoms and functional impacts to well-being and satisfaction with life domains [6,14]. People with BD have highlighted the importance of life areas directly affected by BD (mood, sleep, physical health, and cognition), functioning and participation (home, work, education, leisure, finances, and relationships), and subjective experiences (self-esteem, spirituality, identity, and independence), which form the basis of BD-specific QoL assessment [14,15]. Self-management interventions align well with QoL-oriented treatment frameworks by assisting an individual with the process of monitoring, responding to, and coping with the impacts of BD [16]. Although psychoeducation about self-management strategies is increasingly incorporated into BD treatment guidelines [17-19], there are substantive barriers to accessing such support. Only 50% of patients in treatment for BD receive psychosocial services such as psychoeducation [20], and people with BD report receiving inadequate knowledge of QoL-focused self-management strategies [21]. Stigma and mistrust in the health care system may also discourage seeking psychoeducation about self-management [16,22]. Unfortunately, the COVID-19 pandemic has introduced additional barriers to obtaining psychosocial interventions [23,24].

Digital health interventions have been suggested as a means to improve access to self-management information and support [16,25]. A total of 2 innovative digital health projects were recently developed with a focus on optimizing QoL in BD. First, only the BD-specific QoL instrument (Quality of Life in Bipolar Disorder [QoL.BD] scale [14]) was adapted to a web-based format (the QoL Tool [26]). The QoL Tool has comparable psychometric properties with those of the pen-and-paper version [27], and individuals with BD reported positive experiences using the web-based format [28]. Second, a novel web-based suite of multimedia evidence–informed self-management tools for people with BD (the Bipolar Wellness Centre [29]) was developed as a partner website to the QoL Tool and has been found to enhance both subjective recovery and QoL [30]. Although these websites have each produced positive impact, they are not integrated, and unlike smartphone apps are not able to provide *in the moment* responsive support. Moreover, mobile app–based self-management and self-monitoring interventions have been shown to have higher levels of engagement than analogous web-based versions [31].

Interest in and use of apps to address mental health needs is high among people with BD. A recent survey found that 93% of people with BD own smartphones, and 77% expressed willingness to receive support with self-management strategies via an app [32]. However, to capitalize on the potential of app-based interventions for BD, the field must address the pressing challenge of user engagement and retention [33]. Evidence from the broader field of digital mental health research suggests that user interest does not necessarily translate to sustained use of web- or app-based interventions. For example, clinical trials of apps for depression have demonstrated high dropout rates [34], and data on publicly available digital self-help interventions for depression or anxiety suggest that program completion and long-term use are rare [35].

Although engagement with mobile apps for BD has not been widely formally evaluated, a qualitative analysis of app store reviews highlighted several unmet user needs related to features and content [36]. QoL-focused app-based interventions have the potential to increase engagement and retention by addressing some of these unmet needs for 3 reasons. First, given the breadth of the QoL construct, such interventions could address the full spectrum of life domains that individuals with BD nominate as important foci for self-management [37-40]. Second, in contrast to traditional symptom-focused monitoring, which tends to highlight dysfunction and can sometimes increase depressive symptoms in BD [41], QoL-focused self-monitoring may help draw attention to personal strengths [28]. Third, as the QoL framework aligns with the treatment goals of many patients, therapeutic alliance and motivation to engage in treatment may be enhanced by a QoL-focused app [42,43]. Indeed, individuals with BD have described participating in a QoL-focused intervention as empowering [21] and that QoL self-monitoring encourages behavior change [28].

The alpha version of the app that will be evaluated in this study, the PolarUs app, builds on and advances a decade of research by the Collaborative Research Team to Study Psychosocial Issues in Bipolar Disorder (CREST.BD). Specifically, the PolarUs app synthesizes and advances the evidence and resources contained in the QoL Tool and Bipolar Wellness

Centre and incorporates additional features and content nominated as important by individuals with BD [33]. Furthermore, individuals with BD and BD researchers co-designed the PolarUs app, which incorporates evidence-informed self-management strategies. Although human or peer support has been shown to enhance engagement with digital health interventions [44,45], this comes with a trade-off in terms of feasibility, particularly in terms of scale-up. Unfortunately, research-led interventions are rarely publicly available [46,47], and researchers are increasingly encouraged to formulate plans for sustainable dissemination beyond the clinical trial [48]. Although the PolarUs app can be used to facilitate or support one-to-one therapy, it has primarily been designed for use as a self-guided program. In this paper, we describe the procedures to be used in a mixed methods study that will explore the feasibility and impact of the PolarUs app and allow for an exploration of patterns of engagement with the app.

Objectives and Hypotheses

There are 3 overarching objectives for this pilot study.

Objective 1: Evaluating PolarUs App Feasibility

To explore feasibility, we will assess rates of adherence and use of the alpha version of the PolarUs app over a 12-week study period.

Objective 2: Evaluating PolarUs App Impact

To evaluate the impact of the alpha version of the PolarUs app, we will assess QoL (using the Brief QoL.BD, our primary outcome measure) over the 12-week study period; we hypothesize that QoL will improve over that time. In addition, we will explore the impact of the app on our secondary outcome measures (ie, mood symptoms, self-efficacy in illness management, subjective recovery, and self-compassion).

Objective 3: Exploring PolarUs App Engagement

Given the relative immaturity of methods for measuring mobile health (mHealth) app engagement (*Discussion* section), we will apply a mixed methods approach to more deeply explore patterns of engagement with the PolarUs app.

Methods

Design

Overview

A sample of 150 adult research participants with a confirmed diagnosis of BD will be recruited to evaluate the alpha version of the PolarUs app. Our chosen assessment period for the evaluation of the PolarUs app is 12 weeks. Most app evaluation studies are 4 to 8 weeks [49], but this may be an insufficient time period within which to assess trajectories of change in self-management behaviors, QoL, or app engagement.

A mixed methods research approach [50] is embedded in the design of this study. Qualitative methods are added to a traditional quantitative design as a single approach, and data set will not be adequate to successfully address our 3 objectives. In the case of this research, qualitative interviews with a purposefully selected subsample (approximately, n=30) of participants will be conducted to explore in more depth feasibility, impact, and engagement with the PolarUs app over the 12-week study period. Qualitative methods are used to enhance our understanding of the quantitative results, improving the overall design through these complementary approaches [50].

Co-design of the PolarUs App

CREST.BD specializes in community-based participatory research, where researchers and knowledge users (in this case, people with BD, their supporters, and BD health care providers) work hand in hand [51]. Lived experiences of BD and co-design methods were integrated into all aspects of PolarUs app development and the design of the evaluation study. For example, the colead principal investigator of the project (SJB) lives with BD, as do some of the coinvestigators. Moreover, the app and study design are guided by a 7-member advisory group, which meets approximately monthly. All members of the advisory group have lived experience of BD as well as a diverse array of additional expertise, including user interface design, interactivity, graphic design, writing, and patient-engaged research.

In addition to our co-design approach, input from a broader international community of individuals living with BD was gathered through a survey. This survey was used to solicit community perspectives on features and content deemed important for inclusion in a BD-specific mHealth app [33].

Functionality of the PolarUs App

The PolarUs app incorporates and expands upon the evidence, resources, and tools currently provided in CREST.BD's Bipolar Wellness Centre [29] and the QoL Tool [26]. As with the Bipolar Wellness Centre, content in the PolarUs app is organized according to the 14 life areas assessed by the QoL.BD. After completing a QoL.BD assessment (Figure 1) at baseline, users will be able to select up to 3 QoL.BD life areas they would like to improve, after which they can select up to 4 relevant self-management strategies to implement over a subsequent 4-week period. During each 4-week period of this 12-week study, users are encouraged to self-monitor their QoL, mood, and sleep at regular intervals (Figure 2). Users receive encouragement while using the app in various forms, including notifications and some types of gamification.

Figure 1. PolarUs app users will complete a self-assessment using the Quality of Life in Bipolar Disorder (QoL.BD) scale at the end of each week and at the end of each month. The image on the left illustrates the presentation of a question from the QoL.BD. The image on the right illustrates a summary screen that is presented to users once they complete the QoL.BD.

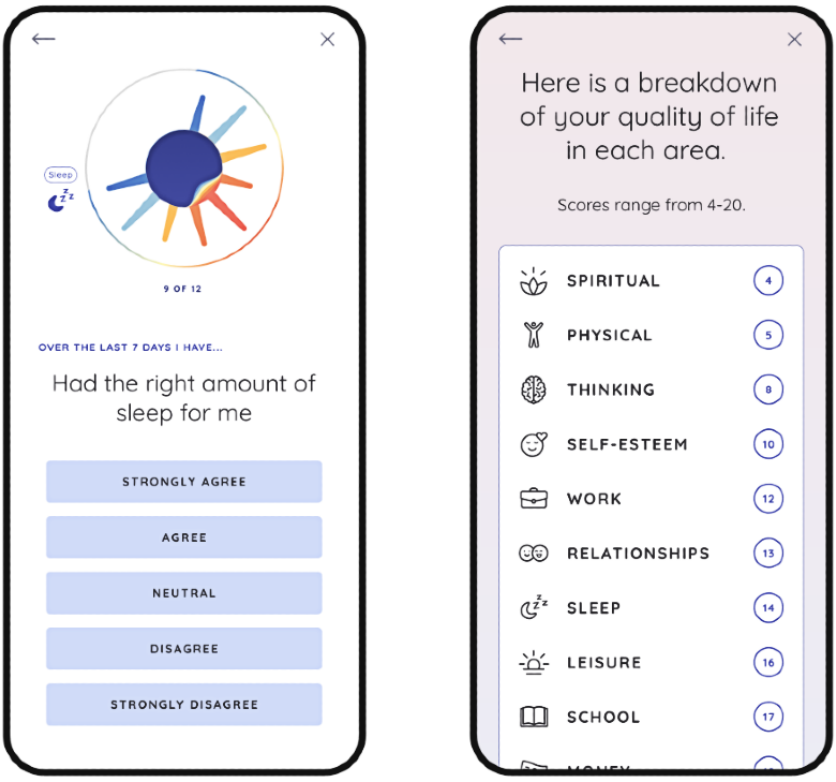
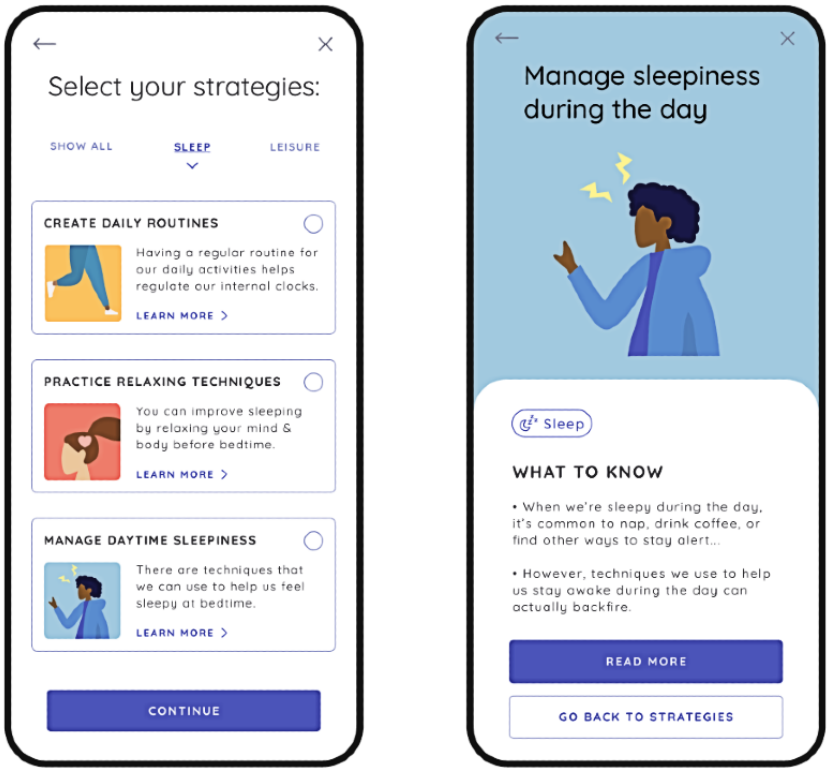


Figure 2. Participants will be prompted (eg, "How are you feeling today?") to complete the Quality of Life in Bipolar Disorder and other self-monitoring activities at regular intervals during the 12-week study. The image on the left illustrates a prompt to do a daily mood check-in. The image on the right illustrates how users can view the history of their Quality of Life in Bipolar Disorder (QoL.BD) scores over the 12-week period of the study. Participants can peruse any one of many resources that might help them with the self-management strategies they are currently using at any time (eg, bottom portion of left image).

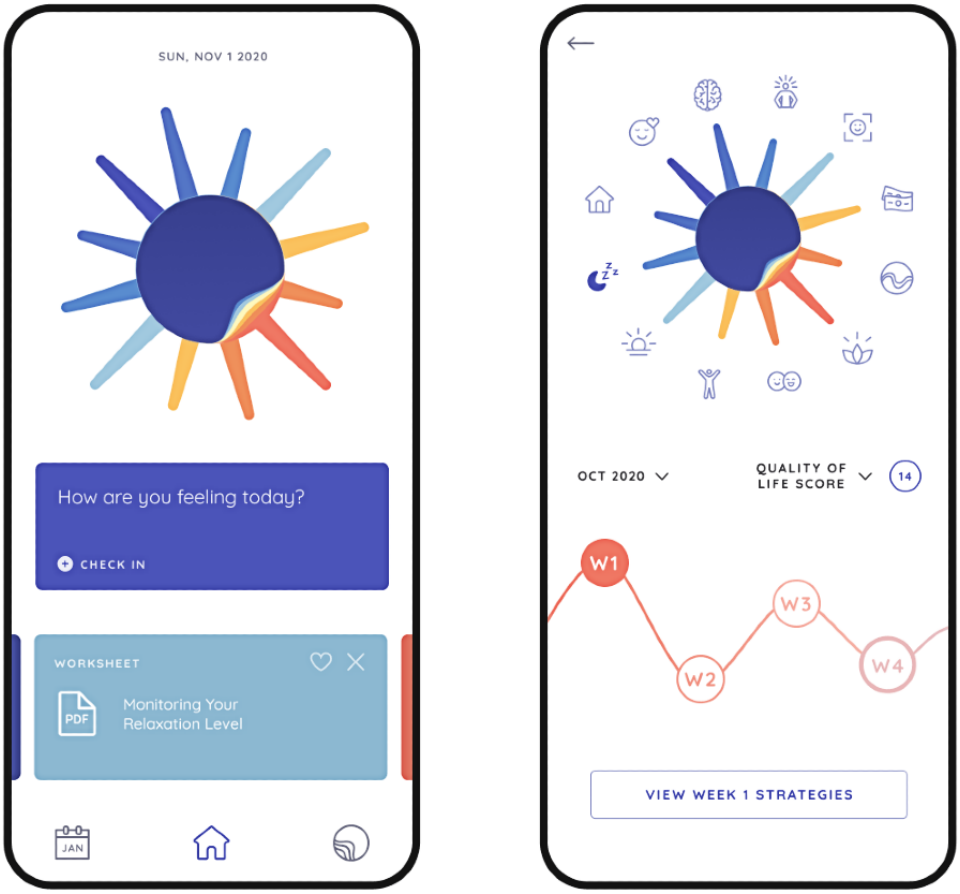


Typical Use Scenario for the PolarUs App in This Study

A typical PolarUs user will engage in the following in-app activities during the course of this study, in the following sequence:

1. Users begin by completing an in-app baseline full QoL.BD assessment (Figure 1).
2. Users then have the opportunity to review their baseline QoL.BD assessment (right image in Figure 2).
3. Users are then prompted to choose up to 3 QoL.BD life areas to focus on over the next 4 weeks.
4. Users are then prompted to choose up to 4 relevant self-management strategies to use over the next 4 weeks (Figure 3).
5. Users are then encouraged to engage in those self-management strategies over the next 4 weeks. They are free to change their self-management strategies over the course of the 4-week period.
6. Once they select their self-management strategies, users are provided with a list of resources related to each strategy that they can review at their leisure.
7. Users are prompted to perform a daily *check-in* regarding their sleep quality and mood (left image in Figure 2).
8. After each period of 7 days, users are prompted to complete the Brief QoL.BD. They can review all their QoL.BD data at any time by navigating to the history screens (eg, right image in Figure 2).
9. At the end of each 4-week period, users are prompted to complete the full QoL.BD, and then steps 3 to 9 are repeated until the 12-week period of this study ends.

Figure 3. The PolarUs app contains information on evidence-informed self-management strategies for each Quality of Life in Bipolar Disorder (QoL.BD) life area. This figure shows 2 screens from the PolarUs app: one with information about the sleep life area (right image) and one with a list of strategies for improving the sleep life area that a user can choose to focus on.



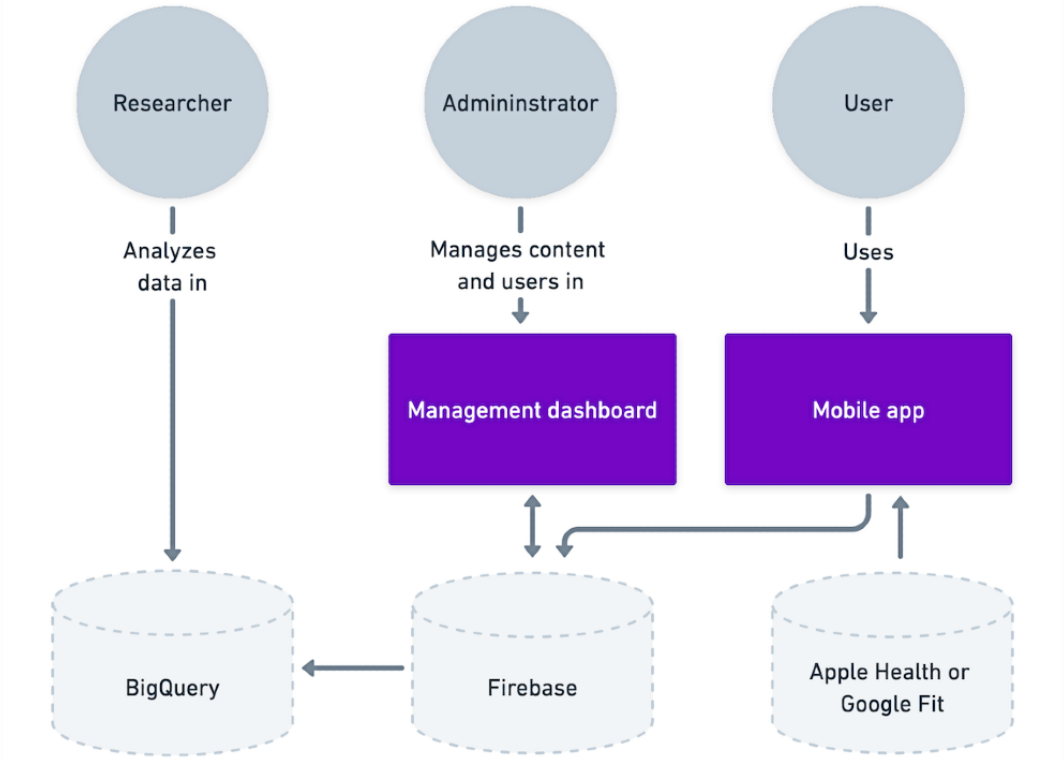
Technical Specifications of the Alpha PolarUs App

The alpha version of the PolarUs app operates on either the Android or iOS smartphone platform. It was built using the open-source Maslo platform (maslo.ai; [52]), which incorporates several technologies. For its frontend, the Maslo platform uses React Native [53], Three.js [54], and Javascript or Typescript. For its backend, the Maslo platform uses Firebase. In addition to using the Maslo platform, the PolarUs app uses Neo4J [55] as its graph database. The architecture of the PolarUs app is illustrated in Figure 4.

Recruitment notices will be circulated to CREST.BD partner organizations and promoted on multiple CREST.BD social media platforms (eg, Facebook, Twitter, and Instagram), on the CREST.BD website [56], and via a project-specific landing page [57]. Participants will be residents of North America, aged >18 years, with a primary Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision diagnosis of BD type 1, BD type 1, or BD not otherwise specified as assessed by the Mini-International Neuropsychiatric Interview version 7.0 [58]. Minimally restrictive diagnostic exclusion criteria will be set to aid generalizability; those currently experiencing

psychosis and those with active suicidal ideation as assessed by diagnostic interviews will be excluded [58]. Participants will also need to be smartphone users, agree to install the app, agree to receive notifications from the app, and have sufficient understanding of written and spoken English to provide informed consent and engage with the app. In addition, participants will, for the purposes of the research study, have the option of consenting to the sharing of their health and behavioral data from the PolarUs app and from the Apple Health or Google Fit apps on their smartphone. Apple Health and Google Fit will not have access to the data unless the user gives permission to share their data with Apple or Google independent of the app. Participants will be invited to consent separately to engage with the qualitative arm of the study.

Figure 4. PolarUs app architecture.



Ethics Approval

Ethics approval for the study has been granted by the University of British Columbia Behavioural Research Ethics Board office (H21-02042).

Assessment and Data Collection Procedures

Overview

Table 1 summarizes the assessment procedures used. The Mini-International Neuropsychiatric Interview version 7.0 will be administered by experienced research assistants at baseline via the Zoom teleconferencing platform or telephone to confirm diagnostic eligibility (ie, a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision diagnosis of BD type 1, BD type 2, or BD not otherwise specified) and identify any comorbid diagnoses [58]. This structured baseline interview will also be used to record sociodemographic variables and conduct the objective mood rating scales.

Clinician-administered and self-report scales (see *In-app QoL.BD: Primary Outcome Measure*, *Clinician-Administered Scales*, and *Qualtrics-Administered Self-Report Scales* sections) will be completed at baseline and at monthly intervals during the 12-week pilot study. Most self-report measures will be conducted via a secure, encrypted web-based survey platform (ie, UBC Qualtrics) that stores its data on Canadian servers. Research assistants (Caden Poh, Bryn Manns, and Priya Johal) will monitor the completion of Qualtrics questionnaires on a regular basis and contact participants to facilitate completion when such support may be required.

Some self-report measures (eg, QoL.BD) will be administered within the app. App use data will be automatically collected in real time. All data collected by the PolarUs app will be transmitted using end-to-end encryption to a secure database on a Canadian server.

At the end of the 12-week evaluation period, a subset of participants will be invited to participate in qualitative interviews. The assessment procedures and instruments to be used in this study are described below, in relation to our study objectives.

Table 1. Summary of self-report, clinician-administered, behavioral, and qualitative data to be collected.

Data type	Outcomes	Scale	Delivery method (frequency)
Self-report	• Condition-specific QoL[a] • General QoL • Chronic Disease Self-Efficacy • Mood • Personal recovery • Self-compassion • Subjective app engagement • App acceptability	• Full QoL.BD[b] • Brief QoL.BD • WHOQOL-BREF[c] • Stanford's Chronic Disease Self-Efficacy: "Manage Disease in General" subscale • Positive and Negative Affect Schedule • Bipolar Recovery Questionnaire • Self-Compassion Scale-Short Form • User Engagement Scale-Short Form • Mobile App Rating Scale (user version)	• In-app (monthly) • In-app (weekly) • Qualtrics (monthly) • Qualtrics (monthly) • Qualtrics (monthly) • Qualtrics (monthly) • Qualtrics (monthly) • Qualtrics (monthly) • Qualtrics (first month)
Behavioral	• Adherence (number of log-ins per week and number of Brief QoL.BD completed) • App use (number and frequency of pages accessed; time spent on the app per session and overall; time spent on specific pages; number and length of unique sessions; length of time between unique sessions) • Behavioral health data (eg, daily activity, heart rate, sleep data, and nutrition)	N/A[d]	• In-app (real-time) • In-app (real-time) • Apple health (iOS) or Google Fit (Android)
Clinician-administered	• Diagnosis • Depressive symptoms • Manic symptoms	• MINI[e] • Montgomery-Asberg Depression Rating Scale • Young Mania Rating Scale	• Telephone (baseline) • Telephone (monthly) • Telephone (monthly)
Qualitative	• Subjective app engagement and impacts	N/A	• Telephone or Zoom (after intervention)

[a]QoL: quality of life.

[b]QoL.BD: Quality of Life in Bipolar Disorder.

[c]WHOQOL-BREF: Brief World Health Organization Quality of Life.

[d]N/A: not applicable.

[e]MINI: Mini-International Neuropsychiatric Interview.

Objective 1: Evaluating PolarUs App Adherence

Our first objective will be to evaluate levels of adherence with and use of the alpha version of the PolarUs app over the 12-week study period. For the purposes of this study, adherence will be defined as beginning to use the app and continuing to do so in a prescribed manner; adherence is rooted in use behaviors (eg, frequency and duration of app or specific app feature use) as opposed to subjective experience [59].

Key use behaviors will be assessed primarily by the number of weekly QoL.BD questionnaires completed by participants over the 12-week study period. These use data will be used to produce a profile for each participant for each 4-week period. Then, those participant use profiles will be used to classify participants into use clusters, such as *regularly used*, *intermittently used*, and *initially used*, to explore use patterns associated with use of the PolarUs app. Additional use data will also be collected, including the number and frequency of the QoL domain and self-management strategy content pages accessed, time spent in the app, both per-session and overall time spent on a specific domain and self-management strategy content pages, number and length of unique sessions, and length of time between unique sessions.

Objective 2: Evaluating PolarUs App Impact

Overview

Our second objective will be to evaluate the impact of the alpha version of the PolarUs app for improving QoL, as measured weekly across the 12-week period of the study using the in-app Brief QoL.BD—our primary measure of impact. Exploratory analyses will examine whether the app affects our secondary outcome measures, as assessed by clinician-administered and self-report scales: mood symptoms, self-efficacy in illness management, subjective recovery, and self-compassion (described below).

In-App QoL.BD: Primary Outcome Measure

The QoL.BD is the first and to date only instrument developed to specifically assess QoL in terms of the life areas prioritized by individuals living with BD [14]. QoL.BD items were derived from interviews with people with lived experience of BD [15], health care providers, and BD subject matter experts, in combination with a comprehensive literature review.

The full 56-item QoL.BD assesses 12 core (physical, sleep, mood, cognition, leisure, social, spirituality, finance, household, self-esteem, independence, and identity) and 2 optional (work and study) life areas, each containing 4 self-report Likert scale

items (1=strongly disagree to 5=strongly agree). An overall score (range 48-240) can be calculated by summing the responses to the 48 items of the 12 core domains. Higher overall scores represent greater satisfaction with life. The Brief QoL.BD is an abbreviated version of the full scale that contains 12 items representing the core domains (overall score range 12-60). During initial field testing, both versions of the QoL.BD had excellent internal reliability (Cronbach α>.8), and the Brief QoL.BD demonstrated a higher sensitivity to changes in clinician-rated symptoms of depression than generic QoL measures [14]. The QoL.BD has been used in international clinical trials, with sensitivity to treatment effects demonstrated [10]. Construct validity of the Brief and full QoL.BD has been demonstrated through associations with symptoms of mania and depression, generic QoL instruments, and functioning [10,14]. A web-based adaptation of the full instrument, the QoL Tool, has been psychometrically validated [27].

Clinician-Administered Scales

The 10-item Montgomery-Asberg Depression Rating Scale [60] will be administered using a structured interview guide [61]. Scores on the Montgomery-Asberg Depression Rating Scale range from 0 to 60, with higher scores indicating greater severity of depressive symptoms. Symptoms of mania will be assessed using the Young Mania Rating Scale [62], a 11-item scale with scores ranging from 0 to 60, with higher scores indicating greater severity of manic symptoms.

Qualtrics-Administered Self-report Scales

The Brief World Health Organization Quality of Life (WHOQOL-BREF) scale [63] will be used to assess non–BD-specific aspects of QoL (ie, domains assumed to be relevant to the general population). The WHOQOL-BREF is one of the most commonly used generic QoL instruments in the BD literature [6], and is included in addition to the QoL.BD to facilitate comparisons with other populations. This instrument is reliable and valid for populations with psychiatric illnesses [64]. The WHOQOL-BREF has 26 Likert scale items that are used to calculate QoL for 4 domains: physical, psychological, social, and environmental. Higher scores for these QoL domains (range 0-100) indicate greater life satisfaction.

Chronic Disease Self-efficacy will be assessed using the 5-item *Manage Disease in General* subscale of Stanford's Chronic Disease Self-Efficacy Scale [65,66]. Higher scores (range 1-10) indicate greater confidence in managing the impact of a chronic health condition. Self-reported mood will be measured using the Positive and Negative Affect Schedule [67]. Higher scores on the two 10-item subscales (range 10-50) indicate greater levels of positive and negative affect.

The 36-item Bipolar Recovery Questionnaire was informed by qualitative research on the experiences of personal (as opposed to clinical) recovery in BD [68]. Higher scores (range 0-3600) indicate better self-appraised recovery. The Bipolar Recovery Questionnaire has good internal consistency and test-retest reliability and has been found to be sensitive to change in an evaluation of a cognitive behavioral therapy–based BD intervention [69].

The Self-Compassion Scale-Short Form will be used to measure self-reported self-compassion [70,71]. A total of 12 items are used to assess 6 dimensions of self-compassion: self-kindness, self-judgment, common humanity, isolation, mindfulness, and overidentification. Higher scores (range 1-5) indicate more frequent experiences of self-compassionate behaviors and attitudes.

The subjective acceptability of the PolarUs app will be assessed by using the user version of the Mobile App Rating Scale [72]. This scale contains subscales that measure attitudes toward app engagement, functionality, aesthetics, and information quality.

Objective 3: Exploring PolarUs App Engagement

Our third objective will apply a mixed methods approach to more deeply explore the patterns of engagement with the PolarUs app. Our quantitative scale to measure subjectively experienced engagement will be the User Engagement Scale (UES) Short Form [73,74]. Both the UES Long Form (31 items) and UES Short Form (12 items) consist of 4 subscales: focused attention (feeling absorbed in interaction with the system and losing track of time), perceived usability (negative affect experienced because of effort expended to use the system), aesthetic appeal (visual appeal of the interface), and reward (perceived benefits and interest experienced because of using the system). The UES has been used internationally by academic and industry researchers and has been found to be a reliable, valid, and sensitive measure for evaluating engagement with a range of technologies, including digital health applications [75]. Both subscale and the overall engagement scores can be calculated as the average of the included items (range 1-5), with higher scores indicating higher levels of subjective engagement with the app. The UES will be administered as a Qualtrics survey every 4 weeks and at study completion.

In-depth qualitative interviews (approximately 1 hour) will be conducted with a subsample (approximately, n=30) of participants immediately after the end of the 12-week study period. Potential interviewees will be invited primarily based on their engagement patterns (assessed quantitatively). Specifically, we will seek to capture major variations in adherence and engagement by purposeful sampling according to the individual's use cluster (eg, *regularly used*, *intermittently used*, and *initially used*). Purposeful sampling will be used to ensure representativeness of the subsample [76] according to diversity in gender, age, ethnocultural background, and BD diagnosis.

Interviews will be semistructured, and the topics discussed will include (1) perceptions of the PolarUs app (eg, attitudes toward specific features and content), (2) experiences of engaging with the app across the intervention period, (3) facilitators and barriers to app use, and (4) subjective impacts (eg, QoL, self-management behaviors, and self-efficacy). All interviews will be conducted remotely via Zoom or telephone and will be recorded and transcribed for later analysis.

Sample Size

To inform sample size, we benchmarked a recent meta-analysis of clinical trials of smartphone apps for depressive symptoms, which estimated dropout rates of 25% to 50% [77]. Allowing

for a 33% dropout rate, 90% power, an effect size of 0.5 SD, and a nonsphericity correction of 0.7 for the final monthly QoL.BD scores for each participant, the required sample size for addressing objective 2 is estimated at 150 participants. This sample size also allows similar power levels to address the exploratory analyses related to the other measures collected monthly through Qualtrics. A challenge in estimating the sample size required is the heterogeneity in prior research that has used QoL.BD (or a variant thereof). In 2020, a search identified 13 clinical trials of psychosocial interventions in BD that reported on any QoL.BD outcomes. Significant changes in scores were uncommon, but the studies were generally limited by small sample sizes. In addition, as QoL was often used as a secondary outcome, the effect sizes were not consistently reported. However, promising effect sizes (0.4-1.42) were observed for recovery-focused cognitive behavioral therapy, dialectical behavior therapy, and web-based recovery-focused psychoeducation and mindfulness interventions [10].

Regarding our sample size for the qualitative interviews, although an approximation of sample size is informative for planning, in practice the appropriateness of the sample must be evaluated during the research process. There are no firm recommendations on the precise number of participants to include; rather, sample size is informed by attention to a number of dimensions related to the research aims, informed by pragmatic considerations and the researcher's own experiences [78]. Given our broad aims (objectives 1-3) and our prior experiences of using qualitative methods to explore the use of digital health tools for BD [21,28], we estimate our chosen sample size of approximately 30 for the interviews to be sufficient to support meaningful thematic analyses.

Data Management and Statistical Analyses

Responses to the Qualtrics and in-app questionnaires will be made mandatory to reduce the likelihood of missing data. Comprehensive data cleaning will occur before analyses with range and distributional checks and comparisons with published norms, where appropriate.

Objective 1: Examining PolarUs App Feasibility

To describe and categorize levels of adherence with and use of the PolarUs app over the 12-week study period, our behavioral measures (described above) will be used to produce a profile for each participant for each 4-week period; these profiles will then be used to classify participants into use clusters, such as *regularly used*, *intermittently used* and *initially used*. The number of categories and initial seeds for these categories will be established using an agglomerative hierarchical clustering approach (eg, Ward method) and then refined using mean values to define the participant engagement profile for each of the clusters.

Objective 2: Evaluating PolarUs App Impact

To provide a preliminary evaluation of the impact of the alpha version of the PolarUs app on our primary (ie, weekly Brief QoL.BD) and exploratory outcome measures (described above), we will use mixed effects modeling with random intercepts and slopes to track changes in these measures over the 12-week study period.

Objective 3: Exploring PolarUs App Engagement

To explore engagement patterns with the PolarUs app, two types of analyses will be used to explore the relationships between engagement and outcome trajectories of individual participants: (1) quantitative analyses of the longitudinal impact and engagement data (see above) and (2) qualitative analyses of the interview data.

In terms of the quantitative analyses, the moderating effects of participant engagement cluster on our primary and secondary measures of impact will be explored statistically by using mixed effects modeling with random intercepts and slopes and with the engagement cluster × time interaction as a fixed effect. Mixed effects modeling will allow changes in the primary and secondary measures to be explained in terms of engagement cluster membership by estimating and testing time-by-cluster interactions. The participant clusters showing the greatest benefit will be used to benchmark the best engagement behaviors over time. Mixed effects modeling will be used in the same way to assess the correlation between subjective app engagement scores and actual engagement behaviors identified with the use clusters. To appreciate the extent to which the PolarUs app is aligned with users' self-management goals and user expectations, we will compare use data (eg, time spent) for the various self-management strategy content pages and specific QoL domains using nonparametric repeated measures analyses (eg, Friedman test). The self-management strategy content pages and specific QoL domains on which more time is spent are likely to be most closely aligned with a user's self-management goals and expectations. All of these analyses will be further informed by qualitative analysis of the interview data.

Thematic analysis will be used for qualitative analyses [79]. Through a careful reading and rereading of the interview data, the data will be compared, contrasted, and categorized (both within and across transcripts) to identify themes. NVivo (version 12; QSR International) will be used to manage the data and facilitate data analysis.

Exploratory Economic Evaluation

An exploratory economic evaluation will be conducted at the end of the study, using a health care payer perspective to estimate the cost per incremental unit of QoL. These estimates will be summarized using an incremental cost-effectiveness ratio [80] and an incremental net benefit statistic [81,82]. The uncertainty of the estimates will be characterized using cost-effectiveness acceptability curves and 95% CIs [83,84].

Results

Participant enrollment has begun in June 2022. Data collection is expected to be completed by December 2022.

Discussion

Overview

This protocol paper describes a pilot study designed to assess the feasibility, impact, and engagement with the alpha version of the PolarUs app for BD. This study has the following objectives: (1) to describe and categorize levels of adherence

with and use of the PolarUs app over a 12-week study period; (2) to assess the impact of the PolarUs app on QoL, as assessed by our primary outcome measure, the QoL.BD; and (3) to leverage mixed qualitative and quantitative methods to provide deeper insights into engagement patterns associated with the PolarUs app and subjective experiences of app use. The remainder of this discussion is divided into 3 major focus areas. The first section discusses our definitions of app use and engagement and the associated theoretical issues. The second section examines the strengths and limitations of this protocol. The third section discusses implications of this protocol. The discussion concludes with an overview of our next steps.

Defining App Use and Engagement

The purpose of the PolarUs app is to enhance QoL for people living with BD, and this has shaped the design of the app to include self-management tools and educational content; these app design features are also of interest in defining the user engagement metrics for this study. User engagement is the cognitive, temporal, affective, and behavioral investment a person makes when interacting with a digital system [75] and is a foundational element supporting the efficacy of mental health apps [85]. The quality and impact of this investment must be assessed "in relation to the purpose of a particular intervention, and can only be established empirically, in the context of that intervention" [86]. Many digital health interventions focus solely on behavioral engagement (eg, frequency and duration of app use or specific app feature use) [87]. Computing the number of log-ins, pages, modules, or features that have been accessed and the length of time spent on these components are commonly used as proxies of engagement breadth and depth [88], but do not consider individual differences in user expectations and use patterns or the dynamic needs of people managing a mental health condition; for example, mood fluctuations and stage of illness [59].

To appreciate the extent to which the PolarUs app is aligned with self-management goals of users [86,89] and clinically relevant outcomes [90], we will analyze use data alongside questionnaire and interview data. The use of mixed methods will allow us to explore engagement trajectories and determine effective use benchmarks by examining behavioral measures with users' subjective experiences and insights and clinical outcomes. This study design will advance our understanding of the relationship between behavioral and self-report data to deepen our understanding of patterns of engagement with the PolarUs app in particular and mHealth apps in general.

Limitations

There are several notable limitations to this protocol, the first of which relates to the generalizability of the findings from the study. First, as the PolarUs app is currently only available in English, this will restrict the study to participants with English language skills, thus limiting the generalizability of the findings. To address this limitation, the PolarUs app will soon support Canada's second national language, French. Indeed, there is already a validated French version of the QoL.BD [91]. This version of the QoL.BD will allow us to build the PolarUs app to support French initially, with the long-term goal of supporting other languages.

Second, it is likely that people with a specific interest in mHealth apps and self-management strategies for BD will self-select into this study. Although this limitation cannot be addressed in this study, future studies could use a more general recruitment strategy, such as advertising a study for self-management strategies for BD in general, rather than for a self-management app for BD. Such a recruitment strategy would also support a study that could compare the efficacy of the PolarUs app to more traditional ways of learning about and using self-management strategies (eg, browser-based psychoeducation, such as the Bipolar Wellness Centre [29]). Future research may also address a possible bias for higher levels of digital health literacy in this study.

Although we aimed to make the PolarUs app as accessible as possible through community consultation, consideration of accessibility issues specific to serious mental health during the design phase [92], and attention to reading level in content writing, it is still likely that individuals with more familiarity with apps and computers will be better able to engage with the intervention and complete all required research tasks (ie, web-based questionnaires) [93]. Although it is not feasible for us to offer dedicated support to upskill participants in technological abilities in the context of this study, future research may evaluate whether adjunctive interventions can enhance the feasibility of mHealth interventions in populations with BD.

A third limitation relates to the purposive sampling strategy used to select participants for qualitative interviews, as this selection process may be subject to researcher bias. Probability-based sampling was considered but ultimately not chosen for reasons of feasibility, given that not all participants will start and conclude the intervention at the same time. Interviewing people as close as possible to the period in which they used the PolarUs app will limit potential recall bias and enhance the depth of information available and will help ensure that our target sample size is achieved. To address the potential bias in our interpretation of engagement with the PolarUs app, we aim to recruit individuals to ensure diversity in levels of engagement with the intervention and demographic characteristics. Further, to ensure transparency, we will report on the demographic characteristics of the qualitative subsample relative to the overall sample.

Finally, it is possible that the user engagement metrics deployed in this study may be influenced by the study design. For example, prior research has shown that user engagement with web- and app-based mental health programs may be influenced by frequent interactions with research assistants [94]. In this study, participants will interact with research assistants at least once a month over the 12-week study period.

Implications of This Research

This study has several implications. First, in this protocol, we use QoL as the primary outcome variable to determine the impact of our mHealth app. As emphasized previously, QoL is an important outcome variable for any intervention or treatment

of a health condition, given that improvements on specific clinical scales do not necessarily translate to tangible improvements in day-to-day life. However, relatively few clinical trials have used QoL outcomes to assess the impact of psychosocial interventions, both in BD and in mental health more generally. It is our hope that assessments of the potential efficacy of mHealth apps via examination of QoL outcomes (combined with more traditional outcomes) will soon become ubiquitous.

Second, the design of the PolarUs app has emphasized co-design with individuals living with BD, clinicians who specialize in the treatment of BD, and BD researchers. The design of this study will allow us to indirectly explore the effectiveness of such community-engaged app design. That is, if the PolarUs app is found to be effective, it will reinforce the notion that mHealth app co-design is critical for the impact of an mHealth app [95]. Future studies should examine which elements of the co-design process are critical for mHealth app efficacy and uptake.

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Authors' Contributions

EEM and SJB conceptualized and designed the overall study. EM, HLO, GM, RH, and DM contributed to study design. All authors provided critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Conflicts of Interest

SJB, EM, HLO, GM, RH, and DM declared no potential conflicts of interest with respect to the research, authorship, and publication of paper. EEM received funding to support patient education initiatives from Otsuka.

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Abbreviations

BD: bipolar disorder
CREST.BD: Collaborative Research Team to Study Psychosocial Issues in Bipolar Disorder
mHealth: mobile health
QoL: quality of life
QoL.BD: Quality of Life in Bipolar Disorder
UES: User Engagement Scale
WHOQOL-BREF: Brief World Health Organization Quality of Life

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Protocol

Design and Rationale of the National Tunisian Registry of Percutaneous Coronary Intervention: Protocol for a Prospective Multicenter Observational Study

Rania Hammami[1], MD; Selim Boudiche[2], MD; Tlili Rami[3], MD; Nejeh Ben Halima[4], MD; Ahmed Jamel[4], MD; Bassem Rekik[2], MD; Rym Gribaa[5], MD; Ben Mrad Imtinene[6], MD; Salma Charfeddine[1], MD; Tarek Ellouze[1], MD; Amine Bahloul[1], MD; Ben Slima Hédi[7], MD; Jamel Langar[8], MD; Habib Ben Ahmed[9], MD; Zied Ibn Elhadj[10], MD; Mohamed Hmam[8], MD; Mohamed Aymen Ben Abdessalem[11], MD; Sabri Maaoui[12], MD; Sana Fennira[6], MD; Laroussi Lobna[10], MD; Majed Hassine[13], MD; Sami Ouanes[13], MD; Drissi Mohamed Faouzi[8], MD; Souad Mallek[1], MD; Abdallah Mahdhaoui[11], MD; Dghim Meriem[14], MD; Walid Jomaa[15], MD; Sofien Zayed[3], MD; Tawfik Kateb[8], MD; Nidhal Bouchahda[13], MD; Fares Azaiez[3], MD; Helmi Ben Salem[16], MD; Morched Marouen[17], MD; Aymen Noamen[14], MD; Salem Abdesselem[8], MD; Denguir Hichem[18], MD; Hassen Ibn Hadj Amor[19], MD; Farhati Abdeljelil[2], MD; Amine Amara[17], MD; Karim Bejar[20], MD; Ben Hamda Khaldoun[15], MD; Chiheb Hamza[8], MD; Mohsen Ben Jamaa[21], MD; Sami Fourati[17], MD; Faycal Elleuch[17], MD; Zeineb Grati[8], MD; Slim Chtourou[17], MD; Sami Marouene[8], MD; Mohamed Sahnoun[17], MD; Morched Hadrich[17], MD; Maalej Mohamed Abdelkader[17], MD; Hatem Bouraoui[11], MD; Kamel Kamoun[8], MD; Moufid Hadrich[8], MD; Tarek Ben Chedli[8], MD; Mohamed Akrem Drissa[8], MD; Hanene Charfeddine[17], MD; Nizar Saadaoui[17], MD; Gargouri Achraf[8], MD; Siala Ahmed[17], MD; Mokdad Ayari[8], MD; Marsit Nabil[8], MD; Sabeur Mnif[17], MD; Maher Sahnoun[17], MD; Helmi Kammoun[17], MD; Khaled Ben Jemaa[21], MD; Gharbi Mostari[22], MD; Nebil Hamrouni[21], MD; Maazoun Yamen[17], MD; Yassine Ellouz[8], MD; Zahreddine Smiri[8], MD; Amine Hdiji[17], MD; Jerbi Bassem[17], MD; Wacef Ayadi[17], MD; Amir Zouari[17], MD; Chedly Abbassi[8], MD; Boujelben Masmoudi Fatma[17], MD; Kais Battikh[21], MD; Elyes Kharrat[17], MD; Imen Gtif[14], MD; Milouchi Sami[19], MD; Leila Bezdah[9], MD; Salem Kachboura[11], MD; Mohamed Faouzi Maatouk[15], MD; Sondes Kraiem[6], MD; Gouider Jeridi[11], MD; Elyes Neffati[5], MD; Samir Kammoun[1], MD; Youssef Ben Ameur[3], MD; Wafa Fehri[14], MD; Habib Gamra[13], MD; Lilia Zakhama[14], MD; Faouzi Addad[10], MD; Mourali Mohamed Sami[2], MD; Leila Abid[1], MD

[1]Department of Cardiology, Hédi Chaker Hospital, Faculty of Medicine of Sfax, University of Sfax, Sfax, Tunisia

[2]Department of Cardiology, La Rabta Hospital, Faculty of Medicine of Tunis, University of Tunis, Tunis, Tunisia

[3]Department of Cardiology, Mongi Slim Hospital, Faculty of Medicine of Tunis, University of Tunis, Tunis, Tunisia

[4]Department of Cardiology, Kairouan Hospital, Faculty of Medicine of Sousse, University of Sousse, Kairouan, Tunisia

[5]Department of Cardiology, Sahloul Hospital, Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia

[6]Department of Cardiology, Habib Thameur Hospital, Faculty of Medicine of Tunis, University of Tunis, Tunis, Tunisia

[7]Department of Cardiology, Menzel Bourguiba Hospital, Faculty of Medicine of Tunis, University of Tunis, Bizerte, Tunisia

[8]Cardiologist, Private Sector, Tunis, Tunisia

[9]Department of Cardiology, Charle Nicole Hospital, Faculty of Medicine of Tunis, University of Tunis, Tunis, Tunisia

[10]Department of Cardiology, Abderrahmen Mami-Ariana Hospital, Faculty of Medicine of Tunis, University of Tunis, Ariana, Tunisia

[11]Department of Cardiology, Farhat Hached Hospital, Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia

[12]Cardiologist, Private Sector, Monastir, Tunisia

[13]Department of Cardiology A, Fattouma Bourguiba University Hospital, Faculty of Medicine of Monastir, University of Monastir, Monastir, Tunisia

[14]Department of Cardiology, The Main Military Instruction Hospital of Tunis, Faculty of Medicine of Tunis, University of Tunis, Tunis, Tunisia

[15]Department of Cardiology B, Fattouma Bourguiba University Hospital, Faculty of Medicine of Monastir, University of Monastir, Monastir, Tunisia

[16]Cardiologist, Private Sector, Sousse, Tunisia

[17]Cardiologist, Private Sector, Sfax, Tunisia

[18]Department of Cardiology, Gabes Hospital, Faculty of Medicine of Sfax, University of Sfax, Gabes, Tunisia

[19]Department of Cardiology, Habib Bourguiba Hospital, Faculty of Medicine of Sfax, University of Sfax, Medenine, Tunisia

[20]Cardiologist, Private Sector, Nabeul, Tunisia

[21]Cardiologist, Private Sector, Medenine, Tunisia

[22]Cardiologist, Private Sector, Bizerte, Tunisia

Corresponding Author:
Rania Hammami, MD
Department of Cardiology, Hédi Chaker Hospital
Faculty of Medicine of Sfax
University of Sfax
3029 Al Ain Road
Sfax, 3029
Tunisia
Phone: 216 24056985
Email: raniahammami@yahoo.fr

Abstract

Background: Coronary artery diseases remain the leading cause of death in the world. The management of this condition has improved remarkably in the recent years owing to the development of new technical tools and multicentric registries.

Objective: The aim of this study is to investigate the in-hospital and 1-year clinical outcomes of patients treated with percutaneous coronary intervention (PCI) in Tunisia.

Methods: We will conduct a prospective multicentric observational study with patients older than 18 years who underwent PCI between January 31, 2020 and June 30, 2020. The primary end point is the occurrence of a major adverse cardiovascular event, defined as cardiovascular death, myocardial infarction, cerebrovascular accident, or target vessel revascularization with either repeat PCI or coronary artery bypass grafting (CABG). The secondary end points are procedural success rate, stent thrombosis, and the rate of redo PCI/CABG for in-stent restenosis.

Results: In this study, the demographic profile and the general risk profile of Tunisian patients who underwent PCI and their end points will be analyzed. The complexity level of the procedures and the left main occlusion, bifurcation occlusion, and chronic total occlusion PCI will be analyzed, and immediate as well as long-term results will be determined. The National Tunisian Registry of PCI (NATURE-PCI) will be the first national multicentric registry of angioplasty in Africa. For this study, the institutional ethical committee approval was obtained (0223/2020). This trial consists of 97 cardiologists and 2498 patients who have undergone PCI with a 1-year follow-up period. Twenty-eight catheterization laboratories from both public (15 laboratories) and private (13 laboratories) sectors will enroll patients after receiving informed consent. Of the 2498 patients, 1897 (75.9%) are managed in the public sector and 601 (24.1%) are managed in the private sector. The COVID-19 pandemic started in Tunisia in March 2020; 719 patients (31.9%) were included before the COVID-19 pandemic and 1779 (60.1%) during the pandemic. The inclusion of patients has been finished, and we expect to publish the results by the end of 2022.

Conclusions: This study would add data and provide a valuable opportunity for real-world clinical epidemiology and practice in the field of interventional cardiology in Tunisia with insights into the uptake of PCI in this limited-income region.

Trial Registration: Clinicaltrials.gov NCT04219761; https://clinicaltrials.gov/ct2/show/NCT04219761

International Registered Report Identifier (IRRID): RR1-10.2196/24595

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KEYWORDS

percutaneous coronary intervention; 1-year outcome; Tunisia; national; multicentric; registry; percutaneous; coronary; artery disease

Introduction

Coronary artery diseases remain the leading cause of death in the world [1]; the management of this condition has improved, thanks to new technical tools and multicentric registries. Recently, in Tunisia, the number of intervention procedures has markedly increased, given the explosion of cardiovascular risk factors among Tunisians [2]. However, there is a paucity of data about the short- and long-term results of percutaneous coronary intervention (PCI) in different hospitals in Tunisia, and thus, a registry of PCI procedures was initiated. Currently, there is a need to know the PCI outcomes by using this registry data and any deficiencies in patient management to help formulate improvement strategies. We will conduct this national registry to determine the current practice of PCI at our hospital in Tunisia, including the clinical characteristics, angiographic profile, and in-hospital and 1-year clinical outcomes of patients who have undergone PCI. Furthermore, this registry could be used to determine clinicians' adherence to the published guidelines for PCI, including the different gaps in real-world practice. The aim of this study is to report the in-hospital and 1-year clinical outcome of consecutive patients undergoing PCI. This study would also generate local data that can be compared

with those in other parts of the world, which would help local health care authorities to plan PCI strategies in Tunisia [3,4].

Methods

We will conduct a prospective multicentric observational study of all patients who underwent PCI in Tunisia between January 31 and June 30, 2020 with a 1-year follow-up. Written informed consent will be obtained from all the patients. Males and females older than 18 years, admitted in public sector as well as in private sector catheterization laboratories, and who underwent a PCI during the study period will be included in this study. Each patient will be included only once during index PCI admission. Repeat admission for PCI of other vessels will be considered during the follow-up of the patients. Data will be collected from computer medical records and captured for analysis by Dacima Consulting according to the Food and Drug Administration 21 Code of Federal Regulations part 11, Health Insurance Portability and Accountability Act, and the International Conference on Harmonization requirements. One-year follow-up data will be collected either from clinic visits or by telephone. For this study, institutional ethical committee approval was obtained (0223/2020).

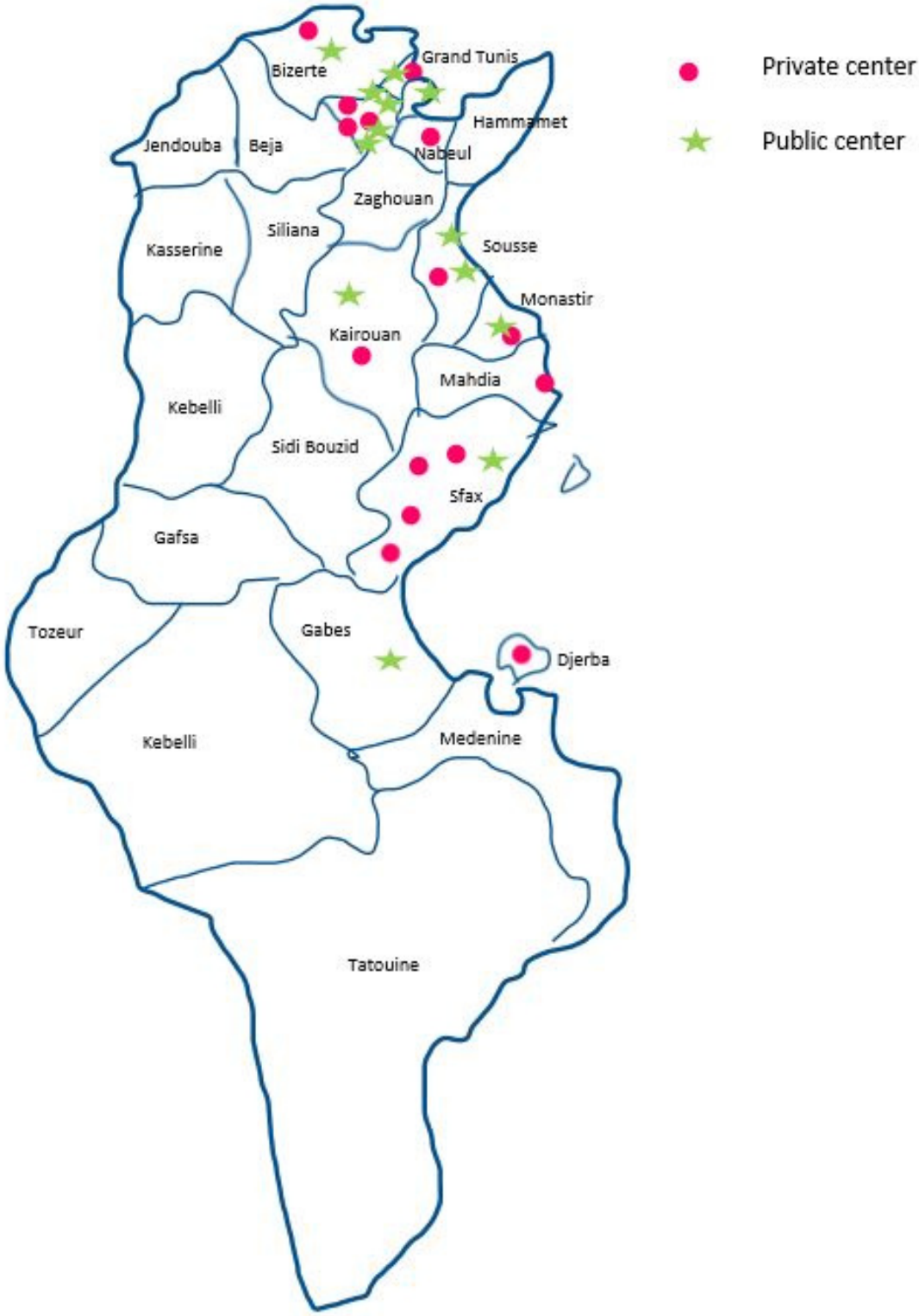
Statistical analyses will be performed for the risk factors, clinical presentation, angiographic profile, PCI details, stents, medication use, and in-hospital and 1-year outcome following PCI. Baseline characteristics of the patients will be analyzed in terms of frequencies and percentages for categorical variables and means and standard deviation for continuous variables. The definitions of data variables in the case report form are based on the American College of Cardiology/American Heart Association guidelines [5,6]. Conventional risk factors, including age, gender, diabetes, hypertension, dyslipidemia, current smoking (within 1 year), and family history of coronary artery disease, will be noted. Previous conditions such as myocardial infarction, PCI, coronary artery bypass grafting (CABG), peripheral vascular disease, cerebrovascular accident or transient ischemic attack, and chronic kidney disease will be assessed. Diabetes is defined according to the guidelines of the American Diabetes Association 2020, as having a history of diabetes diagnosed and treated with medication and insulin, or fasting blood glucose of 7 mmol/L (126 mg/dL), or hemoglobin A_{1c} ≥6.5%, or signs of hyperglycemia associated with a random plasma glucose of ≥200 mg/dL (11.1 mmol/L) [7]. Hypertension is defined as having a history of hypertension diagnosed and treated with medication or blood pressure ≥140 mm Hg systolic or 90 mm Hg diastolic on at least 2 occasions [8]. Hyperlipidemia is defined as a history of dyslipidemia diagnosed or treated by a physician or total cholesterol >2 g/L. Current smoker is defined as smoking cigarettes, water pipe, cigar, or chewing tobacco within 1 year of admission. Moderate chronic kidney disease is defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 for 3 months or more, with or without kidney damage or on dialysis. Angiographic and procedural notes were reviewed. Single vessel disease was considered present if there was more than 70% diameter stenosis on visual assessment in the left anterior descending, left circumflex, or right coronary arteries, or a major branch, or more than 50% for left main stenosis and in-stent restenosis. The stented artery, number of stents used, type of stent (bare metal stent or drug-eluting stent), procedural success, and complications were noted. Left ventricular ejection fraction was noted from echocardiography. PCI was performed according to standard clinical practice. The vascular approach as well as complications related to this route will be noted. A large hematoma will be defined as >5 cm. Significant bleeding will be defined as hemoglobin drop >5 g or required >2 packs of red blood cells for transfusion.

All patients will be followed up daily until discharge. The control of the renal function will be ensured if possible. Contrast-induced nephropathy is defined as either a 25% increase in serum creatinine from baseline or 44 µmol/L increase in the absolute value within 48-72 hours of PCI. The primary end point of this study is the occurrence of major adverse cardiovascular events, defined as cardiovascular death, any myocardial infarction, cerebrovascular accident, and target vessel revascularization with either repeat PCI or CABG. Myocardial infarction is documented by the highly sensitive troponin T rise (>14 pg/mL) with either ischemic symptoms or ST elevation/depression or new pathologic Q waves on electrocardiogram after discharge or as documented in outpatient notes. Post-PCI infarction is considered as >5 times rise in troponin T from baseline levels. Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel, which was stented before. The secondary end points are (1) procedural success rate, defined as successful PCI without associated in-hospital major clinical complications; (2) stent thrombosis, defined as definite stent thrombosis occurring when clinical presentation was consistent with acute coronary syndrome and angiography examination confirmed stent occlusion or thrombus; and (3) rate of in-stent restenosis, defined as >50% angiographic restenosis on follow-up within 1 year, resulting in either repeat PCI or CABG.

Results

This study will enroll 97 cardiologists and 2498 patients with a 1-year follow-up period (Multimedia Appendix 1 and Multimedia Appendix 2). Twenty-eight catheterization laboratories, that is, 15 laboratories from the public sector and 13 laboratories from the private sector will enroll patients after receiving informed consent. Of the 2498 patients, 1897 (75.9%) are managed in the public sector and 601 (24.1%) are managed in the private sector (Figure 1). The COVID-19 pandemic started in Tunisia in March 2020; 719 patients (31%) were included before the COVID-19 pandemic and 1779 (60%) were included during the pandemic. The results of this study are expected to be published by the end of 2022.

Figure 1. Repartition of the investigating centers in this study.



Discussion

This is the first observational registry of PCIs in Africa, which included 2498 patients. Although results from randomized controlled trials provide the highest level of evidence regarding the efficacy of interventions, they have well-recognized limitations. Randomized controlled trials may not always reflect "real-world" medical settings and often underrepresent significant portions of the community such as women and older adults [9].

Clinical registries have consequently emerged as a powerful tool to assess health care effectiveness and safety and improve quality of care, as well as to inform on the real-world impact of new interventions or medications outside the confines of randomized controlled trials. Over the last 2 decades, there has been a substantial growth in national and major regional PCI registries, predominantly in high-income countries. Numerous

registries and surveys have been described in different European, Asian, and American countries, but there are only few contemporary data on the demographic characteristics and outcomes of interventional cardiology practice in low-income countries owing to concerns about costs [10]. Invasive cardiology was initiated in North Africa more than 50 years ago, with the first catheterization procedure performed in Tunis in 1968. The first coronary angiogram was performed in 1983, and the first coronary angioplasty was performed in 1989 [11]. Since its emergence as a new subspecialty, interventional cardiology has evolved quite rapidly in North Africa compared to that in other African countries apart from South Africa. The proximity of these African countries to Europe and particularly to France has helped that progression, as trainees have relatively easy access to French centers for subspecialty training.

According to a recent epidemiologic study (Tunisian Association on Study and Research on Atherosclerosis Survey), the prevalence of cardiovascular risk factors has increased widely; more than half of Tunisians have hypertension and 19% have diabetes [2]. Certainly, these conditions will affect the long-term outcomes of PCI in Tunisia, especially that the use of drug-eluting stent has many cost concerns. In Tunisia, this interventional activity is performed in 28 catheterization laboratories, located mostly in the northern and the middle-eastern region of the country. Fourteen catheterization laboratories are in the public sector. More than 100 interventional cardiologists perform at least one PCI per week.

Recently, a Tunisian national registry of myocardial infarction (FAST-MI) was set up by the Tunisian Society of Cardiology and Cardiovascular Surgery to assess the demographic and clinical characteristics, management, and hospital outcomes of patients with ST-elevation myocardial infarction (STEMI). Data for 459 consecutive patients (mean age 60.8 years, 88.5% male) with STEMI treated in 16 public hospitals (representing 72.2% of the public hospitals in Tunisia treating patients with STEMI) were collected prospectively. The most common risk factors were smoking (63.6%), hypertension (39.7%), diabetes (32%), and dyslipidemia (18.2%) [12]. The limitation of that study was the small number of patients from private hospitals. Our registry will try to project the real-world practice of interventional cardiology, both in private and public sectors. However, the COVID-19 pandemic as well as Ramadan will certainly impact the number of patients in our registry. Given the risk of health care personnel contracting infections, the activities of catheterization laboratories in different countries have dramatically decreased—reduced to nearly 70% of their normal duties.

This large contemporary longitudinal study of Tunisian PCIs will provide a unique opportunity to answer many questions. The National Tunisian Registry of PCI (NATURE-PCI) study is important in several respects. First, systematic observational and outcomes data can be generated from this registry study, which are especially valuable, given that evidence for Tunisian patients undergoing PCI is limited. Second, the follow-ups of complex procedures, especially those of the left main occlusion, chronic total occlusion, and primary PCI are changing dramatically and need to be evaluated in real-world studies. Third, the NATURE-PCI study provides a good opportunity to compare the risk of stent failure in a population with a high prevalence of cardiovascular risk factors, especially diabetes, for comparison with that of populations in other countries and to evaluate clinicians' adherence to the guidelines of the European Society of Cardiology on myocardial revascularization.

NATURE-PCI will fill a significant gap in the dynamic landscape of interventional cardiology practice care and research. It will provide unique and necessary data on the management and outcomes of patients with coronary artery diseases who are treated invasively. This study will yield the largest contemporary longitudinal cohort of PCI in Tunisia and provide a valuable opportunity for real-world clinical epidemiology with insights into the uptake and the difficulties of PCIs. The data of this registry will be useful for considering general health care costs such as the reimbursement of drug-eluting stents in clinical settings.

Acknowledgments

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Authors' Contributions

RH drafted the paper and is the coordinator of the registry. LA revised the paper. All the authors read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Repartition of inclusion procedures according to months (N=2498).
[PNG File , 123 KB - resprot_v11i8e24595_app1.png]

Multimedia Appendix 2
Repartition of inclusion in different Tunisian cities.
[PNG File , 33 KB - resprot_v11i8e24595_app2.png]

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Abbreviations

CABG: coronary artery bypass grafting
NATURE-PCI: National Tunisian Registry of Percutaneous Coronary Intervention
PCI: percutaneous coronary intervention
STEMI: ST-elevation myocardial infarction

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Protocol

The Facilitation of Clinical and Therapeutic Discoveries in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Related Diseases: Protocol for the You + ME Registry Research Platform

Allison Ramiller[1], BSc, MPH; Kathleen Mudie[1], BSc, MSc; Elle Seibert[1], BA; Sadie Whittaker[1], DPhil

Solve ME/CFS Initiative, Glendale, CA, United States

Corresponding Author:
Allison Ramiller, BSc, MPH
Solve ME/CFS Initiative
Suite B #368 Glendale
350 N Glendale Ave
Glendale, CA, 91206
United States
Phone: 1 704 364 0016
Email: research@solvecfs.org

Abstract

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, heterogeneous disease that affects millions and lacks both diagnostics and treatments. Big data, or the collection of vast quantities of data that can be mined for information, have transformed the understanding of many complex illnesses, such as cancer and multiple sclerosis, by dissecting heterogeneity, identifying subtypes, and enabling the development of personalized treatments. It is possible that big data can reveal the same for ME/CFS.

Objective: This study aims to describe the protocol for the You + ME Registry, present preliminary results related to participant enrollment and satisfaction, and discuss the limitations of the registry as well as next steps.

Methods: We developed and launched the You + ME Registry to collect longitudinal health data from people with ME/CFS, people with long COVID (LC), and control volunteers using rigorous protocols designed to harmonize with other groups collecting data from similar groups of people.

Results: As of September 30, 2021, the You + ME Registry had over 4200 geographically diverse participants (3033/4339, 69.9%, people with ME/CFS; 833/4339, 19.2%, post–COVID-19 people; and 473/4339, 10.9%, control volunteers), with an average of 72 new people registered every week. It has qualified as “great” using a net promotor score, indicating registrants are likely to recommend the registry to a friend. Analyses of collected data are currently underway, and preliminary findings are expected in the near future.

Conclusions: The You + ME Registry is an invaluable resource because it integrates with a symptom-tracking app, as well as a biorepository, to provide a robust and rich data set that is available to qualified researchers. Accordingly, it facilitates collaboration that may ultimately uncover causes and help accelerate the development of therapies.

Trial Registration: ClinicalTrials.gov NCT04806620; https://clinicaltrials.gov/ct2/show/NCT04806620

International Registered Report Identifier (IRRID): DERR1-10.2196/36798

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KEYWORDS

myalgic encephalomyelitis/chronic fatigue syndrome; long COVID; data acquisition source; postinfectious; longitudinal cohort study; patient powered; COVID-19; chronic fatigue syndrome; longitudinal health data; symptom-tracking app; health application; mobile health; digital health

Introduction

Background to ME/CFS

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, systemic disease that affects anywhere from 1.5 to 3.4 million people in the United States [1,2], with an estimated annual economic cost of US $36-$51 billion [2]. The etiology of ME/CFS is unknown, but it is associated with infectious triggers or other precipitating events, such as injury, trauma, or exposure to environmental hazards [3]. ME/CFS has not been correlated with age, race, or socioeconomic group; however, 3-4 times as many women as men present with symptoms [3].

The true impact of this disease remains uncertain largely because ME/CFS is commonly misdiagnosed, with primary reasons referenced as a lack of confidence from clinicians and the absence of an established biomarker [4]. Clinicians must rely on a detailed evaluation of the presence of characteristic symptoms, health history, and a physical examination. Although many clinicians are aware of ME/CFS, they often lack essential experience necessary to diagnose this complex disease.

ME/CFS is characterized by debilitating fatigue and other multisystem physical and neurocognitive symptoms, which are exacerbated following minimal physical or mental exertion. Postexertional malaise (PEM) is the hallmark symptom of ME/CFS and is associated with elevated symptom burden and psychological distress [3]. Otherwise, substantial clinical heterogeneity exists among patients, with a range of symptoms that includes orthostatic intolerance (OI), postural tachycardia syndrome (POTS), brain fog, headaches, unrefreshing sleep and other sleep dysfunction, joint pain, and muscle pain/fibromyalgia [3].

Although understanding of biological abnormalities in ME/CFS has increased considerably in recent decades [5-10], the lack of a diagnostic biomarker, complex clinical presentation, and patient heterogeneity have severely hampered progress in the treatment of ME/CFS, causing many patients to have poor outcomes [3,11]. Although there are no treatments approved for ME/CFS, a number of pharmacological and nonpharmacological interventions are used to manage symptoms. There have been a few promising clinical trials undertaken; however, they have not resulted in approved therapies for the ME/CFS population. For example, researchers analyzing data from a phase III trial of rintatolimod found that only a subset of ME/CFS patients defined by relatively short duration of disease (symptom onset within 2-8 years) had improved exercise tolerance in response to rintatolimod [12]. Although this is still an experimental treatment, there is an acute interest in identifying subsets of patients who might be responders [12,13].

Methodological problems, small sample sizes, and selection bias toward those less severely affected by ME/CFS [14] also create persistent roadblocks to progress in the understanding of the disease. An observational study that centralizes clinical data and well-designed patient-reported outcomes collected over time from a large, diverse cohort has the potential to increase research validity and generate new insights.

The You + ME Patient Registry

Patient registries are invaluable resources for collecting real-world clinical data at a large scale that can then be used for research. They comprise a set of systematically collected and stored data that can be harmonized or shared with other research groups, while ensuring a level of data quality and reliability. Patient registries have been effectively used for other complex, heterogenous diseases, such as the Fox Insight study for Parkinson disease [15]; the IBD Partners Registry [16], where IBD refers to inflammatory bowel disease; and ACCELERATE, an international registry for patients with Castleman disease [17].

In May 2020, the Solve ME/CFS Initiative (Solve M.E.), a nonprofit organization whose mission is to make ME/CFS and other postinfection diseases widely understood, diagnosable, and treatable, launched the You + ME Registry and Biobank (Registry) [18]. The Registry is a secure online data repository where people with ME/CFS, people with related diseases, and control volunteers can enter information on their health.

Given the strong evidence for the viral etiology of ME/CFS and experience from the SARS-CoV-1 pandemic of 2003 [19-21], there is a potential for the current SARS-CoV-2 pandemic to lead to a substantial increase in the number of ME/CFS cases. There is evidence that some people experience long-term effects from COVID-19 (termed “long COVID” [LC]) with a constellation of symptoms reported that are strikingly similar to those reported for ME/CFS [22-27]. The COVID-19 pandemic and emergence of long-term symptoms in some individuals present a unique scientific opportunity to understand factors of resistance and susceptibility to long-term, postviral impacts. In December 2020, in response to the increasing number of individuals with LC, the Registry was adapted and opened up to those who are suffering from the long-term effects of COVID-19 and control individuals who had COVID-19 but do not have long-term effects.

The Registry is designed to be a foundational resource for research, and it is unique for several reasons:

- It integrates a symptom-tracking app that can provide more data points for dynamic/cyclic chronic diseases.
- It is a rigorous, systematic infrastructure for collecting data that were cocreated with the ME/CFS and LC communities.
- The data and patient cohorts are available to all qualified researchers, supporting numerous scientific studies and engaging a network of expertise.
- The Registry is centered around principles of data harmonization and collaboration with other research studies to accelerate the search for causes and therapies.

In this paper, we describe the protocol for the Registry, present preliminary results related to participant enrollment and satisfaction, and discuss the limitations of the Registry as well as next steps.

Methods

Human-Centered Design

The creation of the Registry integrated community input and human-centered design (HCD) methodologies [28]. Originally developed in the field of computer science and artificial intelligence, it has been adapted so that engagement with and understanding of the needs of users are common to all design disciplines and can be applied to a range of complex questions, from process optimization to product design [29-31]. We gathered qualitative narratives and quantitative data from multiple stakeholders to inform the Registry and symptom-tracking app product development, user experience, and data collection.

One-on-one unstructured phone interviews were conducted with stakeholders and experts. Interviewees included 4 people with ME/CFS across the disease severity spectrum, 1 care partner, and 3 individuals with expertise in disease registries, informatics, and HCD. Notes from the calls were transcribed and summarized into key themes and insights (Table 1).

Table 1. Key insights from HCD[a] interviews with the ME/CFS[b] community.

Category of expertise	Key insights
People with ME/CFS	• Elevate individuals with ME/CFS to partner/contributor status. • Create mechanisms that will enable participation and insights for people with severe ME/CFS. • Include measures that will corroborate or add on to the symptom data, including a measure to assess functional status.
ME/CFS clinicians and researchers	• Ensure collection of information on autonomic function. • Track regularly whether the person's medications have changed and whether they have been diagnosed with new conditions/diseases.
Informatics	• Foster a social component because people who engage socially are more likely to continue to enter data. • Provide the ability for participants to report quantified self-data and self-experiment (eg, supplements and medications being used).
HCD	• Consider more innovative approaches to enable participation of extremes in your patient population.
Informal caregiver	• Create a formal, defined user group involved throughout the cycle of the process.
Community relations expert	• Partner with advocacy groups for the community, both national and local chapters. • Create an advisory board including active patient advocates to review proposals for research.

[a]HCD: human-centered design.

[b]ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.

An online survey collected anonymous perspectives from 251 people with ME/CFS regarding symptoms they experience, the method/frequency of data capture that would work best, and how data should be reported back through a mobile app. The results were compared to a community survey developed by collaborators at Columbia University (unpublished), for a combined response set from over 1200 people with ME/CFS.

Symptoms endorsed by most of the survey respondents (ie, fatigue, PEM, cognitive impairment, unrefreshing sleep) were included in a core set of symptoms that autopopulate for app users. However, community feedback made it clear that capturing a complete range of symptoms would be critical for relevancy of the app to the individual, so we included the ability to add custom symptoms. Although most said they would use the app daily or weekly, about one-third indicated this was too frequent.

To accommodate variation in disease severity and function, we set up the app to allow data capture as often as daily and included communications every 3 days to encourage data entry. We also added screens to track activities (eg, work, social, leisure) in the first build of the mobile app because respondents were highly interested in understanding the links between activities and symptoms.

Over 30 individuals tested a beta version of the registration process and tracking app on their Apple and Android phones—including people with ME/CFS, care partners, researchers, and clinicians. Most beta testers used a template form to provide feedback with yes/no options, numerical ranking scales, and open comment fields. Version 2.0 of the app was developed in response to tester input with enhanced user guidance and prompts, the ability to add narratives through a journal screen, and the addition of a calendar functionality. When the Registry was adapted and opened for the post–COVID-19 cohort, we utilized a similar community testing and feedback process. The user experience and data collection are continuously improved based on feedback from patients and researchers.

Technical Infrastructure

The Registry data are securely stored in an encrypted database hosted in a cloud-based instance [32]. The database stores data records as documents, which are collated into collections (analogous to tables in a relational database) and linked according to unique identifiers. Participant data are encrypted in transit using industry-standard Transport Layer Security/Secure Socket Layer to protect sensitive information when it is transmitted to and from the front-end apps and

backend database. Amazon Cognito is used for user authentication and access control. Strict security and access standards are in place to protect participant data.

The Registry is designed to be a globally shared repository that removes data silos and increases collaboration. The digital tools and services that comprise the registry are setup for Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulation (GDPR) compliance to ensure the highest international standards of data privacy are met and to allow enrollment and collection of self-report survey data from participants worldwide. We plan to work with local partners to ensure regional data privacy and regulatory requirements are fulfilled for the collection of future data types (eg, health care data, biological samples).

Data Harmonization

The validated data collection instruments within the Registry (see the Data Collection section) are aligned with those used by other researchers and clinicians studying patients with ME/CFS. They include the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements [33] to facilitate aggregation of data across studies. After consulting with community members, additional data fields were included to build a richer understanding of each participant's health history. The Registry also integrates the NINDS centralized Globally Unique Identifier (often referred to as GUID) solution, a secure tool that generates unique IDs without exposing personally identifiable information (PII) to allow data sharing and collaboration across research groups.

Participant Recruitment

The Registry is open to all individuals with ME/CFS, those with LC, and other populations, including individuals with other chronic diseases and individuals considered healthy controls. The aim is to enroll a diverse global cohort of participants who are representative of the broader ME/CFS and LC communities and to create the largest-possible global data set to interrogate.

The Registry is promoted via Solve M.E.'s and You + ME's dedicated @youmeregistry social media channels (Facebook, Twitter, Instagram), on a dedicated online informational website [18], printed newsletters, and email to the Solve M.E. listserv. It is also promoted in webinars and conference presentations.

Additional recruitment is conducted through partners in both ME/CFS and LC by leveraging their social media channels and email listservs. This is particularly important for recruitment to our ME/CFS and LC cohorts, given that many in these communities are connected via robust social media groups [34]. Our LC recruitment strategy specifically is multipronged (Table 2). Outreach is focused on areas with historically high incidences of COVID-19 cases (eg, New York City, New Orleans, and Los Angeles). Future plans for recruitment include referrals from clinicians and health systems.

Table 2. Overview of current and planned recruitment strategies for the Registry[a].

Type of outreach	Target organizations/partners and strategy
Solve M.E.[b] communication channels	Promote the Registry to our established network via (1) a database of over 34,000 active contacts; (2) organizational and Registry social media accounts with a combined following of 6772 on Twitter, 34,114 on Facebook, and 2256 on Instagram; and (3) our educational webinar series for researchers, clinicians, and patients.
COVID-19 survivor postacute sequelae of COVID-19 (PASC) patient groups	Partner with established groups serving COVID-19 survivors and individuals with PASC, including online forums and support groups on social media, to promote the Registry to their networks.
LC[c] alliance	Partner with members to create a referral pipeline to the Registry from over 50 science, postviral disease, and patient advocacy and research organizations working together to find answers for LC and postviral illness.
Internet and social media advertising	Google Ads and social media posts directed toward individuals who have experience in COVID-19 and primary care providers who may be treating those with persistent symptoms of COVID-19.
Clinics/health systems	Partner with health systems, clinics, and hospitals serving our populations of interest to provide a postcard that will be handed out to their patients with COVID-19. The postcard will ask about the development of persistent postviral symptoms and direct patients to the Registry for voluntary sign-up.
Membership organizations/trade associations	Partner with health care workers and emergency medical services (EMS) unions; other unionized or nonunionized essential workers, such as large grocery/drug store chains, transit workers, and delivery services; university-based, countrywide student organizations, athletic associations. and student health networks; and medical specialty associations to share the recruitment notices to their membership.

[a]Registry: You + ME Registry and Biobank.

[b]Solve M.E.: Solve ME/CFS Initiative, where ME/CFS refers to myalgic encephalomyelitis/chronic fatigue syndrome.

[c]LC: long COVID.

Criteria for Selection

The Registry is open to individuals of all genders, with an anticipated gender split between males and females reflective of the gender prevalence of ME/CFS and LC. Adults (aged 18 years and above) are eligible for participation. All races and ethnic origins are included. Although we do not limit enrollment from control volunteers, we will be making every effort to ensure controls are adequately matched to patients by age, sex, race, and other key demographic indicators.

People With ME/CFS

People with ME/CFS self-diagnosed or diagnosed by a clinician are eligible to enroll. Many patients with ME/CFS struggle for

years before being diagnosed; it has been estimated that up to 90% of people with ME/CFS have not received an official diagnosis from a clinician [35,36]. Rather than exclude participants based on a lack of clinical diagnosis at enrollment, we include these individuals and record the method of diagnosis for each participant. We also have a recurring question about clinician diagnosis to track any changes.

People With COVID-19

People who had COVID-19, whether confirmed or not confirmed by a lab test, are eligible to enroll. Access to and reliability of COVID-19 lab tests caused difficulties to confirm an infection, particularly in the early period of the pandemic. Therefore, we allow self-reporting of COVID-19 infection and record the method of initial COVID-19 diagnosis for each participant.

Control Volunteers

Control volunteers are made up of individuals without ME/CFS or LC, including individuals considered healthy controls and those with other chronic illnesses (eg, fibromyalgia).

Symptom Assessment and Algorithm for ME/CFS Case Criteria

For all participants, the Registry scores responses to the UK ME/CFS Biobank (UKMEB) Symptoms Assessment Questionnaire to determine fulfillment of distinct ME/CFS case criteria [37], including the CDC-1994 (Fukuda) criteria [38], the Canadian Consensus criteria [39], the International Consensus criteria [40], the Institute of Medicine criteria [41], and the Oxford criteria [42]. This is to align with what has been proposed for use in clinical practice and currently being used by ME/CFS researchers worldwide [43]. Questionnaire responses are fed to a digitized version of the algorithm licensed from the UKMEB to the Registry, which is coded into the online platform in a separate endpoint that securely runs the data for scoring.

Data Collection

Participants sign up for the Registry via a secure website interface. Participants are asked to complete an electronic informed consent form for collection of data and to be recontacted for optional biosample collection or other study opportunities. After consenting to the Registry, they are guided through a series of baseline surveys (Table 3), including medical history, diagnosed conditions, symptoms and quality of life, and medication history.

Table 3. Surveys used in the Registry[a] and what they measure.

Survey	Measures
ME/CFS[b] Disease History[c,d]	Disease-specific history (triggers, onset, disease course)
COVID-19 History[e]	Infection status, acute illness, clinical course
UKMEB[f] Symptoms Assessment [37][e,g]	Symptom experience and fulfillment of ME/CFS case definitions
Short Form-36 [44][e,g]	Health-related quality of life
Karnofsky Performance Status (modified) [45][e]	Functional status
Multidimensional Fatigue Inventory [46,47]	General fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue
Demographics[g]	Basic demographic information, including age, race, ethnicity, income, education, employment status
My Conditions[h]	Diagnosed conditions
My Treatments[h]	Medications, supplements, and other treatments
Family Health History[d]	Information about disorders from which a direct blood relative may or may not have suffered
Beighton Score[d]	A screening tool for hypermobility
Fibromyalgia Impact Questionnaire Revised[d,i]	Physical functioning, work status, depression, anxiety, morning tiredness, pain stiffness, fatigue, and well-being
COVID-19 Vaccination Status	Vaccination status, symptoms (pre-existing and following the vaccine), and reasoning for not getting vaccinated (if indicated)

[a]Registry: You + ME Registry and Biobank.

[b]ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.

[c]The survey is only presented to those who indicate they have ME/CFS.

[d]A one-time survey.

[e]The exact same questionnaire asked at follow-up timepoints.

[f]UKMEB: UK ME/CFS Biobank.

[g]Abbreviated/modified version of the questionnaire asked at follow-up timepoints.

[h]A form that can be revised/added to on an ongoing basis.

[i]The survey is only presented to those who indicate they have fibromyalgia.

Longitudinal characterization is imperative to understanding chronic illnesses that are evolving and have a cyclical nature. Volunteers with ME/CFS and control volunteers are sent email reminders to complete an abbreviated set of surveys every 90 days following registration (Figures 1 and 2). We hypothesize that biologically or clinically distinct factors drive divergent outcomes in post–COVID-19 patients toward complete recovery or long-term sequelae. So, the post–COVID-19 cohort is sent follow-up surveys every 30 days in the initial 6 months and then every 90 days for longer-term follow-up (Figure 3). Through more frequent data collection during this critical period following recent infection, we aim to identify factors driving or predictive of this bifurcation in outcomes.

Figure 1. Overview of the first 6 months of longitudinal Registry data collection, which includes electronic surveys administered at enrollment (baseline) and follow-up time intervals in adults with ME/CFS. Individuals with ME/CFS can opt to track their symptoms using a numerical scale from 0 (symptom absent) to 4 (very severe) in a mobile app. Severity scores are defined as follows, according to the DePaul Symptom Questionnaire: 0=symptom not present, 1=mild, 2=moderate, 3=severe, 4=very severe. ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome; Registry: You + ME Registry and Biobank.

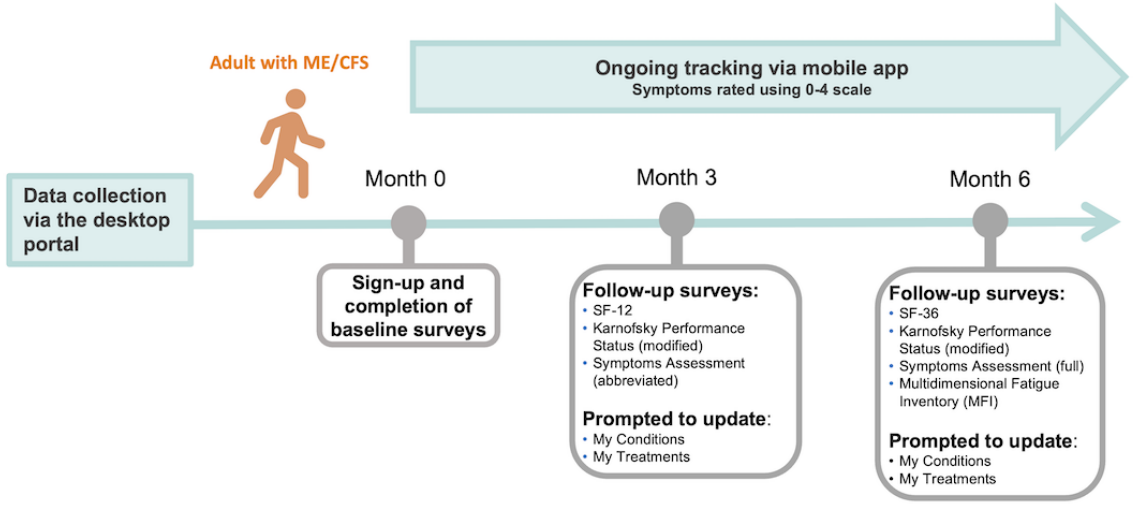


Figure 2. Overview of the first 6 months of longitudinal Registry data collection, which includes electronic surveys administered at enrollment (baseline) and follow-up time intervals in adult control volunteers. ME: myalgic encephalomyelitis; Registry: You + ME Registry and Biobank. SF-12: 12-item Short Form Survey; SF-36: 36-item Short Form Survey.

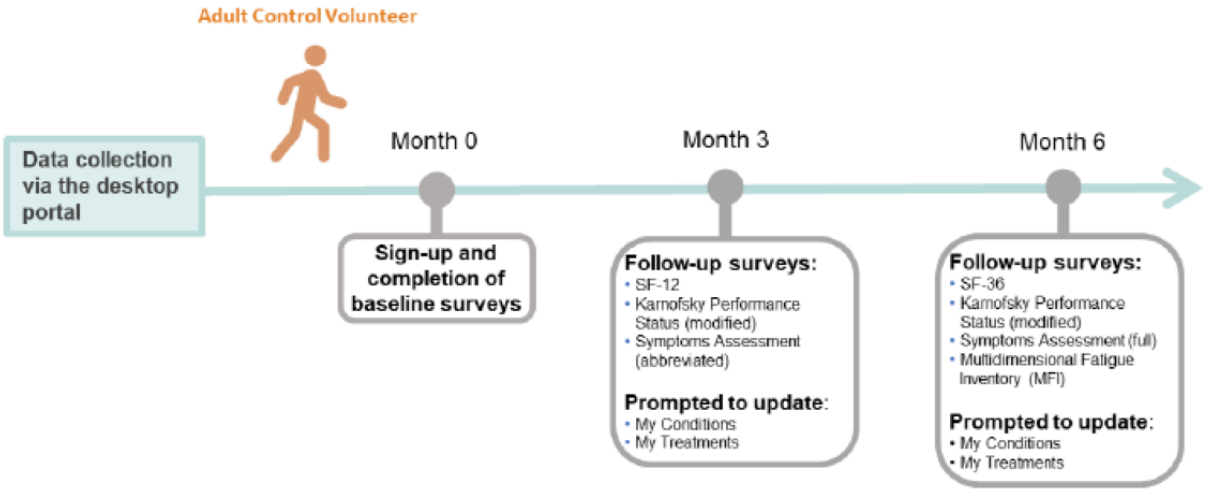
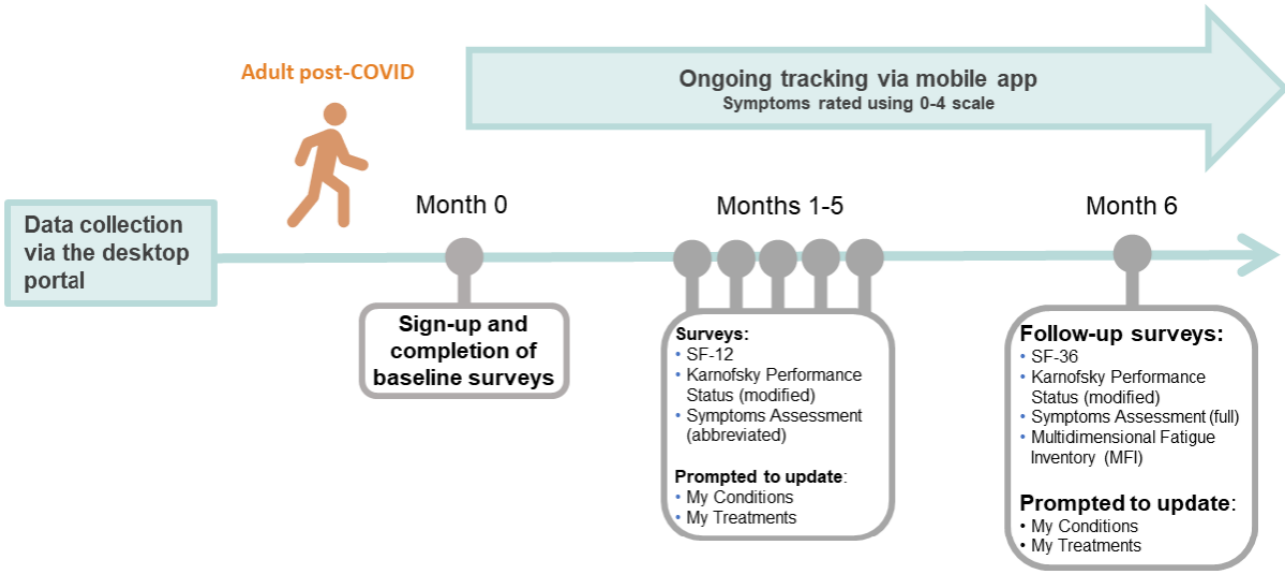


Figure 3. Overview of the first 6 months of longitudinal Registry data collection, which includes electronic surveys administered at enrollment (baseline) and follow-up time intervals in adults post–COVID-19. Individuals can opt to track their symptoms using a numerical scale from 0 (symptom absent) to 4 (very severe) in a mobile app. Severity scores are defined as follows, according to the DePaul Symptom Questionnaire: 0=symptom not present, 1=mild, 2=moderate, 3=severe, 4=very severe. ME: myalgic encephalomyelitis; Registry: You + ME Registry and Biobank. SF-12: 12-item Short Form Survey; SF-36: 36-item Short Form Survey.



One-time questionnaires are also deployed through the Registry, in addition to the regular longitudinal assessments. These questionnaires collect cross-sectional data from unique instruments that are not part of the routine longitudinal assessments, and currently include surveys on family health history, joint hypermobility (self-report Beighton), and COVID-19 vaccination experience.

Data are aggregated into a single table and are available as a comma-separated value file. Values of variables are encoded according to a data dictionary, which accompanies each data file and describes the metadata available for each survey question in the routine longitudinal assessment and one-time surveys. The complete data dictionary includes over 800 collected variables and is available upon request.

Symptom Tracking

Upon completion of the first set of surveys, participants are sent an email with a link to download the You + ME symptom-tracking mobile app. The symptom-tracking app allows individuals with ME/CFS, LC, and other chronic diseases to record symptoms, lifestyle factors, life events, and any activities on an ongoing basis (Figures 4-6).

Figure 4. Using the mobile app tracking screen, users can report the presence and severity of symptoms felt.

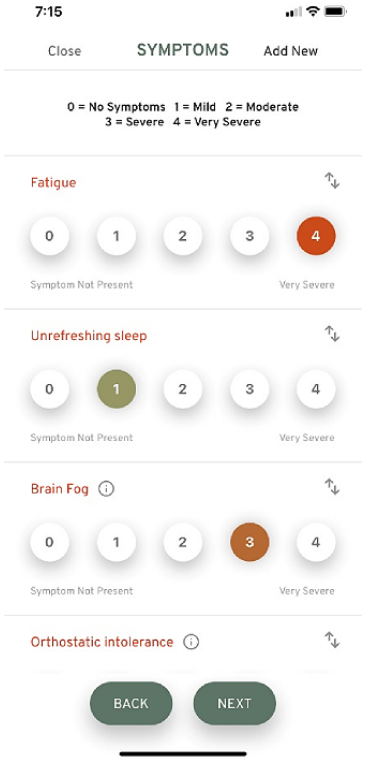


Figure 5. Using the mobile app tracking screen, users can log which treatments were taken that day. ME/CFS: myalgic encephalomyelitis/ chronic fatigue syndrome.

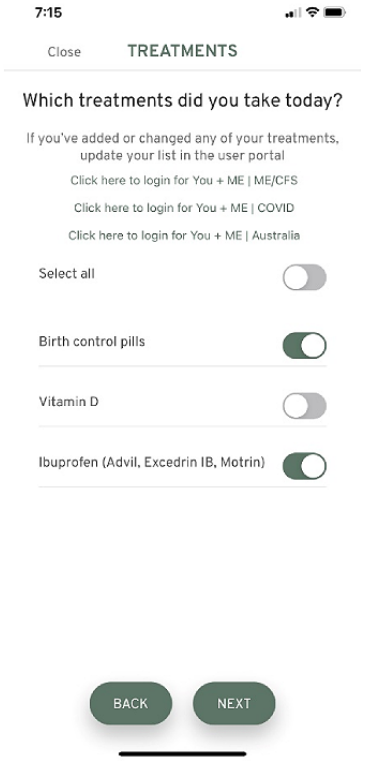
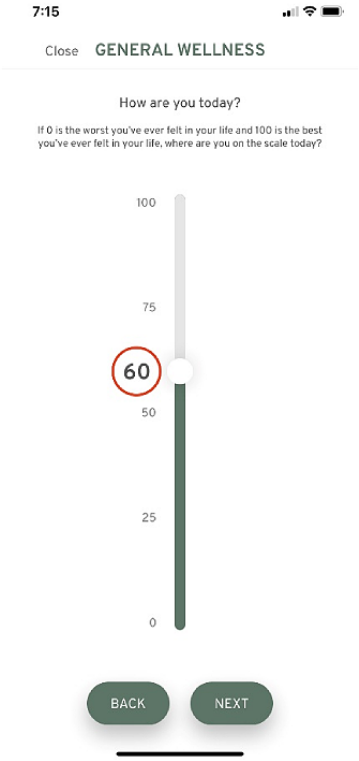


Figure 6. Using the mobile app tracking screen, users can provide a rating of general wellness.



Data Management

The principal investigator is responsible for overseeing data quality and reliability and ensuring safeguards are in place to protect participant privacy and safety. The Registry data manager audits the data biweekly to improve quality, ensure validity and reliability, and guarantee the integrity and credibility of output.

Data Sharing

Researchers who want to access the data for research apply to Solve M.E. with information required to review their request, including their name, institution, terminal degree, relevant publications, and research interest. The application is reviewed by the You + ME Innovation Council, a group of approximately 12 individuals with deep expertise in ME/CFS and chronic disease research or data science (clinicians, researchers, data scientists, and individuals with ME/CFS and other chronic diseases). Data are stripped of identifiers and shared with researchers through secure means of transfer. Researchers who use the data are required to sign a data use agreement that includes a guarantee to share their methods and findings with the ME/CFS and LC patient communities.

Ethical Considerations

The Registry was approved and is overseen by the Western Institutional Review Board (Protocol #20193104).

Results

Participant Enrollment

As of September 30, 2021, the Registry had over 4200 participants: 3033/4339 (69.9%) people with ME/CFS, 833/4339 (19.2%) post–COVID-19 people, and 473/4339 (10.9%) control volunteers. Recruitment to the Registry continues at a steady pace, with an average of 72 new people registered every week, responding to social media and other outreach efforts.

The Registry includes participants from all 50 states of the United States (see Figures 7 and 8). Participant-provided zip codes matched to rural-urban commuting area codes from the 2010 Census indicate that 256/2085 (12.3%) of ME/CFS and 42/387 (10.9%) of LC registrants who provided zip code data live in nonurban areas. The Registry is open to LC registrants internationally. The highest concentration of LC registrants is in the United States (n=651, 78.2%), the United Kingdom (n=44, 5.3%), and Canada (n=72, 8.6%); in total, there is representation from 32 countries (see Figure 9).

Although a major goal of the Registry is to open up participation in research to underrepresented groups, enrollment to date is largely consistent with previous ME/CFS research cohorts. The male-to-female sex ratio for the entire Registry cohort is 23:100, meaning for roughly every 23 males, there are 100 females (intersex individuals make up 0.001% of the participants). Registry participants are predominantly non-Hispanic White. An area of divergence from most previous studies is the significant proportion of individuals in the Registry who are severely-to-very-severely ill, including nearly one-third (581/1096, 30.5%) of our ME/CFS cohort and 123/782 (15.7%) of our post–COVID-19 cohort who have provided a response to the Karnofsky Performance Status survey. These patients, who are house- or bed-bound, are underrepresented in traditional research settings.

Figure 7. Registry enrollment of adults with ME/CFS in the United States by state (as of September 30, 2021). Map based on longitude (generated) and latitude (generated). Each state with ME/CFS and control volunteers enrolled shows a color corresponding to enrollment count aggregated from zip code data provided by participants (N=2085). ME/CFS: myalgic encephalomyelitis/ chronic fatigue syndrome; Registry: You + ME Registry and Biobank.

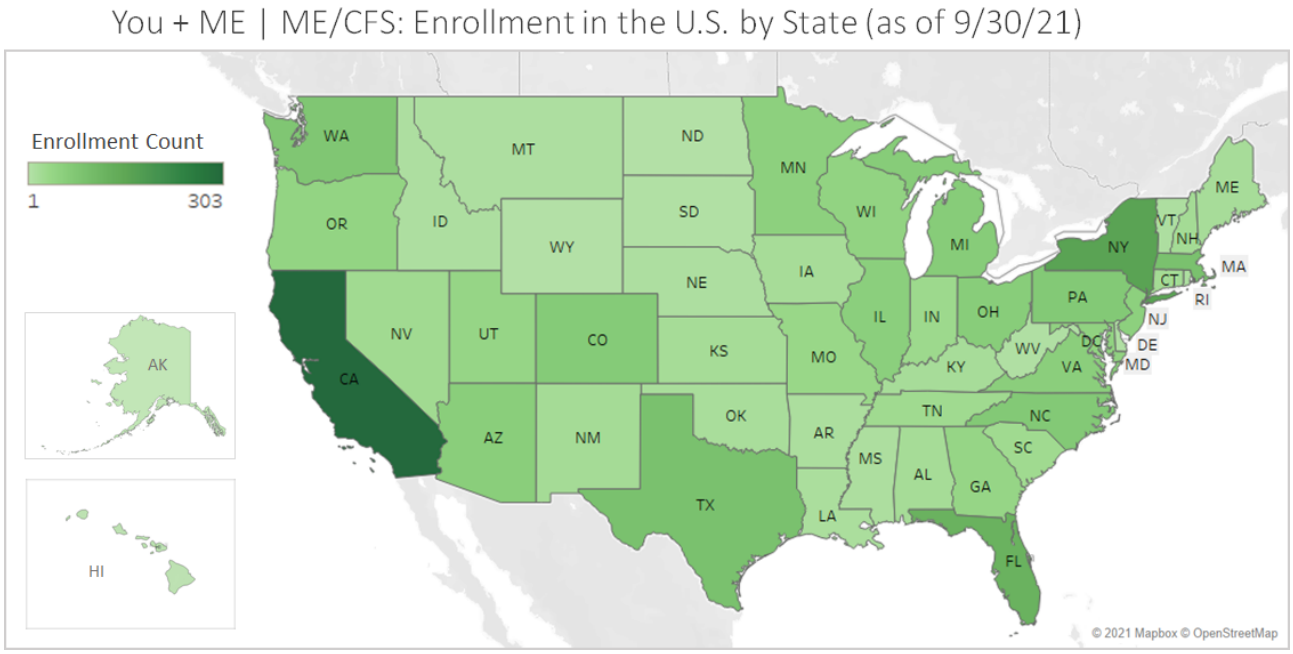


Figure 8. Registry enrollment of adult control volunteers in the United States by state (as of September 30, 2021). Map based on longitude (generated) and latitude (generated). Each state with participants enrolled shows a color corresponding to post–COVID-19 enrollment count aggregated from zip code data provided by the participants (N=387). ME: myalgic encephalomyelitis; Registry: You + ME Registry and Biobank.

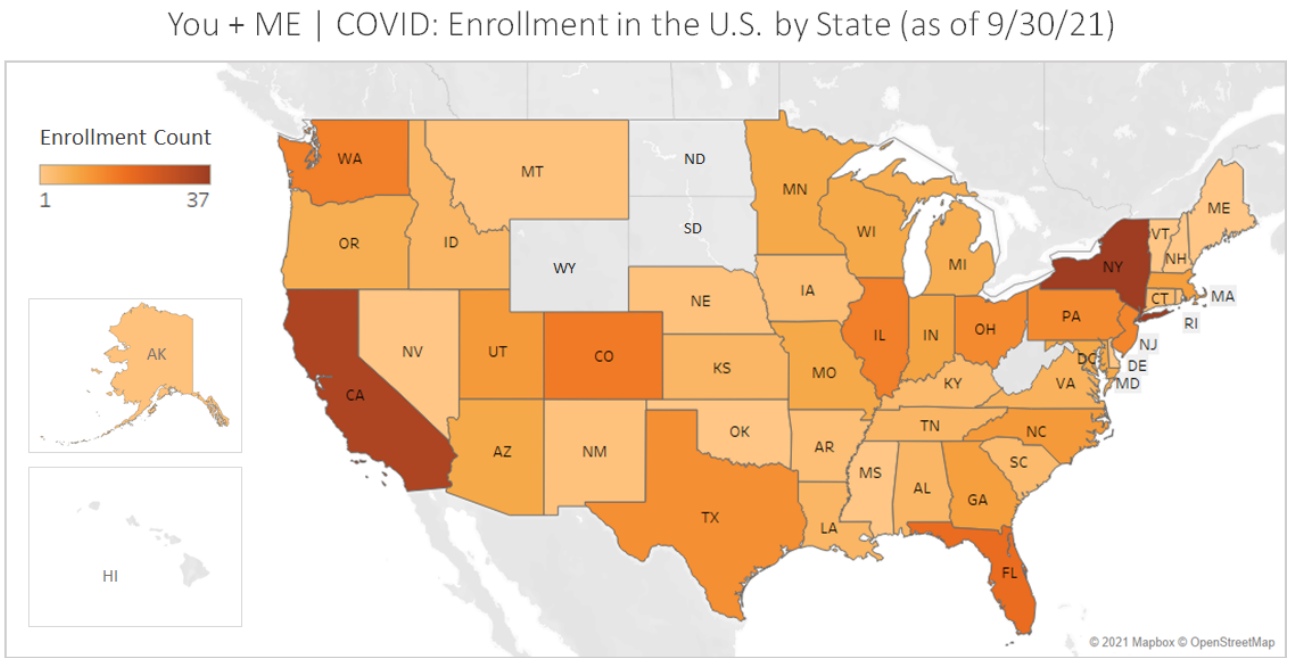
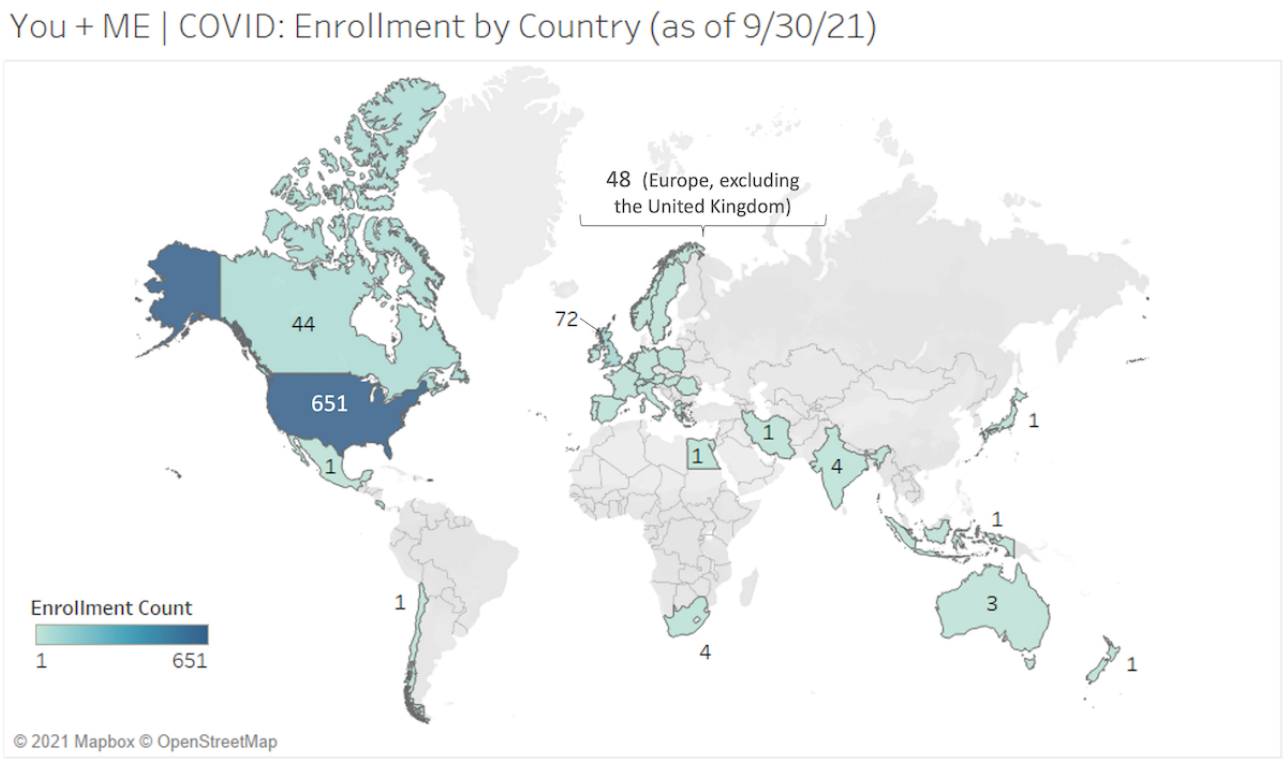


Figure 9. Registry enrollment of adults post–COVID-19 by country (as of September 30, 2021). Map based on longitude (generated) and latitude (generated). Each country with participants enrolled shows a color corresponding to post–COVID-19 enrollment count from country of residence data provided by the participants (N=836). ME: myalgic encephalomyelitis; Registry: You + ME Registry and Biobank.



Overall enrollment targets by cohort for the first 3 years of the Registry are summarized in Table 4. The goal is for 30% of the ME/CFS and post–COVID-19 cohorts to be controls (in the post–COVID-19 cohort, controls are individuals who had COVID-19 but fully recovered and never experienced LC). Another goal is for 25% of the entire Registry cohort to be based outside the United States by the end of year 3.

Table 4. Registry[a] enrollment targets by cohort for years 1-3.

Cohort	Year 1 (N=3800), n (%)	Year 2 (N=9000), n (%)	Year 3 (N=15,000), n (%)
ME/CFS[b] cohort[c]	3000 (78.9)	7000 (77.8)	10,000 (66.7)
LC[d] cohort[e]	800 (21.1)	2000 (22.2)	5000 (33.3)

[a]Registry: You + ME Registry and Biobank.

[b]ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.

[c]Includes control volunteers without ME/CFS.

[d]LC: long COVID.

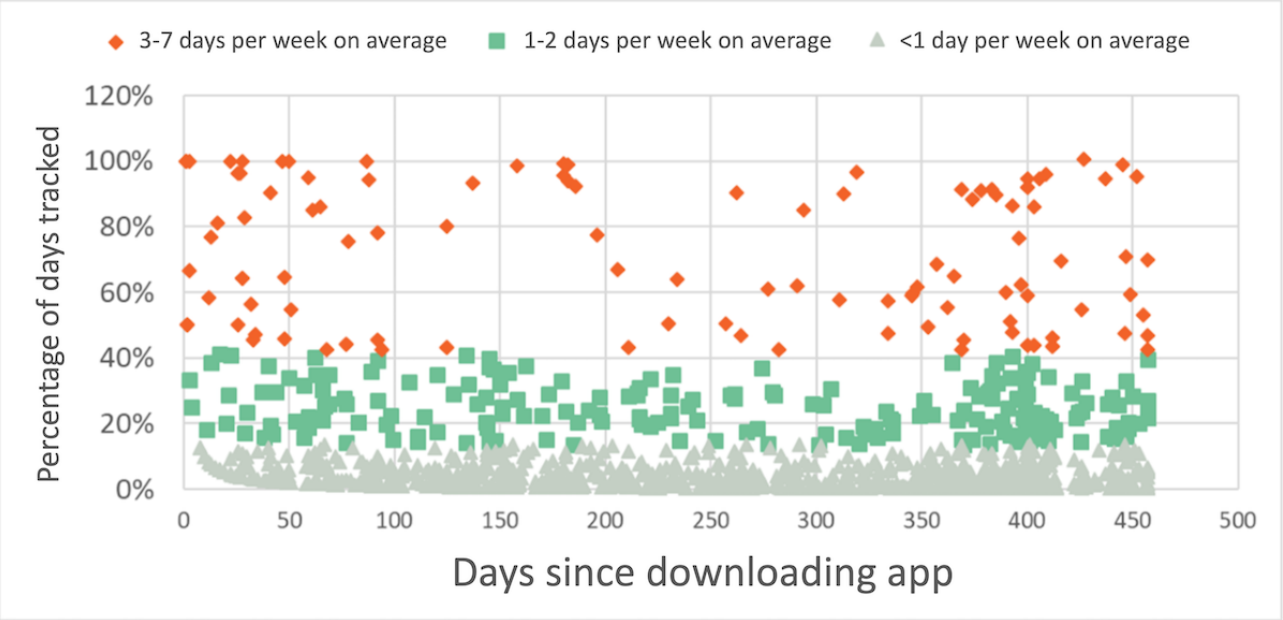
[e]Includes controls (COVID-19-recovered).

Mobile App Engagement

According to an analysis completed in August 2021, 1358 participants (56.1% of those who had enrolled by the end of July 2021) with ME/CFS and LC had downloaded the mobile tracking app and over 1264 (93.1% of those who had downloaded the app) initiated tracking. Nearly half of the app users had tracked symptom and other health data on 10 or more days. Collectively, mobile app users had logged 38,242 tracking days.

The days per week tracked by users (on average) showed high engagement (3-7 days per week) from a superuser group comprising 106 (8%) of users. In addition, 207 (16%) had moderate engagement (1-2 days per week), and three-quarters (n=951) had low engagement (less than 1 day per week); see Figure 10.

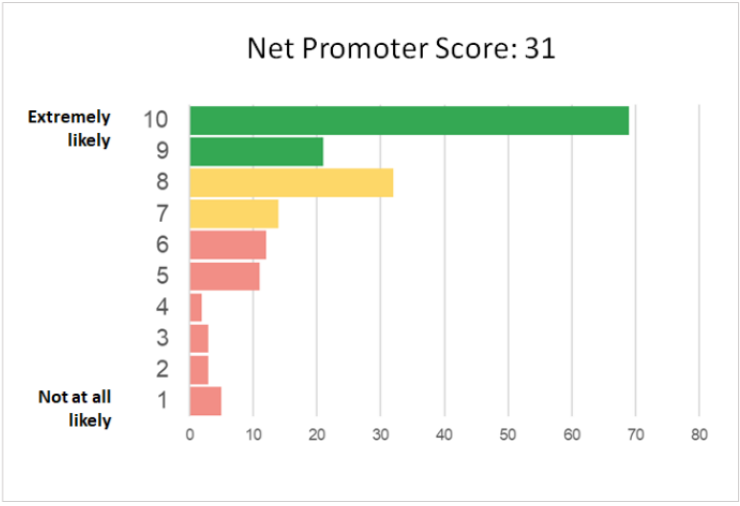
Figure 10. Percentage of days tracked per week (on average) by each symptom-tracking mobile app user since date of app download. The percentage of days tracked were bucketed into three categories and color-coded in the graph: high engagement (3-7 days per week) moderate engagement (1-2 days per week) and low engagement (less than 1 day per week).



Participant Satisfaction

Of 172 participants who completed our community feedback survey as of September 30, 2021, 122 (70.9%) rated their overall satisfaction with the Registry as 7 or higher (on a scale of 1-10). The Registry has qualified as "great" using a user satisfaction index measurement called a net promoter score, in which respondents are asked how likely they are to recommend it to a friend (see Figure 11).

Figure 11. You + ME user satisfaction index measured by the net promoter score (as of September 30, 2021). ME: myalgic encephalomyelitis.



Discussion

Preliminary Results: Participant Enrollment and Satisfaction

This paper describes the design, operation, recruitment, geographical coverage, and overall participant satisfaction for the Registry. With a plan to enroll a large and diverse cohort for longitudinal data collection, this data resource has the potential to improve the understanding of ME/CFS and LC, facilitate translational research, and inform clinical care and improve the quality of life for people living with ME/CFS and LC.

Resources such as the UK Biobank and other large-scale research efforts have demonstrated the power of large cohorts for biomedical discovery [48] and motivated our goal to collect data from tens of thousands of individuals. Enrollment in the Registry has been robust, with over 4000 participants registered within 2 years of opening; participant accrual and the trajectory toward enrollment targets have been consistent with similar online disease registries [15,16].

Compared to traditional, in-person studies, online studies and web-based recruitment can enable participation from people with diverse geography, backgrounds, and disease experiences [15-17]. The Registry has successfully enrolled some hard-to-reach participants, including people from nonurban

areas and severely ill patients, who are house- or bed-bound. In addition to the convenience of online participation, strong enrollment in the Registry is likely driven by the broad eligibility criteria and highly motivated patient populations who want to contribute to research [49] that will help them and others, as has been observed in other disease registries.

Users have reported finding the mobile app useful for ongoing tracking of their symptoms and other factors, but use of the app is extremely variable. Others only use it for a limited period due to a multitude of factors, including the burden of frequent tracking, mobile app functionality (eg, periodic bugs or personal preferences around app functionality), or an aversion to being reminded of their health. Deploying strategies that encourage more frequent tracking with the app is an ongoing priority.

The high degree of satisfaction with both the data collection process and the digital tools reported by the You + ME community members reflects the incorporation of perspectives from multiple stakeholders into the Registry design and the benefits of cocreation and HCD in the development of digital health tools [28,50-52]. Facilitating a mechanism for those living with an illness to share the unique insights of their lived experience and partnering with them on the development of tools to capture that experience are best practices that should be universally adopted to improve our understanding and therapeutic development.

Participant satisfaction and commitment to the Registry will be key to continued success and further expansion. We learned from other efforts that a meaningful approach to maximizing retention and engagement in a research study over time is sharing individualized data and research results back [53,54]. You + ME registrants have access to the survey information they provide, as well as readouts of symptom data from the tracking app that provide a resource for self-management and sharing of information with health care providers and loved ones.

Using the Data to Drive Research

The overarching goal of the Registry is to serve as a catalyst for critical research into diagnostics, treatments, and cures for ME/CFS, LC, and other postinfection diseases using the power of a large cohort with prospectively collected data. The data collection combines patient-reported outcomes that are important to community members with validated scales. These data can be used for researching associations between numerous characteristics and disease courses and to validate outcome data reported by patients as benchmarks for future approval of treatments [15,16].

One of the benefits of this data set is the ability to look across cohorts to understand the similarities and differences between ME/CFS and LC. Cross-disease and disease subtype comparisons using data from registries have produced valuable insights, including clarification of clinical profiles and implication of targeted therapies [55,56]. The establishment of the Registry during the COVID-19 pandemic, during which case numbers have been highly concentrated over a short period, presented an opportunity to track and study trajectories of symptom improvement or worsening in a population with a singular infectious trigger. Clues about susceptibility and resilience to long-term effects of COVID-19 could also benefit the millions of Americans already diagnosed with ME/CFS [56].

The Registry has started to support data analysis by the internal research team and in partnership with external researchers. One example of active promotion of the Registry is through the Solve M.E. Ramsay Grant Program, an annual peer-reviewed competition for grants in support of pilot studies that first launched in 2016. In 2021, the Ramsay Grant Program opened a new funding mechanism to analyze Registry data, ultimately funding 2 projects [5].

To further increase accessibility and utility of the Registry research data set, we plan to build an interface that allows vetted researchers to query and use the data for a range of scientific projects. Researchers will be required to share their results so a community of researchers can further test the findings or build from them in new work.

Limitations

Despite these successes, the current Registry study design and data set has some limitations, including reliance on self-report data, which can produce a measurement error due to participant recall, interpretation, or other factors [57]. The Registry is also subject to selection bias, including sociodemographic and other differences between participants and nonparticipants, selective participant drop-off, and missing data. These are frequent concerns in registry-based research and introduce data accuracy, interpretation, and generalizability issues. We are therefore planning a number of actions to improve the representativeness of the Registry cohort and pursuing studies to evaluate our measurements, guide development of the protocol, and examine the quality and usefulness of the data.

Engagement and Data Completeness

Both ME/CFS and LC are illnesses that evolve and change over time. Although the Registry and symptom-tracking app are specifically designed to capture this, they are dependent on continued engagement from the Registry community, both within visits and over time. Data completeness, potential bias in completion rates, and data quality will be continuously monitored. Developing novel approaches for engagement and learning from others [50,52] who have successfully achieved this will be an ongoing priority.

Diversifying the You + ME Community

The Registry is predominantly made up of White non-Hispanic individuals. Ethnic minorities are underrepresented as participants in biomedical and public health research, due to a multitude of personal (eg, cultural distrust and perceptions of research), social (eg, expenses, work, and home responsibilities), and research-related (eg, inaccessibility of study documents and materials, travel to study locations) factors [58]. The use of online surveys that can be completed at home addresses some of these barriers to participation, but there are still reported ethnic and socioeconomic status (SES) differences in web-based research study participation [59]. In collaboration with partners, a directed effort will be made to increase Registry inclusivity

and participation and to develop strategies that address recruitment bias.

Expanding Our Control Cohort

The existing control cohort represents a little more than 10% of overall participants; the target is 30%. To ensure the control cohort is adequately matched on key demographic variables and therefore able to serve as a comparison group to our ME/CFS and LC cohorts, direct, targeted outreach and more innovative approaches, including partnership with other disease registries to share a control data set, will be explored.

Next Steps for the Registry

Meeting the Needs of Adolescents

Both ME/CFS and LC affect adolescents; this group is often underrepresented in clinical research [60-62]. The symptom clusters experienced by this population are often distinct from the adult population; for example, many adolescents with ME/CFS have OI as a predominant symptom [63,64].

Development of a version of the Registry for adolescents aged 13-17 years is currently underway. It will be designed specifically for this age group, so it includes an appropriate consent and data collection process.

Biosample Collection

To accompany the rich longitudinal phenotypic data collected in the Registry, biological samples will be collected from a subset of the larger Registry cohort to both support specific research projects and create a biorepository of samples for future research. Samples will include 1 or more of the following:

- Dried blood spot (DBS) cards (DNA, RNA, protein expression, and metabolomics analyses)
- Dried urine strips (DUS; metabolomics)
- Fecal samples for analyses of microbiome composition and metagenomics (determination of potential microbial metabolites that affect gastrointestinal, immune, metabolic, neurologic, and systemic health)
- Saliva (salivary biomarkers)
- Venipuncture blood draw, and processing and storage of blood components (immunologic, metabolomics, microbiome/virome)

These sample types can support a range of research and make up the immediate biosample collection protocol, but studying other tissue types, such as cerebrospinal fluid, is possible in the future. Samples will be stored by a certified good clinical practice (GCP) provider indefinitely in the Solve M.E. Biobank but destroyed upon request if a participant withdraws.

Expanding the Registry to Integrate New Data Types

Although the current capabilities of the Registry can support expansive data collection, the platform is also built with the capacity to integrate new data types (eg, passive monitoring from wearables and health care data from participants' clinicians). This gives great potential for multimodal data, in particular physiological data, that can be combined with self-reported data to significantly increase the accuracy and validity of results and to reduce bias.

Acknowledgments

We are incredibly grateful to the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and long COVID (LC) community members who have continually contributed insights and ideas for the You + ME Registry and Biobank (Registry), helped to design the data collection process, spent hours testing the platform and mobile app, and spent extensive time and energy enrolling and completing surveys.

Special thanks also go to Rochelle Joslyn (PhD), Rachael Carder, and Beth Mazur for their wisdom and expert advice on numerous aspects of the Registry design and data collection process.

We are deeply appreciative of the scientists and clinicians who provided advice and input, particularly Anthony L Komaroff (MD), and others in the field who shared their protocols for data collection so we could work to harmonize data: Jarred Younger (PhD), Luis Nacul (MD, PhD), Eliana Lacerda (MD, PhD), Lucinda L Bateman (MD), and Nancy Klimas (MD), to name a few.

We are incredibly grateful to our partners at Topflight Apps, who partnered with us on the development of the Registry platform, with particular thanks to Francesco Mantovani and Alex Lorincz for their dedication and creativity.

Thank you to the UK ME/CFS Biobank (UKMEB) and CureME team and the London School of Hygiene and Tropical Medicine for licensing their Symptoms Assessment and scoring algorithm to the Registry.

This work would not be possible without funding from countless individual donors to the Solve ME/CFS Initiative (Solve M.E.).

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Authors' Contributions

Conceptualization was performed by SW and AR; data curation by ES and AR; visualization by KM and AR; and drafting of the manuscript by KM, AR, and SW. All authors have approved the final draft of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

HCD: human-centered design
LC: long COVID
ME/CFS: myalgic encephalomyelitis/ chronic fatigue syndrome
OI: orthostatic intolerance
PEM: postexertional malaise

Registry: You + ME Registry and Biobank
Solve M.E.: Solve ME/CFS Initiative
UKMEB: UK ME/CFS Biobank

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Protocol

Digital Interventions Supporting Self-care in People With Type 2 Diabetes Across Greater Manchester (Greater Manchester Diabetes My Way): Protocol for a Mixed Methods Evaluation

Joanna Goldthorpe[1], PhD; Thomas Allen[2], PhD; Joanna Brooks[1], PhD; Evangelos Kontopantelis[3], PhD; Fiona Holland[4], MSc; Charlie Moss[4], MSc; Deborah J Wake[5,6], PhD; Doogie Brodie[5], MSc; Scott G Cunningham[5,7], PhD; Naresh Kanumilli[8,9], MCRP; Hannah Bishop[10], MSc; Ewan Jones[10], BSc; Nicola Milne[9], RGN; Steve Ball[9], PhD; Mark Jenkins[11], MD; Bogna Nicinska[11], MSc; Martina Ratto[12], MA; Michael Morgan-Curran[13], BSc; Gemma Johnson[14], PG Cert; Martin K Rutter[9,15], MD

[1]Manchester Centre for Health Psychology, School of Health Sciences, University of Manchester, Manchester, United Kingdom

[2]Manchester Centre for Health Economics, University of Manchester, Manchester, United Kingdom

[3]Division of Informatics, Imaging and Data Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

[4]Division of Population Health, Health Services Research and Primary Care, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

[5]My Way Digital Health, Dundee, United Kingdom

[6]Centre for Medical Informatics, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom

[7]Population Health & Genomics, School of Medicine, University of Dundee, Dundee, United Kingdom

[8]Northenden Group Practice, Manchester, United Kingdom

[9]Diabetes, Endocrinology & Metabolism Centre, Manchester Royal Infirmary, Manchester, United Kingdom

[10]Greater Manchester & Eastern Cheshire Strategic Clinical Networks, Greater Manchester Health & Social Care Partnership, Manchester, United Kingdom

[11]Oviva Health, London, United Kingdom

[12]Beingwell Group, English Institute of Sport, Sheffield, United Kingdom

[13]MyCognition Ltd, London, United Kingdom

[14]Changing Health Limited, Newcastle upon Tyne, United Kingdom

[15]Division of Diabetes, Endocrinology & Gastroenterology, School of Medical Sciences, University of Manchester, Manchester, United Kingdom

Corresponding Author:
Martin K Rutter, MD
Division of Diabetes, Endocrinology & Gastroenterology
School of Medical Sciences
University of Manchester
Oxford Road
Manchester
United Kingdom
Phone: 44 161 276 6880
Email: Martin.Rutter@mft.nhs.uk

Abstract

Background: Type 2 Diabetes (T2D) is common, with a prevalence of approximately 7% of the population in the United Kingdom. The quality of T2D care is inconsistent across the United Kingdom, and Greater Manchester (GM) does not currently achieve the National Institute for Health and Care Excellence treatment targets. Barriers to delivery of care include low attendance and poor engagement with local T2D interventions, which tend to consist of programs of education delivered in traditional, face-to-face clinical settings. Thus, a flexible approach to T2D management that is accessible to people from different backgrounds and communities is needed. Diabetes My Way (DMW) is a digital platform that offers a comprehensive self-management and educational program that should be accessible to a wide range of people through mobile apps and websites. Building on evidence generated by a Scotland-wide pilot study, DMW is being rolled out and tested across GM.

Objective: The overarching objectives are to assess whether DMW improves outcomes for patients with T2D in the GM area, to explore the acceptability of the DMW intervention to stakeholders, and to assess the cost-effectiveness of the intervention.

Methods: A mixed methods approach will be used. We will take a census approach to recruitment in that all eligible participants in GM will be invited to participate. The primary outcomes will be intervention-related changes compared with changes observed in a matched group of controls, and the secondary outcomes will be within-person intervention-related changes. The cost-effectiveness analysis will focus on obtaining reliable estimates of how each intervention affects risk factors such as HbA1c and costs across population groups. Qualitative data will be collected via semistructured interviews and focus groups and organized using template analysis.

Results: As of May 10, 2021, a total of 316 participants have been recruited for the quantitative study and have successfully enrolled. A total of 278 participants attempted to register but did not have appropriate permissions set by the general practitioners to gain access to their data. In total, 10 participants have been recruited for the qualitative study (7 practitioners and 3 patients). An extension to recruitment has been granted for the quantitative element of the research, and analysis should be complete by December 2022. Recruitment and analysis for the qualitative study should be complete by December 2021.

Conclusions: The findings from this study can be used both to develop the DMW system and improve accessibility and usability in more deprived populations generally, thus improving equity in access to support for T2D self-management.

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KEYWORDS

diabetes; electronic health; self-management; complex intervention

Introduction

Background

Type 2 diabetes (T2D) is a common long-term condition that affects 7% of the population in the United Kingdom. Compared with people without T2D, those with the condition are at higher risks for a number of complications, including myocardial infarction, stroke, renal replacement therapy, blindness, and major amputation [1,2]. Psychological comorbidities are also common, with depression affecting approximately 1 in 5 adults with T2D and diabetes-related distress affecting approximately 1 in 5 adults with T2D [3]. Self-care (eg, diet, physical activity, and medication adherence) plays a critical role in the management of T2D. Poor self-care can lead to serious diabetes-related complications. Low levels of patient knowledge about T2D contribute to poor glycemic control, and there is evidence in the United Kingdom of major variation in the level of knowledge that people with T2D have about their condition [4].

The management of people with noncommunicable long-term conditions, including T2D, presents a significant challenge to health care systems globally [1]. In the United Kingdom, routine management of T2D is primarily undertaken in primary care settings. There is considerable variation in the quality of diabetes care provided across different services and localities [5]. In Greater Manchester (GM), a mainly urban area in North West England, with a population of 2.8 million people, there are approximately 150,000 adults with T2D. Across GM, there is a poor achievement of national treatment targets for delivering T2D management. Practical and financial challenges exist in delivering interventions aimed at improving T2D knowledge and self-management skills. Current self-management and learning offer in GM is a traditional group-based *structured education* service, and its uptake is low, with attendance rates of approximately 15% [6].

Digital diabetes management systems have the potential to deliver cost-effective self-management support. Diabetes My Way (DMW) is a platform for an open access website (*My Diabetes My Way*) that has been available in Scotland since 2008 to people with diabetes and their carers. Originally, the system included various multimedia resources aimed at improving self-management; from 2010, it offered users access to their clinical data in the form of an electronic personal health record. DMW aims to improve both the outcomes and the experience of people with T2D and provide them with a single care record that is shared with their clinicians. With increased access to and control of their own data, the intention is that patients are able to share decision-making and care planning with clinicians, family, and carers. Through a partner application (MyDiabetesClinical), clinicians can access patient recorded information (with patients' permission) and provide support for clinical decision-making, care planning, and self-management advice.

By 2020, more than 60,000 people have registered for DMW (including approximately one-third of all people with type 1 diabetes). Evaluations of the system have been encouraging, with 90% of respondents to 1 survey of users reporting that engagement with DMW helped them make better use of their consultation, improved their diabetes management and improved their condition-related knowledge [7]. However, despite positive feedback from users in the Scottish cohort, the overall uptake of DMW was low, with only 5.7% of eligible patients having registered by September 2015, steadily moving to less than 20% in 2020. There was also a disproportionately lower use of DMW among older populations, lower socioeconomic groups, and minority ethnic groups [8].

DMW has evolved based on the evidence base generated from the Scottish pilot and now incorporates an app to be used with mobile devices, which includes tailored *push* decision support, including health warnings and reminders to patients and

clinicians. It is this enhanced version of DMW that, as part of the GM Diabetes My Way project, will be offered to all patients with T2D in GM from August 2019 to March 2022. DMW in GM is a collaborative led by the Greater Manchester and Eastern Cheshire Strategic Clinical Networks. Their aim is to provide a more comprehensive self-management and learning offer than is currently available to people with T2D in GM by delivering an enhanced version of DMW across the region. An additional aim is to improve the uptake of the system across all patient groups.

Integrated Digital Interventions Offered Through the DMW Platform

Overview

This work is part of a wider project that aims to test offer a range of other digital supporting services and materials aimed at providing flexible access to support for a wider range of people with T2D. In addition to the DMW platform, this project will offer a range of other digital supporting services and materials through the DMW platform, which will form a package of multiple offerings [9]. The adjunct interventions will include digital support around techniques to change health behaviors (Oviva and Changing Health) and digital support, which aims to assess and improve cognitive functioning (MyCognition).

Oviva offers 12-week personalized, frequent, one-to-one care from a diabetes specialist dietician using behavior change techniques [10]. The app or telephone is also used to maintain regular contact with the dietician. The intervention has been evaluated in 204 people with T2D recruited from practices in London. Engagement with the *Oviva* intervention was associated with a 12.8 mmol/mol reduction in hemoglobin A_{1c} (HbA_{1c}) level, a 4.3 kg reduction in body weight, and a 24% diabetes remission rate [11]. In our study, we will build on this previous work by increasing the number of participants recruited from an ethnically and socially diverse population.

C*hanging Health* offers a 12-week personalized program consisting of a National Health Services (NHS)-digital-approved and Quality Institute for Self-management Education and Training–accredited app supported by a lifestyle coach trained in behavior change techniques [12]. The educational content on the app consists of short videos, articles, and interactive activities on diet and exercise that participants can view at their convenience on their mobile phone or computer. Upon completion of the educational content, participants can book telephone appointments with their lifestyle coaches at the time of their convenience. All participants will receive 100 minutes of coaching (1×20 minutes introductory call, followed by 8×10-minute calls) across the 12 weeks. The intervention was evaluated in 41 people with T2D recruited from practices in London, and engagement with the *Changing Health* intervention was associated with a 4-mmol/mol reduction in HbA_{1c}, a 1.5 kg reduction in body weight, and a 1 mmHg fall in systolic blood pressure [11]. In our study, we will build on this previous work by increasing the number of participants recruited from an ethnically and socially diverse population.

MyCognition is designed to improve cognitive performance, enhance mental resilience, and reduce the impact of stress through cognitive training exercises. The MyCognition intervention can be accessed via a mobile phone or a computer. A web-based assessment tool (taking 15 minutes to complete) provides a personal report on cognitive fitness [13]. A web-based program of personalized educational resources designed to increase cognitive performance follows this. MyCognition also provides access to a personalized game-based training application that can be used for 10-15 minutes per day is also designed to increase cognitive performance. Healthy lifestyle choices are encouraged by the application. Several studies have shown statistically significant improvements in cognitive performance using the application [14-18]. Other interventions designed to improve cognitive performance appear to improve T2D self-management in small studies [18]. In the study we plan to assess the impact of MyCognition on diabetes-related distress in a large cohort of patients with T2D.

Acceptability

Acceptability is an important component of the successful implementation of complex interventions. Evaluations of effectiveness can be undermined by the problems of acceptability to stakeholders (patients, carers, and health service staff). If the key protagonists involved encounter barriers to engagement with the components of an intervention, the outcomes can be affected. Assessment of acceptability to participants (patients and staff) is therefore an important part of the DMW GM evaluation that could provide important insights into usability and uptake of the intervention. This is particularly pertinent, given the findings of the study indicating low and divided uptake [7].

Acceptability has been recognized as an important feature of implementation research in the Medical Research Council guidance for the development and evaluation of complex interventions [9]. This guidance recommends that acceptability is explored both in terms of stakeholders' engagement with the components of an intervention and (for pilot and feasibility studies) with regard to aspects of an associated research study, such as randomization of participants to a control group and completion of outcome measures [19,20] published research into acceptability of complex interventions has increased in number since this guidance was issued. This work has generally focused on barriers and facilitators to engagement [21-23], and *acceptability* has lacked a coherent definition within health services research in terms of its meaning, significance, and theoretical underpinnings. In response, a theoretical framework of acceptability (TFA) has been developed by identifying a relevant and comprehensive theoretical and empirical evidence base. Although this framework is relatively new and has not been widely used and validated, it has been developed from a robust evidence base and offers researchers a useful and unique tool for quantitatively and qualitatively assessing the acceptability of complex interventions [24]. The TFA will be used to inform qualitative data collection and analysis in this study.

Aims and Objectives

The primary aim is to assess whether digital interventions (DMW and the adjunct interventions) improve T2D self-management across GM using quantitative methods. The primary outcomes will be intervention-related changes compared with changes observed in a matched group of people with T2D not using the interventions (controls), and the secondary outcomes will be within-person intervention-related changes.

The secondary aims are (1) to assess cost-effectiveness in comparison with other services, (2) to assess the acceptability of this package of interventions using qualitative methods, and (3) to perform a process evaluation.

Specific Objectives

The specific objectives are listed in Textbox 1.

Textbox 1. Specific objectives.

Diabetes My Way–related objectives

- To assess intervention-related changes in hemoglobin A_{1c} (HbA_{1c}) levels, systolic blood pressure, cholesterol, smoking, and body weight or BMI (compared with controls and within-person changes).
- To assess patient uptake (proportion offered intervention who take it up), engagement (time spent on the web and content viewed), user experience (usability, knowledge, and ability to self-manage), retention (proportion of people interacting with the intervention more than once), completion (proportion of people interacting with the intervention who use it within 2 months of the end date (March 31, 2022), and health care use (clinic and hospital attendance and medication use).
- To assess how Diabetes My Way (DMW) is integrated into care pathways in primary care.

Behavioral interventions (Oviva and Changing Health)–related objectives

- To assess average changes in HbA_{1c} levels, systolic blood pressure, cholesterol, smoking, and body weight or BMI in participants using the intervention (compared with controls and within-person changes).
- To assess patient uptake, engagement, retention, completion, and health care use (defined for DMW above except for completion, which in the case of the behavioral interventions, will be completion of the course).

MyCognition-related objectives

- To assess average within-person changes in *diabetes distress scores*.
- To assess changes in cognition scores.
- To assess changes in referral rates for traditional psychological interventions (compared with controls and within-person changes).

Health economics objectives

- To assess the net financial costs of the intervention for the health system.
- To assess the costs to innovation partners of participating in the Test Beds program.
- To assess the net financial benefits of intervention for the health system.

Process evaluation objectives (addressed in a brief narrative report)

- To describe the process through which the study was designed.
- To explain if the interventions were delivered in line with original plans.
- To explain if the governance arrangements for the intervention were effective and why.
- To describe whether the partnership of National Health Services (NHS) with innovator firms worked as intended and why.
- To describe whether the innovator partnerships resulted in improved technology *pull-through*.
- To describe whether the NHS has received better products or processes as a result of collaboration, testing, or learning.
- To describe the benefits to innovation partners of being part of the Test Bed program.
- To describe whether engagement by each party to the partnership been sufficient and why.
- To describe whether changes were made during implementation to ensure effective delivery of the intervention and why.
- To describe whether there were barriers and facilitators to effective delivery (and uptake of technology or services) and how were they overcome or ensured.
- To describe any unintended consequences that needed to be managed and how was this done.
- To describe to what extent is the intervention likely to be scalable and why.

Acceptability objectives

- To explore acceptability of DMW and any adjunct interventions.
- To explore possible mechanisms of change.
- To explore barriers and facilitators to engagement and sustained use.
- To explore any perceived benefits or drawbacks of using DMW and adjunct interventions.
- To explore and barriers and facilitators to implementation (eg, usability, information technology issues, and skills required).

Methods

A mixed methods approach will be used [25] using a quantitative study with a nested study using qualitative data collection and analysis.

Ethics

Ethical approval has been granted for this work through the appropriate governing body: NHS West Midlands Black Country Research Ethics Committee reference 265621 (qualitative research) and North West—Greater Manchester South Research Ethics Committee reference 261268 (full study).

Quantitative Study

Design

DMW, behavioral interventions (Oviva and Changing Health) and MyCognition will be prospective controlled cohort studies. Intervention-related changes in outcomes such as glucose levels will be assessed after adjusting for prospective changes observed in matched cohorts of patients not receiving any intervention.

Participants and Recruitment

We will take a census approach to recruitment in that all eligible participants in GM will be invited to participate. Identification of potential participants will take place primarily through searches of primary care practice databases to identify patients with T2D. Practice searches will be facilitated by the staff of the Greater Manchester Diabetes Clinical Research Network whenever possible. Letters from the practice, in most cases, will make initial contact with potential study participants. In some cases (according to practice preference), a text message from the practice to the patient or an email sent from the practice to the patient will be used. Posters advertising the study will be made available in practice clinics and waiting rooms.

We expect that a small number of patients with T2D will be identified through their clinical teams based in hospital outpatient clinics (most people with T2D are managed in primary care) and those attending Allied Health clinics (eg, eye screening and podiatry).

Inclusion and Exclusion Criteria for the Main Intervention (DMW)

The inclusion and exclusion criteria for the main intervention are presented in Textbox 2.

The goal will be to offer DMW to all 140,000 people with T2D in GM, and a clinician-facing version will be offered to all GM primary care staff. Behavioral interventions (Oviva or Changing Health) will be offered to a total of 600 patients each. MyCognition cognitive assessment will be offered to all DMW participants, and the intervention on cognitive function will be offered to the first 600 participants. Other digital interventions will be offered to DMW participants through the DMW interface as shown in Figure 1. Participants will be offered access to *additional digital interventions* through DMW.

Textbox 2. Inclusion and exclusion criteria for the main intervention.

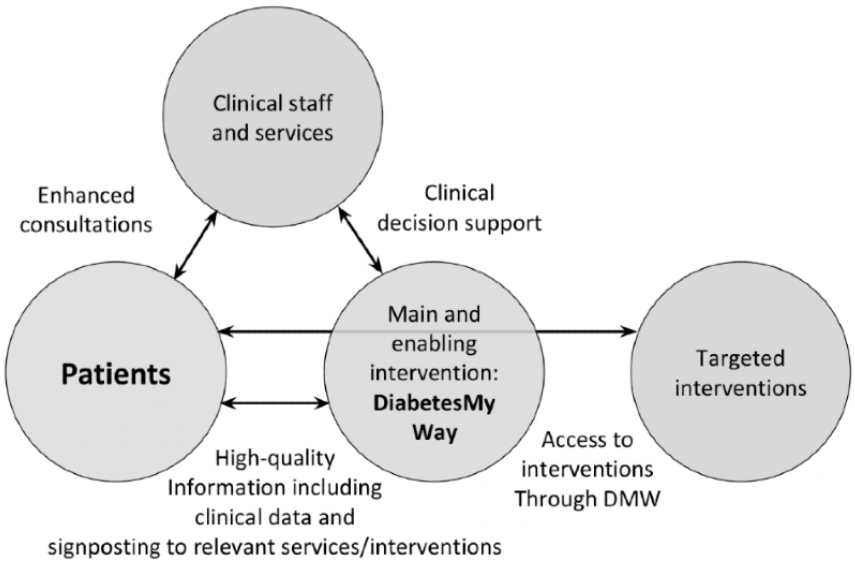
Inclusion criteria

- Age ≥18 years
- Type 2 diabetes (as determined by primary or secondary care records)
- Self-certified understanding of written English
- Registered with general physician in Greater Manchester

Exclusion criteria

- Self-reported *severe mental illness not currently managed by a physician*.

Figure 1. Diabetes My Way: The Main and Enabling Interventions.



Enrollment and Informed Consent

Enrollment to the DMW intervention will be facilitated through the website, and patients will be directed to the participant information sheet. Providing patients are aged ≥18 years and have a diagnosis of T2D, they will be able to express their interest in taking part in the study by submitting their contact details via the DMW website. Patients will register for web-based services via their general practitioner (GP) who will confirm their identity by checking their documentation. Patients are required to use these web-based service codes to register for DMW and answer a number of inclusion and exclusion criteria. Once registered (and where they match the criteria), the study consent form will be introduced. If and when completed and submitted, the patient's account is activated, and they are enrolled in the study. When registered, but not matching the study criteria, the patient will be given access to DMW, but not entered into the study or consent process.

Enrollment to other digital interventions will also occur via the DMW website. On the basis of the inclusion and exclusion criteria, participants enrolled and using the DMW intervention will be invited to take part in additional substudies involving an additional digital intervention (Oviva or Changing Health allocated to alternate eligible participants or MyCognition). The above procedure for communicating participant information and obtaining informed consent will be repeated.

We will invite participants to enroll with either Oviva or Changing Health behavioral interventions until 600 have attended each intervention. These interventions will be offered to alternate participants enrolling with DMW, ensuring that the numbers receiving each intervention remain similar.

All DMW participants will be provided with the option of completing the MyCognition web-based cognitive assessment and will be offered the MyCognition intervention until 1000 have completed the intervention. When 1000 people have completed the intervention, DMW participants will continue to be offered the option of completing the MyCognition web-based cognitive assessment but will not be offered the MyCognition intervention. Participants will be invited to complete the MyCognition web-based cognitive assessment every 3 months during the study (a maximum of 3 times). Those completing these assessments, but without receiving the intervention, will act as a control group.

DMW study participants will be invited to access the other interventions through a notice shown at the top of the home dashboard page of the DMW. Opportunities to enroll will be available instantly upon successful log-in and acceptance of the study criteria.

Comparison Group

Within the short time frame available for the study, a randomized controlled trial will not be possible; therefore, the effectiveness of the interventions will be compared with groups of people choosing not to take up the offer of interventions. Data on this comparison group will be sourced from NHS Digital as part of the national GP Data for Planning and Research program. The comparison group will be sourced from patients registered in GM, the other inclusion and exclusion criteria being applied. Controls (not using the intervention) will be matched (up to 10:1) with study participants on age (+2 or −2 years), gender, ethnicity, and general practice. When appropriate, we will increase the number of controls per participant to enable additional matching on baseline levels of outcome measures, such as HbA_{1c} levels. Where there are clinically important differences between participants and controls in relation to other characteristics such as prevalent cardiovascular disease, we will include these variables as covariates regression models.

Outcomes

Overview

The primary outcomes will be intervention-related changes compared with changes observed in a matched group of controls, and the secondary outcomes will be within-person intervention-related changes (Textbox 3).

Textbox 3. Primary and secondary outcomes.

Diabetes My Way, Oviva, and Changing Health behavioral interventions

- Primary outcome
  - Change in hemoglobin A_{1c} levels [26,27].
- Secondary outcomes
  - Changes in body weight or BMI, blood pressure, cholesterol, and smoking [28].
  - Uptake, engagement, user experience, retention, completion [29], and health care use (clinic and hospital attendance and medication use).
  - Impact of primary care staff on knowledge, skills, and confidence in diabetes management [30].
  - Modifying effect of cognitive function [31].

MyCognition

- Primary outcome
  - Change in diabetes distress score [32-34].
- Secondary outcomes
  - Change in cognition scores.
  - Changes in referral rates for traditional psychological interventions compared with controls and within-person changes.

User Engagement With Digital Intervention

A range of metrics will be gathered remotely with no additional burden on the participants. Measures will include the number of users offered the intervention, number of users expressing an interest in the intervention, number of active users, number of inactive users (registered but not logged onto the intervention), number of users and percentage who have viewed all learning content, number of users and of participants who have booked a coaching session (for behavioral interventions), number of coaching sessions attended, and number and percentage of participants completing digital structured education (for behavioral intervention).

Overview of Data Items and Source of Data by Intervention in the Quantitative Study

Diabetes My Way

To evaluate the DMW intervention, the University of Manchester will obtain participant data from GP records via DMW, between April 1, 2016, and March 30, 2022. These data will include the following: age, sex, ethnicity, GP postcode (to assess the degree of socioeconomic deprivation) [35], diabetes type and duration, blood pressure, cholesterol, creatinine, estimated glomerular filtration rate (eGFR), smoking and body weight, height, BMI, medication, diabetes clinic attendance in primary care, and hospital visits including emergency visits.

Participant data from DMW or NHS Digital will also include ethnicity (self-provided, sometimes unreliable from primary care due to missing data), user experience or usability, service use (medication, diabetes clinic attendance in primary care, and hospital visits including emergency visits), and website activity.

Data on control participants (not using DMW) will be obtained from NHS Digital, from April 1, 2016, to March 30, 2022, and will include the following: age, sex, ethnicity, GP postcode (to assess socioeconomic deprivation), diabetes type and duration, blood pressure, cholesterol, creatinine, eGFR, smoking and body weight, height, BMI, medication, diabetes clinic attendance in primary care, and hospital visits including emergency visits.

Behavioral Interventions: Oviva and Changing Health

To evaluate the behavioral interventions, Oviva and Changing Health, the University of Manchester will obtain participant and control data from GP records via DMW and NHS Digital for the period April 1, 2016, to March 30, 2022, as described for DMW. Data on user experience or usability from Oviva and Changing Health participants will be transferred to the University of Manchester via DMW.

MyCognition

To evaluate the MyCognition intervention, the University of Manchester will obtain participant and control data from MyCognition via DMW, from GP records via DMW, and from NHS Digital for the period April 1, 2016 to March 30, 2022. Participant data transferred to the university via DMW will include cognition scores, diabetes distress scores (administered as a web-based questionnaire to participants), and usability data.

Clinical and Biochemical Data in Study Participants

Overview

Clinical data collected by health care professionals during routine clinical care will enter the appropriate clinical management system (eg, GPs using the Elton Medical Information Systems health primary care electronic health record). Pseudonymization is a technique that replaces or removes all information that can be used to identify an individual. The process involves replacing names or other identifiers that are easily attributed to individuals with a study reference number. DMW will provide pseudonymized data on study participants and controls to the University of Manchester.

Clinical Data

The clinical data of interest includes age, sex, ethnicity, socioeconomic deprivation, diabetes type, weight, height, BMI, HbA_{1c}, blood pressure level, diabetes medication, blood pressure medication, lipid lowering therapy, and service use data (attendance and nonattendance at diabetes clinics and emergency hospital visits) will be obtained from primary care records. Ethnicity will be taken from self-reported data provided at enrollment with DMW (White, South Asian, Black, mixed, or other, if *other* participants will be invited to specify using text). Socioeconomic deprivation will be assessed from the GP postcode to reduce the likelihood of participants being identified.

Biochemical Data

All blood sampling (eg, HbA_{1c} and serum lipids) will be conducted via routine clinical care. Participants who did not have a blood sample taken within the preceding 3-6 months will be advised through a message on the DMW website to arrange a diabetes review (weight, blood pressure, smoking status, medication review, HbA_{1c}, and lipids) with their practice team at the time of enrollment in line with standard clinical care according to National Institute for Health and Care Excellence (NICE) guidance 28 [36] Participants will be advised to have repeat weight, blood pressure, medication review, and blood tests every 3-6 months in line with standard clinical care according to NICE guidance 28 [36]. Study participants will not be subject to any investigations outside of their routine care unless clinically indicated. Blood test results will be transferred to DMW from the primary care record.

Duration of Data Access

The University of Manchester will request primary care data on study participants for the period April 1, 2016, to March 30, 2022, through DMW This will enable a 3-year assessment of *baseline* levels of risk factors such as HbA_{1c} and blood pressure before study commencement (July 2019), and up to the end of the intervention (March 31, 2022).

Clinical and Biochemical Data From NHS Digital in Participants and in Controls not Providing Consent

Our study involves comparing intervention-related changes in risk factors, such as HbA_{1c} levels, in study participants with the changes occurring in a control patient cohort not receiving the intervention.

NHS Digital will use their General Practice Extraction Service (GPES) to provide GP data on all patients with T2D across GM (approximately 160,000 people) between April 1, 2016, to March 31, 2022. The core data items will include age, sex, ethnicity, GP postcode (to assess socioeconomic deprivation), diabetes type and duration, blood pressure, cholesterol, creatinine, eGFR, smoking and body weight, height, BMI, medication, diabetes clinic attendance in primary care, and hospital visits including emergency visits.

To distinguish between DMW participants and nonparticipants in the GPES data, the following steps will be taken:

- DMW will supply NHS Digital with details of DMW participants including NHS numbers, GP practice with which the participant is registered, DMW generated study ID, and whether the participant is using Oviva, Changing Health, or MyCognition.
- NHS Digital will use NHS numbers of participants to create a DMW participant flag within the GPES data for GM. NHS numbers will then be removed.
- NHS Digital will supply the University of Manchester with GPES data for patients from GM with T2D.
- University of Manchester will store and analyze these data in accordance with NHS Digital requirements and Data Sharing Agreement.

Our study design requires that control participants be matched to participants receiving the intervention on age, sex, ethnicity, and socioeconomic deprivation (defined by GP postcode). Therefore, we require information on these 4 characteristics, in addition to the clinical and biochemical data. Socioeconomic deprivation level will be assessed from the GP postcode to minimize the risk of patients being identified. The University of Manchester will not receive any information that will enable DMW participants or control participants to be identified.

Analysis

Overview

First, the generalizability and relevance of the intervention in the context of GM will be assessed. We will descriptively compare participants in the interventions to other populations: those who did not participate, the population of GM, and the population of England. For the comparison to those who did not take up the intervention, we will use data on age, sex, ethnicity, residence location socioeconomic deprivation quintile (2019 Index of Multiple Deprivation) and risk factors (from their electronic record) for a comparison with the participants. For the GM and England comparisons, we will compare patients based on age, sex, risk factors, and comorbidities using data sourced from NHS Digital.

Second, we will examine engagement with the intervention (as quantified by relevant metrics in the app, eg, visits and time spent), and descriptively assess how it varies across age groups, sex, ethnic groups (South Asian, Black, mixed, White, and other populations) and socioeconomic deprivation quintiles. A multiple linear regression model will be used to more formally evaluate the association between the variables listed above (age, sex, ethnicity, and socioeconomic deprivation) and engagement.

Third, we will aim to use quasi-experimental methods to evaluate the effectiveness of the intervention on each outcome by comparing prospective changes in outcomes between matched participants and controls and by performing pre- versus postintervention comparisons in participants only. Matching will be performed using the caliper method, which is a modification of the nearest neighbor matching procedure that imposes a tolerance on the difference in cohort characteristics [37]. Here, we will combine calipers relating to age range (+2 or −2 years) and with exact match of gender, ethnicity, and general practice. In the matched group approach, participants receiving the interventions will be randomly matched to nonparticipants on age, sex, ethnicity, and general practice (as a proxy for socioeconomic deprivation).

Where there are differences between participants and controls in relation to matched characteristics or other characteristics such as prevalent cardiovascular disease, we will include these variables as covariates regression models.

In the presence of time series data, we will use an interrupted time series design for each outcome of interest, which takes into account the preintervention trends of the outcome as well as the information on controls and quantify the effect of the intervention on future outcome levels. If only 2 time points are available (eg, before and after the intervention), we will use a simple linear regression model with clustered errors or a paired 2-tailed *t* test to compare means in each outcome at the 2 time points.

For example, for the main outcome, change in HbA_{1c} levels, we will compare changes from baseline (defined as April 1, 2016, to July 1, 2019) during the intervention period (July 1, 2019, to March 31, 2022) in matched participants and controls after adjusting for clinically significant differences in baseline weight, blood pressure, cholesterol, creatinine, cardiovascular disease, and smoking.

If the numbers of cases and controls are large, we will explore effect heterogeneity in subgroup analyses (as separate models or using interaction terms in the main models described above) by ethnicity, age groups, socioeconomic deprivation quintile, cognitive function (assessed by MyCognition), and level of engagement with digital interventions.

Missing Data

The proposed analysis allows for missing data values. We will use clinical judgment to explore possible mechanisms of missingness, and we will consider including multiple imputation in the primary analysis, irrespective of levels of missingness, assuming a missing not at random scenario is unlikely (although multiple imputation has been found to perform better than complete case analysis, in a simple missing not at random scenario as shown) [38].

Sample Size Calculations

DMW, Oviva, and Changing Health Evaluations

The primary outcome for participants and controls receiving usual care is the HbA_{1c} level after the intervention. With a ratio of 1:10 for participants to controls and assuming an SD of 15 mmol/mol in HbA_{1c} levels [39], a total of 86 participants and 430 controls provides 80% power to detect an HbA_{1c} level difference in means of 5 mmol/mol (5% significance level), which is considered the smallest clinically significant HbA_{1c} change. Assuming that 90% of participants provide data after the intervention, this requires a total of 96 participants.

Therefore, we aim to recruit at least 288 participants (96×3) to DMW from which recruitment to the 2 behavioral interventions (Oviva, n=96 and Changing Health, n=96) will occur.

If the required sample size for any intervention is not achieved, appropriate consideration will be given to the interpretation of the results in light of the large number of objectives and outcomes.

MyCognition Evaluation

The primary outcome is the postintervention diabetes distress score (DDS). Assuming an SD of 0.92 for DDS [34], 89 patients and 445 controls (5% significance level) provide 80% power to detect a difference in mean DDS of 0.3. Assuming 90% of participants provide data after the intervention, this requires a total of 99 participants.

Economic Evaluation

Short-term Health Benefits and Consequences to Costs

In the short term, economic evaluation will focus on the cost-effectiveness of DMW measured over the intervention period (up to December 2020). Data on changes in outcomes from the quantitative evaluation, such as HbA_{1c} levels, will be compared against costs across population groups. Relevant costs will be direct NHS costs assessed from intervention-related costs and changes in routine health care use, as assessed from rates of primary care consultations and hospital attendance during the observation period. The unit costs of delivering traditional face-to-face behavior change interventions and psychological interventions are available in GM, enabling meaningful cost comparisons. Further unit costs will be sources of NHS reference costs and the unit costs of health and social care.

Long-term Health Benefits and Consequences to Costs

Short-term improvements in diabetes management can have longer-lasting impacts on health and costs. Expected reductions in rates of diabetes-related complications and death, by modifying cardiovascular risk factor levels, will be modeled using the United Kingdom Prospective Diabetes Study outcomes model [40]. Differences in quality-adjusted life years between DMW patients and those in the control group will be estimated.

Qualitative Study

We will structure the interviews and analysis in relation to the TFA [24]. The TFA is a multifaceted construct that consists of seven domains:

- Affective attitude (how an individual feels about an intervention).
- Burden (the perceived amount of effort it takes to engage with an intervention).
- Ethicality (the extent to which an intervention is congruent with an individual's belief system).
- Intervention coherence (how an individual understands the aims of an intervention and how it works).
- Opportunity costs (the extent to which an individual needs to compromise existing benefits or values to engage with the system).
- Perceived effectiveness (how well an intervention achieves the desired outcomes).
- Self-efficacy (an individual's level of confidence that they can engage in the behaviors required to participate in an intervention).

Participants and Setting

Patients

The inclusion criteria for patients are presented in Textbox 4.

We will conduct up to 20 interviews with patients currently using DMW and 10 interviews with patients choosing not to use DMW (N=30; identified by potential participant's clinical care team). Following the provision of information relating to the supporting interventions, potential participants will be asked by members of the clinical care team for permission to pass on their contact details to the research team who will then contact the participant directly to obtain informed consent. Purposive sampling will be used to capture a sample of participants representing a range of ethnic and socioeconomic backgrounds. Participants will be offered a choice of interview settings: at the patient's home or in a private room at either the University of Manchester, the Manchester University NHS Foundation Trust Diabetes, Endocrinology and Metabolism Centre or at a mutually agreed public location. Alternatively, participants can choose to interview over the telephone or through videoconferencing.

Textbox 4. Inclusion criteria for patients in the qualitative study.

Inclusion criteria

- Age >18 years.
- Diagnosis of type 2 diabetes (as determined by invite to attend a specialist type 2 diabetes clinic, secondary care sites) or general practitioner records (for general practitioner practices).
- Registered with a general practitioner in Greater Manchester.
- Able to understand written English.
- No self-reported severe mental illness not currently managed by a physician.

Clinicians

The inclusion criteria for clinicians are presented in Textbox 5.

We will conduct up to 15 interviews with clinicians in groups stratified by ethnicity and indication of socioeconomic deprivation according to the lower super output area of the general practice or outpatient clinic. We will also aim to recruit clinicians working in a variety of roles. On the basis of conversations and meetings with the Greater Manchester Clinical Research Network, we anticipate the following key roles: (1) *general practice* (GPs or practice nurses with a specialist interest in diabetes) and (2) *hospital outpatient clinics* (consultants, specialist diabetes nurses, and health care assistants).

We will also conduct 2 focus groups, 1 with each participant group (patients and practitioners) involving 6-10 participants in each group (N=12-20). We will use the focus groups to further explore any issues of contention or special interest arising from the interviews in a peer group setting. The focus groups will take place in a private room at the University of Manchester.

All interviews and focus groups will be audio recorded and transcribed by an independent contractor using an intelligent verbatim approach. The independent contractor has been approved by the University of Manchester and is aware of guidelines relating to good clinical practice and confidentiality. We anticipate that the interviews will take between 30 and 60 minutes and focus groups will take approximately 60 minutes. Experienced interviewers with a background in psychology will conduct the interviews (JG and JB). Interviewers will attempt to make the interview conversational and informal, while remaining mindful of contextual features, such as power structures and professional boundaries. Data collection will be based on an interview schedule that allows for flexibility in pursuing topics of interest. Topic guides for the interviews have been developed based on the TFA [23] and the findings from the Scottish research [7,8]. We will develop topic guides for the focus groups based on findings from data generated by the interviews.

Textbox 5. Inclusion criteria for clinicians.

Inclusion criteria

- Age ≥18 years.
- A registered health care practitioner working with patients diagnosed with type 2 diabetes who have been offered Diabetes My Way intervention in Greater Manchester.
- Self-certified understanding of written English.

Recruitment to the qualitative study

Patients

Overview

Patients will be recruited from 8 GP practices and 2 hospital outpatient clinics across the GM region. When engaging with patients who meet the inclusion criteria, clinicians (GPs, practice nurses, specialist diabetes nurses, health care assistants, and consultants) will invite potential participants to provide consent for the research team to contact them to provide more information about participating in the study. If patients provide consent to contact, clinicians will give them a patient information sheet to take away. Consent to contact forms will be stored safely and securely by a named individual at each recruitment site.

Interviews

A member of the research team will collect consent to contact forms directly from the recruiting practices and clinics weekly and contact the patients directly using the information provided, ensuring that a minimum of 24 hours has passed since consent to contact was given. The researcher will ensure that the patient has understood the participant information, answer any questions relating to participation in the research, and if the patient agrees, will then arrange a time, date, and location for the interview to take place. When interviews have been conducted with 20 patients or data saturation reached, this process will end.

Focus Groups

When enough participants have been recruited to ensure data collection using interviews is complete, the process will be repeated for recruitment to the focus groups until 10 patients have taken part, at which point recruitment will cease.

Clinicians

Interviews

In total, 15 clinicians will be recruited in three different ways:

1. Via the research active clinics assisting with patient recruitment.
2. At the bimonthly GM strategic clinical network for diabetes meeting.
3. At the launch event for the DMW system.

In each of the above settings, a member of the research team will identify key clinicians who are aware of DMW and are engaging with or are likely to engage with patients who are using or have been offered the intervention. The researcher will provide the clinician with a participant information sheet and obtain consent to contact. After a minimum period of 24 hours, the researcher will contact the clinician, ensure that they have understood the participant information, answer any questions relating to the research and then arrange a time, date, and location for the interview to take place. When interviews have been conducted with 15 clinicians or data saturation is reached, this process will end, and we will begin recruitment to the focus groups.

Focus Groups

When enough participants have been recruited to ensure data collection using interviews is complete, the process will be repeated for recruitment to the focus groups until 10 patients have taken part, at which point recruitment will cease.

Informed Consent

Informed consent will be obtained from all participants by an experienced member of the research team immediately before the interview or focus group taking place, at which point participants will have the opportunity to ask further questions about the study. For face-to-face interviews and focus groups, written consent will be obtained. For telephone interviews, the researcher will read aloud the consent form and consent will be provided verbally over the telephone. This exchange will be audio recorded and later transcribed by an independent company, providing a record of the consent process.

Analysis

Data will be analyzed thematically using template analysis [41]. A distinct feature of template analysis is the structured development of a hierarchically organized coding template. This coding template is initially developed based on subset of data (eg, a selection of transcripts that incorporate a range of accounts—in this work, this will allow for analysis of interview data to be undertaken while data collection remains ongoing), then applied to further data and revised and refined as necessary. Codes are organized into meaningful clusters (including hierarchical relationships between codes in a cluster and lateral relationships across clusters) and a full thematic structure developed iteratively.

A further feature of template analysis is that it permits the use of *a priori* themes—themes that are identified in advance of coding as likely helpful or relevant to the analysis but which are understood as tentative and may be refined or discarded if they do not prove to be useful or appropriate. As in previous work that used the constructs of a theoretical model as *a priori* themes to facilitate initial coding [42], in this work (reflecting our particular research aims), the constructs of the TFA [23] will be drawn on as *a priori* themes to initially focus our coding.

We will use established quality-checking procedures, including critical scrutiny and constant comparison of coding. Two researchers will independently code a subset of interviews, discuss to reach consensus, and generate a first version coding template, encompassing both *a priori* and emerging themes. Once the provisional coding template is discussed and agreed, the researchers will then independently apply the coding template to further data in blocks of 5 interviews, then again meet to similarly discuss and reach full consensus. This iterative process will produce a final version template encompassing all relevant materials, which will then be applied to the full data set. At each stage of the analysis, the full research team will check the validity and consistency of coding and agree upon the final thematic framework. An audit trail will be kept, and the staged analysis process will ensure both coding and interpretation are regularly cross-checked.

Process Evaluation

In collaboration with the digital intervention provider teams, the study team will provide a narrative report on the following observed experiences and outcomes:

- The process through which the study was designed.
- Explore whether the interventions were delivered in line with original plans.
- Explore whether governance arrangements for the intervention were effective and why.
- Explore whether the partnership of NHS with innovator firms worked as intended and why.
- Explore whether the innovator partnerships resulted in improved technology use.
- Explore whether the NHS has received better products or processes as a result of collaboration, testing, or learning.
- Explore any benefits to innovation partners of being part of the Test Bed program.

- Explore whether engagement by each party to the partnership been sufficient and why.
- Describe any changes made during implementation to ensure effective delivery of the intervention and why these were made.
- Explore barriers and facilitators to effective delivery (and uptake of technology or services) and how were they overcome or ensured.
- Report any unintended consequences that needed to be managed and how this was done.
- Explore scalability of the intervention.

Patient and Public Involvement

DMW has had patients involved in every stage of the design, prototyping, development, implementation, and review phases of the intervention. The company receives regular feedback from patients via email, secure messaging, and web-based surveys to ensure that the intervention is genuinely patient-centered and holds regular steering group meetings, including representation by patients. In addition, all new product development work involves users. This is usually conducted through design workshops and user prototype testing in the field. Early feedback (and ongoing feedback on rollout) continues to drive changes in the DMW product range. Furthermore, our partner services engage in ongoing dialogue with its users. A person living with diabetes will be enrolled in the study steering group.

Oviva Diabetes Support conducts patient and public involvement through its continuous patient feedback via surveys, which is reviewed monthly, and changes to the intervention are made as appropriate.

Changing Health sends out feedback surveys to all users at baseline and subsequently every 3 months. The data from these surveys are used to identify potential issues and to continually refine their programs. In addition to this formal channel, *Changing Health* also has a presence on social media (Facebook and Twitter) through which they share user stories and original content of interest to the public.

Dissemination

We will take the following steps to ensure that results are useful to the NHS and the global clinical community: *ensure effective dissemination of results, such as* (1) deliver conference presentations; (2) peer-review publications; (3) run an engagement workshop on *digital solutions to improve diabetes self-management*, which will involve senior clinicians, NHS England, public health staff, diabetes charities, academics, patients, and the general public; (4) social media postings; and (5) give radio and television interviews and p*resent the results in ways that create maximum utility for clinical users (*eg, clearly describe the practical steps necessary to introduce the system). Participants will be provided with a summary of the main study findings through the DMW website.

Results

As of May 10, 2021, a total of 316 participants have been recruited for the quantitative study and have successfully enrolled. A total of 278 participants attempted to register but did not have appropriate permissions set by the GPs to gain access to their data. A total of 10 participants have been recruited for the qualitative study (7 practitioners and 3 patients). An extension to recruitment has been granted for the quantitative element of the research, and analysis should be complete by June 2022. Recruitment and analysis for the qualitative study should be complete by June 2021.

Discussion

Principal Findings

The GM DMW project seeks to implement innovative solutions to clinical and system-wide challenges in learning and self-management in T2D. The overall aim of the intervention is to deliver optimized clinical care, and the electronic provision of patients' medical information to patients and practitioners in a timely and accessible way should contribute to achieving this aim. Patients currently struggle to effectively self-manage, and clinicians are limited by not having all relevant information in a unified care record. Furthermore, there is major variation in the level of knowledge that patients have about their diabetes, major variation in the quality of diabetes care across general practices in GM, and major practical and financial challenges in delivering behavioral interventions that support healthier lifestyles and major blocks in clinical care because of diabetes-related psychological distress. These factors are all compounded by low clinic and structured education attendance rates in some patient groups.

There is a clear need to improve patients' ability to self-manage T2D, and the DMW electronic platform offers an accessible alternative to the current, mostly unsuccessful method of traditional classroom-style education. DMW has been proven popular with patients and practitioners in Scotland; however, uptake across Scotland has been ≈13% (in 2020), with disproportionately lower use in older populations, lower socioeconomic groups, and minority ethnic groups and risks perpetuating or augmenting health inequalities [8]. Exploring issues around the acceptability of the implementation of DMW in GM with both patients and practitioners could offer important insights into possible reasons for the lack of engagement and uptake in certain populations. The findings from this study can be used both to further develop and enhance the DMW system and to improve accessibility and usability in more deprived populations, thus improving equity in access to support for T2D self-management.

If the evaluation demonstrates that DMW and the linked digital behavioral interventions (Oviva and Changing Health) can improve self-management and risk factor levels in people with T2D, then this could lead to a step-change in diabetes management across the NHS and wider. If the economic analysis shows cost savings compared with traditional care, then this would lead to global changes in health care delivery. Therefore, the clinical, psychological, social, economic, and health care resource benefits observed through this application could have a global reach. Furthermore, other adjunct offerings could impact clinical outcomes. If MyCognition improves psychological health in people with T2D, then these data could be used to promote this approach being rolled out across the

NHS, which could reduce the huge public health burden of psychological illness associated with T2D.

Strengths and Limitations

The main strength of the qualitative study is that we will draw on the experience of a wide range of stakeholders with the aim of capturing the most diverse possible range of perspectives to inform the development of DMW and improve the overall number of patients choosing to engage with the intervention.

One of the limitations of the study is that we will not be recruiting patients who do not understand written English. This may result in a biased patient sample, which is not representative of the diverse population of GM, where an estimated 200 different languages are spoken. However, this may provide a topic for future research. Another limitation is that the study will not formally evaluate the influence of digital exclusion on study outcomes. We anticipate differences in digital literacy and the factors that influence this between participants and controls. However, our matching process, followed by multivariable regression that controls for clinically important covariates not included in the matching process, may help to reduce the influence of digital exclusion. We expect that the results of the qualitative work may provide further insights into the role that digital exclusion might have in the results.

Conclusions

Exploring the acceptability of DMW will provide valuable insight into how stakeholders engage with the intervention and how to improve implementation and uptake within diverse populations. It will compliment a larger body of quantitative research on efficacy, generated by the wider GM Test Bed study and the mixed methods Scottish research [7,8]. By using the TFA [23], an evidence-based framework for researching the acceptability of complex interventions, we will also add to a wider body of evidence around the utility of this tool and increase the transparency and replicability of our findings.

If the use of DMW by patients with diabetes has major clinical, societal, and economic benefits, this will be a global stimulus for research in this area. Researchers and health care managers will be interested in the context in which the interventions were delivered (patients and health care system) and the methods of implementation adopted in the Test Bed. The research will have implications for pharmaceutical companies and other companies involved in producing treatments, interventions, and digital interventions in diabetes care.

This study has multiple potential impacts. In 2011, diabetes consumed 10% (£10 billion; US $13.25 billion) of the NHS budget, and when indirect costs were included (mortality data, sickness data, loss of productivity, and informal care), the cost was estimated at £23 billion (US $30.47 billion). If digital interventions have only a small impact on the self-management of T2D and its complications, then the absolute economic benefits may still be large. The largest cost of managing diabetes comes from the cost of managing its complications. If interventions targeting the management of cardiovascular risk (DMW and behavioral interventions primarily) are successful, then this could have major financial benefits in the United Kingdom and globally.

The treatment of T2D is central to the government's 2011 National Service Framework (NSF) for diabetes. Our research addresses key NSF standards. The NSF standard 4 states the following:

> *All adults with diabetes will receive high-quality care...to optimise the control of their blood glucose, blood pressure and other risk factors for developing the complications of diabetes.*

If our research shows the expected outcomes, then we will work with leading figures in the Department of Health, Public Health England, NHS England, and NICE to ensure that future policies and guidance include appropriate reference to our work. This project also maps to the aims of (1) the NHS 10-year plan (2019), (2) the NHS England Digital Health Strategy, (3) the National Information Board Personalised Health and Care 2020 plan, and (4) the *State of the Nation* report (2016) produced by Diabetes UK.

Digital interventions have the potential to transform the self-management of T2D and deliver major clinical, psychological, and economic benefits. This Test Bed project aims to assess the impact of a range of digital interventions delivered through DMW in an ethnically and socially diverse group of people with T2D across GM.

Note on the COVID-19 Pandemic

The plans in relation to the study participants have not been modified because of the COVID-19 pandemic. We expected digital interventions to be effective in improving self-care. However, in the context of the COVID-19 pandemic, it is clear that digital interventions could be even more valuable to people with diabetes because access to face-to-face primary care interventions for people with T2D has been extremely limited and may remain so for many months.

Before the pandemic, the study team was in contact with NHS Digital to obtain data on control participants through the Data Access Request Service. The COVID-19 pandemic provided an alternative route to obtaining these data from NHS Digital through a notice under Regulation 3 (4) of the National Health Service (Control of Patient Information Regulations) 2002. This regulation requires NHS Digital to share confidential patient information with organizations entitled to process this under Control of Patient Information Regulations for COVID-19 purposes.

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test combinations of digital technologies with pathway redesign in real-world settings [43]. The goal is to use the potential of digital technologies to positively transform the way in which health care is delivered to patients and caregivers.

Conflicts of Interest

DJW is a cofounder and shareholder of MyWay Digital Health, who run the Diabetes My Way platform. DB is an employee of MyWay Digital Health. NM has received honoraria for various educational activities from the following companies: Novo Nordisk, Boehringer Ingelheim, Napp, Abbott, Sanofi, MSD, Astra Zeneca, Eli Lilly, and Takeda. SGC is a cofounder, shareholder and director of MyWay Digital Health who are the developers of the GM Diabetes My Way software. M Ratto is currently an employee of the Beingwell Group, the business providing the digital health intervention MyCognition.

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Abbreviations

DMW: Diabetes My Way
eGFR: estimated glomerular filtration rate
GM: Greater Manchester
GP: general practitioner
GPES: General Practice Extraction Service
HbA_{1c}: hemoglobin A_{1c}
NHS: National Health Services
NICE: National Institute for Health and Care Excellence
NSF: National Service Framework
T2D: type 2 diabetes
TFA: theoretical framework of acceptability

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Protocol

Remote Follow-up of Self-isolating Patients With COVID-19 Using a Patient Portal: Protocol for a Mixed Methods Pilot Study (Opal-COVID Study)

David Lessard[1,2,3*], PhD; Kim Engler[1,2*], PhD; Yuanchao Ma[1,2,3,4], MSc; Adriana Rodriguez Cruz[1,2,3,5], PhD; Serge Vicente[2,6], PhD; Opal-COVID-19 Patient Expert Committee[2*]; Nadine Kronfli[1,3], MD; Sapha Barkati[3], MD; Marie-Josée Brouillette[3,7], MD; Joseph Cox[3], MD; John Kildea[8], PhD; Tarek Hijal[9], MD; Marie-Pascale Pomey[10], MD; Susan J Bartlett[11], PhD; Jamil Asselah[12], MD; Bertrand Lebouché[1,2,3,5], MD, PhD

[1]Research Institute of the McGill University Health Centre, Centre for Outcomes Research & Evaluation, Montreal, QC, Canada

[2]See Acknowledgments

[3]Department of Medicine, Division of Infectious Diseases and Chronic Viral Illness Service, McGill University Health Centre, Montreal, QC, Canada

[4]Department of Mechanical Engineering, École Polytechnique de Montréal, Montreal, QC, Canada

[5]Department of Family Medicine, Faculty of Medicine, McGill University, Montreal, QC, Canada

[6]Department of Mathematics and Statistics, Université de Montréal, Montreal, QC, Canada

[7]Department of Psychiatry Faculty of Medicine, McGill University, Montreal, QC, Canada

[8]Medical Physics Unit, McGill University, Montreal, QC, Canada

[9]Department of Radiation Oncology, McGill University Health Centre, Montreal, QC, Canada

[10]Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada

[11]Department of Medicine, Divisions of Experimental Medicine, Clinical Epidemiology, Respiratory Medicine, and Rheumatology, McGill University, Montreal, QC, Canada

[12]Department of Medicine, Division of Medical Oncology, McGill University Health Centre, Montreal, QC, Canada

[*]these authors contributed equally

Corresponding Author:
Bertrand Lebouché, MD, PhD
Research Institute of the McGill University Health Centre
Centre for Outcomes Research & Evaluation
5252 de Maisonneuve West
Montreal, QC, H4A 3J1
Canada
Phone: 1 514 934 934 ext 31342
Email: bertrand.lebouche@mcgill.ca

Abstract

Background: People with COVID-19 are instructed to self-isolate at home. During self-isolation, they may experience anxiety and insufficient care. Patient portals can allow patients to self-monitor and remotely share their health status with health care professionals, but little data are available on their feasibility.

Objective: This paper presents the protocol of the Opal-COVID Study. Its objectives are to assess the implementation of the Opal patient portal for distance monitoring of self-isolating patients with COVID-19, identify influences on the intervention's implementation, and describe service and patient outcomes of this intervention.

Methods: This mixed methods pilot study aims to recruit 50 patient participants with COVID-19 tested at the McGill University Health Centre (Montreal, Canada) for 14 days of follow-up. With access to an existing patient portal through a smartphone app, patients will complete a daily self-assessment of symptoms, vital signs, and mental health monitored by a nurse, and receive teleconsultations as needed. Study questionnaires will be administered to collect data on sociodemographic characteristics, medical background, implementation outcomes (acceptability, usability, and respondent burden), and patient satisfaction. Coordinator logbook entries will inform on feasibility outcomes, namely, on recruitment, retention, and fidelity, as well as on the frequency and nature of contacts with health care professionals. The statistical analyses for objectives 1 (*implementation outcomes*), 3 (*service outcomes*), and 4 (*patient outcomes*) will evaluate the effects of time and sociodemographic characteristics on the

outcomes. For objectives 1 (*implementation outcomes*) and 4 (*patient outcomes*), the statistical analyses will also examine the attainment of predefined success thresholds. As for the qualitative analyses, for objective 2 (*influences on implementation*), semistructured qualitative interviews will be conducted with 4 groups of stakeholders (ie, patient participants, health care professionals, technology developers, and study administrators) and submitted for content analysis, guided by the Consolidated Framework for Implementation Research to help identify barriers to and facilitators of implementation. For objective 3 (*service outcomes*), reasons for contacting health care professionals through Opal will also be submitted for content analysis.

Results: Between December 2020 and March 2021, a total of 51 patient participants were recruited. Qualitative interviews were conducted with 39 stakeholders from April to September 2021. Delays were experienced owing to measures taken at the McGill University Health Centre to address COVID-19. The quantitative and qualitative analyses began in May 2022. As of June 2022, a total of 2 manuscripts (on the implementation and the patient outcomes) were being prepared, and 3 conference presentations had been given on the study's methods.

Conclusions: This protocol is designed to generate multidisciplinary knowledge on the implementation of a patient portal–based COVID-19 care intervention and will lead to a comprehensive understanding of feasibility, stakeholder experience, and influences on implementation that may prove useful for scaling up similar interventions.

Trial Registration: ClinicalTrials.gov NCT04978233; https://clinicaltrials.gov/ct2/show/NCT04978233

International Registered Report Identifier (IRRID): DERR1-10.2196/35760

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KEYWORDS

SARS-CoV-2; coronavirus; infectious disease; implementation science; Canada; patient portal; telehealth; telemedicine; app; health information technology; remote monitoring; mobile phone

Introduction

Background

As of December 13, 2021, over 267 million people worldwide have had COVID-19, including almost 2 million in Canada [1]. In 2020, without effective vaccines or treatments, governments and public health agencies enforced lockdown and distancing measures to limit the spread of COVID-19 and the burden on health care systems. At the time, in the Canadian province of Québec, 95% of people diagnosed with COVID-19 were instructed to self-isolate at home and contact health care services if their health deteriorated. While most patients with COVID-19 have mild to no symptoms in the first week following infection [2,3], patient health can rapidly deteriorate in the second week and opportunistic infections can appear [4]. Quick recognition of worsening health is crucial to avoid delays in health care and improve prognosis. However, most self-isolating patients lack tools to self-monitor their illness and maintain contact with health care professionals to ensure timely care. Self-isolation for COVID-19 can also cause anxiety, especially among vulnerable, older, or low-literacy patients [5,6], owing, in part, to inadequate information [7]. Furthermore, it can contribute to numerous other problems, including substance use or addictions [8], self-harm [9], and interpersonal difficulties [10]. Interventions to help self-isolating patients monitor symptoms and vital signs, provide them with educational materials, and facilitate communication with health care professionals could increase the safety and timeliness of care, while reducing psychological distress [5-7].

Health information technologies (HITs) offer solutions in this regard, and the pandemic has propelled their use, including in the form of telehealth and education platforms [11]. Among HITs, patient portals can provide important information and facilitate interactions between self-isolating patients and health care professionals. Their use is also associated with improved patient engagement, empowerment, and satisfaction [12]. One such portal, Opal, was initially created for use at the Cedars Cancer Centre at the McGill University Health Centre (MUHC) in Montreal, Canada, where our team is based. Implemented in 2018, it was co-designed by health care professionals, patients, and HIT developers [12]. It includes a patient smartphone app and a physician desktop dashboard. With Opal, among other advantages, oncology patients can view their diagnostics and treatment plan, laboratory test results, appointment and test schedules, clinical consultation notes, and tailored educational material. Using a dashboard designed for them, health care professionals can administer patient-reported health measures and communicate with patients between consultations [13].

To support self-isolating patients with COVID-19, our team decided to configure Opal for this purpose. This involved applying an existing HIT to a novel and different context of use. Although the benefits of HITs are well-documented for the follow-up of chronic conditions [14-16] such as cancer, little is known about their transferability to acute and typically short-term conditions such as COVID-19. Studying their implementation in this context, particularly with stakeholder engagement, a recognized key to successful HIT projects [17], would generate important data.

Aim and Objectives

Drawing on implementation science, this mixed methods pilot study will evaluate the implementation of a patient portal (Opal) to follow-up with patients recently diagnosed with COVID-19 who were instructed to self-isolate at home. The intervention centers around daily patient self-reports of symptoms, vital signs, and mental health via Opal for remote review by a hospital-based clinical monitoring team. In line with the outcome categories proposed for implementation research [18], the study objectives are as follows: (1) to quantitatively evaluate the

implementation outcomes of this intervention (in terms of predefined benchmarks for acceptability, usability, response burden, feasibility [recruitment and retention], and fidelity); (2) with qualitative data, identify the barriers to and facilitators of implementation (based on semistructured interviews with 4 stakeholder groups); (3) describe service outcomes (in terms of the rates and nature of contact with the health care professionals involved); and (4) describe patient outcomes (based on the daily self-reported health data, including symptoms, use of health services beyond the intervention, and patient satisfaction with teleconsultations, if received).

Methods

Study Design

This single-center pilot study follows the guidance provided by the CONSORT (Consolidated Standards of Reporting Trials) statement for pilot and feasibility studies [19,20]. It uses a mixed methods embedded design, with qualitative methods introduced secondarily to extend the breadth of inquiry [21].

Ethics Approval

Ethics approval was obtained from the MUHC Research Ethics Board on October 5, 2020 (approval number 2021-6763), and the procedures are in accordance with the Helsinki Declaration of 1975, as revised in 2000. Participants provided informed consent and could withdraw from the study at any time. To protect their identity, no identifying information appears in any manuscript or presentation based on this study.

Setting and Participants

Study Site

This study will be conducted at 2 large hospitals of the MUHC, the Glen Hospital and the Montreal General Hospital, both located in Montreal, Québec, Canada. When planning this study, from May to July 2020, at the end of the first wave of the pandemic in the province [22], approximately 150 people from local communities were tested daily for COVID-19 at the MUHC, of which approximately 15% tested positive.

Eligibility Criteria

The participant inclusion criteria are as follows: aged ≥18 years; fluent in French or English; a positive diagnosis at the MUHC with a polymerase chain reaction test for the virus that causes COVID-19 (SARS-CoV-2) and instruction to self-isolate at home; enrollment in Québec's provincial health or public prescription drug insurance plan; access to a smartphone, tablet, or computer; having a home internet connection; and comfortable using a health-related smartphone app or having someone close by who is. Exclusion criteria are being hospitalized, concurrent enrollment in a COVID-19 clinical trial, and having a cognitive impairment that prevents participation.

Recruitment and Sample

To recruit patients, the MUHC test center staff will briefly explain the study and ask about people's interest in participating when calling to inform them of their positive SARS-CoV-2 test result. The study coordinator will then contact interested persons to schedule a videoconferencing appointment, at which time the coordinator will request to see proof of identification (eg, passport and driver's license) and, if applicable, collect consent. To comply with COVID-19 prevention and control measures, explicit oral consent will be obtained from all study participants via videoconferencing. An impartial witness will be present to ensure that all aspects of free and informed consent are respected. If consent is provided, the coordinator will further explain study procedures and provide baseline training on Opal.

For the collection of quantitative data (objectives 1, 3, and 4) using convenience sampling, recruitment will begin in December 2020 and continue until 50 patient participants are enrolled. This sample size meets rule-of-thumb recommendations for 1-arm pilot studies that are not designed to test effects [23,24].

For the collection of qualitative interview data (objective 2) using purposive sampling [25], the 50 MUHC participants and other stakeholders (HIT developers, administrators, and health care professionals) involved in implementing Opal for the pilot study will be invited to be interviewed. After consenting at baseline, patient participants will be asked if they would like to be contacted later for the interview. For nonpatient stakeholders, the study coordinator will record the contact information. Approximately 1 month after all patient follow-up on Opal has ended, potential interviewees will be sent an email to schedule a videoconferencing interview.

We expect that the sample achieved for objective 2 will allow for adequate saturation of the qualitative analyses, as a ≥90% representation of the main study themes is attainable with 10 to 12 qualitative interviews [26].

Procedures

Table 1 details all study procedures related to the patient participants, including the tasks to be accomplished throughout the 14 days of their follow-up.

Table 1. Study procedures for patient participants in the Opal-COVID Study[a].

Procedure	Days of follow-up				
	Before enrollment	1	2 to 14	More days, if needed	1 month after follow-up
Preparation					
COVID-19 test at MUHC[b]	✓				
Notification of positive test result by phone and survey of interest in participation	✓				
Study coordinator call to schedule consent process	✓				
Informed consent and eligibility screen		✓			
Registration and installation of Opal on participant's device		✓			
Educational meeting on Opal's main functions		✓			
Delivery of pulse oximeter or thermometer		✓			
Data collection					
Daily self-assessment					
Severe COVID-19 symptoms and other symptoms		✓	✓	✓	
Vital signs		✓	✓	✓	
Mental health (5 items)			✓ (except Days 7 and 14)	✓	
Mental health (16 items)		✓	Only Days 7 and 14	Weekly	
Study questionnaire					
Sociodemographic and medical background information		✓			
Implementation outcomes		✓	Only Days 7 and 14	Weekly	
Satisfaction with care (after teleconsultations)		✓	✓	✓	
Qualitative semistructured interview					✓

[a]Compensation: CAD $50 (CAD $1=US $1.3).

[b]MUHC: McGill University Health Centre.

Provision of Medical Devices

The coordinator will verify whether the person owns a pulse oximeter and a thermometer, which are necessary to self-monitor vital signs during the study. Those without these devices will be able to receive them free of charge. The pulse oximeter provided will be one that is cleared by the United States Food and Drug Administration. Participants will have the option of receiving the devices through a mailing company with specific guidelines for delivery to patients with COVID-19. Alternatively, they may have them picked up by someone else at the MUHC.

The Opal-COVID Intervention

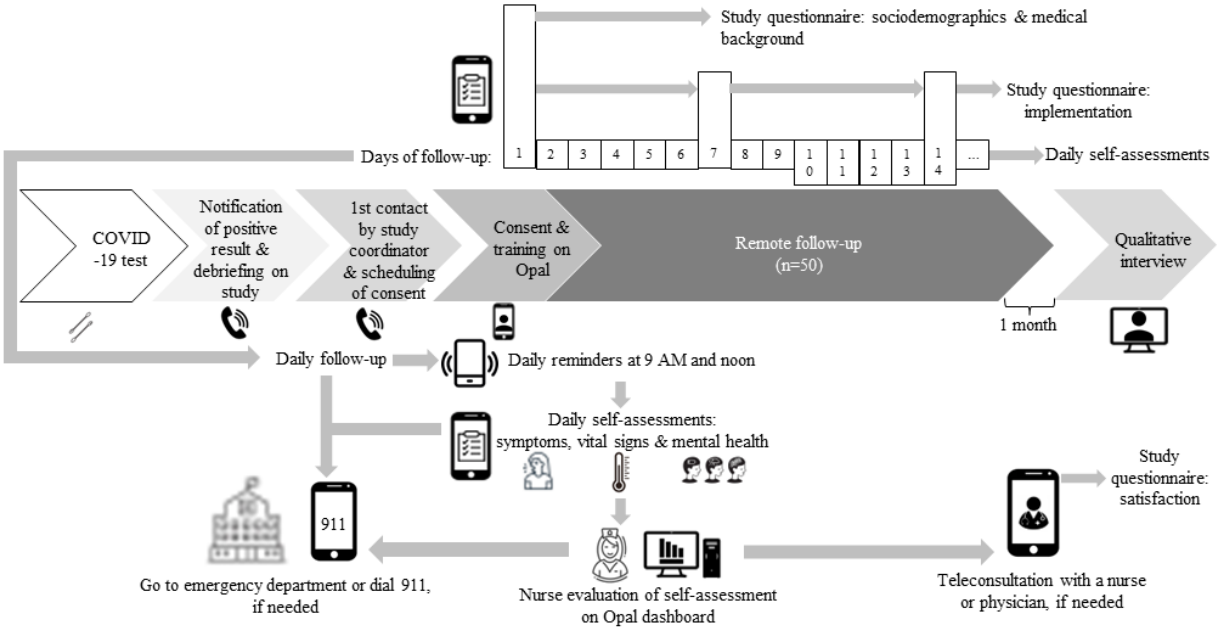
Registration and Training on Opal

Patients must register to use the Opal patient portal. To do so, participating patients will be guided by a research staff member who will confirm their identity and explain Opal's functionalities. The remote registration system will send a unique verification code to the user's smartphone with a link to the registration page where the code will be entered. This is done to ensure the security and privacy of patient information. As shown in the provided screenshot (Multimedia Appendix 1), the user must then confirm their identity with their provincial health insurance card number, fill in some basic account information for log-in and security measures, select a data access level (ie, to allow access to their medical data or not), and accept the terms of use.

Duration

Participant follow-up is expected to last for 14 days. However, it will be prolonged in the following cases: (1) patients being diagnosed with a SARS-CoV-2 variant; (2) patients reporting fever in the last 48 hours on day 14; or (3) patients reporting other acute symptoms in the last 24 hours, except cough or loss of smell, which can take longer to subside [27]. Figure 1 shows the patient participant path in the Opal-COVID intervention.

Figure 1. Opal-COVID Study patient participant path.



Daily Self-assessments

Daily self-assessments form part of the intervention and provide most of the patient outcomes data described in objective 4. They are filled out on the Opal app in either English or French (the full self-assessment can be found in Multimedia Appendix 2; screenshots of the self-assessment are provided in Multimedia Appendix 3). From day 1 to the last day of their follow-up, these self-assessments allow patients to report symptoms, vital signs (using the pulse oximeter and thermometer), and mental health indicators to the clinical monitoring team.

The self-assessment was developed using existing COVID-19 symptom evaluation tools [27-30] and stakeholder feedback. It asks about the following: (1) the presence of severe COVID-19 symptoms (eg, severe difficulty breathing, severe chest pain, heart palpitations, feeling confused, and loss of consciousness in the past 24 hours); (2) the presence of other possible symptoms of COVID-19 (eg, pain, persistent cough, chills, runny or blocked nose, shortness of breath, loss of appetite or sense of smell or taste, sore throat, nausea or vomiting, diarrhea, abdominal cramping, unusual fatigue, and skin changes); (3) vital signs measured and reported by participants, including current temperature, respiration rate, oxygen saturation, heart rate, and, if possible, blood pressure; and (4) mental health symptoms in the past 24 hours, based on the 4-item short form versions of the Patient-Reported Outcome Measurement Information Systems (PROMIS) scales for anxiety, depression, fatigue, and sleep disturbance used under license agreement [31]. To limit response burden, participants will complete all 16 of the PROMIS items on days 1, 7, and 14, whereas on other days, they will respond to only 5.

Reminders

Each day, automated reminders to complete the self-assessment will be sent at 9 AM and then again at noon to participants who did not do so.

Monitoring

The clinical monitoring team will be composed of up to 3 nurses and 1 physician (assigned on a weekly basis).

Physicians will be available for teleconsultations conducted on the Zoom (Zoom Video Communications Inc) platform [32] and to refer patient participants to the psychiatrist (M-JB) in cases of psychological distress. All members of the clinical monitoring team will refer patient participants to emergency services as needed. The normal hours of operation for the team will be from 9 AM to 8 PM. Completed self-assessments will be reviewed by nurses on the Opal Room Management System clinical dashboard and systematically acknowledged. Each nurse will monitor up to 6 patients simultaneously. With the information provided by the self-assessment, nurses will determine a course of action, including the sending of standardized SMS text messages.

In this regard, several scenarios are possible (Multimedia Appendix 4 provides example SMS text messages sent by the nurse). For instance, if a patient's symptoms and vital signs are stable, an SMS text message with positive feedback will be sent. If the nurse judges that a patient needs to be under closer observation, an SMS text message will be sent asking them to complete the self-assessment again. If a patient requests to speak with the nurse or is in poor condition, the nurse will book a teleconsultation for the afternoon. Opal will display the consultation time in the patient's appointment calendar and provide a description of the consultation to help them prepare.

Triggered by the nurse, an SMS text message will be sent to the patient with a link to the teleconsultation (Multimedia Appendix 5 provides screenshots relevant to teleconsultations). After each teleconsultation, to evaluate patients' satisfaction with the care received (part of objective 4), a notification will be sent to patients through the Opal app to complete a survey based on the *Short Questionnaire for Out-of-Hours Care* [33]. It contains 7 items that are rated on a 5-point scale of satisfaction. For this study, a "not applicable" response option was added. All ratings are averaged to generate an overall score (range 1-5). Here, a mean score of ≤4 ("satisfied") will signify adequate patient satisfaction with the teleconsultation.

If the patient completes the self-assessment after 8 PM, the clinical monitoring team will examine their responses and provide feedback early the next morning (note that the self-assessment contains instructions to go to an emergency department or call 911 if symptoms or vital signs reach specific thresholds). If no self-assessments are received from a patient for 2 consecutive days, the clinical monitoring team will reach out to them or to their emergency contact. During enrollment, these monitoring procedures are explained to participants.

Implementation Strategies

Overview

This study draws on recognized implementation strategies [34] (indicated by italics). Implementation strategies are methods that are intended to foster the adoption or implementation of an intervention. The selected strategies are presented based on their corresponding main phase of implementation: preimplementation, implementation, or postimplementation.

Central to many of these strategies is our aim to *involve patients and stakeholders* through different engagement approaches. Engagement emphasizes the coconstruction of knowledge [35-38] and accountability to stakeholder values, expertise, and perspective relative to a health condition and its associated care [39]. Engagement can take many forms and encompass research and intervention development processes [40]. Importantly, it can help to detect and address challenges associated with recruitment, accessibility, acceptability, and the comprehensibility of procedures and instruments [41]. It can also increase the relevance and meaningfulness of research results [39].

Our stakeholder engagement strategy is enacted by a core multidisciplinary research team. Within this team, YM (junior engineer), BL (physician), and DL (anthropologist) were appointed to engage HIT developers, health care professionals, and patients recovered from COVID-19, respectively.

Strategies During the Preimplementation Phase

To *centralize technical assistance*, YM will communicate with the Opal development team (TH and JK) and maintain, configure, and update the patient portal. Regular meetings will be held to discuss the configuration of Opal for COVID-19 and ensure that it integrates stakeholder recommendations, as obtained from engaged health care professionals and patients recovering from COVID-19. Changes in Opal will be recorded via the Jira software [42]. YM will also be available to patient participants on email to provide technical assistance throughout the study.

To *create a clinical team*, BL will unite 4 physicians and 3 nurses with experience in providing COVID-19 care. Their role is to provide recommendations for the following: the use of Opal for remote COVID-19 follow-up, procedures for distance monitoring, the patient's daily self-assessment, and information or educational material to provide to participants through the patient portal.

To engage patients with COVID-19, DL will meet with 3 people who have recovered from the disease to obtain their feedback on the proposed procedures for remote monitoring and research material (eg, informed consent documents, and all data collection instruments, including the self-assessment). This will help ensure relevance, comprehensibility, and comprehensiveness. Representation will be sought from previously infected laypersons and health care professionals with COVID-19 care experience. They will be recruited by convenience sampling within the research team's networks.

To conduct *cyclical small tests of change*, 4 prototype tests with engaged health care professionals (ie, the clinical team) and patients are planned by YM. For each test, members attend a training on Opal, use it for 4 days, and then meet to discuss their experience, report problems, and make recommendations. Furthermore, a *low-load* run of the patient portal is planned with 5 study participants to adjust the intervention, as needed, before the "full-load" run, with all participants.

Strategies During the Implementation Phase

To *record user feedback*, coordinators will fill out daily field notes in a logbook. Interactions involving participants or other stakeholders, including unforeseen challenges, technical issues encountered, and any implemented solutions, will be recorded (all entry types in the coordinator logbook are provided in the Study Data Collection and Metrics section).

As described, the initial consent process with participants includes an *educational visit* to introduce Opal and its features and provide training. We will also select and create *education material*, that is, videos, frequently asked questions, and reading material, to integrate into the Opal app. This material will include COVID-19 breathing exercises [43], guidelines for self-isolation [44], pulse oximeter and thermometer user guides (Multimedia Appendix 6), and a calendar of study participant tasks. All involved stakeholder groups will review this material.

We will *promote adaptability* of the intervention and implementation by enabling adjustments to the concerns and recommendations expressed by stakeholders or participants throughout the study. Peripheral aspects of the intervention (eg, timing and content of reminders, timing of consultations, and duration of participation) are adaptable to participant needs and circumstances. For instance, every time they complete a self-assessment, participants are asked whether they wish to speak to a nurse (irrespective of their reported symptoms, vital signs, etc).

Strategy During the Postimplementation Phase

Our final strategy is to *purposely re-examine the implementation*. We will do this by analyzing participant and stakeholder perspectives on barriers to and facilitators of implementation after implementation (based on the qualitative interviews).

Study Data Collection and Metrics

Study Questionnaires

In part to describe the sample, on day 1, participants will complete a study questionnaire that covers the following: (1) sociodemographic characteristics, including gender, age group, annual income, current occupation, postal code, ethnicity, living arrangements (eg, living alone), and job title; and (2) medical background, including smoking; other medical conditions, such as lung disease or asthma, heart disease, diabetes, kidney disease, and cancer; recent vaccination for influenza and pneumococcal disease; and use of specific medications (eg, nonsteroidal anti-inflammatory drugs, aspirin, acetaminophen, immunosuppressants, and blood pressure medication).

To assess implementation outcomes (for objective 1), a study questionnaire will be administered on a weekly basis (days 1, 7, and 14), with questions on acceptability, response burden, and usability. Acceptability indicates how agreeable, palatable, or satisfactory an intervention is to stakeholders [18]. It will be evaluated with an adapted version of the *Acceptability of Intervention Measure* [45]. The scale has 6 items rated on a 5-point Likert scale. Item scores are averaged to produce a summary score (range 1-5). In accordance with the developers' recommendations, a minimum average score of 4 will indicate high acceptability and act as our benchmark of success.

Perceived response burden refers to the effort required to answer a questionnaire [46] and can be considered an aspect of acceptability [18]. It will be measured with a single question and a 5-point response scale that was adapted from a survey question of the United Kingdom Office for National Statistics [46]. Consistent with the previous threshold, the target will be ≥80% (41/51) of participants rating the daily self-assessments as (2) "quite easy" to (1) "very easy" to complete.

Usability refers to the "extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction" [47] and can be considered to crosscut aspects of several implementation outcomes (feasibility, appropriateness, and acceptability) [17]. It will be assessed with 3 subscales of the *Health Information Technology Usability Evaluation Scale* [48]. This questionnaire is customizable and specifically designed to evaluate mobile health technology. The selected subscales concern perceived impact (3 items), usefulness (9 items), and ease of use (5 items). Items are rated on a 5-point scale of agreement and averaged to generate subscale scores (range 1-5). A mean score of at least 4 on each subscale, indicating agreement that the technology is impactful, useful, and easy to use, will be our metric of success.

Satisfaction with teleconsultations (for objective 4) will be evaluated with a separate questionnaire sent to patients after each teleconsultation.

Coordinator Logbook

The coordinator logbook will capture qualitative data that will be used to assess feasibility and fidelity (for objective 1) and the rates and nature of contacts with health care professionals (for objective 3). It will include entries on the following: (1) participant questions or challenges during consent and baseline educational meetings; (2) participant recruitment, retention, and fidelity to the intervention; (3) the content of spontaneous discussions with participants or other stakeholders during implementation (eg, the object of participant calls to the coordinators); (4) all contacts with the clinical monitoring team, including clinical notes on teleconsultations with participants; (5) details on those who eventually went to an emergency department; and (6) participant compensation.

Feasibility relates to the extent to which an intervention can be successfully used in a given setting [18]. In this case, it will mainly be assessed by the following: (1) the recruitment rate, that is, the proportion of contacted eligible individuals who are included in the study and (2) the retention rate, defined as the proportion of included participants who are retained over the full follow-up period, both with a target of 75% (38/51) [49].

Fidelity, the degree to which the intervention was implemented as intended [18], will be measured as the proportion of included patients who complete their daily self-assessments over the full follow-up period, with a target of 75% (38/51).

Contacts with the clinical monitoring team will be calculated as the proportion and frequency of participants who (1) wish to talk with the nurse (based on self-assessment data); (2) receive a teleconsultation with a nurse; (3) receive a teleconsultation with a physician; (4) receive mental health support; and (5) eventually go to an emergency department for COVID-19 complications. On the basis of the details recorded in the coordinator logbook, the source of much of these data, that is, the reasons for each of these activities, will also be categorized and described.

Qualitative Interviews

All qualitative interviews will be conducted individually and preferentially by videoconferencing and, if not, by phone. Each interview will be recorded, last for approximately 20 minutes, and follow a semistructured guide with open-ended questions and specific prompts. Although adapted to each stakeholder group, the guide includes ≤5 broad questions on the individual's experience of and thoughts on using Opal for COVID-19 follow-up, with prompts on challenges and facilitators [50]. Interview guides for each stakeholder group can be found in Multimedia Appendix 7.

Data Analysis

All statistical analyses will be performed with the R software (R Foundation for Statistical Computing) [10,51].

Sample Description

Descriptive statistics will be used to present the participants' sociodemographic and medical background characteristics. For continuous variables, the minimum, maximum, mean, and SD will be reported. For ordinal and nominal qualitative variables, we will report absolute and relative frequencies (proportions).

Objective 1: Assess Implementation Outcomes With Predefined Success Thresholds

Implementation outcomes will be summarized using descriptive statistics. Acceptability, usability, perceived response burden, and fidelity will be summarized at days 1, 7, and 14. Feasibility will be summarized at the end of the recruitment period (recruitment rate) and at the end of patient follow-up (retention rate). For continuous outcomes, the minimum, maximum, mean, and SD will be reported. For ordinal and nominal outcomes, we will report the absolute and relative frequencies (proportions). The descriptive statistics will also be stratified by gender, age group, and ethnicity.

Acceptability and usability will be evaluated using a linear mixed model (LMM) for each corresponding outcome. The dependent variable of each model will be the outcome and the independent variables will be time (days 1, 7, and 14) and 3 sociodemographic variables reported to influence patient portal use (gender [man or woman], age [≤50 years or ≥50 years], and ethnicity [White or other]) [52]. The goal of each model is to test whether the outcome's mean score changes significantly over time and whether it differs significantly between the groups represented by the sociodemographic variables over time. LMMs are commonly used in longitudinal studies and allow participants with missing data to be retained in the analysis. Finally, if, at each time point (days 1, 7, and 14), the outcome's mean score is greater than or equal to the predefined success threshold, we will consider the target to be met. If it is below the threshold, we will use a unilateral *t* test to test the null hypothesis of threshold attainment, since being slightly below this mark does not imply failure, given the sample mean's variability.

The evaluation of perceived response burden and fidelity will be performed using a generalized LMM (GLMM) for each corresponding outcome, as it is appropriate when the dependent variable is not continuous. The parameters will be estimated using generalized estimating equations (GEEs), as estimates are sensitive to the specified correlation structure, particularly in noncontinuous outcomes. The independent variables will be time (days 1, 7, and 14) and the 3 sociodemographic variables. To evaluate threshold attainment, if the observed proportion is under the predefined success threshold, we will use a unilateral *z*-test, which is appropriate for hypothesis testing with proportions.

The evaluation of feasibility will be performed by confronting the observed recruitment and retention rates with the predefined success thresholds at the end of the recruitment period and patient follow-up, respectively. If the observed rates are over or equal to the success threshold, we consider that the target is met. If it is under the success threshold, we will use a unilateral *z*-test to test the null hypothesis of threshold attainment.

Objective 2: Identify Implementation Barriers and Facilitators

Overview

To identify implementation barriers and facilitators, as well as their proposed or enacted solutions, 2 trained coders will conduct a content analysis focusing on the manifest content [53] of this study's qualitative material. This will include interview transcripts, nurses' and physicians' clinical notes, and coordinators' logbook entries. Analysis will involve three phases [53]: (1) preparation, when analysts get familiar with the data set through immersion in the data; (2) organization, when they deductively code the data using the NVivo software, following a categorization matrix based on Consolidated Framework for Implementation Research (CFIR) constructs [49] to help identify barriers to and facilitators of implementation while remaining open to emerging categories; and (3) reporting, which involves presenting the analytical categories and discussing them during periodic team meetings, as well as any discrepancies in coding or interpretation, to help ensure trustworthiness [53].

Conceptual Framework

The CFIR will guide our qualitative analyses to categorize the barriers and facilitators identified and, quite possibly, to help interpret our findings overall. The CFIR was chosen because it includes 39 distinct constructs grouped within 5 domains of potential influence on implementation, including features of the intervention, the inner and outer settings, the individuals involved, and the implementation process [49].

Objective 3: Describe Service Outcomes

Service outcomes will be summarized with absolute and relative frequencies (proportions) at days 1, 7, and 14. The frequencies will also be stratified by gender, age group, and ethnicity.

Service outcome evaluation will follow the same procedure as for objective 1. As each service outcome is noncontinuous, we will use a GLMM, with parameter estimates obtained by GEE, with the same independent variables.

For objective 3, a qualitative analysis will also be performed on the reasons underlying participant contacts with the clinical monitoring team (eg, teleconsultations) and patient care-seeking in an emergency department, as textually recorded in the coordinator logbook, including the clinical monitoring team's clinical notes. Content analysis [53], as previously described, will be used for this purpose. This will provide more context to the quantitative data on service outcomes.

Objective 4: Describe Patient Outcomes

The patient outcomes collected from the daily self-assessment will be summarized each day with descriptive statistics. For continuous outcomes, the minimum, maximum, mean, and SD will be reported. For ordinal and nominal qualitative outcomes, we will report absolute and relative frequencies (proportions). The descriptive statistics will also be stratified by gender, age group, and ethnicity.

The evaluation of the patient outcomes will follow the same procedure as for objective 1: an LMM for each continuous outcome and a GLMM for each noncontinuous outcome with parameter estimates obtained by GEE, using the same independent variables except for time, which will be expressed daily (day 1 to day 14). Attainment of the patient satisfaction target will also follow the procedure for objective 1, with a unilateral *t* test, when the observed mean score is below target.

Mixed Methods Analysis

The quantitative and qualitative data will be analyzed separately and brought together during the interpretation of results for triangulation, comparison, and improved understanding [21]. More precisely, the barriers and facilitators identified through qualitative methods (objective 2) will be used to help interpret the quantitative findings on implementation, service, and patient outcomes (objectives 1, 3, and 4).

Confidentiality, Data Management, and Cybersecurity

The study coordinator will assign a participant number to all participants in this study to protect their identity. A digital file will contain both the participant numbers and identifying information. This file will be stored in a password-protected folder on a secure MUHC server. Interview recordings will be destroyed after transcription. Transcripts will be anonymized and stored as previously described.

Data obtained from patient participants during their follow-up (eg, sociodemographic information, daily self-assessments, and feasibility) will be electronically collected directly through Opal. The Opal team (YM, TH, JK, and JA) will oversee the management of these data, which will also be held in a secure MUHC server.

Opal conforms to security and governance recommendations for the development of patient portals, as identified by the MUHC Security and Governance team. Details are presented in Multimedia Appendix 2 of Kildea et al [12].

Anticipated Risks and Benefits

There are no direct risks to the participants in this study. For Opal, data security risks were addressed with numerous measures, such as disclosing and explaining these to patients, logging users out after 5 minutes of inactivity, sandboxing data on the users' device and deleting it on log-out, and including security questions in the authentication process [12]. However, patient participants may have unrealistic or unmet expectations of the intervention or a false sense of security [54] with Opal. For instance, they may overly rely on nurses to respond to the information they transmit via Opal instead of taking medical action when needed. To prevent this, the self-assessment instructs patients to seek out emergency services when specific symptoms or vital sign thresholds are attained. For various reasons (eg, ability), participants may also over- or underestimate their symptoms and vital signs, thus affecting the response they receive from the clinical monitoring team.

In addition, the study questionnaires and semistructured interviews may lead to distress related either to the experience of COVID-19 (for patients) or to providing COVID-19 care (for health care professionals). Hence, these research tasks carry a risk of emotional vulnerability. Individuals who experience psychological distress because of their involvement in the study are instructed to inform a study staff member. Resources such as a teleconsultation with a mental health professional or other support services will be made available to them.

The benefits of participating in this study for those with COVID-19 include access to the proposed intervention and follow-up. They will be compensated with CAD $50 (US $65) in the form of a gift card or, in exceptional cases, a money transfer at the end of their participation in the study.

Results

Status

This study secured funding from the McGill Interdisciplinary Initiative in Infection and Immunity Emergency COVID-19 Research Funding (grant ECRF-R2-44) on April 20, 2020, and from the Canadian Institutes of Health Research Strategy for Patient-Oriented Research (Quebec) Support Unit-Methodological Developments (grant M006) on February 12, 2021. Recruitment of patient participants occurred from December 2020 to March 2021, during the second wave of the pandemic in Québec, with a final sample of 51 participants [22]. Qualitative interviews were conducted between April and September 2021 during the third and fourth waves [22], with 57% (39/68) involved stakeholders, among which were 53% (27/51) patient participants, 54% (6/11) health care professionals, 100% (4/4) administrators, and 100% (2/2) HIT developers. The quantitative analyses and the qualitative content analysis of the interviews began in earnest in May 2022. The methods of this pilot study have been the object of 3 conference presentations as of June 2022 [55-57]. In addition, at this time, 2 manuscripts were being prepared, 1 involving a mixed methods analysis of the implementation (objectives 1 and 2) and the other involving patient outcomes (objective 4).

Impact of COVID-19 on Study Progress

Early in the COVID-19 pandemic, tighter regulatory measures for data security were implemented at the MUHC. Complying with these measures delayed the acquisition of Research Ethics Board approval and study initiation. Research staff and data analysts also worked remotely to comply with social distancing measures at the MUHC, which created delays in task delegation and communication. We also experienced a shortage of trained research staff. As a result, most interviews were sent for transcription only once they had all been conducted.

Discussion

Anticipated Results and Contributions

We anticipate reaching the success thresholds for the studied implementation and patient outcomes. By triangulating quantitative and qualitative findings, we also expect a more complete understanding of institutional (eg, infrastructure, regulations, and human and material resources), professional (eg, expert networks), and medical (eg, symptomatology and evolution of COVID-19 infections) factors that influence the implementation of the intervention and shape its unfolding in the real world. This study will also address several gaps in the literature. Research is limited on the remote monitoring solutions for self-isolating patients with COVID-19 [58], and few such interventions have been evaluated using a mixed methods approach [59] that includes qualitative input from both patients and clinicians. Furthermore, little work has explored the configuration of HIT for chronic care management for use in acute care, such as for COVID-19 and our work will provide an example for how to proceed.

Strengths and Limitations

Strengths of this study include its pragmatism and response to a locally identified gap in the care of people with COVID-19. Its multipronged implementation strategy, with an emphasis on stakeholder engagement and iterative feedback processes, promises to enhance intervention configuration, implementation, and evaluation. The intervention and study also benefit from the pre-existing successful use of the Opal patient portal in oncology at the study site (MUHC) [60] and collaborations between the investigators and Opal developers on other projects (eg, the studies by Chu et al [61] and Engler et al [62]). Thus, the rapid scale-up of this precise intervention at other institutions may be limited.

Limitations of this study also include several sources of potential bias. Indeed, enrollment in Québec's provincial public health insurance plan (Régie de l'assurance-maladie du Québec) was necessary for patient inclusion, which may have introduced selection bias. Those potentially excluded include members of vulnerable populations, such as resettled refugees [63] and international students [64], groups particularly impacted by the pandemic in Canada, in part, by high COVID-19 incidence rates. In addition, for feasibility, the qualitative interviews were conducted after completing the quantitative data collection. For some participants, interviews took place several months after their follow-up ended. This time lapse may affect the reliability of the qualitative results, in part, because of recall bias. This also meant that this patient input could not be used to adjust the intervention or its implementation during enrollment and follow-up, leading to possible missed opportunities for improvement [65].

Conclusions

Overall, this protocol is designed to generate multidisciplinary knowledge on the configuration and piloting of a patient portal–based intervention for remote COVID-19 follow-up and will lead to a comprehensive understanding of feasibility, stakeholder experience, and influences on implementation that may help in the testing or scale-up of similar interventions. It also promises to produce data that are useful for a wide range of stakeholders, including academics, researchers, health care professionals and administrators, implementation scientists, and HIT developers, who are interested in fostering feasible patient-oriented remote care for COVID-19 and beyond.

Acknowledgments

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The names of the members of the Opal-COVID-19 Patient Expert Committee cannot be provided as they are patients and their names must remain confidential.

Data Availability

The data sets generated and analyzed for this study are available from the corresponding author (BL) on reasonable request.

Authors' Contributions

In no order of contribution, ARC, YM, KE, DL, NK, SB, BL, and the Opal-COVID-19 Patient Committee helped design the study, the intervention, and data collection tools. DL, KE, ARC, SV, YM, and, BL wrote the manuscript. SV planned the statistical analyses. YM, JK, TH, and JA, configured the Opal app for the COVID-19 follow-up. ADP, NK, SB, JC, CC, AH, NZN, and BL participated in the teleconsultations with the study participants. ARC, YM, and DL contributed to data collection. All authors critically reviewed the manuscript and approved the final version.

Conflicts of Interest

BL has received research support and consulting fees from ViiV Healthcare, Merck, and Gilead. NK reports research funding from Gilead Sciences, advisory fees from Gilead Sciences, ViiV Healthcare, Merck, and AbbVie, and speaker fees from Gilead Sciences and Merck, all outside of the submitted work.

Multimedia Appendix 1
Screenshot of the Opal remote registration system.

[PNG File , 128 KB - resprot_v11i8e35760_app1.png]

Multimedia Appendix 2
Content of the daily self-assessment questionnaire.
[DOCX File , 33 KB - resprot_v11i8e35760_app2.docx]

Multimedia Appendix 3
Screenshots of the daily self-assessment questionnaire on Opal: (A) questionnaire introduction, (B) example question, and (C) answer revision before submission.
[PNG File , 164 KB - resprot_v11i8e35760_app3.png]

Multimedia Appendix 4
Screenshots of different standardized SMS text messages sent by nurses to patient participants, following review of their daily self-assessments: (A) positive feedback, (B) teleconsultation needed, and (C) closer monitoring needed.
[PNG File , 153 KB - resprot_v11i8e35760_app4.png]

Multimedia Appendix 5
Screenshots relevant to procedures involving teleconsultations: (A) teleconsultation shown in the appointment calendar, (B) appointment description to help prepare patients, and (C) teleconsultation SMS text message.
[PNG File , 196 KB - resprot_v11i8e35760_app5.png]

Multimedia Appendix 6
Instructional video created for participants on how to use the pulse oximeter.
[PNG File , 662 KB - resprot_v11i8e35760_app6.png]

Multimedia Appendix 7
Qualitative interview guides for each of the stakeholder groups.
[DOCX File , 36 KB - resprot_v11i8e35760_app7.docx]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
CONSORT: Consolidated Standards of Reporting Trials
GEE: generalized estimating equation
GLMM: generalized linear mixed model
HIT: health information technology
LMM: linear mixed model
MUHC: McGill University Health Centre
PROMIS: Patient-Reported Outcome Measurement Information Systems

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Protocol

Contextual Conversational Agent to Address Vaccine Hesitancy: Protocol for a Design-Based Research Study

Youness Zidoun[1], PhD; Sreelekshmi Kaladhara[1], BSc; Leigh Powell[1], EdD; Radwa Nour[1], DDS; Hanan Al Suwaidi[2], MBBS; Nabil Zary[1], MD, PhD

[1]Institute for Excellence in Health Professions Education, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates

[2]College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates

Corresponding Author:
Nabil Zary, MD, PhD
Institute for Excellence in Health Professions Education
Mohammed Bin Rashid University of Medicine and Health Sciences
Building 14, Dubai Healthcare City
PO Box 505055
Dubai
United Arab Emirates
Phone: 971 585960762
Email: Nabil.Zary@mbru.ac.ae

Abstract

Background: Since the beginning of the COVID-19 pandemic, people have been exposed to misinformation, leading to many myths about SARS-CoV-2 and the vaccines against it. As this situation does not seem to end soon, many authorities and health organizations, including the World Health Organization (WHO), are utilizing conversational agents (CAs) in their fight against it. Although the impact and usage of these novel digital strategies are noticeable, the design of the CAs remains key to their success.

Objective: This study describes the use of design-based research (DBR) for contextual CA design to address vaccine hesitancy. In addition, this protocol will examine the impact of DBR on CA design to understand how this iterative process can enhance accuracy and performance.

Methods: A DBR methodology will be used for this study. Each phase of analysis, design, and evaluation of each design cycle inform the next one via its outcomes. An anticipated generic strategy will be formed after completing the first iteration. Using multiple research studies, frameworks and theoretical approaches are tested and evaluated through the different design cycles. User perception of the CA will be analyzed or collected by implementing a usability assessment during every evaluation phase using the System Usability Scale. The PARADISE (PARAdigm for Dialogue System Evaluation) method will be adopted to calculate the performance of this text-based CA.

Results: Two phases of the first design cycle (design and evaluation) were completed at the time of this writing (April 2022). The research team is currently reviewing the natural-language understanding model as part of the conversation-driven development (CDD) process in preparation for the first pilot intervention, which will conclude the CA's first design cycle. In addition, conversational data will be analyzed quantitatively and qualitatively as part of the reflection and revision process to inform the subsequent design cycles. This project plans for three rounds of design cycles, resulting in various studies spreading outcomes and conclusions. The results of the first study describing the entire first design cycle are expected to be submitted for publication before the end of 2022.

Conclusions: CAs constitute an innovative way of delivering health communication information. However, they are primarily used to contribute to behavioral change or educate people about health issues. Therefore, health chatbots' impact should be carefully designed to meet outcomes. DBR can help shape a holistic understanding of the process of CA conception. This protocol describes the design of VWise, a contextual CA that aims to address vaccine hesitancy using the DBR methodology. The results of this study will help identify the strengths and flaws of DBR's application to such innovative projects.

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KEYWORDS

conversational agent; design-based research; chatbot; Rasa; NLU; COVID-19; vaccine hesitancy; misinformation; vaccination; iterative design; health communication; health information; System Usability Scale

Introduction

Background

Conversational agents (CAs), sometimes known as chatbots, are an emerging technology for facilitating health communication. They are becoming increasingly popular in various professions, including education, entertainment, and health care. Furthermore, CAs are becoming more widespread in formal health care settings to aid with essential duties including appointment scheduling and health monitoring [1,2]. As technology advances, more advanced CAs that can engage humans in natural communication are beginning to appear. As a result, these technologies are becoming more common in daily health-related activities [3], medical care such as orthopedics [4], virtual medical consultations [5], pediatric care [1], geriatric care [6], public health and surveillance [7], large-scale monitoring systems [8], etc. CAs are typically deployed through a variety of platforms such as social networks (eg, Facebook and Twitter), messaging apps (eg, WhatsApp, Discord, and Telegram), or even emails and webpage widgets, making them highly accessible and sustainable [9].

Already deployed in the fight against the COVID-19 pandemic, many authorities and health organizations, including the World Health Organization (WHO) [2], the UK government [10], the US Department of Veterans [11], and the Saudi Ministry of Health [12], have embraced these emerging technologies. In addition, health CAs have been introduced as an innovative digital intervention to support the fight against the pandemic [13]. However, the efficiency of design and best practice for development remains a field of exploration for researchers. The effectiveness of a CA's design remains key to its success, mainly when its purpose is to address serious concerns such as misinformation, mental health, or behavior change.

Many design approaches have been presented in the literature [14,15], ranging from early forms of hard-coded response generators to advanced artificial intelligence (AI) development methodologies. These can be divided into two categories: rule-based and neural network-based methodologies. A neural network is based on deep learning models, whereas a rule-based system is based on established templates and answers.

Most of these design strategies use ontologies, which are based on the domain's knowledge base and may be utilized to interpret the user's intentions and address the difficulty of interpreting the user's phrases [16].

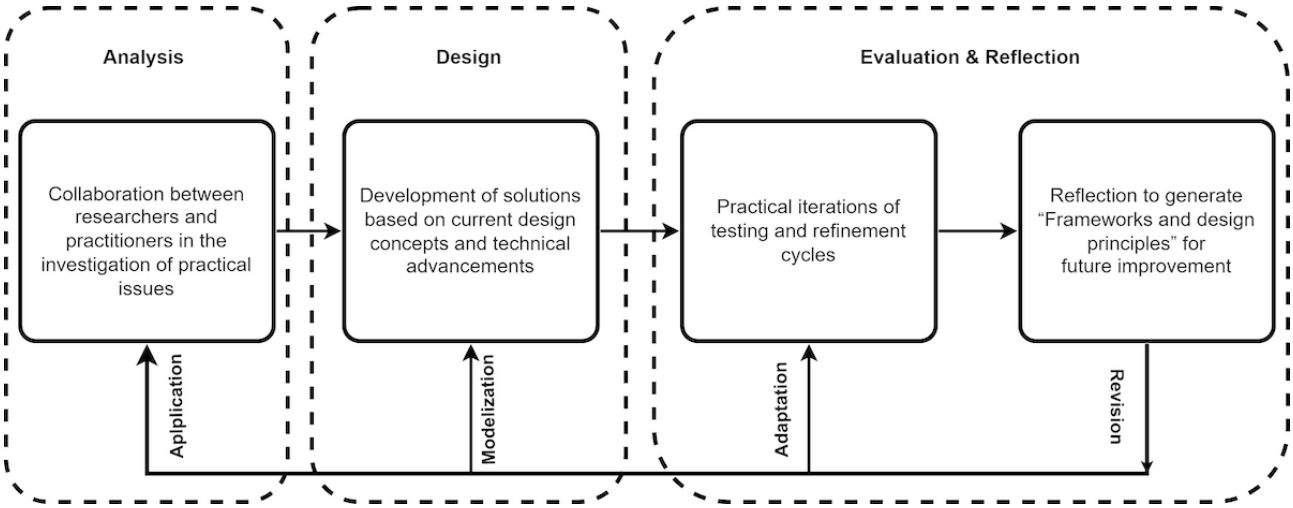
On the other hand, model-driven chatbot development is a different approach. It comprises a neutral meta-model and a domain-specific language for chatbot description, code generators and parsers for several chatbot platforms, and a platform recommender. This approach supports forward and reverse engineering and model-based analysis. The feasibility of this later is presented via a prototype tool and an evaluation based on migrating third-party Dialogflow bots to Rasa [17].

AIML, an XML derivative, is also a widely used approach. The purpose of the AIML language is to simplify the role of conversational modeling in relation to a "stimulus-response" process. It is also a mark-up language based on XML and depends on tags that are the identifiers that make snippets of codes to send commands into the Chatbot [18].

Design-Based Research to Design a CA

Aligned with research methods from other fields in which products are developed for specific purposes [19-21], design-based research (DBR) is a methodological approach that relies on an iterative process. First, the problem that needs to be addressed is identified. Next, theoretical tools including models or frameworks are created to represent the potential solution to the problem. These are later tested in a real environment to measure their impact. As the testing progresses, the theoretical tools are assessed on the basis of new evidence of their positive or lack of effectiveness, and real-time revisions are made if needed [22]. Different ideas can be found in the literature regarding the definition of DBR; however, all agree that it is divided into many stages [23-25]. The most common way of picturing the DBR process is shown in Figure 1.

Figure 1. Design-based research approach adapted from Reeves [26].



Evidence from the literature agrees that DBR is a long-term approach that includes multiple iterations of design, development, and evaluation [27,28]. However, this is not always applicable for short-time-frame projects. This highlights how DBR may be effectively translated and utilized in CA projects, especially how many cycles are necessary to develop valid and meaningful design principles in a very short-term project.

A team of researchers conducted a study using a DBR approach to promote self-direction training and problem-based learning (PBL) for medical students in a clinical context [29]. Another design-based study [18] was conducted with the primary objective of improving the professional performance of higher education teachers by considering various pedagogical aspects and the need for communication and alignment of pedagogy and assessment.

In another DBR, researchers conducted a study aiming to promote and strengthen clinical reasoning and competencies and develop essential clinical skills for nurses. The study's primary aim and approach were to create and construct a web-based learning management system that could promote PBL to students and define their clinical goals [30].

Another study shows that DBR contributed to advancing the practice by encouraging collaboration and coordination between practice and theory [31].

The findings of all these studies and more [32-34] were mostly reported as a basis for reproducing such digital projects and interventions, which helped DBR to demonstrate its potential as a methodology suitable for research and design technology-enhanced learning environments.

Objective

This study protocol describes the use of DBR methodology to conceive a CA that aims to address vaccine hesitancy through a contextualized conversation. Three complementary objectives will be considered in the CA design: (1) combat misconceptions through the dissemination of trustworthy information in accordance with the WHO's frequently asked questions (FAQs) (the updated version of January 2022 from the WHO's FAQs [35] as a baseline data set feeding the AI model of the CA), (2) user profiling (a vaccine hesitancy profile is defined for users through the conversation), and (3) redirection and dissemination (users can disseminate good information and advocate for vaccination literacy). We hypothesize that DBR methodology improves the usability and accuracy of CAs. This intervention will use validated instruments to assess key metrics and present data interpretation.

Methods

Overview

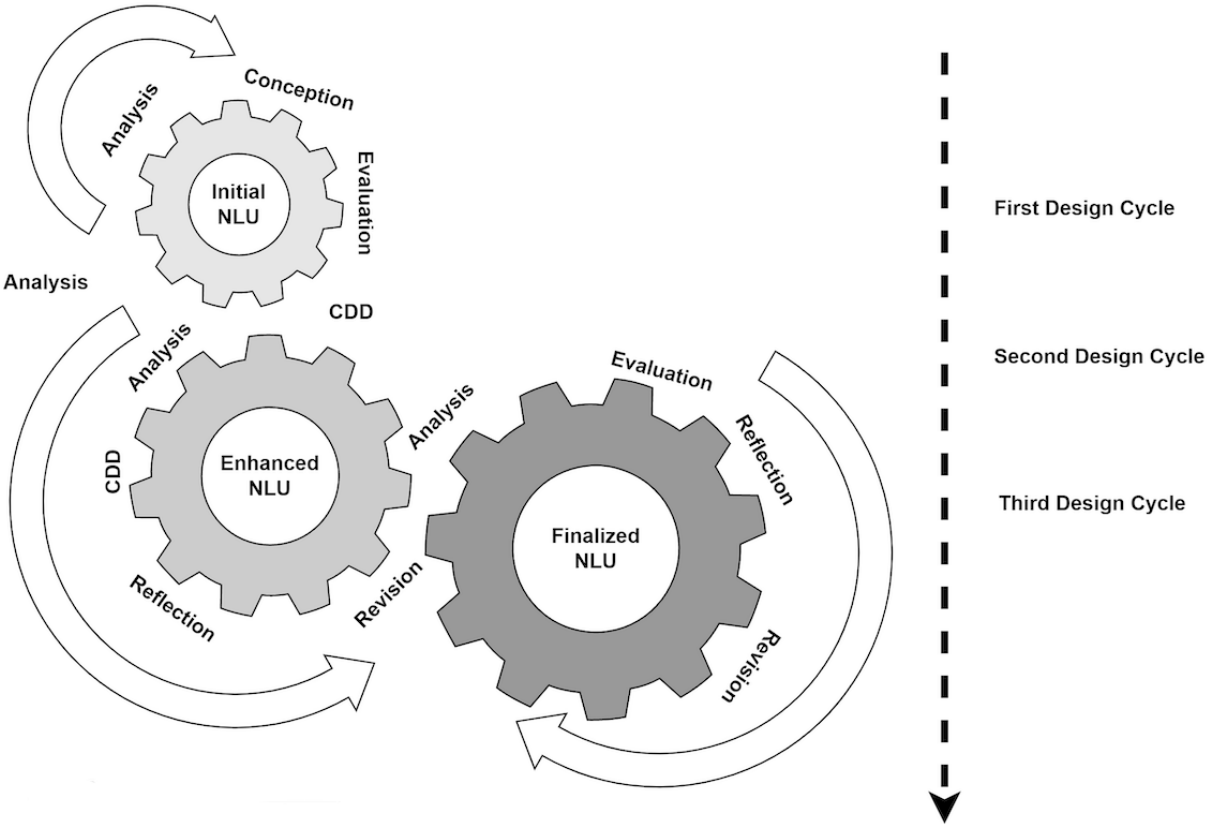
This study entails a pragmatic approach that focuses on the practical application of the DBR methodology. Pragmatism is closely connected with DBR [36] as it allows one to go deeper into a data set to comprehend its significance and utilize the experimental approach to validate conclusions with consideration to subsequent iterations of the design.

As a public health education intervention, VWise CA conception will be considered an educational innovation potentially compatible with all generic DBR frameworks that aim to help design such a technological tool.

Study Phases

Aligned with DBR principles, this study will proceed in iterative cycles, as illustrated in Figure 2. The final objective is to finalize a natural-language understanding (NLU) model developed through cycles of analysis, design, evaluation, and reflection.

Figure 2. The study iterations cycles. CDD: conversation-driven development; NLU: natural-language understanding.



First Design Cycle: WHO-Based CA

Every complete cycle of design consists of three phases: analysis, design, and evaluation. In the first cycle, the analysis and exploration phase will begin with a need analysis establishing deficiencies of current public health education interventions related to vaccine hesitancy. Next, research questions are formulated, and a scoping review is conducted. The purpose at this stage is to understand the use of CAs in health education interventions. Another goal in the analysis phase is to identify the different aspects considered during the design.

In the design phase, the initial NLU model based on the WHO's FAQs data set is developed and integrated using Rasa, an open-source platform for building CAs. During this phase, FAQs are mapped into intents and utters, and the development team creates a set of initial training data to build the first NLU prototype.

Conversational design (CD) will then be implemented to engage the users in the conversation. This helps to elevate the bot from an FAQ level to a more conversational context. The CD part of the CA is based on the Motivational Interviewing (MI) phases [37]. Figure 3 shows the conversation framework based on the MI phases.

A dialogue map defines various dialogue stages that constitute the conversation flow in each MI phase. Each phase can be divided into sub- or microphases (1.1, 1.2, etc). Rasa Map defines the technical aspect of, for example, how a concern is identified and stored in a database for analysis at a later stage.

The first step is bot introduction, where greeting and collection of user demographics (Vaccine status, age, and gender) occur. Concern identification is a crucial part of the whole process determining the framework's branching. Then, the user's knowledge is challenged to establish the level of awareness and readiness for the educational part. Education is thereby provided in accordance with previous data collected. Finally, opinion about the new information presented is gathered at the latest stage.

Best practices from Rasa documentation [38] are also considered in this phase. This means that remarks and observations made from a project management perspective during the analysis phase are encapsulated in the initial model. This basic chatbot is then tested within the team (team members who were not part of the bot's development to avoid biasing) in 5 testing rounds, each being a microcycle in the design phase.

The evaluation and reflection phase consists of several internal testing cycles. In addition, a conversation-driven development (CDD) process, which is a method that encourages listening to users and using their insights to improve the AI assistant, is also initiated at this stage [39]. As an overarching best practice approach for chatbot development, the CDD approach includes the following actions: (1) we will share the assistant with users as soon as possible, (2) we will review conversations regularly, (3) we will annotate messages and use them as NLU training

data, (4) we will test that the assistant always behaves as expected, (5) we will track when the assistant fails and measure its performance over time, and (6) we will fix how the assistant handles unsuccessful conversations.

As illustrated in Figure 4, the CDD method is not a linear process; the chatbot designer should iterate repeatedly as the development and improvement of the bot are needed.

Figure 3. Conversation framework based on Motivational Interviewing (MI) techniques.

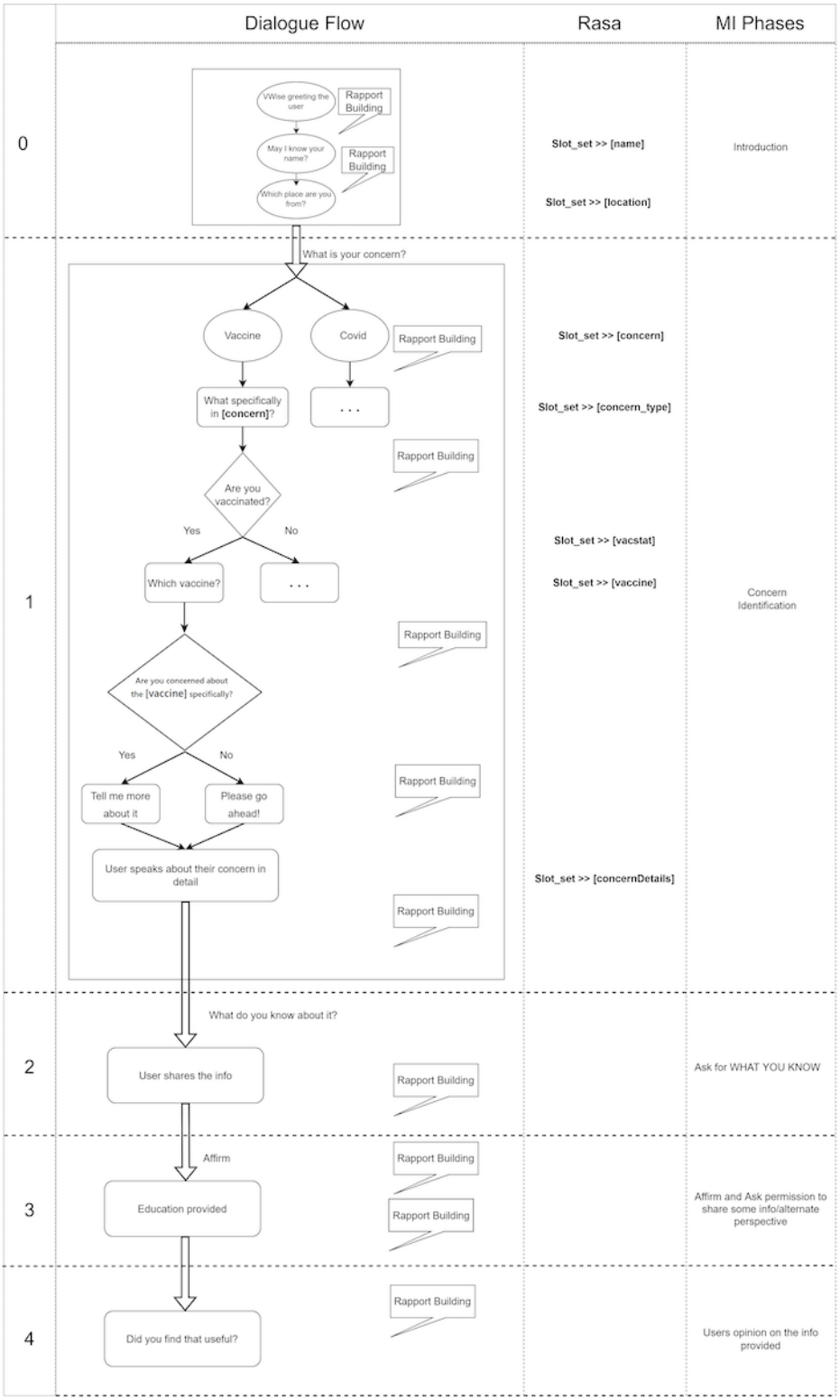
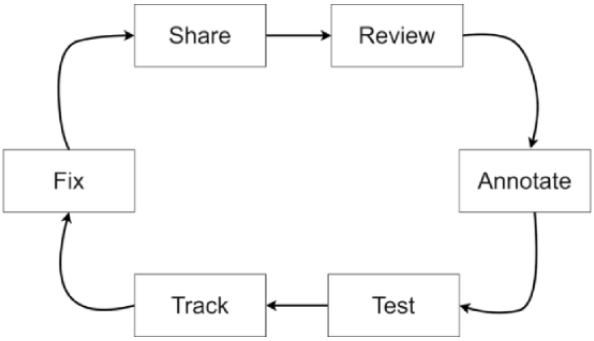


Figure 4. The iterative conversation-driven development (CDD) process.



The System Usability Scale (SUS) will be adopted in the reflection phase since it is a well-established usability instrument that has been used repeatedly [40,41]. It should be noticed that this is not a standardized way of assessing CAs, as in many cases, a single survey question was utilized as an alternative [30]. Unlike evaluating the CA performance in terms of usability, performance evaluation will also improve the intent-utter predictions. First, we shall calculate the conversations' precision, recall, and F1-score by establishing a confusion matrix of intents. The three measurements are defined as follows:

Precision (P) = (True positives) / (True positives + False positives)

Recall (R) = (True positives) / (True positives + False negatives)

F1-score = 2 × [(P × R) / (P + R)]

Second, the PARADISE (PARAdigm for Dialogue System Evaluation) framework [29] will provide better conversational value to the CA.

This method uses a decision-theoretic framework to specify the relative contribution of various factors to an agent's overall performance. The method states that the performance of a chatbot can be associated with the external criteria (user satisfaction), which is the goal of chatbot development. Task success and dialogue costs are the two factors that contribute to achieving this goal. The κ coefficient is used to understand the task success. Cost measures considered in PARADISE reflect both naturalness and efficiency of a chatbot's behavior.

An attribute value matrix is constructed, which represents the dialogue tasks. This consists of the information that must be exchanged between the agent and the user during the dialogue. It is represented as a set of ordered pairs of attributes and their possible values.

Performance evaluation for an agent requires a corpus of dialogues between users and the agent, in which users execute a set of scenarios. κ is calculated from a confusion matrix that summarizes how well an agent achieves the information requirements of a particular task for a set of dialogues instantiating a set of scenarios.

The values in the matrix cells are based on queries and their corresponding responses by the CA. For a particular user query, if the predicted response matches the intended response, the number in the appropriate diagonal cell of the matrix is incremented by 1. The off-diagonal cells represent misunderstandings that are not corrected in the dialogue. For example, "mourn" could be confused with "morning." The effect of misunderstandings that are corrected during the dialogue is reflected in the costs associated with the dialogue. An example of a confusion matrix built on a subset of intents is shown in Table 1.

Table 1. An example of the confusion matrix.

Intents	greet	Side-effect	Vaccine safety	mRNA	affirm	Recall	Precision	F1-score
greet	10	—[a]	—	—	1	0.091	0.909	0.165
Side-effect	—	13	7	—	—	0.65	0.867	0.743
Vaccine safety	—	2	5	—	—	0.714	0.417	0.527
mRNA	—	—	—	8	—	1	1	1
affirm	1	—	—	—	9	0.9	0.9	0.9

[a]—: Not applicable.

Columns represent the key, specifying which information values the agent and user were supposed to communicate to one another given a particular scenario. Rows represent the data collected from the dialogue corpus (final NLU), reflecting what attribute values were communicated between the agent and the user.

In a confusion matrix M, success in meeting the information requirements of the task is measured by κ [42]:

$$\kappa = [P(A) - P(E)] / [1 - P(E)]$$

P(A) is the proportion of times the actual answer matches the prediction. P(E) is the proportion of times the actual response and prediction should coincide by chance. The value of κ is always between 0 and 1. If no random match is expected, κ would be 0. If there is a complete match, κ=1 [43].

Second Design Cycle: Subject Matter Expert–Based CA

As explained previously, DBR is an iterative process; therefore, the three phases of analysis, design, and reflection are continuously repeated in each design cycle. In addition to the results of the preceding cycle, the new input to this new cycle of analysis and exploration will be the intervention of subject matter experts as part of the CDD process. They will analyze, review, annotate, and correct the previous NLU model through conversations data that will result from the previous iteration. Errors and imperfections will be flagged and annotated for the technical team to adjust and incorporate during the new design cycle. A revised NLU model will be generated, trained, and then integrated to fuel a new pilot round that will provide data for reflection and revision. All evaluation metrics used during the first design cycle will be repeated to compare the evolution of the CA design.

Third Design Cycle: Final CA

To complete the third iteration of the design cycles, the three phases will again be conducted, but this time as a consolidation iteration that explores previous flaws, mismatches, and analyses recurring errors and identify deep issues in the prior design of the NLU model. The correction will then be implemented and tested for compliance and alignment with the final expected outcomes. Thus, the last pilot will be carried out as part of the evaluation and reflection phase to ensure the reliability of the NLU model and conclude the design cycles to implement the CA for a larger group of participants via social media platforms.

Data Collection

This study will utilize a convenience sampling approach to recruit participants. Since no sample size recommendation is noticeable in the literature as data sufficiency, a sample size of 500 participants is expected throughout the entire design iterations. New participants are needed for each iteration in accordance with Rasa's best practice for building CAs. Data will be collected via a web server hosted locally at Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU), and only the research team will be accessing data. Participants will be prompted to conversate with the chatbot directly. First, a consent form is completed, and then the conversation begins in accordance with the dialog flow designed. Demographic data such as age, gender, nationality, and vaccination status will be collected from participants anonymously. Concerns and specific knowledge are then discussed, as well as readiness to receive new information.

Users will be invited to interact with the chatbot as much as they want with only a notice that they must respect a minimum of 10 minutes to be considered valid entry data to the analysis. They can ask questions about COVID-19 and vaccination in their own words. Participants will then be asked about their experience with the chatbot using the SUS.

Ethical Approval

The research protocol was approved by the Ethical Review Board of MBRU, located in Dubai, United Arab Emirates, in October 2021 [Approval no MBRU IRB-2021-67].

Data Analysis

Conversation data are reviewed at each evaluation iteration through the Rasa X graphical user interface to improve the NLU model on the basis of messages from the same real conversations. Annotating user messages is a great way to understand the bot's successes and failures and add data that reflect what real users are saying to the assistant. The Insights section in Rasa X will help understand how to improve NLU training data. It will also provide various suggestions for the messages in the NLU inbox.

Among other things, Rasa X uses cross-validation results to identify problems in the training data. It uses 4-fold cross-validation, meaning that it trains four models on 80% of the training data and evaluates them on the remaining 20%. A minimum number of examples calculator ensures that each intent has at least this number of examples (20 by default); otherwise, a new insight is created [44].

When reviewing conversations, tags are created to track what happened in conversations and mark specific messages to pinpoint problems. In addition, these tags can filter conversations to help find successful and unsuccessful conversations.

Using the examples provided as training data, a confidence score is computed for each user's intent. The confidence value is computed as a similarity index after deriving appropriate features embedded in a high-dimensional plane. The response corresponding to a higher confidence value is selected as the response from CA to the user intent. The confidence values for each user query and intent are available in the tracker memory and can be written to a database for further analysis.

To measure users' satisfaction with VWise, usability will be evaluated after the testing phases of each design cycle using SUS. As a nonproprietary and technology-agnostic metric, this user experience assessment will help inform every new design cycle for quality improvement. The precision, recall, and F1-score will be calculated through the confusion matrix, giving insight into how well VWise is achieving the information requirements of a task for a set of dialogues. The dialogue success will be captured later from κ as part of the PARADISE paradigm that will be adopted carefully to the application of this study [42].

Results

As of this writing (April 2022), an initial NLU model was designed. The research team reviews the model as part of the CDD process, preparing it for the first pilot that will wrap up the first design cycle of the CA. Conversational data collected via Rasa X will be analyzed quantitatively and qualitatively (see *Methods*) to inform the reflection and revision phase. Three iterations are identified in this project, resulting in several studies disseminating findings and conclusions. The first study describing the full initial design cycle will be submitted for publication before the end of 2022.

We aim to report all findings in a final scientific paper describing the results of using DBR to conceive a CA that

profiles participants on the basis of their hesitancy to get vaccinated and addresses their concerns by the end of the three design cycles.

Discussion

Expected Findings

This research examines the hypothesis that DBR can improve the accuracy and performance of a CA.

This protocol describes the research and design methods and processes to develop a contextual CA to address, profile, and inform about vaccine hesitancy. In addition, this study protocol contributes to understanding how DBR can drive chatbot design and conception and enhance its performance for public health education interventions starting from FAQ data sets and AI best practices.

This protocol needed researchers from different disciplines to establish a common ground for combining machine learning mechanisms and some learning design technics during designing cycles. In addition, some DBR principles and models were expanded or adapted to clarify the overall design process and how to perform such research with the support of this methodology [24].

The perspectives of AI, public health education, and learning design are combined to generate insight into vaccine hesitancy attitudes and behaviors when confronted with CAs as health education tools. This resulted in the approach that combines these perspectives inside a generic iterative methodology that can inform similar research interventions.

Owing to its holistic approach, this protocol is particularly valuable. In this approach, the respect for the three iterative phases in a design cycle plays an essential role in generating the final NLU model. The more traditional ways of applying DBR are often too generic to accommodate the design of a health education tool such as the VWise agent.

A more generic strategy is provided to start the following design cycle process by complementing the first iteration of the designing cycle. The adaptation and expansion of such a methodology have been discussed before in the literature [24,27,45]. For example, it is emphasized that it is required to build on the generic concept of DBR as traditionally perceived by addressing the process's subcomponents in terms of different-sized cycles, notably micro-, meso-, and macrocycles [24,45].

This research can bring together multidisciplinary teams to understand the CA design process. Furthermore, this novel approach will help establish DBR in the AI environment, bridging engineering principles and research methodologies to serve different applications that can benefit multiple fields.

Owing to the multidisciplinary nature of this research project, we hope that our efforts to describe the research approach will contribute to the reliability and reproducibility of this type of research, particularly in public health education.

Limitations

One of the limitations of the protocol is the convenience sampling approach utilized in the pilot studies during the evaluation phases.

While convenience sampling could potentially introduce bias to the study results [46], there is another problem that is of great concern in this context—outliers. Because of the high possibility of self-selection in nonprobability sampling, the effects of outliers can be even more devastating in this type of subject selection. Outliers are cases that are considered not to belong to the data. In a random sample, however, neither outliers nor their probabilities are quantified [47]. The researcher does not know how well a random sample represents the population in terms of the characteristics or mechanisms being studied. What makes samples so unpredictable is their susceptibility to serious hidden biases [48].

On the other hand, this method is still a practical approach used by various studies, especially in the absence of a sampling frame. However, we expect this to be a minor issue of the study as this phase aims to test the NLU models only, and all revisions will be based on the researchers' consensus regarding the best way to correct and address flaws. Another limitation is the lack of models and frameworks that can guide this approach as a reference to DBR application to the CA's field.

Conclusions

Developing a highly accurate CA is vital to delivering any behavioral health outcomes. To develop a CA that can significantly impact vaccine hesitancy, it is crucial to address real users' needs that are exposed daily to an enormous amount of misinformation, offer consistent and reliable data to gain trust and credibility, and most importantly, adapt and contextualize responses. DBR can enhance chatbot performances by providing a pragmatic framework for continuous development and iterative correction. This study will not only offer researchers a validated methodology for designing a CA, but it will also provide a path for scaling public health education projects.

Acknowledgments

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Data Availability

Supporting data cannot be made public owing to ethical concerns. Upon reasonable request to the corresponding author and after the study's findings have been published, data may also be made available.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence

CA: conversational agent
CD: conversational design
CDD: conversation-driven design
DBR: design-based research
FAQ: frequently asked question
MBRU: Mohammed Bin Rashid University of Medicine and Health Sciences
MI: motivational interviewing
NLU: natural-language understanding
PARADISE: PARAdigm for Dialogue System Evaluation
PBL: problem-based learning
SUS: System Usability Scale
WHO: World Health Organization

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Protocol

Continuous Remote Patient Monitoring in Patients With Heart Failure (Cascade Study): Protocol for a Mixed Methods Feasibility Study

Courtney Reamer[1], MD; Wei Ning Chi[2], MBBS, MPH; Robert Gordon[1], MD, PharmD; Nitasha Sarswat[1,3], MD; Charu Gupta[1], MD; Safwan Gaznabi[1], MD; Emily White VanGompel[4], MPH, MD; Izabella Szum[5], RN; Melissa Morton-Jost[5], MBA; Jorma Vaughn[6], BA; Karen Larimer[6], PhD; David Victorson[7], PhD; John Erwin[1,3], MD; Lakshmi Halasyamani[1,3], MD; Anthony Solomonides[2], PhD; Rema Padman[8], PhD; Nirav S Shah[1,3], MPH, MD

[1]Department of Medicine, NorthShore University HealthSystem, Evanston, IL, United States

[2]Outcomes Research Network, NorthShore University HealthSystem, Evanston, IL, United States

[3]Department of Medicine, Pritzker School of Medicine, University of Chicago, Chicago, IL, United States

[4]Department of Family Medicine, NorthShore University HealthSystem, Evanston, IL, United States

[5]Home and Hospice Services, NorthShore University HealthSystem, Evanston, IL, United States

[6]physIQ, Inc, Chicago, IL, United States

[7]Department of Medical Social Sciences, Northwestern University, Evanston, IL, United States

[8]Heinz College of Information Systems and Public Policy, Carnegie Mellon University, Pittsburgh, PA, United States

Corresponding Author:
Courtney Reamer, MD
Department of Medicine
NorthShore University HealthSystem
2650 Ridge Avenue
Evanston, IL
United States
Phone: 1 847 570 2000
Email: CReamer@northshore.org

Abstract

Background: Heart failure (HF) is a prevalent chronic disease and is associated with increases in mortality and morbidity. HF is a leading cause of hospitalizations and readmissions in the United States. A potentially promising area for preventing HF readmissions is continuous remote patient monitoring (CRPM).

Objective: The primary aim of this study is to determine the feasibility and preliminary efficacy of a CRPM solution in patients with HF at NorthShore University HealthSystem.

Methods: This study is a feasibility study and uses a wearable biosensor to continuously remotely monitor patients with HF for 30 days after discharge. Eligible patients admitted with an HF exacerbation at NorthShore University HealthSystem are being recruited, and the wearable biosensor is placed before discharge. The biosensor collects physiological ambulatory data, which are analyzed for signs of patient deterioration. Participants are also completing a daily survey through a dedicated study smartphone. If prespecified criteria from the physiological data and survey results are met, a notification is triggered, and a predetermined electronic health record–based pathway of telephonic management is completed. In phase 1, which has already been completed, 5 patients were enrolled and monitored for 30 days after discharge. The results of phase 1 were analyzed, and modifications to the program were made to optimize it. After analysis of the phase 1 results, 15 patients are being enrolled for phase 2, which is a calibration and testing period to enable further adjustments to be made. After phase 2, we will enroll 45 patients for phase 3. The combined results of phases 1, 2, and 3 will be analyzed to determine the feasibility of a CRPM program in patients with HF. Semistructured interviews are being conducted with key stakeholders, including patients, and these results will be analyzed using the affective adaptation of the technology acceptance model.

Results: During phase 1, of the 5 patients, 2 (40%) were readmitted during the study period. The study completion rate for phase 1 was 80% (4/5), and the study attrition rate was 20% (1/5). There were 57 protocol deviations out of 150 patient days in

phase 1 of the study. The results of phase 1 were analyzed, and the study protocol was adjusted to optimize it for phases 2 and 3. Phase 2 and phase 3 results will be available by the end of 2022.

Conclusions: A CRPM program may offer a low-risk solution to improve care of patients with HF after hospital discharge and may help to decrease readmission of patients with HF to the hospital. This protocol may also lay the groundwork for the use of CRPM solutions in other groups of patients considered to be at high risk.

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KEYWORDS

continuous remote patient monitoring; remote patient monitoring; feasibility; heart failure; wearable biosensor; preliminary efficacy; mobile phone

Introduction

Background

Heart failure (HF) is a growing global public health concern. Worldwide, the estimated prevalence of HF has increased to >37.7 million cases, and in the United States the estimated prevalence is 6.5 million cases [1,2]. HF is associated with increased mortality, morbidity, and loss of quality-adjusted life years [3]. HF also has a significant economic burden; it is estimated that the overall cost of HF in the United States was US $30.7 billion in 2012, and the total cost of HF hospitalizations in the United States was US $11 billion in 2014 [4,5]. HF is a leading cause of hospitalizations among adults in the United States, and Medicare patients with HF have the highest readmission rates, ranging from 17% to 28.2% [3,5].

HF readmissions have become an increasing focus of quality improvement, and many readmissions are viewed as preventable [4,5]. The Affordable Care Act initiated the Hospital Readmission Reduction Program, which imposes a financial penalty on hospitals with excess 30-day unplanned readmissions [6]. Although these measures have been somewhat effective, additional strategies are necessary to continue improvement in this metric [5]. A promising strategy for improving outcomes in HF, including readmissions, is the use of mobile health (mHealth) solutions.

Related Works

The use of mobile apps is an area of mHealth strategies that have the potential to improve care for patients with HF. Patient-facing apps that focus on self-care and self-monitoring constitute one such area of interest. A meta-synthesis of mobile apps in cardiovascular disease found that mobile apps can help to improve modifiable risk factors for cardiovascular disease [7]. Schmaderer et al [8] developed a mobile app that enabled patients to record their daily weight and medication and provided patients with reminders and educational tips. The authors completed a randomized 3-arm trial that found that patients randomized to the mobile app group or the mobile app plus internet-based–visit group had a trend toward improvement in health-related quality of life [8]. Another study performed a randomized controlled trial on the impact of a mobile app that promoted self-management and daily self-monitoring and found a statistically significant improvement in the Minnesota Living with Heart Failure Questionnaire score at 6 weeks but not at 12 weeks [9]. Overall, interventions using mobile apps alone, without other support built in, have had limited success in improving outcomes in patients with HF [8,9]. However, mobile apps have the potential to improve health, given their prevalence and portability, as well as their ability to record data, connect people, monitor activity, and provide patient-centric health care solutions. Ultimately, there is a further need for systemic assessment of potential mobile apps [10]. In addition, it is possible that mobile apps built in as part of an mHealth solution, as opposed to being the sole intervention, might lead to a more significant improvement in health-related outcomes.

Another possible mHealth approach for improving HF outcomes is remote patient monitoring. These solutions include the use of wearable or implanted devices, mobile apps, or other electronic devices that transmit data to health care providers. Implantable devices have shown potential as one such option for remote patient monitoring. The CardioMEMS Heart Sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA Functional Class III Heart Failure Patients trial evaluated the use of CardioMEMS, an implanted pulmonary artery pressure–monitoring device, and demonstrated a reduction in morbidity, mortality, and hospitalization rate in patients with HF [11]. Hindricks et al [12] performed a randomized controlled trial evaluating the use of implant-based multiparameter telemonitoring compared with usual care in patients with new implantable cardioverter defibrillators or cardiac resynchronization therapy defibrillators and found that the telemonitoring group had a lower mortality score. Overall, some invasive remote monitoring solutions have demonstrated improvements in mortality [11,12] and a decrease in health care costs [13], but they have the large disadvantage of the need for an implantable device, leaving a gap for less-invasive monitoring.

Several studies have investigated forms of noninvasive remote monitoring and their efficacy in improving outcomes in HF [14-30]. A study showing a benefit was the Telemonitoring in the Management of Heart Failure study, a randomized controlled trial that evaluated a remote monitoring device that measured body weight, blood pressure, and heart rate [17]. These parameters were obtained daily, and email alerts were sent to providers when predefined criteria for interventions were met. This intervention, compared with usual care, reduced mortality, number of days lost to hospitalization, and death [17]. Overall, results of noninvasive remote monitoring studies have been mixed, with some showing a benefit in reducing mortality [15,17,30], improvement in quality of life [14,19,24,25,28], and

reduction in readmissions [15,18,23,24,28,30], whereas some showed an improvement in outcomes [9,23,24]. Nonetheless, most remote patient monitoring solutions have yet to take advantage of recent advances in biosensor devices and machine learning technologies and thus do not provide intelligent continuous patient monitoring. Furthermore, raw data are typically collected from patients and required to be funneled through already overtaxed clinical providers [31]. In addition, many of the noninvasive remote monitoring solutions for patients with HF have depended on data collected at discrete time points, as opposed to continuously collected data.

Data collected at discrete time points might limit insight into the patient's health status and may not reflect their condition during activities of daily living. There is some evidence that continuous remote patient monitoring (CRPM) might improve outcomes for patients [32-35]. For example, Downey et al [32] compared continuous vital sign monitoring with discrete vital sign monitoring in patients hospitalized after surgery and found that the continuous remote monitoring of vital signs group had a shorter length of stay and had fewer readmissions than the discrete vital signs monitoring group. Several studies have demonstrated that noninvasive CRPM can be used to help predict readmissions in patients with HF [36-38]. For example, Anand et al [36] completed a nonrandomized, prospective trial of 314 patients with HF where they used vital signs collected from an external chest sensor to develop and validate an algorithm to predict decompensation in patients with HF. They found that the algorithm had 63% sensitivity and 92% specificity in the validation cohort [36].

The latest advance in CRPM is pairing it with advanced machine learning analytics. By using a patient's continuous physiological data stream and applying machine learning analytics, it is possible to detect a change in health status that is unique to that patient and not measured against population norms. Promising data supporting this were presented in phase 1 of this study. We found that elevated respiratory rate for individual patients may be associated with readmission [39]. Furthermore, the Multisensor Non-invasive Remote Monitoring for Prediction of Heart Failure Exacerbation study found that with a sensitivity of 87.5% and specificity of 86%, the analytics were able to predict worsening HF (rehospitalization), with a median time between the initial notification of a variance in vital signs and readmission of 6.5 (IQR 4.2-13.7) days [38]. This suggests there may be time to intervene before decompensation and readmission.

Study Development

Because of the complex medical needs of patients with HF, it is thought that interventions to improve quality of life and health-related outcomes will need to be multipronged and complex [27,40]. Given this, small-scale feasibility pilot studies are useful to determine the feasibility of intricate interventions and allow for refinement of the intervention [41]. We developed an interest in the potential of mHealth solutions to improve outcomes in patients with HF and specifically wanted to study a CRPM system with machine analytics because we feel that this is an untapped area that has the potential to improve outcomes [32-36,38,39]. We therefore developed a cascading-alert continuous remote monitoring system. Because of the complexity of this intervention, we have opted to develop a multiphase pilot feasibility study, with plans for a separate efficacy trial at a later date after the system has been fine-tuned and determined to be feasible.

Objectives

We hypothesize that a continuous noninvasive remote monitoring solution with machine learning analytics used in a population with HF will lead to an earlier and more accurate prediction of decompensation and help to prevent readmissions. Therefore, the objective of the Cascade study is to evaluate the feasibility and preliminary efficacy of a CRPM program at NorthShore University HealthSystem (NSUHS).

Methods

Study Design and Implementation

This is a prospective, mixed methods, nonrandomized, open-label feasibility study. Phase 1 (n=5) was the soft launch and has already been completed [39]. Phase 2 (n=15) is a calibration and testing period to evaluate, adjust, and optimize the alerting criteria, monitoring protocol, and workflows. Phase 3 (n=45) is the pilot period of the optimized study protocol. The study outcomes include feasibility and preliminary efficacy, as well as operational, process, and patient-related outcomes. Feasibility will be determined by evaluating provider and patient acceptability and satisfaction and by evaluating the study attrition and study completion rate. Provider and patient acceptability and satisfaction will be assessed through qualitative measures using the affective adaptation of the technology acceptance model (A-TAM) [42]. Preliminary efficacy will be determined by comparing the study group readmission rate with a retrospective cohort readmission rate.

The study will use the pinpointIQ (physIQ) solution to continuously remotely monitor patients with HF for 30 days after discharge. We will use rules-based and machine learning algorithms to analyze patients' physiological data collected from the VitalPatch biosensor (VitalConnect) to identify patients potentially at risk of decompensation. A structured cascading escalation and management care pathway will be used to intervene on patients determined to be at risk for decompensation.

Participants

Participants will be recruited at NSUHS, which is a 9-hospital integrated health system in Chicago and surrounding suburbs in Illinois, United States. The intervention will be implemented at Evanston Hospital, a 354-bed hospital located in the Chicago suburbs, which has a cardiac care unit and an advanced HF cardiology consult service.

Recruitment

Eligible participants are recruited from patients hospitalized at NSUHS with an HF exacerbation. A daily enterprise data warehouse query is executed to identify patients hospitalized with an HF exacerbation who meet the eligibility determined by specific inclusion and exclusion criteria. Patients considered for participation have an HF diagnosis, have New York Heart

Association functional class II to class IV symptoms, have received at least one dose of an intravenous (IV) diuretic during their hospitalization, have a plan for discharging with partnering home health services, speak English, and are in the top 50% of the patients stratified using NSUHS's 30-day readmission risk–prediction model called the clinical analytics prediction engine [43]. Patients are not considered if they meet any of the exclusion criteria, which include having a CardioMEMS device; having an allergy to hydrocolloid gel adhesive; being pregnant; being on dialysis; or having a documented visual, cognitive, or physical impairment that would interfere with the ability to comply with the study procedures.

Device and Notification Mechanisms

The study uses the pinpointIQ solution, which includes Food and Drug Administration–cleared analytics that can provide early indication of patient deterioration and is capable of generating clinician-defined–event notifications. This is a closed loop monitoring solution that comprises a medical-grade biosensor with remote data collection capabilities, a smartphone app that acts as a data hub and electronic patient-reported outcome (ePRO) interface, a cloud computing platform for applying personalized analytics to patient data, a clinician portal for viewing biosensor data and analytics results that generate notifications (Figure 1), and an application programming interface. An overview of the clinician portal interface is shown in Figure 2.

Study participants are provided a chest-worn VitalPatch biosensor to wear, which collects near–real-time continuous ambulatory vital signs, including heart rate, respiratory rate, heart rate variability, activity level, sleep-wake determination, position, and atrial fibrillation detection (includes single-lead telemetry) once discharged. The biosensor is a disposable noninvasive patch that lasts 7 days and is replaced multiple times by the patient in the postdischarge period to have active monitoring for 30 days in total. This biosensor is a vendor medical device and has been tested separately from this study.

A study-specific smartphone is provided to the participant. The vendor developed an Android smartphone app that serves as the gateway for real-time data acquisition through Bluetooth from the biosensor. It also provides an interface for ePRO questionnaires (Figure 3). The vendor used data from focus groups of patients with chronic illness in the age range of the typical user to inform the smartphone app design. The app runs on a dedicated locked smartphone that is configured only to run the app, which has been validated to reliably interface with, and collect data from, the biosensor. The app interacts with the biosensor in real time and uploads data directly to the vendor platform over a secure cellular network connection. The app also provides patients with indications for proper data collection and escalating notifications of potential data loss, including connectivity issues, low battery, low memory, and unanswered questionnaires (Figure 4). If a patient is out of range with the smartphone, the data are still collected and stored by the VitalPatch biosensor for 8 hours. When the patient comes back into range with the smartphone, the collected and stored physiological data start uploading to the cloud again. The study smartphone's battery life is approximately 12 hours, and the patients are trained to charge the study smartphone daily.

The patient is given a separate study smartphone as opposed to using their own mobile phone for a few reasons. First, many older patients with HF do not own a smartphone; providing them with a study smartphone helps to include patients with HF who may otherwise be excluded from the study. Second, the study smartphone only contains the vendor's app; if the patient ever loses the study smartphone, the vendor can remotely wipe the smartphone's data to ensure that patient privacy is protected. The study smartphone is slim and easy to carry, and most patients do not find having 2 mobile phones inconvenient.

The physiological data are transmitted from the study smartphone to the cloud and analyzed by rules-based and machine learning algorithms to help identify risk of decompensation in patients with HF. The data transmission pathway is shown in Figure 5. Rules-based notifications include tachypnea, tachycardia, bradycardia, atrial fibrillation, and atrial fibrillation with rapid ventricular response. The multivariate change index (MCI), a machine learning–based notification, is also calculated from the physiological data [38]. The MCI is a nonspecific patient deterioration model that trains on the first 48 hours of a patient's physiology and then measures the difference between expected and observed physiology and signals in the clinician portal when there is a significant difference in these measurements. The system specifically calculates an MCI in relation to heart rate and respiratory rate and evaluates for 3 different MCI notifications: MCI elevated heart rate, MCI depressed heart rate, and MCI elevated sleeping respiratory rate.

Figure 1. Overview of the clinician portal showing the portal, possible clinician-defined events, and a notification. HR: heart rate; MCI: multivariate change index; RR: respiratory rate; RVR: rapid ventricular response.

Figure 2. The clinician portal showing an alert and clinical events, where green dots represent events that have been seen already, and red dots represent new events.

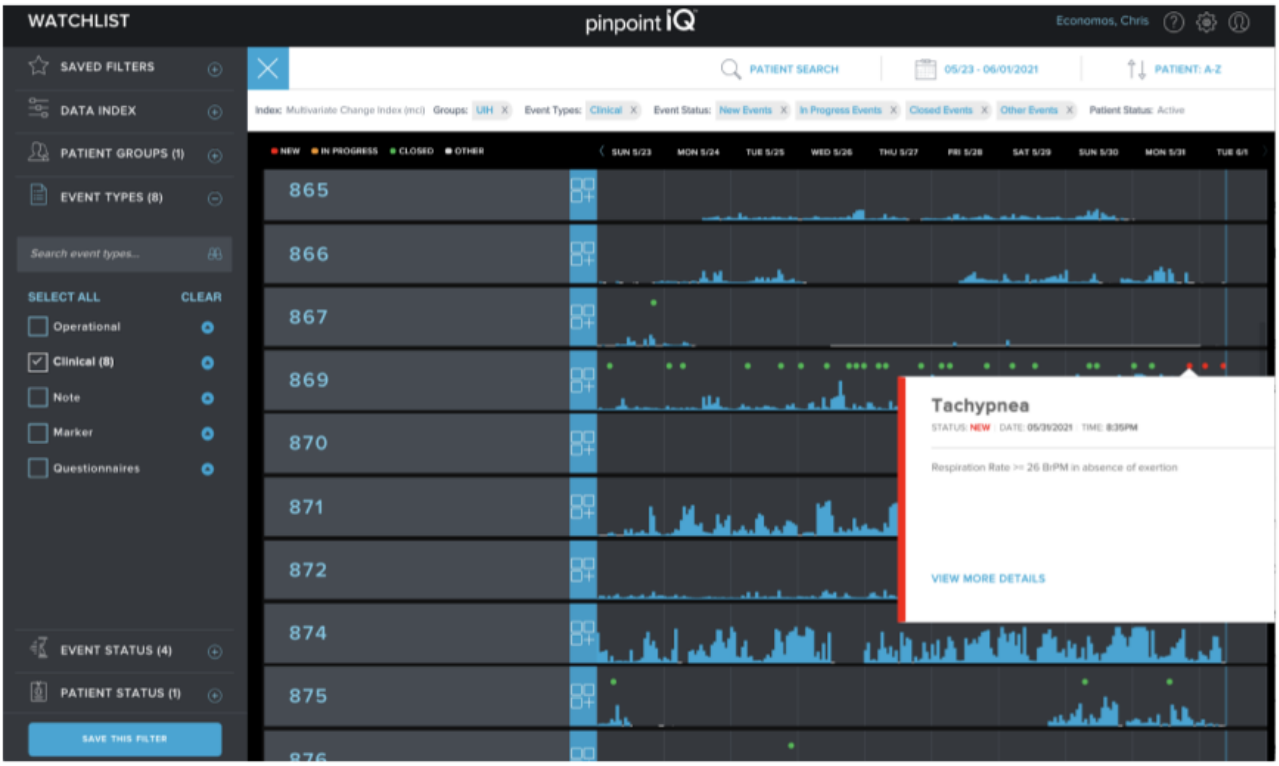


Figure 3. The daily symptom survey on the mobile app.

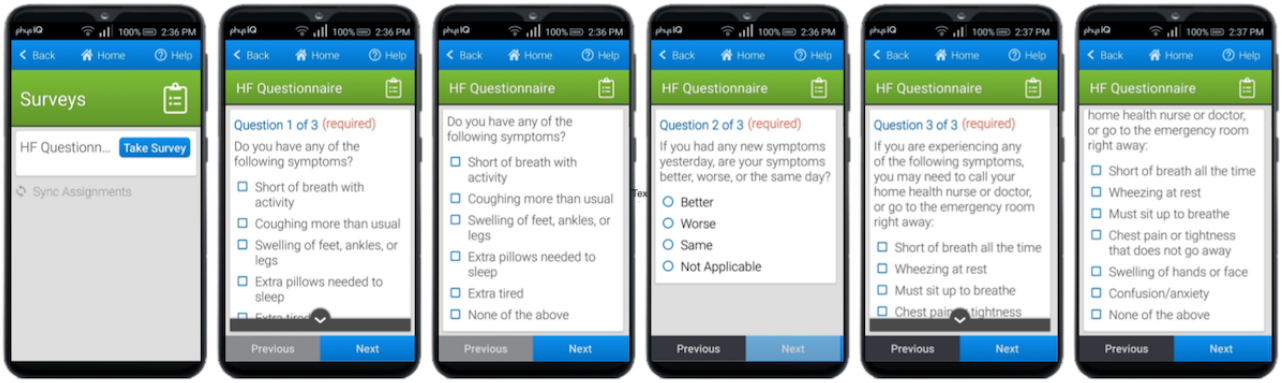
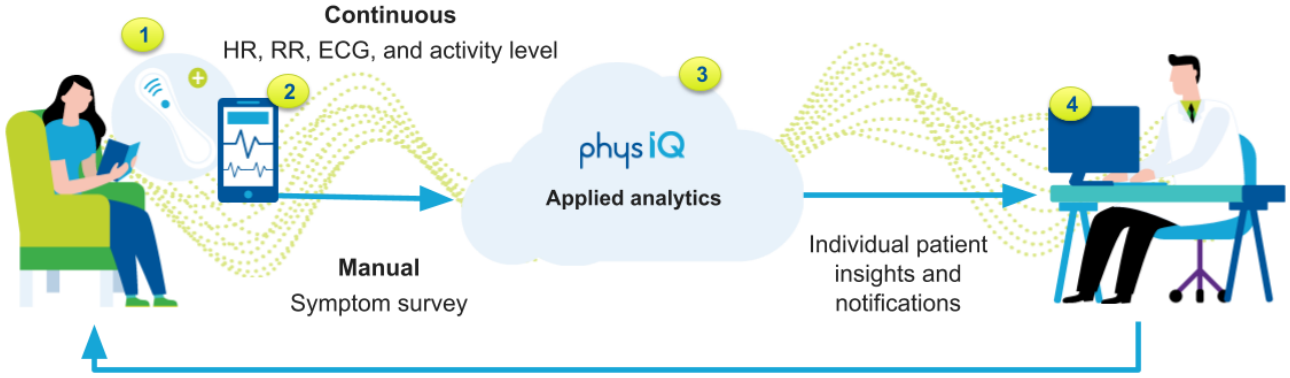


Figure 4. Mobile app alerts.

Figure 5. Data transmission pathway. ECG: electrocardiogram; HR: heart rate; RR: respiratory rate.



The patients also complete a daily symptom survey (Figure 3) on the study smartphone based on the criteria from the HF zone tool, which is transmitted to the clinician portal [44,45]. Physiological notifications and daily symptom survey data (ePROs) are visible to the home health nurse (HHN) on the clinician portal. If predetermined criteria from the physiological events and ePRO responses are met, a structured and predefined electronic health record (EHR)–based pathway of health care provider telephonic management is initiated. The HHN is the first human in the loop in the cascade. If HHN escalation criteria are met, advanced practice providers (APPs) and potentially HF specialists are notified based on the acuity, type of clinical event, and call roster.

Workflow and Clinical Management

The workflow process map is shown in Figure 6. The HHN reviews the web-based platform daily for any clinical event–driven notifications. The daily ePRO, which includes the patient's daily weight and whether they are having symptoms related to HF, is also reviewed [44,45]. If a patient reports any symptoms on a particular day, the patient survey will also ask whether the symptoms are getting better, worse, or the same the following day.

If there are any red zone symptoms reported, which include symptoms of chest pain, shortness of breath at rest, wheezing at rest, swelling of the hands or face, confusion, anxiety, or feeling as though they must sit up to breathe, the HHN will call the HF specialist or send the patient to the emergency department (ED).

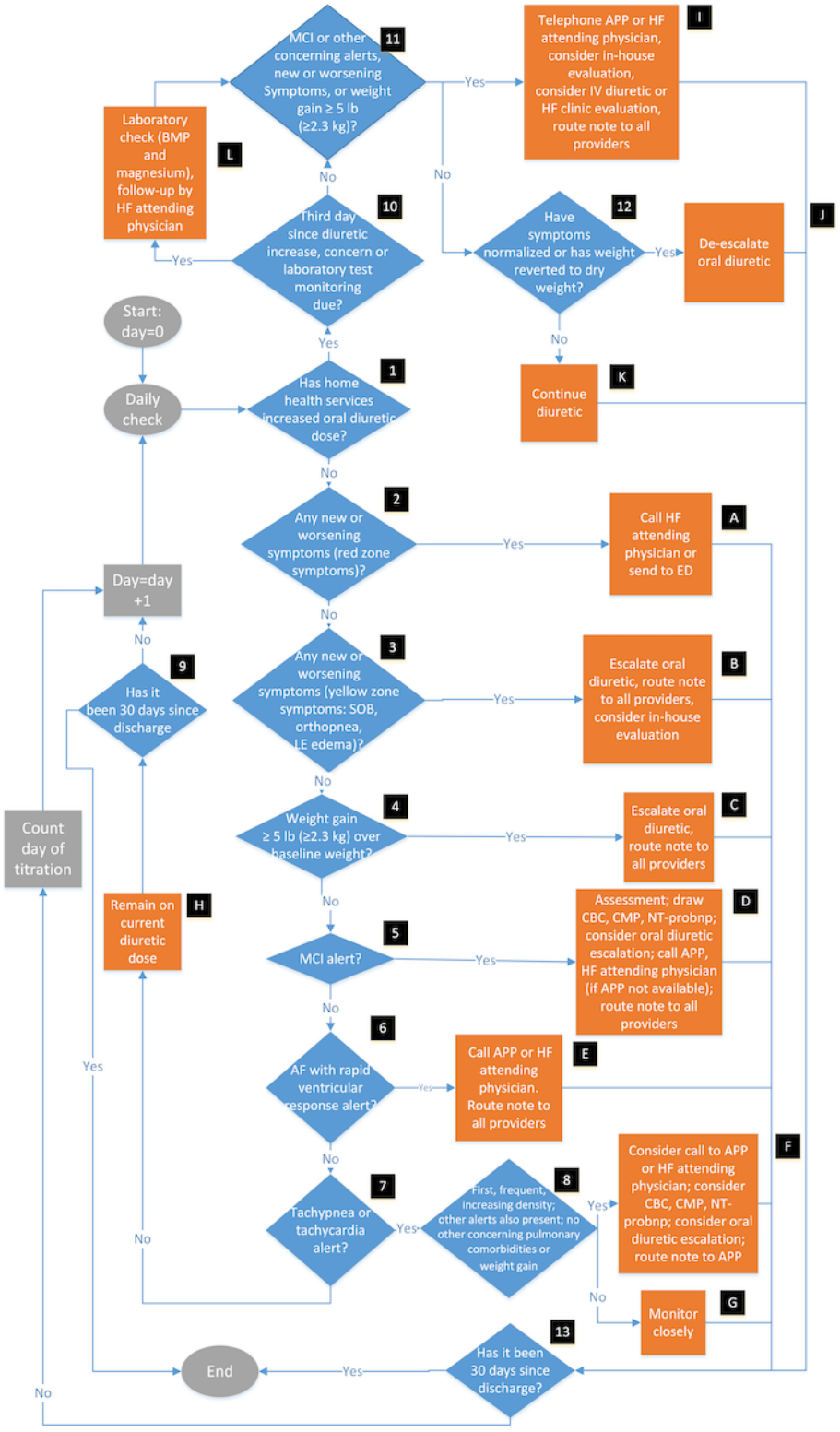
If there are any new or worsening symptoms of shortness of breath, orthopnea, or lower extremity edema (yellow zone symptoms), the HHN will call the patient and complete the structured EHR documentation note. The HHN documentation note provides automated management recommendations based on the information filled out in the note. In the case of a note stemming from new or worsening yellow zone symptoms, recommendations include increasing the oral diuretic dose and considering an in-house evaluation. The note will be forwarded to the APP pool and the patient's HF specialist. The APP in turn will schedule a telephone visit with the patient and determine whether the patient needs home IV diuresis. If so, they will provide a prescription for this, and home health services will start IV diuretics at home. The HF attending physician and the HHN will be alerted of this plan.

If the patient has a weight gain of ≥5 lb (≥2.3 kg) compared with their baseline weight, the HHN will call the patient and complete the structured documentation note. Potential automated recommendations to consider include escalating the oral diuretic dose. The HHN will route the note to both the HF APPs and attending physician. The APP will follow up with the patient and schedule a telephone visit with the patient. The APP will assess whether the patient needs home IV diuresis, and if so, they will prescribe it. This plan will be communicated to the HF attending physician and the HHN.

If there is an MCI event, the HHN will call the patient and complete the structured note. Management recommendations include sending a visiting HHN to draw a complete blood count, a complete metabolic panel, and an N-terminal pro–B-type natriuretic peptide, as well as possible oral diuretic dose escalation. The HHN will also call the APP and route their note to the APP and HF attending physician. The APP will schedule a telephone visit with the patient and follow up on any laboratory test results. On the basis of their telephone visit, the patient's ePROs, and any laboratory test results obtained, the APP will form a clinical assessment regarding the patient. On the basis of this assessment the APP will determine whether any of the following is indicated: an escalation of the oral diuretic dose, an urgent in-person clinic visit, and whether the HF attending physician needs to be alerted.

If there is an atrial fibrillation with rapid ventricular response event, the HHN will call the patient and complete the structured EHR note, call the APP or HF specialist, and route the note to the APP pool and HF specialist, or send the patient to the emergency room. If the APP is alerted to an atrial fibrillation with rapid ventricular response event, they will review the vendor platform to assess the event and the patient's vital signs obtained from the biosensor. They will also schedule an urgent telephone or video visit with the patient to further assess them. The APP will determine whether the patient needs to be sent to the ED or whether the patient can be safely managed at home. The APP will also discuss their assessment with the HF attending physician to ensure that they agree with the plan.

Figure 6. Workflow process map. AF: atrial fibrillation; APP: advanced practice provider; BMP: basic metabolic panel; CBC: complete blood count; CMP: comprehensive metabolic panel; ED: emergency department; HF: heart failure; IV: intravenous; LE: lower extremity; MCI: multivariate change index; NT-proBNP: N-terminal pro–B-type natriuretic peptide; SOB: shortness of breath.



If there is a tachypnea or tachycardia event, the HHN will evaluate whether this is the first time such an event has occurred or whether there is any increasing occurrence of these events. If so, the HHN will call and assess the patient and complete the structured note. Recommendations for management include calling the APP and HF specialist, considering conducting basic laboratory tests, and considering an oral diuretic escalation. If the APP or HF specialist is contacted, they will review the vendor platform and have a telephone visit with the patient. On the basis of their clinical assessment, they will consider an oral diuretic dose increase and determine whether the patient needs to be seen for an in-person visit. The telephone visit assessment will be sent to the HHN.

If the patient's diuretic dose has been escalated or if they are on IV diuretics, the patient's laboratory test results will be checked on the third day of taking an escalated dose. If a patient on an already escalated diuretic dose has an event notification, new or worsening symptoms, or increased weight gain, the HHN will call the APP or HF specialist for further guidance. Recommended interventions include a home evaluation, an urgent HF clinic evaluation, or an IV diuretic at home. A patient's escalated diuretic dose will be de-escalated once their symptoms have resolved or their weight has reverted to their dry weight (normal weight without any extra fluid in the body).

If a patient has >1 alert, the pathway for the alert deemed more severe will be followed. The severity of alerts in order from more severe to less severe are as follows: any new or worsening red zone symptoms, any new or worsening yellow zone symptoms, weight gain of ≥5 lb (≥2.3 kg), an MCI alert, an atrial fibrillation with rapid ventricular response alert, and a tachypnea or tachycardia alert. For example, if the patient has a new red zone symptom and an MCI alert, the pathway for the red zone alert will be followed. The more severe alerts are depicted higher up on the workflow shown in Figure 6.

When the HHN escalates care to the APP or HF specialist, suggested management and treatment plans will be available to the clinical care team, but nuanced clinical judgment is ultimately left to the provider in managing these patients with complex medical needs.

Data Collection and Management

Clinical data, such as demographics, comorbidities, laboratory test results, procedures, medications, communications, office visits, and hospitalizations, as well as outcomes, such as 30-day readmission rates, for each patient are collected from the EHR. CRPM data, including raw physiological and operational data, clinical and operational notification data, and ePRO data, are collected from the vendor platform. All study information is being stored on NSUHS's password-protected encrypted computers and password-protected servers.

Patients are given a unique study record number. The unique study record number is different from their medical record number. This unique record number is used to identify the patient on the vendor web platform. In addition to the study data, the study team collects patient name, medical record number, date of birth, and telephone number for the purpose of conducting the study and links this information to the unique study record number. This information and the key that links the unique study record number to the patient is stored on NSUHS's secure server and only shared with the HHNs and the HF team involved in the study for patient care management. No personal health information is provided to the vendor or other study team members outside of NSUHS. All patient information is aggregated during study analysis, and no identifiers will be provided in the analysis. Upon study completion all study data will be destroyed, and verification will be provided to data governance.

During informed consent and enrollment, the study coordinator makes sure that patients are alone or in a room with family members who the patient agrees can participate in decision-making around the study. The door is closed, and the collection of any study-related information is paused when other staff or visitors enter the room. We allocate 1 hour for consent, and if required, we can extend the amount of time to make sure that the patient has all their questions answered and privacy maintained.

Key Outcomes Measures and Statistical Analysis

We will conduct a mixed methods evaluation of the feasibility of the CRPM solution after the completion of all 3 phases of the study. Our primary end point will be to determine the feasibility of a 30-day CRPM solution and a cascading notification system. Feasibility will be assessed by evaluating the study completion rate and the study attrition rate between consent and end of the intervention and by evaluating provider and patient acceptability and satisfaction using the A-TAM [42]. We will use interviews to evaluate both patients' and providers' degree of technology acceptance; perceptions of, and satisfaction with, wearable biosensor patches; and satisfaction regarding escalation pathways. We will then carry out a directed content analysis of interview transcripts to identify specific themes informed by the A-TAM to help guide future implementations of continuous remote monitoring systems [46]. Specifically, researchers will conduct semistructured interviews with providers and patients. Different researchers will then analyze the interview transcripts and, using the A-TAM framework as a guide, they will identify significant phrases that represent each construct from the A-TAM. We will then develop a synopsis of the significant themes and their relationship to A-TAM constructs.

Preliminary efficacy will be determined by comparing the study group readmission rate with a retrospective cohort readmission rate. The retrospective cohort group will be created from patients with HF who meet the same inclusion and exclusion criteria and received usual care over the previous year. The patients in the control group will be matched based on demographics, discharge home with home health services, and clinical analytics prediction engine risk scores [43]. We will also evaluate whether continuous monitoring can improve care processes through an escalating feedback protocol by comparing clinical and outcome data in the CRPM group with those in a retrospective cohort control group. Comparative analysis will be performed using an interrupted time series design with a propensity-matched control group. The primary outcome measures and methods of evaluation are summarized in Table 1.

Table 1. Primary aims and outcome measures.

Primary aim and measurement	Method of evaluation
Feasibility	
Provider acceptability	Pre-post interview and questionnaire
Provider satisfaction	Pre-post interview and questionnaire
Patient acceptability	Pre-post interview and questionnaire
Patient satisfaction	Pre-post interview and questionnaire
Attrition rate	Study data
Completion rate	Study data
30-day readmission rates	EHR[a] query
Preliminary efficacy	
Mortality	EHR query
Self-care	Pre-post European Heart Failure Self-Care Behavior Scale [47]
Quality of life	Pre-post Minnesota Living with Heart Failure Questionnaire [48]
Self-efficacy	Pre-post Self-Care Self-Efficacy Scale [49]
Social support	ENRICHD[b] Social Support Inventory [50]

[a]EHR: electronic health record.

[b]ENRICHD: Enhancing Recovery in Coronary Heart Disease.

Secondary outcomes, including technical outcomes and process and operational outcomes, will also be assessed (Table 2). Technical outcomes include the usability of the wearable device, usability of the patient smartphone app, usability of the provider portal, and ease of use of the structured clinical HHN note. Operational and process metrics include reasons for attrition, patient adherence to daily weight, patient adherence to daily symptom survey, percentage of notifications responded to in 24 hours, and the number of protocol deviations compared with the total number of patient days. In addition, effective communication of ePROs and physiological signals from the technical platform to the various clinical providers will be assessed by recording significant events and process lapses. CRPM data, clinical and operational notification data, and ePRO data will be analyzed and summarized using standard statistical tests of mean, median, SD, and IQR for continuous measures and count and percentage for categorical measures.

In addition to self-developed questionnaires targeting patient and provider experience in the study, we will also use several validated questionnaires to assess a patient's baseline values and changes before and after the study regarding self-care, quality of life, and social support. Specifically, we will use the following questionnaires:

1. Self-Care Self-Efficacy Scale: a scale to assess a patient's thoughts regarding self-care [47]
2. Minnesota Living with Heart Failure Questionnaire: a patient-oriented measure of the adverse effects of HF on a patient's life [48]
3. European Heart Failure Self-Care Behavior Scale, 9-item version: a scale to measure HF self-care behaviors [49]
4. Enhancing Recovery in Coronary Heart Disease Social Support Inventory: a questionnaire to assess social support [50]

We will also identify valid patterns in the continuous remote monitoring patient data that may be associated with events of interest, such as escalation to IV diuretic at home, escalation to HF specialist, 30-day readmission rates, and ED presentation, using temporal pattern mining and feature extraction methods. Unstructured data in patient reports and clinician notes will be analyzed using simple text analysis methods, including text preprocessing (eg, tokenization and lemmatization) to infer sentiments and extract features in the texts that may be relevant for the events for interest (eg, term frequency–inverse document frequency and term frequency). As this is a feasibility study with a limited sample of patients, we would not have sufficient power to determine statistical significance of the results; therefore, we are not in a position to create a power calculation.

Table 2. Secondary aims and outcome as well as operational and process measures.

Secondary aim and measurement	Method of evaluation
Technical outcomes	
Usability of the wearable device	Interviews and questionnaires
Usability of the patient smartphone app	Interviews and questionnaires
Usability of the provider portal	Interviews and questionnaires
Ease of use of the structured clinical HHN[a] note	Interviews and questionnaires
Operational and process outcomes	
Reasons for attrition	Study data
Patient adherence to daily weight	Study data
Patient adherence to daily symptom survey	Study data
Percentage of notifications responded to in 24 hours	Study data and EHR[b] query
Number of protocol deviations per number of patient days	Study data

[a]HHN: home health nurse.

[b]EHR: electronic health record.

Ethics Approval

The NSUHS Institutional Review Board reviewed and approved this study (EH20-288).

Results

Phase 1

Phase 1 started in December 2020, and the last patient completed the study in March 2021 [39]. Phases 2 and 3 started in April 2021 and are estimated to be completed by the end of 2022.

During phase 1, we enrolled 5 patients, and the results are described in a separate paper [39]. The results of phase 1 are summarized herein. Of the 5 patients, 2 (40%) were readmitted during the course of the study; of these 2 patients, 1 (50%) was readmitted with an HF-related issue and 1 (50%) was readmitted because of an infection. Patient 101 was adherent to completing the daily survey and daily weights 70% of the time, patient 102 was adherent 83% of the time, patient 103 was adherent 90% of the time, patient 104 was adherent 93% of the time, and patient 105 was adherent 12.5% of the time. In total, there were 128 clinical alerts during phase 1. Of the 5 patients, 1 (20%) had atrial fibrillation and bradycardia alerts, 4 (80%) had tachypnea alerts, and 3 (60%) had MCI alerts. The HHN responded to 99.2% (127/128) of the clinical alerts. The observed activity for each patient day was compared with the expected activity to determine the amount of protocol deviations. In total, 57 protocol deviations out of 150 possible patient days were observed in phase 1 of the study.

The results of phase 1 were analyzed, and the study protocol was optimized [39]. During phase 1, the protocol only had tailored recommendations for management for the MCI alert, which led to difficulty in determining what action to take for other clinical alerts. Therefore, the protocol was updated to include tailored recommendations for additional alerts. It was noted that the MCI alert was generated only 1 day before admission for 20% (1/5) of the patients and during admission for another patient. The vendor therefore updated the MCI to make it more sensitive. In addition, the survey used during phase 1 was found to have an insufficient characterization of HF symptoms. Therefore, the study protocol was changed to instead use a validated existing HF symptom survey [44,45]. In addition, originally the study workflow was designed for the HHN to communicate with the HF registered nurse, but it was discovered that the HF registered nurses did not feel comfortable with deciding on patient management. Therefore, the study workflow was redesigned to have the HHNs communicate with the HF APPs and attending physicians. Furthermore, the HF APPs were sometimes unsure of what their response to clinical alerts should be; therefore, specific workflow and recommendations were built out for them.

Phases 2 and 3

Phases 2 and 3 are ongoing; therefore, results are not yet available. Once completed, the data and results from phases 2 and 3 will be published in peer-reviewed scientific journals.

Discussion

Overview

The Cascade study is a feasibility study using an innovative CRPM solution with applied machine learning analytics, linked to an escalating cascading notification system with structured interventions in patients with HF. In this study, patients wear a chest-worn biosensor that collects continuous physiological data that are then analyzed by rules-based and machine learning algorithms to identify physiological perturbation. Patients also complete a daily symptom survey. If criteria based on the physiological data and survey answers are met, notifications are triggered, and a predetermined telephonic management workflow is pursued. As far as we know, this is the first study that integrates CRPM with both machine learning algorithms to provide providers with notifications of physiological decompensation and a cascading notification system and

structured intervention protocols to manage patients after discharge.

The Cascade study is unique in that it evaluates the feasibility of a continuous remote monitoring system with applied machine learning analytics, as opposed to random spot checks of physiological data. Studies have shown that continuous remote monitoring compared with intermittent monitoring in patients admitted to hospital can lead to earlier detection of clinical deterioration and improve patient outcomes [32-35]. We believe that the use of a continuous monitoring system in the postdischarge period may lead to earlier detection of patients at risk for decompensation and may also reduce readmission rates in an ambulatory population with HF.

A unique attribute of this study is the cascading notification system to efficiently identify and communicate with the right provider required to make management decisions. The HHN is the critical gatekeeper in the cascading system. They collect information from the platform and patient and enter it into a structured EHR note that automates recommendations on whether management requires escalation to a different provider. If escalation is required, it targets either the APPs or the HF physicians or both providers. As CRPM has the potential for alert fatigue given the high volume of data collected and analyzed, the cascading system allows for each provider to function at their level of expertise and spreads the clinical decision-making to the right provider at the right time.

The automated EHR note is another innovation within this CRPM pathway. As noted earlier, the HHN assessment in response to notifications includes calling the patient and filling out a structured EHR note. The note was designed for the Cascade study; not only does it orchestrate the cascading system, but it also provides automated recommendations for interventions based on the data elements filled in by the HHN. Ultimately, it guides the HHN to ask the most appropriate questions to the patient and target the patient with a personalized set of interventions, thereby empowering a general HHN to take part in actively managing patients with HF with complex medical needs, while escalating to the most appropriate provider in the most efficient manner when necessary. As was noted in the soft launch, these structured intervention protocols were also enhanced through key learnings on how to interpret continuous data and notifications, which allows for standardization of the initial set of HHN management decisions. We have also created suggested management recommendation workflows for APPs and HF physicians but have left ultimate clinical management to the clinical providers, as described in the Workflow and Clinical Management section.

Another strength of this study is its 3-phase nature, allowing for a soft launch period in the study design to evaluate the CRPM solution on a small number of enrolled participants and a calibration and testing period before the pilot [39]. The soft launch allowed the research team to evaluate the study protocol, notifications, communication pathways, and workflows, as well as make rapid iterative changes [39]. The calibration and testing period is to fine-tune the physiological algorithms, notification scheme, and workflows before arriving at a final fixed state.

Limitations

This study is limited because it is a feasibility study with a population of limited size. More studies with a larger sample size will have to be completed to determine the effectiveness of a remote monitoring solution in preventing hospital readmissions in patients with HF. The study is also limited in that only patients who are eligible and participate in partnering home health services programs are eligible for the study. This decreases the generalizability of this study to other patient populations.

Future Works

This study will enable evaluation of a CRPM program in patients with HF and allow for improvement and modifications to the intervention. This study will pave the way for a larger efficacy trial to determine the effectiveness of a CRPM solution in patients with HF after discharge. In addition, this study will help to create a general framework for CRPM workflow and inform the development and implementation of CRPM programs for other populations categorized as high risk and receiving postacute care.

Conclusions

The results from this study will determine the feasibility of a noninvasive remote monitoring system in recently discharged patients with HF. This study will use multiple validated and self-developed questionnaires and qualitative interviews to assess how this CRPM solution affects patients' self-care, quality of life, and social support. This study's findings will also help to aid earlier detection of patients with HF who are at risk for decompensation. In addition, this study will elicit both provider and patient feedback regarding the use of a remote monitoring system, which will help to determine key stakeholder perceptions regarding the use of CRPM systems and escalation and workflow pathways.

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Conflicts of Interest

The study devices, monitoring platform, and technical support are nonfinancial support by physIQ. KL and JV own shares in, and are engaged in paid employment at physIQ. NSS reports nonfinancial support from physIQ during the conduct of the study. JE reports to, and serves on, the American College of Cardiology MedAxiom Board of Trustees. This is the for-profit arm of the American College of Cardiology Foundation. Although JE has no direct relationships with vendors, the Board approves partnerships with vendors.

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Abbreviations

APP: advanced practice provider
A-TAM: affective adaptation of the technology acceptance model
CRPM: continuous remote patient monitoring
ED: emergency department
EHR: electronic health record
ePRO: electronic patient-reported outcome
HF: heart failure
HHN: home health nurse
IV: intravenous
MCI: multivariate change index

mHealth: mobile health
NSUHS: NorthShore University HealthSystem

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Protocol

Using PrEP and Doing it for Ourselves (UPDOs Protective Styles), a Web-Based Salon Intervention to Improve Uptake of Pre-exposure Prophylaxis Among Black Women: Protocol for a Pilot Feasibility Study

Schenita D Randolph[1], RN, MPH, PhD; Ragan Johnson[1], DNP, FNP-BC; Allison Johnson[1]; Lana Keusch[1], MPH

Duke University School of Nursing, Duke University, Durham, NC, United States

Corresponding Author:
Schenita D Randolph, RN, MPH, PhD
Duke University School of Nursing
Duke University
307 Trent Drive
Durham, NC, 27710
United States
Phone: 1 3363148759
Email: schenita.randolph@duke.edu

Abstract

Background: Multilevel interventions are necessary to address the complex social contributors to health that limit pre-exposure prophylaxis use among Black women, including medical distrust, pre-exposure prophylaxis stigma, and access to equitable health care. Strategies to improve knowledge, awareness, and uptake of pre-exposure prophylaxis among Black women will be more successful if information-sharing and implementation take place within trusted environments. Providing women with information through trusted cultural and social channels can effectively support informed decision-making about pre-exposure prophylaxis for themselves and members of their social networks who are eligible for pre-exposure prophylaxis.

Objective: The goal of this project is to improve knowledge, awareness, uptake, and trust of pre-exposure prophylaxis, as well as reduce pre-exposure prophylaxis stigma, among Black women living in the US South.

Methods: This multilevel, mixed methods study uses a community-engagement approach to develop and pilot test a salon-based intervention. There are three components of this intervention: (1) stylist training, (2) women-focused entertainment videos and modules, and (3) engagement of a pre-exposure prophylaxis navigator. First, stylist training will be provided through two 2-hour training sessions delivered over 2 consecutive weeks. We will use a pre- and posttest design to examine knowledge and awareness improvement of pre-exposure prophylaxis among the stylists. Upon full completion of training, the stylists will receive a certificate of completion and "Ask Me about PrEP" signage for their beauty salons. Second, together with the community, we have codeveloped a 4-part entertainment series (*The Wright Place*) that uses culturally and socially relevant stories to highlight key messages about (1) HIV, (2) pre-exposure prophylaxis, and (3) Black women's social contributors to health. Quantitative and qualitative measures will be used in a pre- and posttest design to examine pre-exposure prophylaxis knowledge, awareness, risk, stigma, trust, intentions, and women's perceptions of the usability and acceptability of the overall intervention and its implementation strategies. A video blog will be provided after each video. Third, participants will have access through an email or text message link to a pre-exposure prophylaxis navigator, who will respond to them privately to answer questions or make referrals for pre-exposure prophylaxis as requested.

Results: This project was funded in October 2020 by Gilead Sciences and was approved by the Duke University School of Nursing institutional review board in April 2021 (Pro00106307). Intervention components were developed in partnership with community partners in the first year. Data collection for phase 1 began in April 2022. Data collection for phase 2 began in May 2022. The study will be complete by October 2022.

Conclusions: Multilevel interventions that consider the assets of the community have promise for promoting health among Black women who have influence within their social networks. The findings of this study have the potential to be generalizable to other populations.

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KEYWORDS

HIV prevention; women; PrEP uptake; application; web-based application; web-based; pre-exposure prophylaxis; prophylaxis; mixed-method; community engagement; pilot test; HIV

Introduction

Background

Pre-exposure prophylaxis (PrEP), taken as prescribed, is an effective HIV prevention strategy, yet uptake remains low among populations at risk for HIV in the US, especially Black women living in the US South [1]. Black women in the US comprise 13% of all women but account for over half (55%) of new HIV infections among women [2], and individuals living in the southern states are at the highest risk of acquiring HIV. Despite the critical need for interventions aimed at this population, no interventions that focus on Black women and PrEP are available in the *Compendium of Evidence-based Interventions and Best Practices for HIV Prevention*, published by the US Centers for Disease Control and Prevention (CDC) [3]. A small study of 10 Black women with sexual partners with HIV showed preliminary acceptability and feasibility of PrEP [4]; however, broad, multilevel interventions that reach Black women beyond those in serodiscordant relationships are needed.

Barriers To Uptake

The barriers to PrEP uptake among Black women in the US are complicated, and individual- and interpersonal-level strategies, as well as community- and structural-level approaches, are warranted [5]. Barriers and challenges to PrEP uptake among Black women include lack of awareness and knowledge of PrEP [5-7], PrEP stigma [6,8], and distrust of medical professionals [6]. Yet interventions to increase PrEP have been (1) primarily focused on men who have sex with men (MSM), (2) implemented on the individual level, and (3) not been aimed at addressing PrEP stigma and medical distrust.

Lack of awareness and knowledge of PrEP among women in the US is prevalent [9,10]. Patel and colleagues [10] found that among 225 women living in the US South, 72% were eligible for PrEP; however, PrEP awareness was extremely low: only 11% of women had heard about PrEP. Signage campaigns such as “Ask Me about PrEP” have been used in clinical settings, but little research has linked their effectiveness to PrEP uptake among this population. To our knowledge, PrEP signage in community settings has not been examined and could be effective in reaching a broader population.

Stigma regarding PrEP is experienced personally among women, who also observe it within their social networks. Several studies show that women may not take PrEP due to fear that their family or friends will assume that the medication has been prescribed to treat HIV rather than prevent it [6-8]. These findings provide evidence that support from social networks plays a crucial role in determining women’s decision to start PrEP [10]. Strategies to reduce PrEP stigma, therefore, should leverage the social networks of Black women within trusted environments.

Finally, medical distrust is a significant barrier to health practices. Black women have been led by historic abuses to distrust the medical system [11], and this can affect their engagement with the health care system in general and with PrEP in particular [12,13]. For example, in a study of 500 female clients of Planned Parenthood living in 3 cities with high HIV prevalence, Black women had higher levels of medical distrust, evidenced by less comfort discussing PrEP with a medical provider [14]. One way to connect Black women with medical providers of PrEP is through linking a PrEP navigator to trusted and commonly frequented environments such as beauty salons. Patient navigators employed by local health departments can effectively decrease barriers faced by minority populations and increase completion of recommended health care utilization behaviors [15].

Salon-Based Interventions

The feasibility and acceptability of interventions to encourage PrEP uptake and reduce barriers is of critical importance. Beauty salons and, in particular, stylists provide women with regular, trusted networks of influence and support; thus, they present unique opportunities to increase awareness of PrEP. The authors have previously shown that a salon-based intervention to promote awareness and uptake of PrEP would be feasible and acceptable among Black female salon customers (n=44), salon owners (n=6), and hair stylists (n=25) [16,17]. Salon-based research interventions have shown promise for promoting health broadly in Black communities, because stylists can share health information in the salon with Black women, who view them as trusted confidantes [16-21]. There is evidence that stylist and customer confidence is increased when stylists undertake training in preparation for sharing information [18], but only a single study conducted in Brazil has evaluated such a training program for beauty salon professionals [19]. Although women customers varied in their perceptions of the role of the stylists in health promotion in the salon setting, all stylists in our study reported the need to have current, factual health information to share with women as conversations arose.

Our previous work suggested that women customers would prefer the use of technology (ie, iPads, text messaging, email, and media) and culturally centered interventions for the delivery of health-related content in salons [16,17]. Technology-based approaches can target a larger number of individuals effectively at a lower cost and are conducive to addressing privacy concerns expressed in previous studies [16,17]. Specifically, the use of entertainment videos was an intervention strategy that was reported as being both culturally and socially relevant and engaging. Entertainment videos have been effective in improving HIV knowledge and HIV testing for women of color [22]. Furthermore, seeing other women who look like them may increase trust in health care systems and delivery.

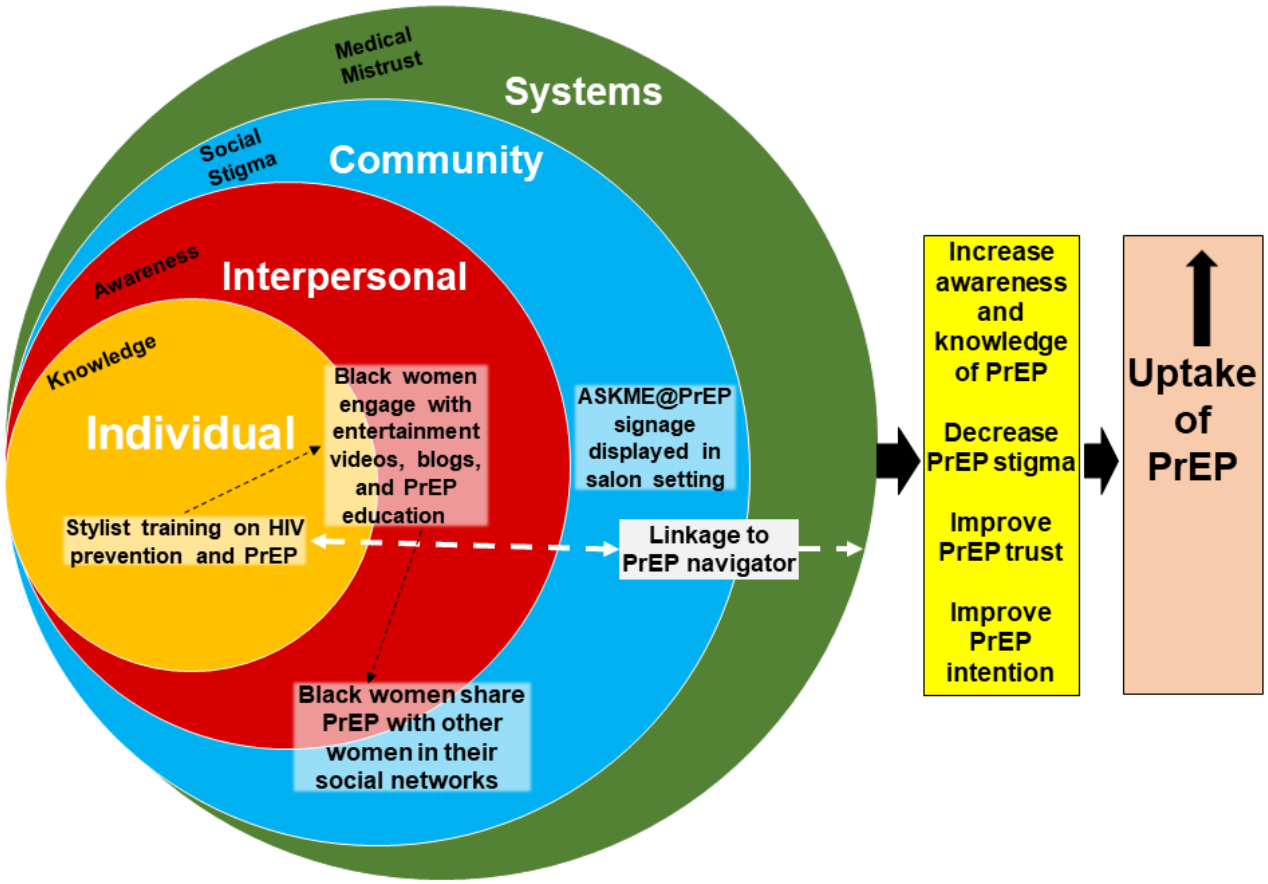
Aims and Objectives

The primary study objective was to develop a study protocol—Using PrEP: Doing it for Ourselves (UPDOs) Protective Styles—to test the feasibility and acceptability of a salon-based intervention to increase awareness, knowledge, and uptake of PrEP and reduce associated stigma and distrust of PrEP among Black women in the US South. UPDOs Protective Styles is a multiphase intervention that encompasses 3 sequential components (Figure 1). The first involves training stylists on women's health and PrEP, virtually or face-to-face. The training protocol was adapted from the CDC's evidence-based intervention "d-up: Defend Yourself!" [23], which enlists trusted community members whose advice is respected to serve as opinion leaders. D-up! is aimed at Black same-sex-loving men and uses opinion leaders to change social norms regarding condom use to prevent HIV [23]; our intervention protocol uses a similar approach. Stylists are respected and trusted in the Black community [16-19], and the training aims to leverage this respect to decrease social stigma associated with PrEP and HIV and increase trust in PrEP.

UPDOs's second component entails entertainment-education, that is, videos designed to entertain while communicating prosocial norms and behaviors [24]. Videos have been used effectively to communicate HIV risk reduction and promote sexual health among Black women using smartphone-delivered, culturally relevant content, as has a stage play to increase awareness and knowledge of HIV produced for a Black community [25]. Both showed acceptability and feasibility and resulted in an increase in knowledge and awareness of HIV and prevention strategies. The videos developed for the current protocol each conclude with a video blog of the research team and community partners discussing its key points and providing resources, information, and links to related content. Community partners were cast members of the entertainment videos, stylists, or members of the community advisory committee. Blogs, in either written or video form, are often associated with popular-culture media and allow an opportunity to clarify, recap, or further explain concepts to the audience.

The final UPDO component is the integration of a local PrEP navigator as a resource for participants. Participants will have access to a recorded overview of the need for and role of PrEP navigators, as well as a digital link to their local navigator's contact information.

Figure 1. Socioecological model for the Using PrEP: Doing it for Ourselves (UPDOs) Protective Styles intervention. PrEP: pre-exposure prophylaxis.



Theoretical Framework for Intervention

The design of this study was informed by the transtheoretical model [26], which posits that health behavior change involves progress through 6 stages of change: precontemplation, contemplation, preparation, action, maintenance, and termination [26]. Based on this model, the protocol-based study will evaluate women's intentions to use PrEP at baseline, upon completion of the intervention, and at 3 and 6 months postintervention. Our multicomponent intervention aims to influence behavior change over time by engaging varied implementation strategies.

Two other frameworks have informed specific aspects of the protocol. Transportation theory [27] proposes that, to the extent that individuals are engaged in a story or "transported into a narrative world," they may show effects of the story on their real-world beliefs and behaviors; this theory informed our development of the sitcom series that was videotaped for salon customers. Finally, a socioecological model [28] that considers the complex interplay between individual, relational, community, and other systems that influence one another guided development of the authors' open-ended probes regarding the network- and health systems–related impact of the UPDOs intervention. These constructs may inform the sustainability of prevention efforts over time and the capacity within a community for longstanding reciprocal relationships that support health.

Methods

Design and Sample

Stylist Training

The training curriculum for stylists is based on d-up!, an evidence-based intervention developed by the CDC. This is a 4-part, 8-hour online learning module developed and facilitated by Black MSM, delivered to community leaders who can create or change social norms to promote condom use and address racial and sexual biases that increase risk for HIV [23]. D-up! has shown significant HIV-related positive outcomes and evidence of efficacy. For UPDOs, we integrated feedback from topic experts and a community advisory council of local stylists into a 2-part, 4-hour curriculum to be delivered face-to-face or by Zoom over 2 weeks. Part 1 includes information on HIV transmission, universal precautions for the stylist, social- and behavioral-level risks (eg, racism and bias) for HIV, and HIV prevention through PrEP. In part 2, stylists learn how to act as opinion leaders to change social norms regarding HIV and PrEP, including the opportunity for participants to practice conversations using case studies. Part 1 must be completed to progress to part 2 of the training. The curriculum is based on the most current evidence available from the CDC and the Black Women and PrEP Toolkit [29]. For reasons of confidentiality, sessions will not be recorded. Two facilitators will conduct each training session with a third team member who will serve as a notetaker.

A convenience sample of stylists in a 3-county catchment area of North Carolina will be recruited via word of mouth, flyers, social media, and active recruitment by study staff. Inclusion criteria include (1) full-time employment as a stylist or beauty industry professional, (2) age 18 years or older, (3) employment at a salon that serves primarily (≥50%) Black women customers, and (4) the ability to speak and understand English. All eligible and willing beauty industry professionals will be enrolled in the first study component in order to increase the number of opinion leaders who have accurate, evidence-based information. Stylists who complete the training are not required, as a part of this study, to have conversations with women customers about HIV and PrEP; such conversations are purely discretionary. Upon completion of their training, stylists will receive a certificate of completion and a QR code with signage ("Ask Me about PrEP") to display in the salon. Finally, eligible stylists will be offered yearly 2-hour refresher training sessions on HIV prevention and PrEP.

Six salons that have completed the training curriculum will be selected to participate in the second component of the study. Stylists must be willing to display recruitment materials in the salon, serve as opinion leaders for their customers, and answer general questions about the study. Stylists who participate in the training will receive continuing education credit through the state's Board of Cosmetology. Each of the 6 participating salons will receive US $500.

Entertainment-Education and Video Blogs

The videos are a series of four 20-minute sitcom episodes with accompanying blogs, titled *The Wright Place.* The series is socially and culturally relevant and was scripted by the study's community partners with input from the research team, Black women, and the community advisory council; it was produced by a local filmmaker and executive producer. *The Wright Place* is grounded in evidence-based information from the CDC, the Black Women and PrEP Toolkit [29], and the extant literature. Each episode aims to improve Black women's agency for their individual health and the health of those within their social networks. PrEP education is integrated with more general women's health information (eg, cardiovascular disease and violence prevention) in the videos and blogs. Cardiovascular risk was chosen as it is the leading cause of death for Black women [30]. The videos and blogs are housed on a web-based platform accessible only to enrolled participants.

Black women will be recruited using rolling enrollment at the 6 salons among customers of stylists who agree to be opinion leaders and display the "Ask me about PrEP" signage in their salons, as well as through word of mouth, flyers, and efforts by research staff. Eligibility criteria include (1) age 18 years or older, (2) frequency of visiting the salon of at least every 2 weeks, (3) self-identification as Black or African American, (4) self-identification as a woman, and (5) ability to speak and read English. Based on their typical frequency of visiting the salon, women should expect to view 1 video and blog every 2 weeks. Participants must self-enroll in the study and will be able to access the videos and electronic surveys on their mobile device by typing in a link or using a QR code provided on flyers available in the salon. The QR code provides access to the consent form. After providing consent, participants will be sent a standardized welcome from the study team and given access to the web-based application link that they can access on their individual computers or smart devices. Thereafter, the study team communicates to the participants solely by email prompts or text messages, delivered from REDCap (Research Electronic Data Capture; Vanderbilt University) [31], to provide access to the web-based application link and administer survey measures. Stylists will not enroll participants nor administer study instruments. Compensation to Black women participants for their participation over 6 weeks will be US $125, which will be delivered in 2 payments.

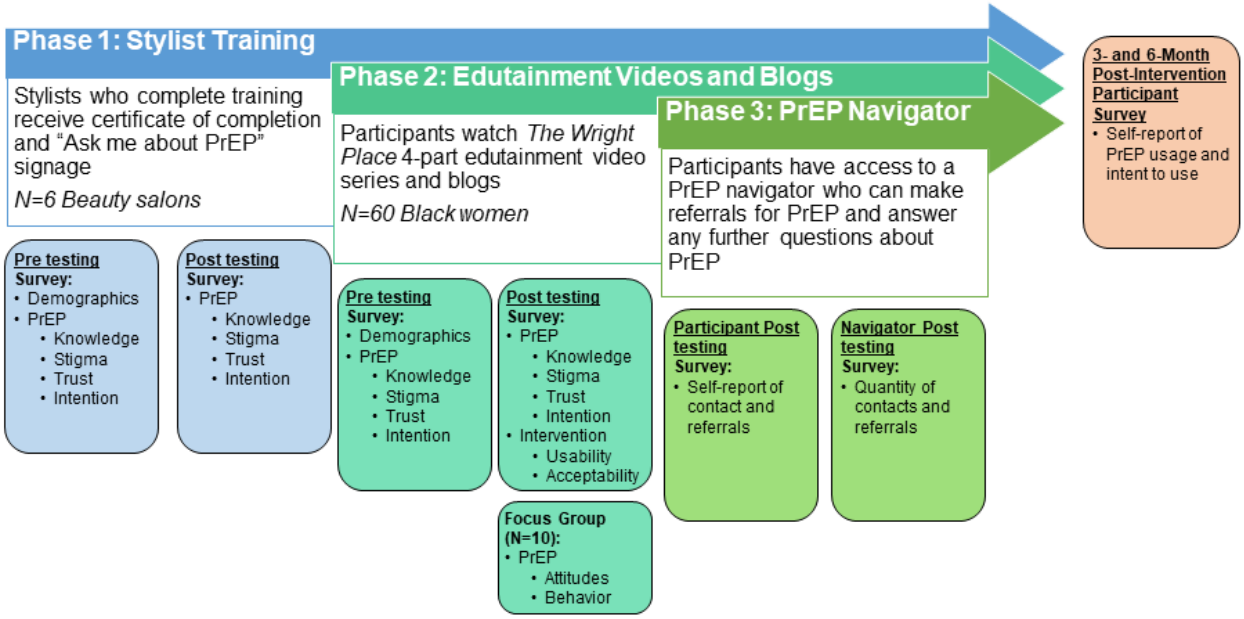
After 60 women have completed the survey questionnaires and engaged in the site, a subsample of participants will be invited to join a single "think-aloud" focus group, with a goal of 10

women who have completed all parts of the intervention. Additionally, a focus group will be conducted with 6 stylists from the salons who have completed training and the full study. The purpose is to provide an opportunity to describe the experience of the UPDOs intervention and provide evaluative feedback to the study team. A lunch will be served at a site convenient to the group. Expected time needed for participation is 1.5 hours.

PrEP Navigator

The final component of the study is a link to a PrEP navigator, an expert available through the state health department. There will be contact information on the web-based application to connect participants with a PrEP navigator; the participants themselves will initiate contact with the PrEP navigator, who will be available to discuss PrEP, answer PrEP-specific questions, and assist participants with obtaining an appointment at a PrEP clinic or beginning a PrEP conversation with their primary care provider or a provider of their choice. Through the web-based application, participants will have opportunities to share links to PrEP resources with members of their social networks through email or text notification; however, in the pilot testing phase, nonparticipants will not have open access to study materials (Figure 2).

Figure 2. Study design schematic. PrEP: pre-exposure prophylaxis.



Measures

Stylists

A demographic questionnaire will be used to assess age, sexual orientation, marital status, zip code, history of sexually transmitted disease, and last HIV test for all participants. Each participant will have the opportunity to select more than one race and ethnicity upon screening and will be included if "Black" or "African American" are selected. HIV status will not be ascertained, in order to increase participation and avoid the potential for stigma.

Table 1 summarizes the measures used in this study. Two items, adapted from Chandler et al [32], will assess knowledge and awareness of PrEP: "Before this study, had you ever heard of PrEP?" (yes or no) and "On a range of 0 = no knowledge to 10 = expert knowledge, what is your knowledge of PrEP?" A further 31 items will be used to assess HIV and PrEP perceived risk (5 items), stigma (8 items), trust (12 items), and intentions (6 items). The perceived risk items are based on CDC guidelines [33]. Stigma will be assessed using 2 subscales (PrEP User Stereotypes and PrEP Disapproval by Others) of the PrEP Anticipated Stigma Scale [14]. Trust was assessed using Avanzo and colleagues' [34] PrEP Trust Scale. Intention to use PrEP will be measured by responses to author-developed questions that are based on a transtheoretical model; for example, "I am not currently considering taking PrEP" (precontemplation) and "I am planning to take PrEP within the next month" (preparation). Responses range from 0 (very unlikely) to 5 (very likely). At 3 and 6 months postintervention, participants will self-report whether they have made and attended a clinic appointment for PrEP initiation, were prescribed PrEP, and utilized PrEP.

Feasibility and acceptability of the stylists' curriculum will be measured with a 15-item pre- and posttest design survey to assess their comfort, willingness, and intention to serve as opinion leaders in their salon. A postquestionnaire will be delivered after the initial training and at the conclusion of the study to assess the acceptability of the content and format, including overall satisfaction with the training, willingness to participate in future training, and intention to share information learned in the training with Black women customers, other stylists, or members of the participant's social networks. Open-ended questions on the postquestionnaire include (1) "Overall, how would you describe your experience with the opinion leader training?" (2) "What did you gain from this experience?" (3) "What were the best parts of the opinion leader training?" (4) "What were the least helpful or engaging parts

of the training?" and (5) "How can the training be improved? Please provide specific recommendations when possible."

Table 1. Summary of concepts and instruments used to collect the data.

Measure	Description	Expected outcome	Evaluation schedule
Systems Usability Scale [35]	A 10-item measure of digital intervention usability that allows evaluation of a wide variety of products and services, including hardware, software, mobile devices, websites and applications. Items are scored on a 5-item Likert scale, ranging from strongly disagree to strongly agree.	Assessment only	Postintervention
Acceptability and feasibility [22]	Video series/episodes	Assessment only	Postintervention
PrEP[a] knowledge/awareness [32]	Two items: "Before this study, had you ever heard of PrEP?" (yes/no) and "On a range of 0 = no knowledge to 10 = expert knowledge, what is your knowledge of PrEP?"	Improved knowledge and awareness of PrEP	Baseline and postintervention
PrEP risk [33]	Five risk questions adapted from the CDC source documents: question 1 and questions 2-5 (yes/no response).	Assessment only	Baseline, postintervention
PrEP stigma [14]	Eight items; responses include "strongly disagree," "disagree," "agree," and "strongly agree." This measure assesses user stereotypes about PrEP and disapproval by others to take PrEP.	Improve stigma related to PrEP	Baseline, postintervention
PrEP trust [34]	Twelve items; responses are on a 10-point Likert scale ranging from "strongly disagree" to "strongly agree." This measure perceptions about trust in the provider and health care interactions.	Improve trust related to PrEP	Baseline, postintervention
PrEP intentions [36]	Six items, including "How likely are you to use PrEP in the future?" Responses range from 0, "very unlikely," to 5, "very likely." This measure is based on the transtheoretical model of change.	Improve intentions of women to take PrEP	Baseline, postintervention, 3-6 months postintervention

[a]PrEP: pre-exposure prophylaxis.

Video/Blog Viewers

Survey items on participant demographic characteristics and barriers to PrEP uptake will be answered by viewers of the sitcom video and blogs using the same method as for the stylists. Although sexual risk is not an outcome of this study, the risk-related items will be included with the understanding that study participants who are not at significant risk themselves may know someone in their social network who is at risk. HIV status will not be ascertained, in order to increase participation and avoid the potential for stigma.

Acceptability and feasibility of the UPDOs intervention will be measured quantitatively using a 14-item evaluation tool (Multimedia Appendix 1**)** modified from a study by Jones et al [24]. Sample questions include "Do the episodes you watched address problems you think are important to women?" and "Do you think the episodes could help a woman make a decision about her sexual health?" Answers are ranked from "definitely no" to "definitely yes." Feasibility data will also include the self-reported completion rate for all modules.

A focus group with a subsample of 10 women participants will be used to assess the implementation strategies and influence of the UPDOs intervention on the attitudes and behavior of the participants. Probes will address the usefulness for raising awareness and increasing uptake of PrEP of the following five aspects of UPDOs, as well as which aspects were most and least liked: (1) the "Ask me about PrEP" signage in salons, (2) the written section of the modules, (3) the entertainment-education videos, (4) the links and access to the PrEP navigator, and (5) impromptu conversations with stylists. To assess reach within social networks, participants will be asked if they shared information they learned about PrEP with their social networks, and if so, how often they shared it and whether they shared it with women, men, or both. The think-aloud protocol is an interview method designed to capture participants' thought processes as they engage with instruments and interventions. The participant is asked to think aloud while solving a problem or completing a task, thus allowing understanding of their problem-solving process [37].

We will also evaluate the usability of the intervention website and application using the System Usability Scale (SUS) [35]. The SUS provides a reliable tool for measuring the usability of a wide variety of products and services, including websites and applications. It consists of a 10-item questionnaire with 5

response options for respondents, ranging from "strongly agree" to "strongly disagree." Sample questions include "I think that I would like to use this system (website) frequently," "I found the system (website) unnecessarily complex," and "I thought the system (website) was easy to use."

We will assess the proportion of participants who contact the PrEP navigator by self-report and the report of the PrEP navigator. These data will be deidentified. We have partnered with a local PrEP navigator for the development and implementation of the study protocol.

Analytic Strategy

All assessments will be conducted using REDCap technology. Demographic information will be summarized as the mean and standard deviation for continuous variables and frequency and percentage for categorical variables.

Stylist training data will include training recruitment and completion rate as well as average time to complete surveys. Descriptive analyses will be conducted to describe pre- and posttraining PrEP awareness and knowledge and measures of barriers to PrEP uptake, and will be summarized as means, standard deviations, medians, interquartile ranges, and ranges. Given the small sample, a Wilcoxon test (or Wilcoxon signed-rank test) will be used to assess participant improvement in knowledge and awareness after completing the training. Descriptive statistics will be used to describe the feasibility and acceptability of UPDOs's training for stylists. If improvement in awareness and knowledge is acceptable for an increase in scores of 2 standard units, we will be able to detect the desired change with 71% power for a sample of 4 and with 99.6% power with a sample of 8 [38].

The video/blog viewers will be assessed before and after completing their initial women's health vignettes and modules on PrEP awareness, knowledge, and uptake. Awareness and knowledge total scores and the uptake of individual items will be descriptively summarized (as means, standard deviations, medians, interquartile ranges, and ranges), then tested using a paired *t* test. With a sample size of 60, for a 2-sided test with significance level set to P=.05, the paired *t* test will have 80% power to detect a mean standard difference of 0.37 [38]. Similarly, the number of women who received education from a stylist and the number of women who were referred to a PrEP navigator will be summarized descriptively.

Improvement in the 2 subscales of the PrEP Anticipated Stigma Scale (ie, PrEP User Stereotypes and PrEP Disapproval by Others) [14] and the PrEP Trust scale [34] (mean score of 12 items) will be graphically depicted over the multiple measurements (baseline, 3 months, and 6 months). A linear model for the longitudinal data will be fitted to estimate the linear improvement gained between baseline and each of the follow-up measurements. The unconditional models of the growth curve of the scores for the PrEP Anticipated Stigma PrEP User Stereotypes scale, the PrEP Anticipated Stigma Disapproval by Others scale, and the PrEP Trust scale have 80% power to detect a linear slope of 0.07 for 3-times measurements for a sample size of 60 [39]. Data collected on whether a woman customer saw a PrEP navigator or started PrEP, as well as on the number of referrals provided by women in the project, will be descriptively summarized.

The talk-aloud process and individual interviews will be audio-recorded, transcribed verbatim, and analyzed using directed content analysis [37]. We will analyze individual interviews separately using horizontalization, then develop clusters of meaning from significant statements by cross analysis to construct themes. We will perform systematic coding using a well-defined thematic codebook and NVivo data analysis software (QSR International). NVivo allows the coder to create a "tree" of codes that can be used to identify both individual and overlapping thematic units in the data. The research team will code the data separately and compare interpretations on an ongoing basis to achieve intercoder consensus and enhance the reliability and validity of the analyses. The resulting collection of themes will be conceptualized with the goal of creating an initial picture of the acceptability and usability of the salon-based intervention to increase PrEP awareness and uptake.

Ethical Considerations

The study has been reviewed and was approved by the Duke University School of Nursing institutional review board in April 2021 (Pro00106307). The informed consent documents will include detailed information on all study procedures as well as the consent process. Stylists who attend the stylist training will provide electronic consent prior to training and before the start of the pretraining survey. Black women participants completing the video/blog intervention will provide electronic consent. Consent for the focus groups of women who will be engaged at the end of the pilot study will take place via verbal consent if COVID-19 prevents in-person meetings or via written consent if meetings are in person. In-salon discussions regarding PrEP and UPDOs are at the sole discretion of stylists and their customers; all assessments are opt-in opportunities and conducted on a digital device with whatever privacy settings are chosen by those being assessed.

Results

This project was funded in October 2020 by Gilead Sciences, Inc and approved by the the Duke University School institutional review board in April 2021 (Pro00106307). Intervention components were developed in partnership with community partners in the first year. Data collection for the stylists' training began in April 2022. Data collection for the video/blog viewers began in May 2022, and the study will be completed by October 2022. As of June 7, 2022, we have enrolled 3 salons, conducted stylist training with 4 stylists, and enrolled 17 women customers across the 3 salons.

Discussion

Anticipated Findings

This study will provide evidence that builds on the extant literature regarding whether and how partnering with trusted community members, such as salon stylists and PrEP navigators, may affect PrEP awareness, knowledge, uptake related to PrEP stigma, and medical trust among Black women living in the US South. Implementation of the UPDOs protocol will allow the

authors to link their findings in a sample from a new population of Black women to evidence from prior studies among MSM and transgender women. This linkage, in addition to data regarding the feasibility and acceptability of the elements of the UPDOs protocol, may inform future intervention studies and, ultimately, the expansion of future CDC evidence–based interventions to include those specific to Black women, for whom there is a dearth of articles describing culturally appropriate interventions for HIV prevention. This gap is significant, given the size of this target population.

Detailing the lived experiences of Black women throughout the research process will allow evidence to be disseminated that could empower a community that displays significant health disparities [40] to have the information needed to make informed decisions for their own health. This level of engagement allows women to be in a position to share with other women and PrEP-eligible individuals in the community, thus potentially having community-wide impact.

Strengths and Limitations

The design of this study has several strengths, including its focus on Black women, regardless of risk or HIV status, which has the potential to (1) reduce HIV- and PrEP-associated stigma and (2) uncover hidden risks, such as partner infidelity, that are beyond a woman's control. The sample size and analysis by age and socioeconomic status have the potential to illuminate how information is shared among social networks, which are often intergenerational in the Black community. Lived experiences of Black women contributing to this work offer unique insights into the influences of where women work, live, and play. The influence of Black women in the family and community is well documented [41]. This study allows women to be leaders of this information, regardless of their perceived or actual vulnerability. Leveraging trusted spaces and networks of women offers a unique opportunity to change social norms around HIV prevention and the use of PrEP. If UPDOs demonstrates acceptability and feasibility in this pilot study, this approach has potential to have a broad impact on Black women's health and the design of culturally relevant interventions.

The use of a web-based technology that participants can use from their personal device allows intervention testing with a potentially global reach while maintaining privacy, which can be sacrificed in interpersonal settings. An intervention that uses entertainment videos highlighting the social determinants of health for women is relatively novel and allows for a culturally relevant and timely impact on population health that could improve inequities among Black women in health and HIV prevention. Finally, the inclusion of training for stylists is critical, as prior research confirms it is necessary to ensure the comfort of stylists and Black women customers engaged in salon-based interventions. This education will empower stylists with requisite knowledge, as well as critical thinking and communication skills, to foster healthy sexual behaviors and positively influence social norms.

Anticipated limitations of this intervention include the self-reported PrEP uptake, as Black women may visit their primary care providers or other sources to receive PrEP. There is also potential for reporting bias on the initial assessment of PrEP risk; however, this information is not intended to inform the intervention. We also do not assess participants' current HIV status in this study. Finally, the absence of a comparison group may limit the ability to determine whether change was related to the intervention or other factors.

Future Directions

We have developed a strategic dissemination plan in partnership with members of our community advisory council, beauty industry partners, and a hired communication strategist's team. Through our social media outlets, YouTube channel, short clip videos, a community forum led by salon partners, and quarterly newsletters, the research process and study findings will be shared with the community. Additionally, findings will be disseminated in peer-reviewed journals and at academic conferences.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Video Series/Episodes: The Wright Place from UPDOs Protective Styles Project.
[PDF File (Adobe PDF File), 283 KB - resprot_v11i8e34556_app1.pdf]

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Abbreviations

CDC: US Centers for Disease Control and Prevention
d-up!: d-up: Defend Yourself!
HIV: human immunodeficiency virus
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
UPDOs: Using PrEP, Doing it for Ourselves

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Protocol

Enabling Long-term Predictions and Cost-benefit Analysis Related to Housing Adaptation Needs for a Population Aging in Place: Protocol for a Simulation Study

Steven M Schmidt[1], PhD; Carlos Chiatti[2], PhD; Lisa Ekstam[1], PhD; Maria Haak[3], PhD; Christina Heller[1], MSc; Maria H Nilsson[1,4,5], PhD; Björn Slaug[1], PhD

[1]Department of Health Sciences, Faculty of Medicine, Lund University, Lund, Sweden

[2]R&D Unit, Tech4Care srl, Falconara Marittima, Italy

[3]Department of Nursing Education and Integrated Health Sciences, Faculty of Health Sciences, Kristianstad University, Kristianstad, Sweden

[4]Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Faculty of Medicine, Lund University, Malmö, Sweden

[5]Memory Clinic, Skåne University Hospital, Malmö, Sweden

Corresponding Author:
Björn Slaug, PhD
Department of Health Sciences
Faculty of Medicine
Lund University
P.O. Box 157
Lund, 22100
Sweden
Phone: 46 46 222 1838
Email: bjorn.slaug@med.lu.se

Abstract

Background: Policies that promote aging in place are common in Sweden and many other countries. However, the current housing stock cannot sufficiently accommodate a population aging in place considering how functional capacity and housing needs change as people age. To be suitable for all regardless of their functional ability, housing should be designed or adapted to facilitate the performance of activities of daily living. Long-term planning and plausible projections of development 20 to 30 years into the future are needed.

Objective: The overall aim is to develop simulation models that enable long-term predictions and analysis of potential consequences in terms of societal gains and costs for different large-scale measures and interventions in the ordinary housing stock.

Methods: This study is designed as a simulation study and will broadly apply health impact assessment methods in collaboration with five municipalities in Sweden. Individual interviews and research circles were used to identify current and prioritize potential new policies to improve the accessibility of the housing stock. We will run a series of simulations based on an estimated willingness to pay from discussions with the municipalities. Two to three different prioritized policies will be compared simultaneously using Markov cohort analysis to estimate the potential costs and health impact on the population. Using data from a systematic review and existing population-based data sets with individual-level data on home and health variables, we will calculate parameter estimates for the relations between housing accessibility and health outcomes. The potential impact of selected policy interventions will be estimated in several microsimulations representing people living in the community. Sensitivity analyses will be conducted for each simulation.

Results: As of April 2022, open access data was collected, and a systematic review was underway and expected to be completed by November 2022. Collaboration with five municipalities was established in autumn 2020. In spring 2021, the municipalities developed a list of prioritized policy interventions to be tested and used in the simulation models. Inventories of barrier frequencies in ordinary housing started in spring 2022 and are expected to be completed in autumn 2022. Data gathering and analyses for simulation inputs will be completed during 2022 followed by the simulation modeling analyses to be completed in 2023.

Conclusions: Improved accessibility of the ordinary housing stock has the potential to maintain or improve the health of the aging population. This study will generate tools that enable long-term predictions and reliable cost-benefit estimates related to the housing adaptation needs for a population aging in place, thus providing support for the best-informed policy decisions.

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KEYWORDS

accessibility; activities of daily living; age-friendly housing; aging in place; demographic aging; functional limitations; housing adaptations; housing policies; person-environment fit; simulation models

Introduction

Background

Policies that promote aging in place are common in Sweden and many other countries. There is a widespread perception, corroborated by research findings, that older people often prefer to stay in their homes as long as possible [1,2]. Moreover, from an economic perspective, aging in place is expected to reduce public expenditures. As people age in their homes—that is, in ordinary nonsheltered housing—the demand for more expensive and care-intensive sheltered housing is lowered [3]. However, for aging in place to be tenable, ordinary housing has to be designed or adapted to the needs of people aging with disabilities and functional limitations, as these become more common with aging.

The standard of ordinary housing is generally high in Sweden, but to be suitable for all regardless of functional ability, there are specific demands put on the design, such as sufficient maneuvering space when using mobility devices, placement and design of controls, and operable hardware that make them easy to reach and operate. The housing environment should be designed or adapted in such a way that it facilitates the performance of activities of daily living (ADL). This degree of fit between the person's functional capacity and the demands of the housing environment is often referred to as housing accessibility [4]. As an example of the serious deficiencies of the existing ordinary housing stock among senior citizens (aged ≥65 years) living in multifamily dwellings, 50% are estimated to live in buildings that lack elevators [5]. Additionally, in many buildings with elevators, residents still need to go up steps or other level differences to enter or exit the building. If not resolved, such problems could constitute fall risks, which may lead to injuries, disabilities, and increased societal costs. It is particularly important to have accessible entrances, so people with disabilities or functional limitations can get to places and activities outside the house and to care for basic needs such as shopping. Moreover, research results indicate that accessible housing that enables senior citizens to stay independent and active is associated with better health and well-being [6], but a systematic overview of such scientific findings is currently lacking. Therefore, the accessibility of the ordinary housing stock must be improved as a matter of public health promotion and to ensure successful aging in place.

Even though building legislation and housing standards in Sweden have incorporated aspects of accessibility for at least 25 years [7], the production of new accessible dwellings is insufficient. More than 90% of senior citizens in Sweden live in ordinary housing, and of those, almost 80% live in less accessible dwellings built during or earlier than the implementation of a national program of massive multi-dwelling block construction in the 1960s and 1970s [8]. The aging of the population in combination with the deficiencies in the ordinary housing stock thus calls for large-scale measures to improve accessibility [9]. However, for such measures to be successful, they must be based on the best knowledge about the ordinary housing stock, the functional status of the population, and the costs, and feasible solutions will require cooperation among many stakeholders [10]. New policies at the local and national level could serve as catalysts to promote such cooperation. Higher costs to build accessible housing and for housing adaptations are often seen as barriers. However, it is important to consider potential gains from improved housing accessibility, such as a presumed decrease in the need for home services because senior citizens can independently manage their ADL [11].

To establish a housing stock that accommodates a population aging in place requires long-term planning and plausible projections of development 20 to 30 years into the future. In this respect, health economic models can serve as useful tools for decision makers, provided that the specificities of this policy sector are taken into account. Health economic models are widely used to extrapolate the costs and effectiveness of different interventions beyond trial data. Using the best available evidence, health economic models serve to compare relevant policy/intervention options, generalize results obtained in one setting to others, inform resource allocation decisions (also in the absence of "hard data"; ie, data from interventions actually carried out), and make head-to-head comparisons of alternative competing interventions.

Traditional health evaluation paradigms have not been used for evaluating typically interrelated interventions in the context of housing accessibility policies, so some exploration of different model options will be needed. Conventional systematic reviews could be used for simple interventions, but it would be difficult to apply in the context of more complex interventions or policies. Previous attempts have been made to improve decision-making in the field of public health (eg, the Disparities Elimination through Coordinated Interventions to Prevent and Control Heart and Lung Disease Risk Alliance applied the logical steps of the realist approach to the field of cardiovascular disease risk), but no evaluation method for understanding the impact of housing accessibility policies has been validated and applied. However, Slaug and colleagues [11] published a pilot study that estimated the potential impact on health-related outcomes by implementing a policy change regarding housing accessibility. This study demonstrated the feasibility and the potential of such an approach, and building on this experience, we aim to develop more sophisticated and realistic simulation models. These models will enable long-term predictions and

estimates of costs and benefits related to policies designed to improve housing accessibility for a population aging in place.

Methodological and Theoretical Foundations

The methodological foundation of this study stems from the Housing Enabler [12], a methodology refined over 20 years of applied research [13] and cooperation with actors in housing provision. The Housing Enabler is an internationally acknowledged instrument for the professional inventory of the functional capacity of individuals, environmental barriers in housing, and analysis of accessibility problems [12,13]. Using the ecological model of aging as the theoretical base [14], the Housing Enabler operationalizes the relationship between a person's capacity and the environmental demand [4]. According to the ecological model of aging, a balance between the person's capacity and the demand of the environment can be achieved by changing one or the other component, or both [14]. Hence, even if the person's functional capacity deteriorates, activity performance can be maintained or improved by lowering the demands of the environment. Moreover, persons with lower capacity are considered more sensitive to the demands of the environment than those with higher capacity.

The Housing Enabler quantifies the magnitude of accessibility problems based on a personal component and an environmental component analyzed in relation to one another. Accessibility problems emerge when the environmental demands exceed the functional capacity of the individual; for instance, stairs without handrails may create severe problems for individuals with poor balance. Accessibility is one (crucial) aspect to enable people with functional limitations to move around in the physical environment; to reach objects; to activate controls and functions, for example, on home appliances; and to manage day-to-day life at home. The validity, reliability, and feasibility of the methodology have been established through empirical studies of >2000 senior citizens and their dwellings across Europe [15].

Study Aim and Objectives

The overall aim is to develop simulation models that enable long-term predictions and analysis of potential consequences in terms of societal gains and costs for different large-scale measures and interventions in the ordinary housing stock. This will be achieved by addressing three objectives:

1. Assess and evaluate societal gains of a more accessible ordinary housing stock
2. Compare potential housing adaptations policies against other possible ageing in place policies (eg, additional home care or meals on wheels)
3. Provide policy makers with powerful tools for preparing and making the most informed housing policy decisions

Methods

Study Design

This study is designed as a simulation study and will broadly apply health impact assessment methods [16,17]. Based on previous experiences (see [18]), we will collaborate with several municipalities in an iterative process to identify and prioritize intervention options that have the potential to improve the accessibility of the ordinary housing stock. The interventions identified should be anticipated to have a positive impact on health. Several of the most promising interventions will be modeled to simulate the costs and health impact on the population. The different models will be demonstrated and discussed with municipal policy makers to enhance and promote the use of research-based decision-making.

Study Population

Data is drawn from multiple sources as described in the sections below, and the study will focus on people 65 years and older living in ordinary housing in Sweden. Depending on the priorities identified by the participating municipalities, different subgroups from this larger population may be selected for different simulation models. People younger than 65 years with functional limitations (eg, due to neurological disorders) may also be targeted because an adequate housing environment is essential for them as well.

Simulation Model Inputs

Input 1: Costs of Housing Adaptations

Sweden has 290 municipalities, and 20 to 30 of those will be strategically selected to have diversity regarding size of the population, geographical area, socioeconomic characteristics, and ethnicity. Data on costs for a comprehensive list of housing adaptations will be gathered by retrieving publicly available data (see Textbox 1) from the municipalities and by interviewing housing adaptation grant managers. The distribution of dwellings regarding building period and type of dwelling will also be gathered from the selected municipalities.

Textbox 1. Data sources for the simulation model inputs.

1. Costs of housing adaptations
- Publicly available data from 20-30 municipalities
- Interviews with housing adaptation grant managers

2. Frequencies/occurrences of environmental barriers in the Swedish housing stock
- Publicly available data from the National Board of Housing, Building and Planning (Boverket)
- Housing Enabler inventory in a total of 50 dwellings in five municipalities
- Home and Health in People Ageing with Parkinson's Disease database
- SNAC-GÅS (The Swedish National Study on Aging and Care in Scania)
- ENABLE-AGE database

3. Population-based functional profiles
- SNAC-GÅS
- Scania Public Health Survey
- National Public Health Survey from the Swedish Public Health Agency (Folkhälsomyndigheten)
- ENABLE-AGE database

4. Costs of existing services
- Statistics Sweden
- The National Board of Health and Welfare
- Annual economic reports and other material from government, municipalities, counties, or other societal institutions

5. Effects of poor accessibility on independence (activities of daily living), health, and well-being
- ENABLE-AGE database
- Home and Health in People Ageing with Parkinson's Disease database
- SHARE (Survey of Health, Ageing and Retirement in Europe)
- SNAC-B, SNAC-N, SNAC-K (The Swedish National Study on Aging and Care in Blekinge, Nordanstig, and Kungsholmen)
- SWEOLD (Swedish Panel Study of Living Conditions of the Oldest Old)

Input 2: Frequencies/Occurrences of Environmental Barriers in the Swedish Housing Stock

Physical environmental barriers are part of housing design features that can hinder ADL. For estimations of the frequency of occurrences of physical environmental barriers (see Textbox 1), we will mainly use detailed environmental barrier inventories of dwellings (N=1023) from three previous research projects (ENABLE-AGE [15], Home and Health in the Third Age [19], and Home and Health in Parkinson's Disease [20]). In all three projects, housing data was collected with the Housing Enabler [13]. In the pooled data sample, 65% of the surveyed dwellings are apartments in multi-dwelling blocks and 35% are one-family houses. Different kinds of tenure are represented. The dwellings are situated in 34 municipalities in the south of Sweden (ranging from 7500 to 320,000 inhabitants), representing urban, semirural, and rural districts. Regarding the year of construction, 39% were built before 1960, 37% were built from 1960 to 1979 (a period in Sweden with massive multi-dwelling block construction), and 24% were built in 1980 or later (a period dominated by one-family house construction). The distribution between building periods and type of dwelling in our pooled data set largely reflects the distribution of the housing stock in Sweden as a whole [5]. Different kinds of tenure are also represented. To use the data for projections at national and municipal levels, we will retrieve data on the distribution of building types, number of rooms, and year built from public sources from the National Board of Housing, Building and Planning (Boverket) in all the municipalities of Sweden. The research databases of environmental barriers will then be matched with national and municipal data, extrapolating environmental barrier frequencies. To validate the extrapolation results, a total of 50 dwellings in five selected municipalities will be inventoried with the Housing Enabler, which is for comparing actual barrier frequencies with frequencies obtained by extrapolating data from the existing research databases.

Input 3: Population-Based Functional Profiles

To estimate the prevalence and incidence of functional limitations in different age segments of the population, we will retrieve source data from open access databases (see Textbox 1). Other metadata from the most recent high-impact scientific publications and from publicly available statistics will also be applied in our estimations. All this data will be used to establish

"functional profiles" that represent large groups of people having certain combinations of functional limitations in common [21]. The population-based functional profiles will be used to calibrate the effects of potential interventions in terms of improved accessibility for different target groups. That is, interventions that address functional limitations such as limitations in movement, sensory impairment, or a combination of different functional limitations.

Input 4: Costs of Existing Services

To estimate the costs of existing home services, other services, and health care provision (eg, sheltered housing forms, institutionalized care, or medical care for fall accidents), we will gather data on different types of services and care, number of individual cases per year, number of hours delivered per year, costs per hour, etc. Data will be retrieved from publicly available sources such as Statistics Sweden; The National Board of Health and Welfare; annual economic reports; and other material from the government, municipalities, counties, or other societal institutions (see Textbox 1).

Input 5: Effects of Poor Accessibility on Independence, Health, and Well-being

Specific assumptions of relationships between the parameters (ie, effect sizes) in the simulation models will be derived from published research results. Parameters included will also cover aspects such as perceived health and well-being. Where no or insufficient results are available in the literature, we will use existing longitudinal data sets (see Textbox 1) to estimate the effects of different functional profiles on health and functioning over time. Our main effect of interest will be the risk of becoming dependent in activities of ADL [22]. ADL is used because the costs for social services in the home setting are likely to increase with increased dependence (eg, need for home health/help services, meals on wheels, or similar). Our previous research has shown that those with more housing accessibility problems in the home are at higher risk of dependence in ADL [17]. Further, higher dependency in ADL has shown to be associated with lower health-related quality of life [23]. To measure effects in terms of accessibility, the Housing Enabler methodology [12,13] will be applied. As we are also interested in the general health and psychosocial relationships with accessibility, in a similar manner, we will identify/develop effect estimates for secondary outcomes of health and perceived well-being.

Prioritizing Interventions

The simulations will estimate the cost to implement a new policy across Sweden and the potential savings achieved by preventing dependence in ADL. The policy that will be implemented in the simulation models will be selected from a prioritized list developed with representatives of five municipalities. In a subsample of five municipalities (Eslöv, Perstorp, Östersund, Örebro, and Vänersborg), individual interviews were held with municipality workers to understand their current housing adaptation policies and discuss alternative policy solutions. A prioritized list of new policies (eg, large-scale housing interventions, additional home care, or meals on wheels) was then developed through workshops with the same participants to be used in simulations. To involve the municipality workers more actively and to reach a deeper engagement, the workshops used the research circle methodology [24-26]. This methodology aims to engage the participants in a joint effort to develop new knowledge and new ideas. The research circle methodology differs from the nearby focus group methodology in adopting an explicit participatory design focus where researchers and participants contribute with equal authority. That is, while focus groups are based on a group interview methodology, research circles represent a way to collaborate with users in the generation of new knowledge or new ideas. Research circles include a selected number of people with different backgrounds who meet several times for a predefined period of time in workshop sessions to discuss a common topic. By applying the research circle methodology, we aspire to nurture communication among participants with different backgrounds but with a common goal of generating suggestions for alternative policy solutions and a prioritized list of new policy suggestions to be simulated.

Simulation Methods

We will conduct a series of simulations to model the potential impact on health outcomes and costs of selected policy interventions based on principles of health economic modeling [27]. Intervention costs will be calculated based on inputs 1 (costs of housing adaptations) and 2 (frequencies/occurrences of environmental barriers in Swedish housing stock) by combining the cost of adaptations (barrier removal or amelioration) with the frequency of the barriers in ordinary housing. This will then be adjusted to each of the specific interventions prioritized by the municipalities. Current costs (no new intervention) will be based on input 4 (costs of existing services). Input 3 (population-based functional profiles) will be used to identify target groups for intervention. We will then simulate models including the entire population compared with targeted interventions for people with specific functional profiles. Using a Markov cohort analysis, we will run a series of simulations based on the different profiles using an estimated willingness to pay from the discussions with the municipalities. Two to three different interventions will be compared simultaneously, and we will track the costs and benefits for 10 years with the following end points: independent in ADL, dependent in ADL, or death. Time until death will be estimated based on population statistics for life expectancy among the different ages represented in the simulation, and death will also be estimated based on the effects of poor accessibility identified in input 5 (effects of poor accessibility on independence [ADL], health, and well-being). Other end points and transitions will also be based on input 5. All simulated cohorts will have a starting state of independent and have transition states of independent, dependent, or death. It will also be possible to transition from dependent back to independent in the 10-year model.

Using existing data sets with individual-level data on home and health variables, we will also conduct several microsimulations representing those living in the community aged 80 to 89 and 67 to 70 years, and for those living with Parkinson disease (aged 45-93 years). The same basic model design will be used as

described for the cohort analyses. Sensitivity analyses will be conducted for each simulation.

Ethics

Following the principles of the Helsinki Declaration and current national legislation and policies on ethics for research involving humans, the study has been approved by the Swedish Ethical Review Authority (2020-01643 and 2020-05871).

Results

Five municipalities (Eslöv, Perstorp, Vänersborg, Örebro, and Östersund) were recruited in autumn 2020 as core partners in the study. A reference group consisting of selected policy makers, housing adaptation grant managers, older adults, and municipality workers involved in housing policy or housing adaptation issues was set up and has provided input for the study, with the first meeting in February 2021. During winter 2021, individual interviews with two key persons from each partner municipality were completed to understand current and future housing policies. In spring 2021, a research circle with the key persons from the municipalities, together with two older adults and three researchers, resulted in a priority list of policy suggestions to be tested and analyzed in the simulation models (see [28]).

As of April 2022, data from open access sources for input to the simulation models has been collected, and accessibility inventories on barrier frequencies in ordinary housing are ongoing since spring 2022 and are expected to be completed in autumn 2022. A systematic literature review on the evidence of associations between housing and health was registered in PROSPERO in March 2022. We anticipate the data collection and the systematic literature review to be completed by November 2022. Thereafter, we plan to continue with the simulation modeling analysis starting in late 2022, to be completed by summer 2023. See Textbox 1 for a list of data sources for simulation inputs.

Discussion

Overview

An ordinary housing stock that can accommodate an aging population is of utmost importance from a public health perspective, and improved accessibility of the ordinary housing stock has the potential to maintain or improve the health of our aging population. While accessibility issues have gained attention among policy makers and are now high on the political agenda [29,30], the tools for preparing and making the most informed policy decisions are still largely lacking. By developing simulation models based on the best knowledge available, this project will provide policy makers at different societal levels with the tools they need. That is, tools that enable long-term predictions and reliable cost-benefit analysis related to the housing adaptation needs for a population aging in place, thus providing support for the best-informed policy decisions.

This study also concerns important gender issues, as there are significant differences between men and women with regard to housing conditions and financial possibilities on the housing provision market [5]. Two-thirds of the men and just half of the women in the age group 65-74 years live in one-family houses that they own themselves. Considering those living in multi-dwelling blocks, approximately 85% live in buildings built before 1980 when housing construction was characterized by less concern for housing accessibility issues [9]. With a longer life expectancy, women are also likely to live for a longer period of life in dwellings with accessibility problems. Only one in three women aged ≥75 years can afford to move to a newly built dwelling, while the corresponding number for men is two in three [5]. Consequently, more women than men have to stay in less accessible dwellings, even though the functional decline means that accessibility problems gradually get worse. Though women tend to get housing adaptations more often than men, men tend to get more expensive housing adaptations than women [5]. For these reasons, upgrading the existing ordinary housing stock in terms of accessibility would benefit women more than men and thus serve to promote equality.

A large proportion of immigrants and ethnic minorities live in the less accessible dwellings built during the period of the 1960s and 1970s implementation of a national program of massive multi-dwelling block construction. When people in these groups grow older, they are often already disadvantaged in terms of their social and economic situations. Additionally, if they have to cope with a housing environment that is not adequately designed for the needs of older people, it increases the risks for them to have health problems and lower quality of life. According to a recent report, inadequate housing affects vulnerable groups of the society disproportionately [31]. Therefore, it is particularly important to improve the housing situation for these vulnerable groups.

Problems with housing accessibility are currently mainly addressed by housing adaptations that are typically granted after individuals have already started to have problems performing ADL. Approximately 74,200 housing adaptations are granted each year in Sweden, at a cost of more than US $100 million [32]. Furthermore, many of these houses are restored to the preadaptation design after the person who had them granted moves from the dwelling. These practices will be unsustainable with the growing need for accessible housing, which calls for innovative and large-scale interventions. To support policy makers to take accurate and efficient decisions, it must be possible to evaluate and compare the cost-effectiveness of different interventions targeting the ordinary housing stock. By developing simulation models based on the best knowledge available, this study will provide policy makers at different societal levels with the tools they need, that is, tools that enable long-term predictions and reliable cost-benefit estimates related to the housing adaptation needs for a population aging in place, thus providing support for the best-informed policy decisions.

By using a simulation study design, we will be able to compare the effects of different housing policies to improve housing accessibility in scenarios based on projections of the demographic development, indicators of functional status of the population, data on housing design features that cause accessibility problems, and costs for a range of potential interventions. The use of simulation models such as Markov and microsimulation models [33] will enable us to answer “what

if" questions, for example, related to what policies are most sustainable under critical conditions, such as "What happens when certain policies are applied if birth rates or immigration rates change drastically?" or "What are the probabilities for different outcomes under certain conditions?" Answering such questions is not possible using traditional methods such as empirical studies or randomized trials. Empirical studies can only provide knowledge of the effects of policies already applied, not those not yet applied, and intervention trials would be unfeasible, since the conditions for providing housing adaptations is regulated by law in Sweden and cannot be "experimented" with [34]. Simulations in health sciences could therefore be considered as the equivalent to experiments in natural sciences.

Methodological Considerations

The accuracy and credibility of simulation results are dependent on using the best available knowledge in the research field in question. Therefore, this study will gather both primary source data and metadata from established and verified databases, and apply the most up to date and high qualitative scientific results to formulate assumptions on the associations between parameters used in our models. Our contributions to the research area include this data collection and the building of new data sets, which will enable combining and analyzing existing data in new and innovative ways. Once established, the data sets can be continuously extended and updated, and the assumptions guiding the models can be refined as the knowledge field advances. The new data sets as well as the models we are developing will be of benefit to the research society and serve as incentive for further research.

The literature overview of scientific findings concerning relationships between the key parameters in the simulation models, that is person-environment interactions and health indicators, will be significant in itself as an overview of the best available research evidence. Moreover, this literature overview could serve as a starting point for more advanced meta-analysis projects in this area.

Dissemination and Use of Results

This project engages targeted knowledge users of the simulation models in the research process and throughout the project lifetime. Participatory integration of researchers and knowledge users can be seen as a way to bridge the gaps between theory and practice and between science and everyday experience [25]. As an important part of the strategy for knowledge translation, we formed a reference group and are maintaining close communications with staff in the five municipalities. By working in a participatory manner, regularly discussing and analyzing the emerging results, we are striving to create new knowledge and understanding together. These knowledge users will take part in different knowledge translation activities. For example, workshops will initially be conducted to widen and deepen the knowledge among the end users about estimated frequencies of environmental barriers and their potential consequences for the aging population, housing adaptation costs, and so on. At later stages of the project, seminars and workshops will be arranged to present and discuss the simulation models, the results of policy simulations, and how to use simulations as a tool to support policy decisions. Through these joint activities, we will inform a wider public audience about the project and how it may support decision-making concerning improved accessibility of the ordinary housing stock.

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Authors' Contributions

BS generated the project idea. BS, SMS, and CC designed the project. BS wrote the proposal for funding in collaboration with all coauthors except CH. CH provided details regarding data collection and data sources. SMS and BS wrote the manuscript with critical review and input from all coauthors. All coauthors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Reviewer comments from Forte: Forskningsrådet för hälsa, arbetsliv och välfärd / Swedish Research Council for Health, Working Life and Welfare (Stockholm, Sweden).
[PDF File (Adobe PDF File), 74 KB - resprot_v11i8e39032_app1.pdf]

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Abbreviations

ADL: activities of daily living

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Protocol

Ecological Burden of e-Waste in Bangladesh—an Assessment to Measure the Exposure to e-Waste and Associated Health Outcomes: Protocol for a Cross-sectional Study

Sarker Masud Parvez[1,2], MPH; Shaikh Sharif Hasan[2], MBBS; Luke D Knibbs[3,4], PhD; Farjana Jahan[2], MBBS; Mahbubur Rahman[2], MBBS; Rubhana Raqib[2], PhD; Nafisa Islam[5], PhD; Nirupam Aich[6], PhD; Mohammad Moniruzzaman[7], PhD; Zahir Islam[1], PhD; Masatake Fujimura[8], PhD; Peter D Sly[1], DSC

[1]Children's Health and Environment Program, Child Health Research Centre, The University of Queensland, Brisbane, Australia

[2]Environmental Interventions Unit, Infectious Diseases Division, International Centre for Diarrheal Disease Research, Bangladesh, Dhaka, Bangladesh

[3]School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

[4]Public Health Unit, Sydney Local Health District, Camperdown, Sydney, Australia

[5]Department of Chemical Engineering, Bangladesh University of Engineering and Technology, Dhaka, Bangladesh

[6]Department of Civil, Structural and Environmental Engineering, School of Engineering and Applied Sciences, University at Buffalo, The State University of New York, Buffalo, NY, United States

[7]Bangladesh Council of Scientific & Industrial Research, Dhaka, Bangladesh

[8]Department of Basic Medical Sciences, National Institute for Minamata Disease, Minamata City, Kumamoto, Japan

Corresponding Author:
Sarker Masud Parvez, MPH
Children's Health and Environment Program
Child Health Research Centre
The University of Queensland
62 Graham St
Brisbane, 4101
Australia
Phone: 61 610 480365175
Email: s.parvez@uq.edu.au

Abstract

Background: e-Waste is a rapidly growing waste stream worldwide, and Bangladesh is a hub of e-waste handling. Informal e-waste recycling operations involve crude methods for dismantling, repairing, sorting, and recycling electronic goods with bare hands and without personal health protections. Direct inhalation or dermal exposure to toxicants during informal recycling is common. Evidence suggests that e-waste–derived toxicants pollute the terrestrial ecosystem and have been linked with adverse health effects. However, e-waste recycling–related occupational health hazards have not been adequately explored in the context of Bangladesh.

Objective: Our study aims to expand the current understanding of exposure to e-waste. This study will measure the metal concentrations in biological and environmental samples and evaluate the relationship between heavy metals and the biochemical systems of the e-waste workers.

Methods: The study uses a cross-sectional study design consisting of an exposed site and a nonexposed control site. The trained team collected information on individual exposures, detailed work and medical history, and biological samples (blood, urine, and hair) from each subject. This study will measure heavy metal levels (lead, cadmium, and mercury) and biochemical parameters (hematological, hormonal, renal, and others) from the biological samples with reported physical function as outcomes of interest. In addition, we also collected soil and dust samples from both exposed and nonexposed control sites to measure the health risk. All the environmental samples will be analyzed using inductively coupled plasma mass spectrometer to determine metal concentrations. We will also conduct a qualitative investigation for a deeper understanding of the e-waste management system in Bangladesh.

Results: The protocol has been approved by the Institutional Review Boards of the International Centre for Diarrheal Disease Research, Bangladesh, and The University of Queensland's Human Behavioral Ethics Committee. Informed written consent was

obtained from all participants. We recruited 199 workers from the e-waste sites with at least 5 years of exposure and 104 control subjects with no industrial or e-waste exposure. Sample analysis is estimated to be completed in 2022.

Conclusions: Although many studies have identified potential adverse health outcomes from exposure to e-waste, there is a lack of published epidemiological research in Bangladesh. Research in this field is particularly pressing in the context of the current e-waste trend and the need to deepen the understanding of exposures and outcomes.

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KEYWORDS

e-waste; lead; cadmium; mercury; environment; exposure; recycling; toxicants; health outcomes; Bangladesh

Introduction

Background

e-Waste is a rapidly growing waste stream that poses severe threats to the environment and human health [1,2]. This can be defined as any "electrical or electronic equipment, which is waste, including all components, subassemblies, and consumables, which are part of the equipment at the time the equipment becomes waste" [3]. The exponential growth of the electronic industries in the last couple of decades has resulted in a considerably high volume of obsolete waste flow [4-8]. In 2014 and 2016, the estimated quantity of e-waste was about 41.8 and 44.7 million metric tons, respectively, all over the world, whereas only about 15% (6.5 million metric tons) and 20% (8.9 million metric tons) were formally collected and recycled by a proper channelized system. In 2019, Global E-waste Monitor estimated the global production of e-waste at approximately 53.6 million metric tons. This figure is expected to grow to 74.7 million metric tons by 2030, with the majority of e-waste produced in Asia (24.9 million metric tons) [9]. Low-income countries are attractive destinations for e-waste due to lower labor costs, cheaper disposal, and less stringent or poorly enforced laws, with illegal export from high-income countries accounting for approximately 80% of the burden [10,11].

e-Waste contains large amounts of hazardous material. High concentrations of known neurotoxicants, including lead (Pb), cadmium (Cd), chromium (Cr), polybrominated diphenyl ether, polychlorinated biphenyl compounds, and polycyclic aromatic hydrocarbons are leached or discharged from e-waste [12]. Exposure to these pollutants can cause toxicity to the respiratory, circulatory, nervous, immune, endocrine, urinary, and reproductive systems [13-15]. Additionally, e-waste–derived metals are nonbiodegradable, which adversely affects aquatic and terrestrial environments [16].

e-Waste exposure usually comes from 1 of 3 sources: informal recycling, formal recycling, or environmental contamination [17-20]. Most e-waste recycling processes are carried out in the informal sector, where the recycling process is used to extract valuable metals rapidly. These crude operations are carried out without protective gear or the assistance of technology [21,22]. Workers who handle e-waste as part of their formal or informal occupations are more likely to be exposed through inhalation, ingestion, and dermal absorption, and this is typically known as direct occupational exposure [23-25]. In addition, local inhabitants and workers can also be exposed through indirect routes, including physical contact with contaminated soil, dust, air, water, and food sources [26,27]. Several studies reported that even if the residents live nearby the recycling areas, they are still at risk of exposure due to the high load of contamination [25,28].

Country Context and Rationale of the Study

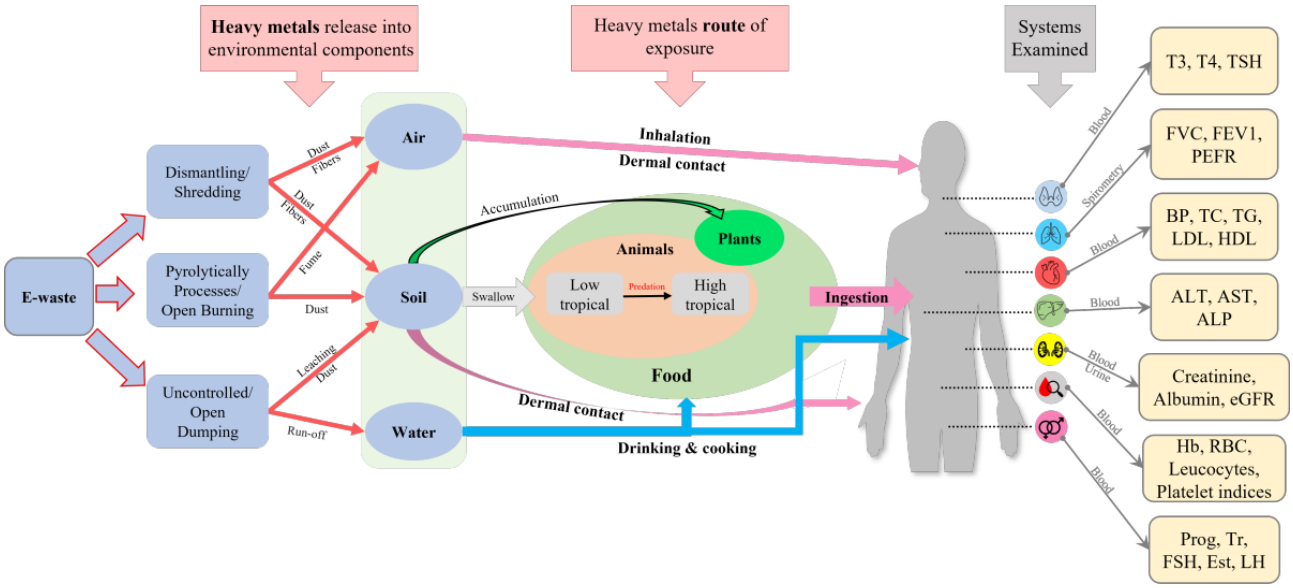
Bangladesh has a rapidly growing economy, which is parallel with the proliferation of e-waste from electronic gadgets, especially mobile phones and computers [29]. The Bangladeshi Department of Environment estimated that 0.40 million metric tons of e-waste were generated in 2018, and this is expected to reach 4.62 million metric tons by 2035 with an annual growth rate of around 20% [30]. However, only 3% of e-waste enters the market of recycling, and the rest is mixed with municipal solid waste and goes to the landfill [30]. Recently, Hazardous Waste (e-waste) Management Rules, 2021 under the Bangladesh Environment Conservation Act, 1995 were approved by the Government of Bangladesh [31]. This initiative has the potential to markedly improve the management of e-waste and reduce the harm to human and environmental health. However, extensive research is required to identify and develop effective policies. Our study aims to fill the gaps in the current understanding of how e-waste handling contributes to adverse consequences on human and environmental health.

Study Objectives

The overarching objective of the study is to improve the current understanding of exposure to e-waste and its adverse consequences. Based on the literature review, we conceptualized a framework for the effects of exposure to e-waste on environmental and human health (Figure 1). We identified hot spots likely to have higher exposures within Dhaka city and the factors that determine the location of hot spots. The specific aims of the project are to (1) explore the management pathway of e-waste from collection to disposal; (2) determine the different types of e-waste that are modified physically and chemically in Dhaka city; (3) measure the frequency of Pb, Cd, mercury (Hg) and other elements (arsenic, Cr, copper, manganese, nickel, zinc, cobalt, selenium, beryllium, and vanadium) contamination of soil and dust in e-waste repair and recycling areas; 4) measure the levels of Pb and Cd in blood and Hg in hair among children, adolescents, and adults working in e-waste repair and recycling area; (5) investigate the characteristics (work exposure, behavioral, and occupational safety) associated with blood Pb and Cd and hair Hg levels

among participating respondents; and (6) measure the association between heavy metals in biological samples and biochemical parameters (hematological, renal, hormonal, respiratory, cardiovascular, and liver function and oxidative damage markers) of the e-waste workers. All of these objectives will be assessed by comparing e-waste workers to those living in unexposed areas.

Figure 1. Study conceptual model of the effects of exposure to e-waste on environmental and human health. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate transaminase; BP: blood pressure; eGFR: estimated glomerular filtration rate; Est: estrogen; FEV_1: forced expiratory volume in 1 second; FSH: follicle-stimulating hormone; FVC: forced vital capacity; Hb: hemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LH: luteinizing hormone; PEFR: peak expiratory flow rate; Prog: progesterone; RBC: red blood cell; T_3: triiodothyronine, T_4: thyroxine; TC: total cholesterol; TG: triglyceride; Tr: testosterone; TSH: thyroid-stimulating hormone.

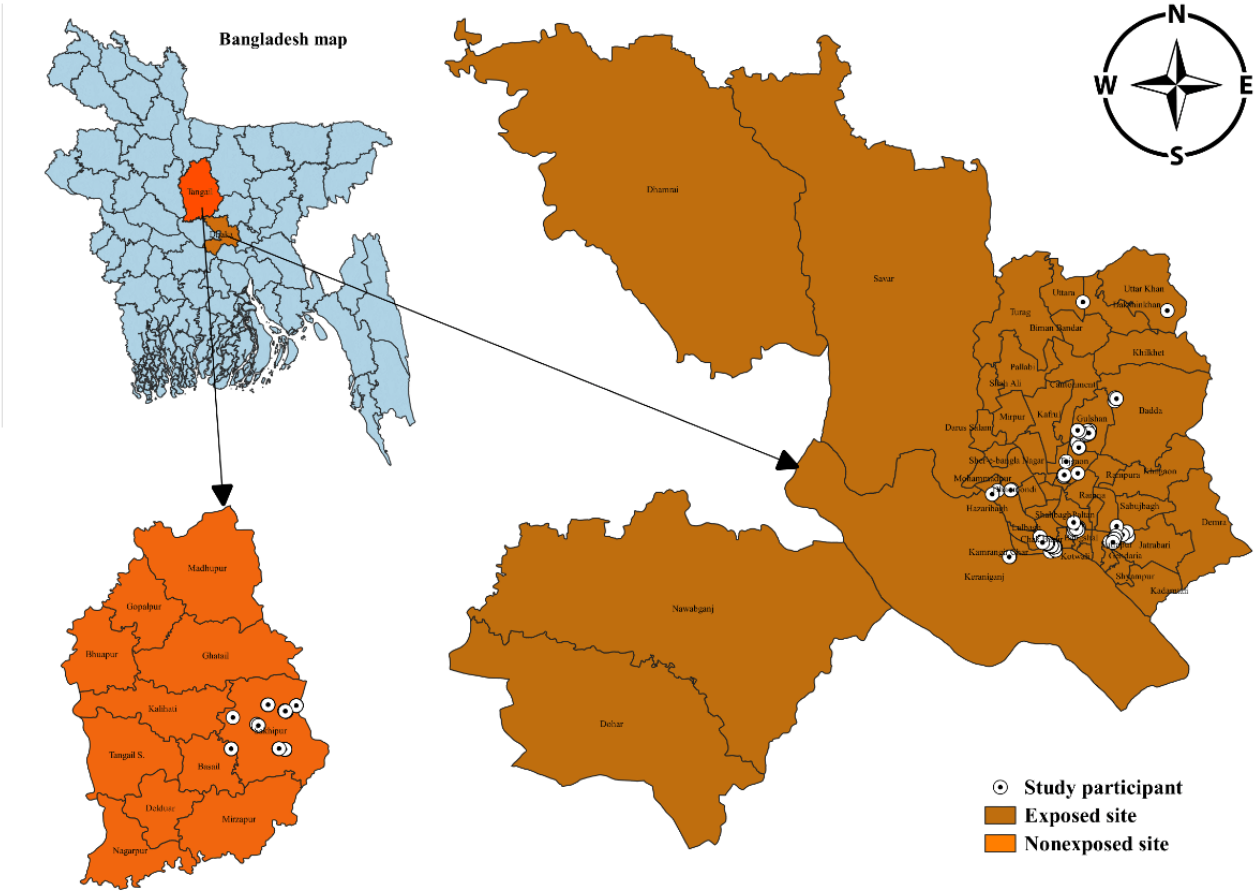


Methods

Study Design

The design comprises both quantitative and qualitative investigations to meet the objectives. Our emphasis is on the quantitative investigation where we use a cross-sectional study consisting of an exposed site and a nonexposed control site (Figure 2). For the in-depth understanding of e-waste management, we will also conduct a qualitative investigation.

Figure 2. Study sites.



Study Site, Population, and Participant Recruitment

The research team identified key informal e-waste recycling sites in Dhaka (Figure 2). The study population included e-waste workers involved in collecting, recycling, repairing, incineration, and other relevant work in these informal e-waste recycling sites (Figure 3). We screened the potential participants to confirm that they fall into one of the recycling activities targeted in our study along with at least 5 years of exposure. We excluded the workers who have had shorter durations of exposure, because chemicals derived from e-waste are potentially toxic and cause adverse health outcomes from chronic exposure. We also selected a nonexposed control site at a distance from Dhaka, where no industrial or e-waste pollution sources existed. All the nonexposed participants were local residents mainly involved in agriculture, small businesses, and teaching, and none of them had previous exposure to e-waste (Figure 2).

Figure 3. e-Waste exposure sites and working condition.

The trained fieldworkers travelled to the eligible areas and asked the leaders or owners for permission to conduct research within their community. The research team briefly explained the study objectives, procedures, and possible measurements that we were interested in. After providing time for discussion among the workers and owners and obtaining verbal interest to participate, a field team member recorded the GPS coordinates at the location of e-waste sites and developed a line list of workers involved in e-waste processing. Later, the field team sought informed consent from the eligible workers during enrollment. The GPS coordinates were compiled and analyzed using QGIS mapping software (version 3.16.1; Open Source Geospatial Foundation).

Sample Size Calculation

The primary outcome of this study is blood Pb and Cd levels among the e-waste exposed and nonexposed individuals. We calculated the sample size using the mean blood Pb and Cd concentration reported by Sirichai et al [32]. They reported mean blood Pb levels of 6.61 (SD 3.07) µg/dL and 2.73 (SD 0.49) µg/dL among Thai exposed and nonexposed controls, respectively. In contrast, the mean blood Cd levels of e-waste and non–e-waste workers were 1.00 (SD 0.33) µg/L and 1.17 (SD 0.39) µg/L, respectively. The estimated sample sizes for a 2-sample means test are 18 (9 per group) and 192 (96 per group) for Pb and Cd, respectively, considering 90% of power and a 95% CI. To meet the study objective, 96 respondents from each group would be required to detect differences between exposed and unexposed individuals. However, there is a paucity of available information on the e-waste–exposed population and the harmful effects from e-waste–derived toxicants in this context. To generate rigorous evidence and to allow for the examination of interactions and mediation pathways, particularly on the e-waste–exposed population, we enrolled 199 exposed and 104 unexposed participants.

Data Collection Procedures

Trained fieldworkers visited the site and approached the eligible participants. The fieldworkers explained the study in detail and obtained written consent from those who agreed to participate.

Exposure Assessment

A data collection tool was developed and piloted prior to being administered in the field. All questionnaires were administered by trained research staff and collected electronically. The team collected data in several domains:

- general characteristics (ie, age, sex, income, education, and dwelling environment),
- detailed exposure history (years of involvement, daily/weekly work time, and work type),
- occupational safety equipment, and knowledge and attitudes about harmful effects from exposure to e-waste,
- lifestyle and behaviors, including cigarette smoking, alcohol consumption, and medication use, and
- self-reported disease status, including hypertension, diabetes mellitus, chronic kidney diseases, hepatic diseases, and others.

All interviews were conducted in the workplace with direct observation supporting results.

Biological Sample Collection and Storage

A trained phlebotomist collected venous blood samples (7.5 mL) from the participants using trace metal–free certified needles and tubes. Our team also collected spot urine samples in a 50 mL falcon tube; all samples were transported to the laboratory in a cooler box, maintaining adequate temperature (2°C to 8°C) within 4-6 hours of collection. A medical technologist separated 2 mL of whole blood samples for heavy metal analysis, and 1 mL of blood was immediately transferred to the laboratory to measure hematological variables. Whole

blood was spun (894 G relative centrifugal force) for 15 minutes at ambient temperature for plasma separation. Aliquots of packed blood and plasma were stored at –80°C at the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b). Blood glucose was measured using a rapid field test kit during blood collection. All analyses, as outlined in Table 1, on stored blood and urine analyses will be performed at the Immunobiology, Nutrition, and Toxicology Laboratory of icddr,b. In addition, the trained team also collected 20 strands of hair about 10 cm in length from the scalp to measure Hg exposure. To store hair samples, we used 1 envelope for each participant. We will send the hair samples to the National Institute for Minamata disease study laboratory in Japan, where they will use oxygen combustion–gold amalgamation procedure using a Mercury Analyzer (MA2000; Nippon Instruments) to analyze mercury content in hair [33].

Outcome Assessment

Our primary study outcome is blood Pb and Cd concentrations. Secondary outcomes include the impacts of heavy metals on body function. In our recent published systematic review [34], we have identified the reported health consequences of e-waste exposure (Table 1).

Table 1. Study outcome indicators and measurement tools.

Outcome, measurement type or sample analyzed	Indicator	Measurement tool
Heavy metal detection		
Blood	Pb[a] and Cd[b]	Graphite furnace atomic absorption spectrometry
Hair	Total Hg[c]	Oxygen combustion–gold amalgamation procedure using Mercury Analyzer (MA2000; Nippon Instruments)
Hematological system		
Blood	Hb[d], RBC[e], leukocytes, and platelet indices	Automated 5-part (Diff.26 parameter) hematology analyzer (XS-800i; Sysmex Corporation)
Respiratory System		
Lung function	FVC[f], FEV_1[g], and PEF[h]	Handheld Spirometer (SP-10; Contec)
Respiratory health	Cough, phlegm, wheeze, shortness of breath, chest illness, and family history	Modified Medical Research Council Respiratory Questionnaire [35]
Renal system		
Urinary system assessment	Difficulty emptying bladder, blood or pus in urine, and micturition problem	Self-reported questionnaire
Urine	Creatinine, albumin, and ACR[i]	Enzymatic method on analyzer (cobas c311; Roche)
Blood	Creatinine and eGFR[j]	Semiauto electrolyte analyzer
Cardiovascular system		
Blood	TC[k], TG[l], LDL[m], and HDL[n]	5-part differential semiautomated hematology analyzer (XS-800i; Sysmex)
Blood Pressure	Systolic and diastolic pressure	Digital blood pressure monitor (HEM-907; Omron)
Anthropometry	Height, weight, waist circumference, and hip circumference	Adult portable height-length measuring board (accuracy: 0.1 cm; ShorrBoard) and Body composition monitor (HBF-214; Omron)
Thyroid function		
Blood	T_3[o], T_4[p], and TSH[q]	Electrochemiluminescence immunoassay with automated immunoassay analyzers (cobas e601; Roche)
Liver function		
Blood	ALT[r], AST[s], and ALP[t]	Semiautomatic biochemistry analyzer (Evolution 3000; BSI)
Reproductive system		
Blood	Progesterone, testosterone, follicle-stimulating hormone, estrogen, and luteinizing hormone	Electrochemiluminescence immunoassay with automated immunoassay analyzers (cobas e601; Roche)
Reproductive health assessment for women	Pregnancy history, abortion, stillbirth, menstruation history, and delivery complications	Modified version of the Core Questionnaire from the 2005 World Health Organization Multi-country Study on Women's Health and Domestic Violence Against Women [36] and the reproductive health assessment toolkit from Centers for Disease Control and Prevention [37].
Pro-inflammatory cytokines		
Blood	IL-1β[u], IL-6[v], IL-8[w], IP-10[x], IL-12_p70[y], and TNF-α[z]	Enzyme-linked immunosorbent assay
Oxidative stress		
Urine	8-OHdG[aa]	Enzyme-linked immunosorbent assay

[a]Pb: lead.

[b]Cd: cadmium.

[c]Hg: mercury.

[d]Hb: hemoglobin.
[e]RBC: red blood cell.
[f]FVC: forced vital capacity.
[g]FEV_1: forced expiratory volume in 1 second.
[h]PEF: peak expiratory flow.
[i]ACR: albumin creatinine ratio.
[j]eGFR: estimated glomerular filtration rate.
[k]TC: total cholesterol.
[l]TG: triglyceride.
[m]LDL: low-density lipoprotein.
[n]HDL: high-density lipoprotein.
[o]T_3: total triiodothyronine.
[p]T_4: total thyroxine.
[q]TSH: thyroid-stimulating hormone.
[r]ALT: alanine aminotransferase.
[s]ALP: alkaline phosphatase.
[t]AST: aspartate transaminase.
[u]IL-1β: interleukin 1 beta.
[v]IL-6: interleukin-6.
[w]IL-8: interleukin-8.
[x]IP-10: interferon gamma inducible protein-10.
[y]$IL\text{-}12_p70$: interleukin 12p70.
[z]TNF-α: tumor necrosis factor alpha.
[aa]8-OHdG: 8-hydroxy-2 deoxyguanosine.

Environmental Sample Collection and Health Risk Assessment

A trained team collected dust and soil samples from e-waste processing sites and nonexposed control sites. To collect the dust samples, the team instructed the workers to collect samples at the end of a workday before cleaning the floor. They swept the floor, desks, and shelves using precleaned paintbrushes and collected the sample into a dustpan. After mixing the samples with a hand trowel, 100 to 150 g of homogenous dust was collected and placed inside an airtight Ziplock plastic bag to prevent access to ambient moisture and other contaminants.

Fieldworkers used a stainless steel spade to clean a 1 m^2 area, removing visible dust, paper, plastic, or any other organic or inorganic matter. The cleaned surface was divided into 6 equal quadrangles using the hand trowel. Subsequently, the team collected 6 subsamples using a stainless steel spade from the 6 quadrangles. A total of 100 to 150 g of soil was collected from the top surface layer of soil at a 0- to 6-cm depth to get the most precise examination of soil contamination with heavy metals. Samples were labeled, transported, and stored at room temperature at icddr,b for analyses. In addition, the team recorded GPS information at every sampling site. We will send soil and dust samples to the Bangladesh Council of Scientific and Industrial Research to quantify Pb, Cd, Hg, Cr, zinc, copper, selenium, arsenic, nickel, cobalt, beryllium, and vanadium levels using an inductively coupled plasma mass spectrometer (2000; NexION).

To determine the contamination level of both dust and soil samples, we will calculate and compare the geoaccumulation index between exposed and nonexposed sites [38]. Evidence suggests that workers are typically exposed to heavy metals through ingestion, inhalation, and dermal contact. We will calculate the average chronic daily intake through ingestion, inhalation, and skin according to the Exposure Factors Handbook [39]. Furthermore, the standardized formula will estimate the carcinogenic and noncarcinogenic risks of all available risk-posing species.

Data Management and Quality Assurance

A data management standard operating procedure was developed, in line with the icddr,b data repository system, considering the range and variation in data types. Questionnaires were programmed, and qualified research assistants collected data using handheld computers. The study investigator consulted daily with the research assistants to check data consistency. Data were downloaded from the devices each week and reviewed by the investigator. The statistical team maintains a SQL server database and provides data sets to the investigators in Stata format (.dta). Once data are available to investigators, they will be checked and cleaned for analysis. All data will be stored and periodically updated on icddr,b's data repository system. Appropriately coded exposure, biological, and environmental data will be periodically shared with the investigators and stored on the server.

Statistical Methods

Data will be presented as mean and SD for normal distribution, or median and IQR for nonnormal distribution. Proportions will be calculated for binary and categorical variables, and chi-square tests will examine the distribution differences of categorical variables between 2 groups. We will use Student *t* test (2-tailed) to compare normally distributed data, whereas the

Mann-Whitney *U* test will be used for nonnormal or skewed data. Pearson correlations (2-tailed) will be used to test the associations between different normally distributed variables, whereas Spearman correlation test will be used for the nonnormally distributed data to explore the potential risk factors for heavy metal exposure and the relationships between heavy metals and biological parameters. The correlation result will be presented as correlation coefficients (*r*'s) with *P* values.

Linear regression will be used to measure the impact of possible relevant factors on heavy metal exposure, and multiple stepwise regression will be used to investigate the relevant factors contributing to blood Pb and Cd and hair Hg concentrations considering the collinearity of the independent variables. Multivariable regression analyses will be performed to evaluate the associations between blood Pb and Cd or hair Hg concentrations and clinical parameters. All regression models will be adjusted for potential confounders as covariates; these confounding variables will be identified using directed acyclic graphs. Regression diagnostics will be conducted for all models, including examination of fit, influence, and heteroscedasticity. All statistical tests requiring the assumption of normality will be performed on natural logarithmic-transformed concentrations if required. The significance level will be set at α=.05. Data will be analyzed using Stata statistical software (release 13; StataCorp), and figures will be drawn using R software (version 3.5.2 for Windows; R Foundation for Statistical Computing).

Qualitative Investigation and Analysis

We will conduct a qualitative investigation to understand the overall management system of e-waste in the context of Bangladesh. Since this aim is not testing a hypothesis, we have not conducted a separate sample size calculation for this exploratory qualitative study. We will visit as many respondents as needed to achieve data saturation—the point at which we no longer gain new information [40]. We will conduct interviews with active workers involved in e-waste collection, refurbishment, crude recycling, and disposal. Additionally, we are planning to conduct interviews with key informants, including government officials and stakeholders working on e-waste. We will use a semistructured questionnaire as a data collection tool. All of the qualitative data will be collected by experienced researchers, and they will be trained on the proposed guideline. All the interviews will be recorded using an audio recorder if the participants permit. The research team will also take additional open-ended field notes, including informal discussions and observations. Audio-recorded in-depth interviews and key informant interviews will be transcribed verbatim in the native Bengali language. Data will be analyzed through systematic thematic analysis using the deductive codes generated before data collection, and any inductive codes generated during data analysis. Later, thematic content analysis will be performed to present the result. All the data will be analyzed using ATLAS.ti software (version 5.2; ATLAS.ti Scientific Software Development).

Ethics Approval

Before interviews and sample collection, eligible adult respondents provided written informed consent in the local language (Bengali). We acquired consent from the guardian and assent from the child if a worker was aged <18 years and enrolled as a study participant. To minimize the risk of breach of confidentiality, every effort was made to conduct the interviews in private. We made every effort to put the subjects at ease during discussions of sensitive questions by using culturally appropriate terminology or euphemisms where possible and by reminding the subjects at the outset that they are free to withdraw from the study at any point. We will develop anonymous data sets without personal identifiers and maintain participants' privacy by using deidentified data during storage, analysis, and dissemination. This study protocol has been reviewed and approved by the Research Review Committee and Ethical Review Committee of the icddr,b (PR#19057) and The University of Queensland's Human Behavioral Ethics Committee (2021/HE001648).

Results

Participant Characteristics

A total of 199 exposed and 104 nonexposed individuals were successfully enrolled. Demographics for the participants are presented in Table 2. Participants from the exposed group were younger than the nonexposed participants (31 vs 35 years), and most of participants in both groups were male (160/199, 80.4% and 73/104, 70.2%, respectively). No significant differences were found in terms of marital status, family members, and heights of the participants in the 2 groups (*P*=.85, *P*=.77, and *P*=.46, respectively). The exposed group's weight, hip and waist circumference, and BMI were lower than the nonexposed group's (*P*=.03, *P*<.001, *P*<.001, and *P*=.04, respectively). There were significant differences and higher consumption rates of smoking and alcohol in exposed participants than nonexposed participants (both *P*<.001).

Table 2. Participant characteristics of exposed and nonexposed populations.

Characteristic	Exposed population (N=199), n (%)	Nonexposed population (N=104), n (%)	*P* value
Age (year), mean (SD)	31 (12)	35 (15)	.01[a]
Sex, male, n (%)	160 (80.4)	73 (70.2)	.04[b]
Education, n (%)			<.001[b]
No education	71 (35.7)	28 (26.9)	
Up to primary school	97 (48.7)	20 (19.2)	
Above primary school	31 (15.6)	56 (53.8)	
Married, n (%)	143 (71.8)	76 (73.1)	.85[b]
Self-owned home, n (%)	47 (23.6)	101 (97.1)	<.001[b]
Family members, mean (SD)	4.66 (2.18)	4.74 (2.04)	.77[a]
Monthly income (US $), median (IQR)	234 (140-351)	175.52 (117-234)	<.001[c]
Household have own, n (%)			
Electricity	193 (97)	104 (100)	.07[b]
Mobile phone	183 (92)	103 (99)	.01[b]
Television	138 (69.3)	72 (69.2)	.98[b]
Refrigerator	110 (55.2)	84 (80.8)	<.001[b]
Electric fan	186 (93.5)	103 (99)	.02[b]
Sewing machine	36 (18.1)	33 (31.7)	.01[b]
Occupation, n (%)			<.001[b]
e-Waste workers	199 (100)	N/A[d]	
Farmer	N/A	31 (30)	
Small business	N/A	20 (19.2)	
Student	N/A	18 (17.3)	
Housewife	N/A	15 (14.4)	
School teacher	N/A	5 (4.8)	
Others (service, day labor, tailor, and mason)	N/A	15 (14.4)	
Smoker, n (%)	122 (61.3)	31 (29.8)	<.001[b]
Alcohol consumption, n (%)	37 (18.6)	3 (2.9)	<.001[b]
Height (cm), median (IQR)	157.85 (153.03-163.23)	159.03 (152.53-165.43)	.46[c]
Weight (kg), (median (IQR)	51.9 (44.77-61.1)	55.5 (48.68-64.97)	.03[c]
BMI (kg/m^2), median (IQR)	20.4 (18-24.4)	21.87 (19.25-25.5)	.04[c]
Hip circumference (cm), median (IQR)	33.45 (31.2-35.95)	36.5 (32.77-82.30)	<.001[c]
Waist circumference (cm), median (IQR)	29.35 (25.85-33.75)	33.8 (27.62-74.55)	<.001[c]

[a]Independent-sample *t* test.

[b]Chi-square test.

[c]Mann-Whitney *U* test.

[d]N/A: not applicable.

Dissemination

We will share the study findings with the Department of Environment of the government of Bangladesh and other partner nongovernmental organizations working on environmental issues to ensure a safe environment. We will discuss the scope and limitations of e-waste management based on our study findings. We will develop technical and policy-level interventions and capacity building and increase public awareness of these environmental hazards. We will develop abstracts for international conferences to international audience for dissemination. We will develop manuscripts and submit them to peer-reviewed journals.

Discussion

To the best of our knowledge, this will be the first epidemiological study to assess the health effects of e-waste exposure among current e-waste workers in Bangladesh. This study has several strengths. First, we collect extensive data on potential exposures, covariates, and outcomes that will help determine valid and meaningful associations between different exposure-outcome combinations. We collected biological samples (blood, urine, and hair) from which a comprehensive health assessment can be measured. We also collected environmental samples that allows us to determine the correlation between the concentrations of environmental heavy metals and levels in participants' biological specimens. Second, most of the outcomes planned in this study are objective measures that will increase the validity of our findings and ease the risk of reporting bias.

There are some limitations as well. Study subjects may have been exposed to toxicants other than those we have measured, such as other heavy metals and persistent organic pollutants, and these exposures may be correlated with those we have measured. As such, attributing causality to associations between Pb, Cd, and Hg and adverse health outcomes may be problematic. Moreover, we encountered several obstacles during data collection. First, the COVID-19 surge delayed our data collection process, and we had to halt the data collection on multiple occasions to comply with COVID-19 guidelines. Second, workers had limited work scope during this critical time, and many of them left their job, which may have reduced the continuous exposure. Additionally, there is a possibility of information bias and a possible overreporting of symptoms, especially respiratory and female reproductive issues among the exposed individuals.

Despite these limitations, the danger to the population involved in e-waste handling is largely undocumented, and this study will provide important information. The research findings could provide data to support decision-making and the formation of action plans following the Bangladesh e-waste management road map.

Acknowledgments

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Authors' Contributions

SMP and MR developed the study concept. SMP, MR, and FJ developed the study design. PDS, LDK, RR, MF, NI, ZI, SSH, NA, and MM provided input in environmental and biological sample collection and analysis. SSH provided input in statistical analysis. SMP drafted the paper, and all authors read and commented on the paper and agreed with the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) - Research Review Committee (Dhaka, Bangladesh).
[PDF File (Adobe PDF File), 569 KB - resprot_v11i8e38201_app1.pdf]

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Abbreviations

Cd: cadmium
Cr: chromium
Hg: mercury
icddr,b: International Centre for Diarrheal Disease Research, Bangladesh
Pb: lead

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Protocol

A Novel Theory-Based Virtual Reality Training to Improve Patient Safety Culture in the Department of Surgery of a Large Academic Medical Center: Protocol for a Mixed Methods Study

Lukasz M Mazur[1], PhD; Amro Khasawneh[2], PhD; Christi Fenison[3], MS; Shawna Buchanan[3], BSN; Ian M Kratzke[4], MD; Karthik Adapa[1], MD; Selena J An[4], MD; Logan Butler[1], MS; Ashlyn Zebrowski[1], MS; Praneeth Chakravarthula[5], PhD; Jin H Ra[4], MD

[1]Division of Healthcare Engineering, Department of Radiation Oncology, School of Medicine, University of North Carolina, Chapel Hill, NC, United States

[2]Industrial Engineering Department, School of Engineering, Mercer University, Macon, GA, United States

[3]Academic Technology Services, School of Medicine, University of North Carolina, Chapel Hill, NC, United States

[4]Department of Surgery, School of Medicine, University of North Carolina, Chapel Hill, NC, United States

[5]Department of Computer Science, University of North Carolina, Chapel Hill, NC, United States

Corresponding Author:
Lukasz M Mazur, PhD
Division of Healthcare Engineering, Department of Radiation Oncology
School of Medicine
University of North Carolina
101 Manning Drive
Chapel Hill, NC, 27713
United States
Phone: 1 9196169702
Email: lmazur@med.unc.edu

Abstract

Background: Preventable surgical errors of varying degrees of physical, emotional, and financial harm account for a significant number of adverse events. These errors are frequently tied to systemic problems within a health care system, including the absence of necessary policies/procedures, obstructive cultural hierarchy, and communication breakdown between staff. We developed an innovative, theory-based virtual reality (VR) training to promote understanding and sensemaking toward the holistic view of the culture of patient safety and high reliability.

Objective: We aim to assess the effect of VR training on health care workers' (HCWs') understanding of contributing factors to patient safety events, sensemaking of patient safety culture, and high reliability organization principles in the laboratory environment. Further, we aim to assess the effect of VR training on patient safety culture, TeamSTEPPS behavior scores, and reporting of patient safety events in the surgery department of an academic medical center in the clinical environment.

Methods: This mixed methods study uses a pre-VR versus post-VR training study design involving attending faculty, residents, nurses, technicians of the department of surgery, and frontline HCWs in the operation rooms at an academic medical center. HCWs' understanding of contributing factors to patient safety events will be assessed using a scale based on the Human Factors Analysis and Classification System. We will use the data frame theory framework, supported by a semistructured interview guide to capture the sensemaking process of patient safety culture and principles of high reliability organizations. Changes in the culture of patient safety will be quantified using the Agency for Healthcare Research and Quality surveys on patient safety culture. TeamSTEPPS behavior scores based on observation will be measured using the Teamwork Evaluation of Non-Technical Skills tool. Patient safety events reported in the voluntary institutional reporting system will be compared before the training versus those after the training. We will compare the Agency for Healthcare Research and Quality patient safety culture scores and patient safety events reporting before the training versus those after the training by using descriptive statistics and a within-subject 2-tailed, 2-sample *t* test with the significance level set at .05.

Results: Ethics approval was obtained in May 2021 from the institutional review board of the University of North Carolina at Chapel Hill (22-1150). The enrollment of participants for this study will start in fall 2022 and is expected to be completed by early spring 2023. The data analysis is expected to be completed by July 2023.

Conclusions: Our findings will help assess the effectiveness of VR training in improving HCWs' understanding of contributing factors of patient safety events, sensemaking of patient safety culture, and principles and behaviors of high reliability organizations. These findings will contribute to developing VR training to improve patient safety culture in other specialties.

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KEYWORDS

virtual reality training; patient safety culture; patient safety events; sensemaking; high reliability organizations

Introduction

Background

High-quality health care requires continual efforts to decrease the incidence of medical errors [1]. Surgical patients are at particular risk for error-associated adverse outcomes, given the invasiveness of undergoing surgery [2]. It is estimated that annually over 4000 harmful surgical errors are preventable nationally [1]. Surgical errors may lead to temporary or permanent harm to the patient (eg, physical, emotional, or even death) and may cause harm to care providers (eg, second victim) [3]. For example, unintended retention of foreign objects, which is estimated to occur at least once in every 5500 surgeries, [3] may lead to reoperation, increased hospital length of stay, and sepsis [3]. Moreover, the average additional cost related to unintended retention of foreign objects is estimated to be more than US $200,000 per incident [4]. The common root causes of surgical errors reported to the Joint Commission include the absence of policies and procedures, problems with hierarchy and intimidation, failure to communicate with physicians, and failure of staff to communicate relevant patient information [5]. Additionally, factors such as high workload, time pressure, and the resulting burnout are associated with higher rates of errors. These root causes have been difficult to address, as complex care delivery systems tend to "drift" over time creating new sources of failures and failure pathways [5].

Safety problems in health care persist because they are multifactorial and complex. A barrier to improving safety appears to be a broad lack of appreciation for the underlying causes of safety problems and everyone's role in contributing to these problems. There is a need to collectively strive to build a "culture of patient safety," with excellence at all levels, as is common in high reliability organizations (HROs) [6]. An evolving concept in the area of quality and safety is sensemaking, which is an action taken in response to an individual's interpretation of ambiguous events. Sensemaking is essential to achieve commitment to HRO-like thinking and behaviors [7]. Sensemaking has been shown to improve patient safety by improving health care workers' (HCWs') commitment to a culture of patient safety and the reliability of an organization [7]. For example, by improving sensemaking, bedside nurses can evaluate and determine the appropriate response to safety concerns expressed by patients or their families [8].

Current interventions to improve safety largely address the sharp end of the error. For example, at the resident level, the Accreditation Council for Graduate Medical Education requires residents, including surgical residents, to participate in interprofessional patient safety training and activities such as performing root cause analyses and reporting patient safety events, with evidence that these requirements lead to positive patient safety improvements [9]. Moreover, simulation-based training for attending surgeons appeared to decrease subsequent malpractice claims [10]. Most of these efforts, however, focus on skills needed at the sharp end of the error (eg, communication and teamwork in the operating room, technical skills) yet lack the training on the faulty systems (eg, Swiss cheese model [SCM] [11] of error prevention), the culture of patient safety, and the unreliable thinking and behaviors that lead people to make mistakes or fail to prevent them [12].

The use of virtual reality (VR) training in health care is becoming an increasingly feasible and effective method for training. Research suggests that VR training in health care can improve technical and nontechnical skills (eg, team communication, teamwork), planning and performing surgery, and medical diagnosis [13]. Most importantly, VR appears to be particularly well suited to be modified to address education on nontechnical skills, including the holistic view of the culture of patient safety and high reliability, as well as the sensemaking of patient safety events. Although such VR-based training has not been widely applied in health care, it has been successfully applied in construction [14]. Alternative approaches to providing this type of training within health care are perhaps suboptimal. Major health care systems currently rely on a webpage-based learning management system and the associated PowerPoint presentations. While useful, VR may provide this information more interactively and engagingly. Thus, there is a need to develop a patient safety training program that promotes understanding and sensemaking toward the holistic view of the culture of patient safety and high reliability. Furthermore, the training program must help HCWs better understand the overall extent of patient safety from the blunt to the sharp end of the error and, consequently, emphasize a culture of improvement at all levels of the organization.

VR can give HCWs immersive first-person access to realistic health care scenarios where adverse events occur, thereby enabling a deeper experiential learning exposure to the contextual realities surrounding such events, without posing any risk or harm to a real patient. As a strategic training solution, VR may enable the provision of complex health care training scenarios that would otherwise be inaccessible as real-world observations owing to their unpredictable and high-risk nature, too resource-intensive to re-enact in a live clinical training setting on a per learner basis, and ineffective as a passive 2D module, where the goal of the training is to experientially connect learners to the lived, contextualized realities surrounding an adverse event for situational sensemaking. Among these difficult to train for adverse events is a surgical error in action. Errors are by nature unintended and thus cannot be anticipated

during clinical shadowing. Specifically, surgical errors occur in an operating room, where strict policies for patient safety make observation impossible for most learners and anyone outside of the surgical team itself. This reveals a key experiential exposure obstacle: access to the real context in which a surgical error occurs. Although live mock simulations using standardized patients are used for certain health care scenarios, the resources involved in realistically recreating a surgical scenario include the time and coordination for full representation of a surgical team, time in an operating room, or the creation of a realistic representation of one, patient representation, and an array of special effects that must coincide with the error and necessitate cleanup/reset for each run-through. These resource requirements are immense and thus neither cost-effective nor scalable for multiple realistic per-learner exposures. Additionally, such a live mock simulation continues to fall short in meeting the holistic need, providing insight into the larger contributing factors and consequences that exist beyond the operating room itself. Meanwhile, traditional 2D content may be used in the topical illustration of a surgical error, but by nature, exists as a passively consumed resource disconnected from learners' spatially contextualized, experiential reality. Although this disconnection may or may not impact certain forms of learning such as the ability to recall facts, higher-level central processing of theoretical events, including a simulated engagement in sensemaking of complex situations, may benefit from more experiential learning approaches. Experiential learning involves a personalized and cognitive engagement with the learning content, emphasizing the linkage between learning and its "real world" context. If HCWs are to engage in sensemaking activities regarding the complex lived realities that are connected to adverse events, VR may offer advantages to 2D content in that it allows HCWs to access an immersed perspective of the event as it would occur before one's own eyes.

We have developed an innovative VR-based training to improve patient safety culture and HCWs' understanding of factors contributing to patient safety events, sensemaking, and HRO-like thinking and behaviors. This training is rooted in Reason's SCM [11], which demonstrates how system failures are often the result of a combination of factors. The training is designed for HCWs to build deep emotional connections and to facilitate understanding and sensemaking toward the culture of patient safety and HRO-like thinking and behaviors [12,15]. Our goal is to implement and evaluate this innovative VR training at a large academic medical system in the southeast United States. To the best of our knowledge, this VR training is the first-of-its-kind high-fidelity model focused on the culture of patient safety and HRO thinking and behaviors and designed to help HCWs make sense of patient safety events in health care.

The VR training tool utilizes multiple 360° scenes arranged in a narrative format and delivered within an interactive VR-input enabled application. The 360° videos were recorded with 2 different 360° cameras: first-person perspectives were recorded with a head-mounted GoPro Max in 5.6K resolution and a third-person observer view was recorded for each scene with the Insta360 Titan in 11K resolution. The GoPro Max was selected for the first-person perspectives owing to its small size for head mounting and stabilization features. The Insta360 Titan was also used for its ability to capture the full scene in a higher resolution/level of detail. Each scene within the simulation features a room view as well as a first-person perspective view. The 360° videos include scenes within the operating room where the adverse event occurs, different locations within the hospital, different locations within home environments, and a board room where hospital policies are discussed; each of these locations serves to explore the complex realities of the various perspectives connected to the adverse event. The 360° videos were edited using Adobe Premiere Pro and Boris FX for both cinematic scene composition and special effects as needed, and each scene was exported as its own video file for interactive scene selection options in-app. The initial development of the interactive VR app used 3DVista—a visual scripting tool for the creation of interactive 360° video applications. The 3DVista software was selected for a quicker design iteration process, publishing a product that can be delivered via both WebXR on any device and as a sideloaded local app on the standalone VR headset itself. The app features a welcome user interface menu providing an overview of the simulation content and purpose to provide a background context as well as instructions for VR use prior to starting the simulation. Buttons are present within the app to allow for perspective switching within each scene, as learners can explore the perspective-based contributions and effects surrounding the surgical error featured in the simulation. Within each scene, a few interactive hotspots are present to allow users to further observe the contextual details present. After testing our initial VR tool design, the app's final design choice will be rebuilt in the Unity game engine to enable future C#-based customizations as needed, such as enabling potential eye-tracking-dependent research questions and potential learning management system integrations. This tool is being developed in-house by our research team on behalf of the University of North Carolina (UNC) School of Medicine IT Instructional Media Services.

Objectives

The overall aim of this study is to create a VR-simulated environment where HCWs profoundly experience and learn the concepts of patient safety culture and principles and behaviors of HROs. This will be created in a human factors laboratory and will be used to train HCWs in a large academic medical center. The specific aims of this study are as follows: (1) to assess the effect of innovative VR training on HCWs' understanding of contributing factors to patient safety events, sensemaking of patient safety culture, and principles and behaviors of HROs in the laboratory environment and (2) to assess the effect of innovative VR training on patient safety culture, TeamSTEPPS behavior scores, and reporting of patient safety events in the surgery department of an academic medical center in clinical settings.

We hypothesize that HCWs' understanding of contributing factors to patients' safety events (*hypothesis 1a*), sensemaking process of patient safety culture, and principles of HROs (*hypothesis 1b)* will improve from pre-VR to post-VR training. Further, we hypothesize that there will be an increase in patient safety culture score (*hypothesis 2a)*, TeamSTEPPS behavior

scores (*hypothesis 2b)*, and reporting of patient safety events (*hypothesis 2c)* in pre-VR versus post-VR training.

Methods

Study Design

This study uses a mixed methods approach and a pre-VR versus post-VR training study design. In the first phase of the study, participants will first read a description of a patient safety event and then be asked to evaluate the contributing factors associated with the event. Next, participants will experience a patient safety event in an immersive interactive VR environment, followed by evaluating their understanding of the contributing factors associated with the event. We will use the data frame theory framework [16] supported by a semistructured interview guide to capture the sensemaking process of patient safety culture and principles of HROs for an HCW. We will conduct interviews with the participants after they have experienced the VR training program. The second phase of the study involves comparing changes in the culture of patient safety, TeamSTEPPS behavior scores, and reporting of patient safety events in pre-VR versus that in post-VR training.

Participants

The participants for this study are attending faculty, residents, nurses, and technicians working in the Department of Surgery at UNC Health. This department includes 68 faculty and 75 residents. Residents are divided into general surgery, cardiothoracic, vascular, and plastic surgery. Within general surgery are additional faculty divisions (pediatric, acute care, transplant, oncology, gastrointestinal, burns). Faculty practice mostly at UNC's main medical center, but we also have some faculty at Hillsborough and Rex. All frontline HCWs from operation rooms and the UNC Department of Surgery will also be invited to participate in the study. We will exclude traveler nurses, temporary employees, and administrative staff from this study. An onsite research team member will answer questions from prospective participants, and the principal investigators' contact information will be available on the flyer. A previously used scripted protocol and emails sent through a departmental listserv will be used to inform prospective participants about the study. If they choose to participate, we will obtain consent from the participant before the first phase of the study. An incentive of US $50 will be provided to the participants for the first phase of the study.

Setting

The first phase of the study, which provides participants with experience of a patient safety event in an immersive interactive VR environment, will be conducted in the Human Factors Laboratory located in the Department of Radiation Oncology at UNC.

Intervention

The VR training is guided by Reason's SCM [11,15] and Human Factors Analysis and Classification System (HFACS) [17,18] and targets each layer in the HFACS model. We utilized state-of-the-art filming equipment to capture a 360° view of the event and the perspective of those involved in the event. We built the scripts for the scenes, recruited actors (attendings, residents, students, administrators) with lived experiences in health care to help with the filming, identified filming locations, rehearsed all the scenes, and filmed our scenes. We expect to assemble the complete training program and have the final product ready by July 2022. This training will be delivered to the participants using a VR head-mounted display to ensure an immersive environment. Specifically, we will use Pico Neo 3 Pro Eye [19] with 6DoF VR hardware/software to implement the VR training.

Measures

Primary Measures

Understanding of Contributing Factors

Participants' understanding of contributing factors to an event is assessed using a scale based on the HFACS (Multimedia Appendix 1).

Sensemaking of Patient Safety Culture and Principles of HROs

Participants' understanding of patient safety culture and principles of HROs are assessed by conducting 2 semistructured interviews with each participant after reading the patient safety event description and after completing the VR training. The purpose is to explore participants' baseline understanding of patient safety culture and principles of HROs before taking the training and to examine their experience with the training, including how did the training change their understanding of patient safety culture and principles of HROs. Interviews are guided by a phenomenological approach, which follows the paradigm of subjectivity and emphasizes the importance of understanding personal experience to gain insights into the sensemaking process of patient safety events concept as the individuals take the training program [16]. This approach has been applied in previous studies to examine the sensemaking process of making health care decisions [20]. Interview questions are presented in Multimedia Appendix 2. Face-to-face interviews for 10 minutes are conducted with each participant. If participants permit, interviews are audio-recorded and transcribed for analysis or else, the research team will take detailed handwritten notes.

Secondary Measures

Patient Safety Culture

Patient safety culture is assessed using the Agency for Healthcare Research and Quality (AHRQ) Survey on Patient Safety Culture (SOPS). AHRQ SOPS is a reliable and validated instrument to assess and capture all staff members' perceptions on key components of patient safety culture, such as teamwork, staffing, work pace, organizational learning, response to error, clinical leader support for patient safety, communication about the error, communication openness, reporting patient safety events, hospital management support for patient safety, handoffs, and information exchange [21,22]. The Department of Surgery will take this survey after the intervention to allow for the pre-VR versus post-VR training comparison on patient safety culture.

TeamSTEPPS Behavioral Score

Teamwork is one of the key initiatives within patient safety that can transform the culture within health care. Studies suggest that communication and other teamwork skills are essential for the delivery of quality health care and for preventing and mitigating medical errors and patient injury and harm [23,24]. TeamSTEPPS behavioral scores are currently collected by the operation room nurses as part of regular operations by using the Teamwork Evaluation of Non-Technical Skills (TENTS) tool [25]. TENTS is a valid and reliable instrument to assess a variety of clinical teamwork events. It is a 13-item observational assessment tool used in clinical settings. These scores will be used to compare the results of pre-VR versus those of post-VR training [25].

Reporting of Patient Safety Events

Voluntary reporting of patient safety events is important for achieving the broad goal of error reduction. We will use the events reported in our institutional voluntary reporting system to compare the reporting of patient safety events before versus after the VR training. The events will be classified based on the AHRQ Common Format Harm score. Using the score (1 through 9) and the nature of harm, we will classify each patient safety event as serious safety events, precursor safety events, near-miss safety events, and unsafe condition safety events and compare before and after the VR training. Table 1 provides an overview of the measurement tools.

Table 1. Overview of the measurement tools.

Variable	Measure
Primary outcomes	
Understanding of contributing factors	Human Factors Analysis and Classification System scale
Sensemaking of patient safety culture and principles of high reliability organizations	Semistructured interview
Secondary outcomes	
Patient safety culture	Agency for Healthcare Research and Quality Survey on Patient Safety Culture
TeamSTEPPS behavioral scores	Teamwork Evaluation of Non-Technical Skills tool
Reporting of patient safety events	Institutional voluntary reporting system
Other variables	
Demographics	Questions

Data Collection

All participants will first read a written description of the recorded patient safety event (see Multimedia Appendix 3). Then, they will take the VR training program.

Hypothesis 1a: All participants will rate the perceived contributing factors to the event using a scale based on the HFACS [17].

Hypothesis 1b: We will conduct 2 semistructured interviews with each participant: after reading the patient safety event description and after completing the VR training. The interviews are conducted to (1) explore their baseline understanding of patient safety culture and principles of HROs before taking the training and (2) to examine their experience with the training, including how did the training change their understanding of patient safety culture and principles of HROs.

Hypothesis 2a: The UNC Department of Surgery was scheduled to take the AHRQ SOPS survey in February and March 2022, which will serve as the baseline data. The UNC Department of Surgery agreed to take this survey again in February-March of 2023 (postintervention) to allow us for the pre-VR versus post-VR training comparison.

Hypothesis 2b: TeamSTEPPS behavioral scores are currently informally being collected by the operation room nurses as part of regular operations by using the TENTS tool. As needed, we will modify this data collection to fit the need of this proposal and support this data collection to ensure proper evaluation. We will use these scores to compare the results before versus after the VR training.

Hypothesis 2c: We will extract data on reporting of patient safety events from the Risk Level-6 solution platform (Safety Awareness For Everybody reporting) managed by the risk management department. We will access this data set and compare results before versus after the VR training.

Data Analysis

Hypothesis 1a: A previous study showed that VR in a simulated learning environment can improve empathic clinical communication score by 0.3-1.15 points with a standard deviation (σ) of 0.3-1.1 [26]. To detect a statistically significant change in our study, a sample size of 68 participants is needed to obtain a medium-to-large effect size (d=0.5-0.8) with a power level of .80 and an alpha of .05 [26,27]. We will compare the number of identified contributing factors (after reading the event vs after VR training) by using a within-subject 2-tailed, 2-sample t test with the significance level set to .05.

Hypothesis 1b: We will recruit a subset of the participants who took the training to participate in an additional interview study. Based on the theoretical saturation concept and our prior experience, we estimate to conduct interviews with 20-28 participants (eg, 5-7 faculty, 5-7 nurses, 5-7 staff, 5-7 residents).

However, we will continue to recruit additional participants until our data reach saturation [28]. Interview data will be analyzed using the phenomenological analysis method [29] to understand the different perspectives regarding patient safety culture and principles of HROs before taking the VR training and how the participants make sense of the training and the patient safety events they experienced during the training to adjust their understanding, behavior, and commitment to patients' safety. The qualitative analysis will include 3 steps: (1) develop textual and structural descriptions for each interview, (2) composite all textual and structural descriptions, respectively, and (3) synthesize textual and structural meanings using the data frame theory of sensemaking [16].

Hypothesis 2a: Based on the AHRQ SOPS data collected by the Office of Quality Excellence at UNC Health in 2017 and 2019, we expect that we will need 75 participants to take the survey to obtain a medium effect size (d=0.5) with a power level of .80 and an alpha of .05 [27]. We will use 2-tailed, 2-sample t test to compare pooled and construct-based AHRQ SOPS scores before versus after the VR training.

Hypothesis 2b: We will use a 2-tailed, 2-sample t test to compare pooled and construct-based to assess changes in TENTS scores before versus after the VR training.

Hypothesis 2c: We will use a 2-tailed, 2-sample t test to compare reporting of patient safety events before versus after the VR training.

Ethics Approval and Confidentiality of Data

This study received approval from UNC's institutional review board in May 2022 (22-1150). Handling and storage of data will be done per the general data protection regulation and the institutional review board policies of UNC. Collected research data within this study includes questionnaires and interviews, collected by the researchers from the Department of Radiation Oncology and Surgery at UNC. All data will be deidentified by giving every participant a unique participant ID. All data from the questionnaires shall be stored in a protected folder that can be accessed only by the research team. Physical documents, for example, signed informed consent forms will be stored safely in the Human Factors Laboratory of the Department of Radiation Oncology, UNC. The recordings of the interviews will be stored in a secure encrypted folder that is accessible only to the research team. Research data and analyses will be stored after finishing the research project in accordance with the policies of UNC.

Results

Participant recruitment will start in July-September 2022. Data collection for this study is expected to be completed by November 2023. The analysis will be conducted after data collection and is expected to be completed by December 2023. The results will be published in peer-reviewed journals and presented at national and international conferences.

Discussion

Strengths and Challenges

The VR training on safety culture and principles of HROs continue to be an appreciated topic in many other research areas, and to our knowledge, there is currently no experienced-based training to enhance HCWs' understanding of these topics. The key strengths of this study are as follows:

1. This is a first-of-its-kind VR training to enhance HCWs' understanding of contributing factors to patient safety events.
2. This is also a first-of-its-kind VR training to enhance HCWs' sensemaking of patient safety culture and principles and behaviors of HROs.
3. This study uses SCM, HFACS, and sensemaking theoretical frameworks to guide the development and evaluation of VR training.
4. It involves a multidisciplinary team and promotes collaboration among clinicians, human factors engineers, and multimedia and technology innovation experts.
5. We focus on the department of surgery, which is an innovative environment owing to the complexity of the department, where multiple factors can contribute to the occurrence of a patient safety event (eg, technical and teamwork skills, communication, technology, hierarchy) as well as the high impact of patient safety events.

We recognize that implementation of the training and having most of the department of surgery staff taking the VR training will be challenging. We have already secured the leadership's commitment to supporting this training. Based on our sample size calculations, we need 80 to agree to participate in our VR training, which is reasonable. In our past research, we were able to successfully recruit >80% of staff from various departments at UNC. Further, unanticipated factors (eg, changes in clinical practice, patient volumes, COVID-19 surges) impacting the culture of patient safety, TeamSTEPPS behaviors, and reporting of patient safety events are expected. Surgery department leadership shall inform the research team of any interventions that take place during/after the implementation of VR training, and we will account for them in our statistical analysis.

Scalability and Sustainability

The findings and experience gained by the research team from conducting this study will apply broadly to other departments in UNC Health (eg, neurosurgery, urology, orthopedics, obstetrics-gynecology) as well as other similar surgery departments nationally. We will expand the entire concept to film additional scenarios to capture other contexts (eg, intensive care unit procedures, care transitions, imaging, laboratory studies). Ultimately, if proven successful, VR training could be integrated into training curricula for attending continuous education, resident and student education, including medical and nursing populations. We also plan to work with the UNC Health Office of Quality Excellence and UNC Training and Education to help guide the implementation of our VR training more broadly.

Conclusions

To date, no research has been conducted into the effectiveness of VR in improving patient safety culture and HCWs' understanding of contributing factors of patient safety events and sensemaking of patient safety culture and principles and behaviors of HROs. Our study will be the first to assess the effect of VR-based training on patient safety culture, TeamSTEPPS behavior scores, and reporting of patient safety events in the clinical environment of the department of surgery. Based on the results, VR training can be further developed to improve patient safety culture in other specialties. In addition, the foundation that will be laid with this study allows us to design follow-up studies, for example, to compare the effectiveness of VR with other modes of training.

Acknowledgments

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Authors' Contributions

LMM, AK, CF, IMK, and SB conceived the study. The study design was a collaboration between all authors. The protocol was written by LMM, JHR and KA, with input from all authors. All authors approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participants' understanding of the contributing factors to an event using a scale based on the human factors analysis and classification system.
[DOCX File , 16 KB - resprot_v11i8e40445_app1.docx]

Multimedia Appendix 2
Interview questions.
[DOCX File , 14 KB - resprot_v11i8e40445_app2.docx]

Multimedia Appendix 3
Written description of the recorded patient safety event.
[DOCX File , 13 KB - resprot_v11i8e40445_app3.docx]

Multimedia Appendix 4
Peer-review report from the Center for Health Innovation.
[PDF File (Adobe PDF File), 160 KB - resprot_v11i8e40445_app4.pdf]

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
HCW: health care worker
HFACS: Human Factors Analysis and Classification System
HRO: high reliability organization
SCM: Swiss cheese model
SOPS: Survey on Patient Safety Culture
TENTS: Teamwork Evaluation of Non-Technical Skills
UNC: University of North Carolina

VR: virtual reality

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Protocol

Capturing Diabetes-Related Distress and Burden From the Perspective of Patients With Type 1 or Type 2 Diabetes: Protocol for an Explorative Mixed Methods Study

Sandra Zara[1], MSc; Johannes Kruse[1,2], Dr med; Anna Maria Leveling[1]; Jana Schmitz[1]; Isabelle Hempler[3], Dr Phil; Hanna Kampling[1], Dr Phil

[1]Department of Psychosomatic Medicine and Psychotherapy, Justus Liebig University Giessen, Giessen, Germany

[2]Department for Psychosomatic Medicine and Psychotherapy, Medical Center of the Philipps University Marburg, Marburg, Germany

[3]Institute of General Practice / Family Medicine, Medical Center – University of Freiburg Faculty of Medicine, Freiburg, Germany

Corresponding Author:
Sandra Zara, MSc
Department of Psychosomatic Medicine and Psychotherapy
Justus Liebig University Giessen
Ludwigstrasse 76
Giessen, 35392
Germany
Phone: 49 641 994 5654
Email: sandra.zara@psycho.med.uni-giessen.de

Abstract

Background: Diabetes is one of the most common diseases worldwide and is associated with increased morbidity, mortality, and reduced quality of life. Many patients experience high diabetes-related distress as well as depression and anxiety symptoms, which are associated with poor diabetes self-management. As disease management is a central component in diabetes treatment, poor management enhances the occurrence of micro- and macrovascular complications. This emphasizes the relevance of reducing diabetes-related distress and providing adequate treatment options addressing the individual psychosocial burden of patients with diabetes. Since patients' perspectives diverge significantly from those of practitioners in terms of relevant treatment aspects, the patient perspective on, for example, barriers to and facilitators of diabetes treatment is crucial for adequate and effective treatment as well as improvements to self-management and therefore, needs to be further explored.

Objective: This study aims to examine diabetes-related distress, the course of distress throughout diabetes management, as well as barriers and facilitating factors in dealing with diabetes from the individual perspective of patients with type 1 and type 2 diabetes.

Methods: The study employs a mixed methods design combining qualitative and quantitative data. Semistructured interviews (N=40) will be conducted with patients with type 1 diabetes (n=20) and patients with type 2 diabetes (n=20). The primary outcomes comprise (1) diabetes-related distress, (2) the severity of distress, (3) the course of distress throughout diabetes management, (4) barriers, and (5) facilitating factors. Questionnaires will provide data on the following secondary outcomes: diabetes-related emotional distress (the Problem Areas in Diabetes scale), symptoms of depression and anxiety (Patient Health Questionnaire, German version), personality functioning (Operationalized Psychodynamic Diagnosis-Structure Questionnaire), mentalizing capacities (Mentalization Questionnaire), epistemic trust (Epistemic Trust, Mistrust and Credulity Questionnaire) and experiences of child maltreatment (Childhood Trauma Questionnaire), and the overall health status of the patient (routine medical data).

Results: As of April 2022, the conceptualization phase of the study was finalized. Ethics approval was received in January 2022 from the local ethics committee of the Justus Liebig University Giessen – Faculty of Medicine (AZ 161/21).

Conclusions: This study will provide insights into the individual perspective of patients with type 1 and type 2 diabetes regarding their experiences with diabetes management and what they perceive to be relevant, obstructive, or beneficial. The insights gained could help further tailor diabetes treatment to the individual needs of patients with diabetes and therefore optimize diabetes self-management.

Trial Registration: German Clinical Trial Register DRKS00024999; https://tinyurl.com/2wb4xdh8

International Registered Report Identifier (IRRID): PRR1-10.2196/38477

(JMIR Res Protoc 2022;11(8):e38477) doi:10.2196/38477

KEYWORDS

diabetes; diabetes-related distress; glycemic control; depression and anxiety; mixed methods design; mixed methods; protocol; stress; anxiety; depression; patient perspective; psychosocial; management; treatment; self-management

Introduction

With a global prevalence of 476 million, diabetes is one of the most common diseases worldwide [1]. About 10% of the German population has diabetes [2], with projections indicating a further increase [3]. Diabetes is associated with increased morbidity, mortality, and reduced quality of life [4] and poses growing socioeconomic challenges for the health care system (eg, medication and hospitalization) [5]. Regarding treatment, adequate glycemic control (glycated hemoglobin [HbA_{1c}] <7.5%) and a high degree of self-management are crucial. However, studies have shown that approximately 58.4% of patients with type 1 diabetes and 40.4% of patients with type 2 diabetes do not achieve their target glycemic control [6]. Additionally, as many as 42% of patients with type 1 diabetes and 24% to 36% of patients with type 2 diabetes report pronounced diabetes-related distress [7] (defined as the emotional aspect of the burden of living with a mainly self-managed chronic disease) [8]. High diabetes-related distress is associated with inadequate glycemic control (HbA_{1c}>7.5%) as well as poor diabetes management [9,10], highlighting the relevance of reducing this burden for patients with diabetes.

Further, patients with inadequate glycemic control present elevated depression or anxiety symptoms [11]. Diabetes has been shown to increase the risk of depressive symptomatology [7], while, conversely, depressive symptomatology increases the risk of developing type 2 diabetes by 34% [12]. Patients with diabetes have about twice the risk of developing an anxiety disorder compared to patients without diabetes, with fears of acute complications, such as hypoglycemia or subsequent diseases and complications (microvascular diseases like retinopathies as well as macrovascular diseases) [13]. The presence of psychiatric comorbidity is linked to both morbidity and mortality and decreased quality of life [7], while health care costs and the risk of subsequent diseases are augmented [14]. Since psychological distress and psychiatric comorbidities not only require adequate treatment by themselves but also accelerate the development of diabetes-associated secondary diseases and worsen their course [15], they pose a significant treatment focus in patients with diabetes.

As strict monitoring and regulation of glycemic control are central in diabetes management, factors associated with poor glycemic control are important to consider. Evidence on the association between poor glycemic control and, for example, depression or anxiety symptoms is inconsistent. Some studies showed an association between depression and anxiety symptoms and poor glycemic control in adults with type 1 diabetes [16], while others found no association between depression and poor glycemic control [17,18]. This might be a conceptual issue, as the notion of diabetes-related distress better describes the psychosocial adjustment to diabetes than depression, comprising anger, guilt, frustration, denial, and loneliness [19]. Both constructs seem to overlap and correlate, yet are distinct [20,21], potentially explaining why pharmacological and psychological treatments for patients with depression and type 1 and type 2 diabetes yield inconsistent achievements regarding glycemic control [22,23]. Recently, a multidisciplinary, psychosomatic, psychodynamically oriented, short-term intervention improved glycemic control by focusing on individuals' specific diabetes-related distress [24]. This emphasizes the need to align treatment with individual needs. Studies have shown that the focus of patients and practitioners diverges; patients mainly focus on the importance of diabetes in their daily life whereas practitioners almost exclusively orient toward measurable parameters [25]. This might hinder adequate diabetes management and affect the success of treatment options. Hence, to individualize interventions, further research on patients' perspectives and their diabetes-related distress is needed.

The first aim of this study is to explore individual and specific issues in diabetes management in patients with poor glycemic control in order to better understand barriers and facilitators in their treatment. Based on qualitative data, we will derive patients' perspectives on individual diabetes-related burdens, critical times in the course of their treatment, as well as barriers and support factors. The secondary outcomes will be measured with questionnaires addressing diabetes-related distress in the context of diabetes and treatment requirements, psychological aspects (depression and anxiety symptoms, personality functioning, mentalization capacities, epistemic trust, and experiences of child maltreatment), as well as physical health assessed through routine medical data (diabetes type; HbA_{1c}; medication; weight and height; total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides; and previous illnesses).

Methods

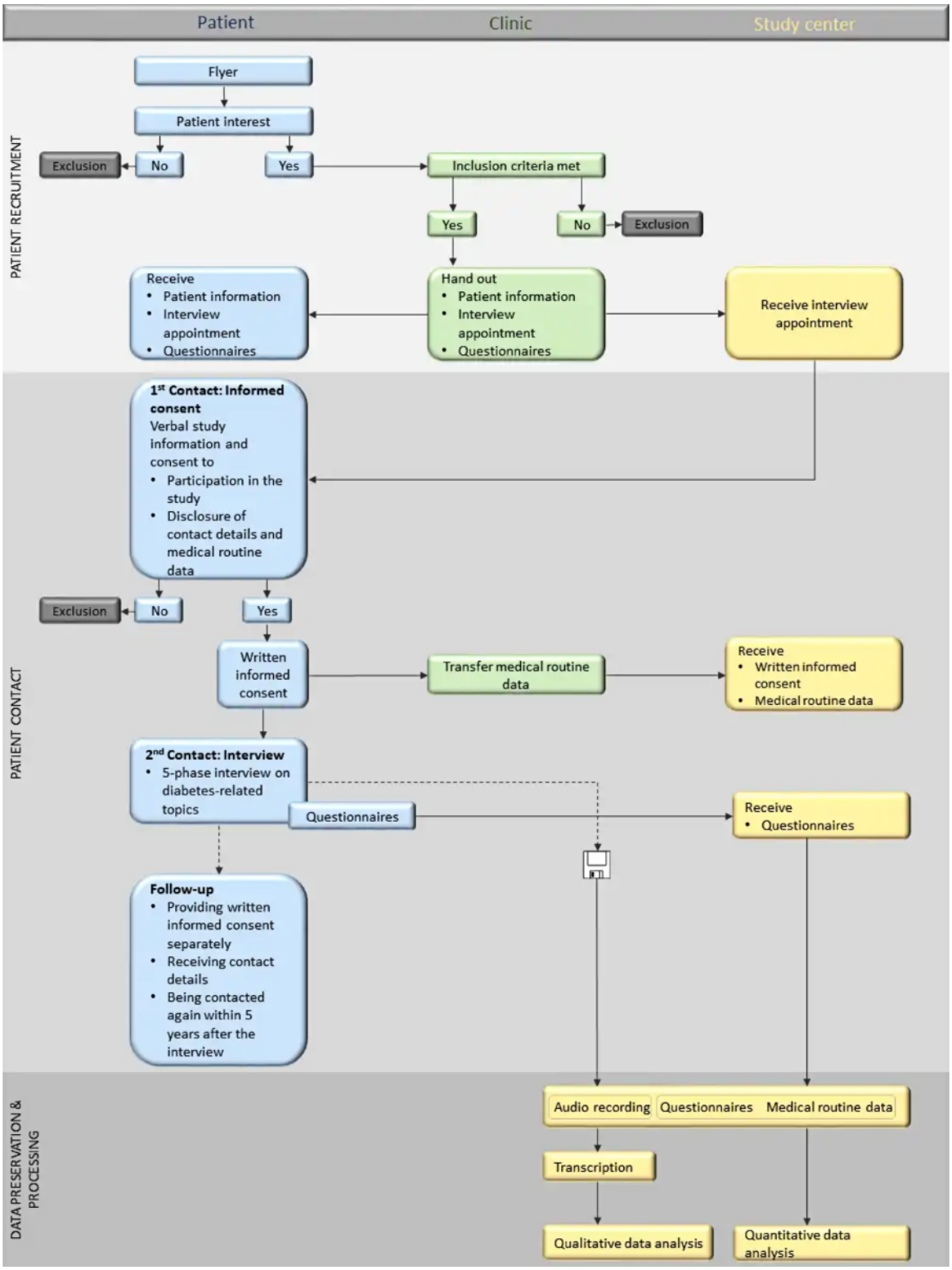
Study Design

The study will be conducted using an explorative mixed methods design and will integrate qualitative as well as quantitative data. Patients between 18 and 69 years with diagnosed type 1 or type 2 diabetes, with an HbA_{1c} value >7.5%, a diabetes duration of minimum 2 years, a completed diabetes self-management program, sufficient German language skills, and cognitive abilities will be included in the study. Patients with type 3 diabetes or gestational diabetes, severe comorbid diseases (eg, dementia, major depressive disorder, psychosis, or addiction), a diabetic foot, and those who are bedridden or are care-dependent patients will be excluded from the investigation.

Figure 1 illustrates the procedure of the study. Recruitment will take place in a clinic that specializes in diabetes. In step 1, the clinic will be equipped with all relevant documents (eg, information on the course of the study, data protection, form

for assessing routine medical data, flyer and information for patients, and questionnaires). In step 2, patients will be asked by clinic personnel to participate in the study or made aware of the study by a flyer. In step 3, patients willing to participate in the study will be given comprehensive information, be informed verbally on the study purpose and procedure, and be assigned an interview appointment by the clinic personnel. In addition, self-report questionnaires will be handed out. In step 4, the researchers conducting the interviews will thoroughly discuss the patient information and the declaration of consent with the patient. After providing written informed consent, the interview will be conducted in the clinic. Due to the ongoing COVID-19 pandemic, the patient interviews will be conducted under strict compliance with the clinics' hygiene regulations by researchers who are familiar with proper patient contact and the special regulations in effect under the pandemic.

Figure 1. Schematic illustration of the study procedure.



Sample Size

A total of 40 patient interviews (20 each for type 1 and type 2 diabetes) will be conducted. Among those, 4 interviews (2 each for type 1 and type 2 diabetes) are planned as a pretest to gain a deeper understanding of whether the developed guideline will work or if questions need to be reevaluated and modified.

Assessment

Interview Guideline

Semistructured interviews will be conducted based on an interview guideline, with each section containing open questions, giving the participant the opportunity to speak openly and introduce new content.

Phase 1: Welcome

The participant will be greeted and—corresponding to the patient information—the interviewer will explain the interview as well as the protection of privacy, including pseudonymization of the data and how the transcript will be handled. After obtaining written informed consent and providing time for questions, the interviewer will start the audio recording and begin to collect sociodemographic information.

Phase 2 – Category I: Diagnosis and Course of Diabetes

This category aims to collect information on the patients' experience with the initial diagnosis, difficult phases including symptoms of depression and anxiety, or diabetes-associated complications, as well as less difficult or good phases regarding diabetes. Sample questions include: "In your opinion, what went badly [when receiving the diagnosis]?" and "What memorable events were there in connection with diabetes and the treatment of diabetes (eg, complications and medication changes)?"

Phase 3 – Category II: Diabetes-Related Distress and Burden

In this category, individual diabetes-related distress and burden, including concerns and behavior changes, will be explored. Sample questions include: "What is it that worries you most about your diabetes?" and "What new experiences—positive and negative—have you had that you might not have had without diabetes?"

Phase 4 – Category III: Barriers and Facilitators

Questions of this category investigate barriers, for example, through doctors, the use of external support offers, as well as difficulties at work and in the social environment. Sample questions include: "What difficulties have arisen in the workplace?" and "Are there any tools (blood sugar diaries, food diaries, or apps) that make it easier for you to deal with diabetes?"

Phase 5: Final Phase

The participant will have the opportunity to tell the interviewer a specific recommendation that they believe to be useful for every patient with diabetes. After time for additional questions, the participant will be thanked for their time and participation.

Problem Areas in Diabetes Scale

The Problem Areas in Diabetes scale [26] includes 20 items to assess different areas of diabetes-related emotional distress. The response options range from 0 ("no problem") to 4 ("major problem"). A sum score is computed and multiplied by 1.25, resulting in a total score between 0 and 100. Higher values represent more severe distress. A value >39 indicates severe emotional distress [19], pointing to significant depressive symptoms [26,27].

Patient Health Questionnaire

The Patient Health Questionnaire (German version; PHQ-D) measures depressive and anxiety syndromes, somatoform syndromes, eating disorders, alcohol abuse, psychosocial functioning, stressors, critical life events, menstruation, pregnancy, and childbirth, and shows good validity [28,29]. The depression module of the PHQ-D corresponds to the PHQ-9 [30]. By providing response options between 0 ("not at all") and 3 ("almost every day"), it allows the calculation of a total score between 0 and 27, with severity classified as no depressive disorder, <5 points; mild depression, 5-9 points; moderate depression, 10-14 points; and severe depression, 15-27 points [30,31]. Anxiety syndromes are assessed with a panic module and a scale for other anxiety syndromes. The panic module consists of a general part on anxiety attacks (questions 3a-d) and a part with questions that refer specifically to the last severe anxiety attack (questions 4a-k). The possible answers are "yes" and "no." A panic syndrome is expected when questions 3a to 3d are answered with "yes" and at least 4 of the questions 4a to 4k are answered with "yes." Other anxiety syndromes (questions 5a-g) have the response options "not at all," "some days," and "more than half the days." Another anxiety syndrome is assumed if question 5a is answered with "more than half of the days" and at least 3 of the questions 5b to 5g are answered with "more than half of the days" [32].

Childhood Trauma Questionnaire

Different forms of child maltreatment will be assessed with the Childhood Trauma Questionnaire (CTQ). Participants answer questions regarding sexual, emotional, and physical abuse as well as emotional and physical neglect on a scale with response options ranging from 1 ("not at all") to 5 ("very often"). Each subscale consists of 5 items, resulting in sum scores from 5 to 25. Severity is classified as none to minimal, low to moderate, moderate to severe, and severe to extreme [33]. The German version of the CTQ [34] shows good internal consistency, except for physical neglect (sexual abuse: α=.89; physical abuse: α=.80; emotional abuse: α=.87; physical neglect: α=.55; and emotional neglect: α=.83).

Operationalized Psychodynamic Diagnosis-Structure Questionnaire

The Operationalized Psychodynamic Diagnosis-Structure Questionnaire (OPD-SQS) is a self-report questionnaire to screen for participants with deficits in personality functioning. It comprises 3 subscales (ie, self-perception, interpersonal contact, and relationship model) with 4 items in each scale. Response options range from 0 ("does not apply at all") to 4 ("fully applies"), resulting in a sum score from 0 to 48, with higher scores indicating impairments in personality functioning. The OPD-SQS showed good internal consistency (α=.88) [35].

Mentalization Questionnaire

The Mentalization Questionnaire [36] is a self-report instrument to assess mentalization capacities from the patient's perspective. It consists of 15 items with response options ranging from 1 ("no agreement at all") to 5 ("total agreement"). Analyses yielded 4 subscales with acceptable reliability and sufficient validity: (1) refusing self-reflection, (2) emotional awareness, (3) psychic equivalence mode, and (4) regulation of affect. The sum score ranges from 15 to 75, with higher scores indicating lower mentalization capacities.

Epistemic Trust

The Epistemic Trust, Mistrust and Credulity Questionnaire by Campbell and colleagues [37] was developed as a self-report questionnaire to assess epistemic trust, distrust, and gullibility. It comprises 15 items with response options ranging from 1 ("strongly disagree") to 7 ("strongly agree") [38], resulting in a score from 15 to 105. High epistemic trust, mistrust, and credulity are indicated by either strong agreement or strong disagreement with the statement.

Routine Medical Data

Routine medical data collected at doctor's appointments comprise diabetes type (type 1 or 2), HbA_{1c} level, and current medication. Weight and height to calculate BMI; total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides to assess lipid metabolism; and information on preexisting conditions (eg, coagulation disorders, cardiovascular disease, neuropathy, retinopathy, peripheral arterial occlusive disease) to assess the patients' health status will be collected.

Outcome Parameters

Primary outcomes: qualitative data from semistructured interviews will comprise (1) diabetes-related distress; (2) severity of diabetes-related distress; (3) general distress at the time of diagnosis notification, medication change, if applicable, and special events regarding the patients' social environment; (4) barriers; and (5) facilitating factors. Secondary outcomes include quantitative data that will comprise self-report questionnaire data to assess (1) diabetes-related emotional distress and (2) psychological aspects (depression and anxiety symptoms, personality functioning, mentalization capacities, epistemic trust, and child maltreatment), as well as (3) routine medical data (diabetes type, HbA_{1c}, medication, weight, height, total cholesterol, LDL and HDL cholesterol, triglycerides, and preexisting conditions).

Data Analysis

Qualitative Data Analysis

The audio recordings of the semistructured interviews will be transcribed. During the transcription process, all personal data (including that of third parties) will be made unrecognizable. The pseudonymized transcript will then be analyzed by means of content structuring qualitative content analysis [39] using MAXQDA (VERBI GmbH). The material will be systematically described with regard to individual categories that are determined in connection with the research question and differentiated during the analysis. Special emphasis will be placed on text comprehension and text interpretation [39]. The evaluation of the transcript will be divided into the following steps:

1. Development of main topics for the semistructured interview guideline
2. Initiating text work on the material
3. Inductive determination of main categories
4. First coding process
5. Compilation of main categories
6. Inductive determination of subcategories on the material
7. Second coding process
8. Simple and complex analyses and visualizations

Quantitative Data Analysis

The descriptive exploratory statistical analyses of the quantitative data (questionnaire data and routine medical data) will be performed using SPSS Statistics (IBM Corp).

Ethics Approval

Ethical approval was obtained from the Ethics Committee of Justus Liebig University Giessen – Faculty of Medicine (AZ 161/21). The study is registered in the German Clinical Trial Register (DRKS00024999). All personal data of the participants are subject to medical confidentiality, the German general data protection regulation (Datenschutz-Grundverordnung), and state and federal data protection acts (Landesdatenschutzgesetz and Bundesdatenschutzgesetz). To maintain anonymity, the data will be pseudonymized and the corresponding codes will be kept by the principal investigator. The data will be stored for up to 5 years after final publication.

Results

As of April 2022, the conceptualization phase of the study conduct has been finalized.

Discussion

Expected Findings

This study aims to gain insights into the individual perspective of patients with type 1 and type 2 diabetes on their experiences with their diabetes diagnosis, diabetes-related distress and burdens, psychosocial aspects, and barriers and facilitators, as well as what they perceive to be particularly relevant, obstructive, or beneficial regarding these subject areas. With the applied mixed methods design we expect to comprehensively explore individual diabetes-related burdens and facilitating factors adding to the numerous well-known challenges of patients with diabetes and, hence, inform diabetes treatment as well as focus on important psychosocial aspects for successful treatment. The results of our study will lay the groundwork for a new questionnaire to systematically assess individual diabetes-related distress, burdens, and facilitators that are useful for diabetologists by informing treatment planning as well as for future research in this field by enabling the systematic assessment of individual challenges and problem areas.

Limitations

Regarding the proposed methodology of this study, a number of possible limitations must be acknowledged. First, due to recruitment taking place in a diabetes clinic, our study population might face particular challenges compared to patients with diabetes who receive outpatient treatment, potentially limiting the generalizability of our findings. Further, we omitted patients with gestational diabetes and other diabetes types. Mixed methods research generally faces the conceptual challenge of how methods should be selected for a given research question, what the mixing of approaches refers to, and, eventually, how a mixed methods methodology should be structured [40]. Further, an immanent part of qualitative research is the possibility of receiving socially desired answers, especially when it comes to sensitive issues. With regard to the time frame of the patient interview (approximately 60 minutes), addressing all aspects that might be of interest will not be possible. For example, suicidal ideation will not be specifically addressed. To account for this, we will end each interview subject with open questions, giving the patient the opportunity to bring subjects to our attention.

Practical Implications

Based on our results, we aim to expand the knowledge about common diabetes-associated challenges and burdens as well as resources by exploring individual and potentially less evident problems from the patient perspective. The findings will be translated into a questionnaire allowing both practitioners and researchers to individually, efficiently, and systematically assess diabetes-related burden and subsequently inform treatment planning regarding the psychological as well as diabetological aspects to improve diabetes treatment.

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Data Availability

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

Conflicts of Interest

None declared.

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Abbreviations

CTQ: Childhood Trauma Questionnaire
HbA_{1c}: glycated hemoglobin
HDL: high-density lipoprotein
LDL: low-density lipoprotein
OPD-SQS: Operationalized Psychodynamic Diagnosis-Structure Questionnaire
PHQ-9: Patient Health Questionnaire–9
PHQ-D: Patient Health Questionnaire, German version

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Protocol

Cardiometabolic and Anthropometric Outcomes of Intermittent Fasting Among Civil Servants With Overweight and Obesity: Study Protocol for a Nonrandomized Controlled Trial

Shazana Rifham Abdullah[1], MPH, DrPH, MD; Nur Hayati Azizul[1], MBBS; Ruziana Mona Wan Mohd Zin[1], BSc; Nur Suffia Sulaiman[1], MBCHB, MPH, DrPH; Norhayati Mustafa Khalid[1], BSc, MSc; Roshan Jahn Mohd Salim Mullahi Jahn[1], BEng, MSc; Muhamad Khairul Nazrin Khalil[1], MB BCh BAO; Norhashimah Abu Seman[1], BSc, PhD; Nur Azlin Zainal Abidin[1], MD; Azizan Ali[1], MBBS, MSc; You Zhuan Tan[1], MD; Azahadi Omar[2], MD, MCommHealth; Mohammad Zabri Johari[3], BSc, MSc, PhD; Nur Shahida Abdul Aziz[4], BSc; Azli Baharudin[4], BSc; Zamtira Seman[2], BSc, MSc; Norazizah Ibrahim Wong[2], BSc; Mona Lisa Md Rasip[5], MPH, MD; Hayati Mohd Yusof[6], BSc, MSc, PhD; Mohd Fairulnizal Md Noh[1], BSc, MSc, PhD

[1]Nutrition, Metabolism and Cardiovascular Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health, Shah Alam, Selangor, Malaysia

[2]Sector for Biostatistic and Data Repository, National Institutes of Health, Ministry of Health, Shah Alam, Selangor, Malaysia

[3]Institute for Health Behavioural Research, National Institutes of Health, Ministry of Health, Shah Alam, Selangor, Malaysia

[4]Institute for Public Health, National Institutes of Health, Ministry of Health, Shah Alam, Selangor, Malaysia

[5]Occupational Safety and Health Unit, National Institutes of Health, Ministry of Health, Shah Alam, Selangor, Malaysia

[6]Faculty of Fisheries and Food Science, Universiti Malaysia Terengganu, Terengganu, Malaysia

Corresponding Author:
Shazana Rifham Abdullah, MPH, DrPH, MD
Nutrition, Metabolism and Cardiovascular Research Centre, Institute for Medical Research, National Institutes of Health
Ministry of Health
Jalan Setia Murni U13/52
Setia Alam
Shah Alam, Selangor, 40170
Malaysia
Phone: 60 333628888 ext 7487
Email: shazana.a@moh.gov.my

Abstract

Background: Overweight and obesity among adults are a growing global public health threat and an essential risk factor for various noncommunicable diseases. Although intermittent fasting is a generally new dietary approach to weight management that has been increasingly practiced worldwide, the effectiveness of 2 days per week dry fasting remains unclear.

Objective: The Cardiometabolic and Anthropometric Outcomes of Intermittent Fasting study aims to determine the cardiometabolic, anthropometric, dietary intake, and quality of life changes among civil servants with overweight and obesity, following combined intermittent fasting and healthy plate (IFHP) and healthy plate (HP) and explore the participants' experiences.

Methods: We designed a mixed methods quasi-experimental study to evaluate the effectiveness of the IFHP and HP methods among adults with overweight and obesity. A total of 177 participants were recruited for this study, of which 91 (51.4%) were allocated to the IFHP group and 86 (48.6%) to the HP group. The intervention comprised 2 phases: supervised (12 weeks) and unsupervised (12 weeks). Data collection was conducted at baseline, after the supervised phase (week 12), and after the unsupervised phase (week 24). Serum and whole blood samples were collected from each participant for analysis. Data on sociodemographic factors, quality of life, physical activity, and dietary intake were also obtained using questionnaires during data collection.

Results: Most of the participants were female (147/177, 83.1%) and Malay (141/177, 79.7%). The expected outcomes of this study are changes in body weight, body composition, quality of life, physical activity, dietary intake, and cardiometabolic parameters such as fasting blood glucose, 2-hour postprandial blood glucose, hemoglobin A1c, fasting insulin, and lipid profile.

Conclusions: The Cardiometabolic and Anthropometric Outcomes of Intermittent Fasting study is a mixed methods study to evaluate the effectiveness of combined IFHP and HP interventions on cardiometabolic and anthropometric parameters and explore participants' experiences throughout the study.

Trial Registration: ClinicalTrials.gov NCT05034653; https://clinicaltrials.gov/ct2/show/NCT05034653

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KEYWORDS

intermittent fasting; dry fasting; obesity; overweight; healthy plate

Introduction

Background

The overweight and obesity epidemic has become one of the most alarming public health threats. Although largely preventable, the worldwide prevalence of obesity nearly tripled between 1975 and 2016 and shows an increasing trend. In 2016, >1.9 billion adults were overweight, and 650 million were obese. If this current trend continues, it is estimated that 2.7 billion and >1 billion adults will be overweight and obese, respectively, by 2025 [1]. In Malaysia, the National Health and Morbidity Survey (NHMS) 2019 reported that 50.1% of adults were either overweight (30.4%) or obese (19.7%), which increased compared with the NHMS 2011 (overweight 29.4% and obesity 15.1%) and 2015 (overweight 30% and obesity 17.7%) findings [2].

The relationship between obesity and poor health outcomes is well established. Despite the increased risk of noncommunicable diseases such as hypertension, diabetes, stroke, coronary heart disease, and certain cancers, a growing body of literature has demonstrated a positive relationship between obesity and various mental health issues such as depression and poor quality of life [3,4]. The World Health Organization has established multiple strategies that describe the actions that need to be taken by stakeholders at the global, regional, and local levels to combat obesity in adults and children. Furthermore, effective and feasible policy actions have been included in the "Global action plan on physical activity 2018-2030: more active people for a healthier world" to increase physical activity globally [1].

As obesity occurs because of a positive energy balance in the body, strategies for preventing and treating obesity mainly focus on dietary modification and increasing physical activity. A form of calorie restriction dietary protocol is intermittent fasting (IF), which encompasses various eating diet plans that cycle between fasting and nonfasting states over a defined period to create a negative energy balance, thereby inducing weight loss. Studies have shown that IF is effective in reducing body weight and improving metabolic outcomes [5,6]. Although the effects of wet IF have been well documented, the benefits of dry IF (except for Ramadhan fasting for Muslims) have not been clearly indicated in previous studies. Wet or water IF is defined as fasting during which all food and drink except water are restricted [7], whereas dry IF is complete fasting without any food and fluid intake [8]. In countries with predominantly Muslims, the practice of dry fasting during Ramadan and the voluntary 2 days per week fasting (Mondays and Thursdays) are widely conducted.

As portion size is a crucial determinant of energy intake, portion control by controlling serving size is another practical method for reducing calorie intake and promoting weight loss. This portion-control method has been widely practiced and studied worldwide, using different portion divisions depending on the culture and eating habits [9,10]. The Malaysia Healthy Plate, a portion-control dietary plan, was created to translate the messages in the Malaysia Dietary Guideline 2010 and Malaysia Food Pyramid 2010 [11]. It is a visual tool that emphasizes the quarter-quarter-half concept and provides a quick visual technique that helps ensure that the intake of food is within the recommended guidelines. Specifically, the Malaysia Healthy Plate is a single-meal guide that divides the plate into a quarter plate of grains or grain products; a quarter plate of fish, poultry, meat, or egg; and a half plate of fruits and vegetables [12].

Objectives

Although weight loss has been reported in studies of conventional IF, the adaptive phenomenon of dry IF on 2 nonconsecutive days per week on cardiometabolic and anthropometric outcomes remain unclear. Similarly, although the Malaysian Healthy Plate policy has been widely practiced and publicized since 2010, the effectiveness of this eating plan in improving cardiometabolic risks and promoting weight loss is still not well documented. Thus, we established the Cardiometabolic and Anthropometric Outcomes of Intermittent Fasting study to determine the cardiometabolic, anthropometric, dietary intake, and quality of life changes among civil servants with overweight and obesity, following combined IF and healthy plate (IFHP) and healthy plate (HP) and explore the participants' experiences throughout the study. We hypothesized that combining dry IF and HP diet protocols will improve these parameters more than HP alone.

Methods

Study Design

This is a quasi-experimental study applying a mixed study method that consists of 2 parts: quantitative and qualitative. The quantitative part involved allocating participants into 2 intervention arms: the combined IFHP group and the HP group and measuring the parameters of cardiometabolic risk and anthropometrics at baseline, month 3 and month 6. The qualitative part aimed to explore the facilitators and barriers that enabled or admonished the success of weight loss in the

IFHP group through focus group discussions (FGDs) conducted at month 6.

Study Site

The participants were allocated to each intervention arm according to the institutes in the National Institutes of Health in Setia Alam; the Institute for Medical Research, Jalan Pahang; and the Institut Latihan Kementerian Kesihatan Malaysia (Teknologi Makmal Perubatan), Jalan Pahang. The distance between Jalan Pahang and Setia Alam is approximately 40 km. The allocation was done in such a manner to avoid contamination bias. The study population had a relatively similar sociodemographic features, environment, facility, and nature of work. The allocation of the intervention was determined a priori and was based on the feasibility of monitoring the study participants.

Study Population

Inclusion and Exclusion Criteria

Workers aged 19 to 59 years with a BMI of ≥23 kg/m^2 (overweight or obese), ready to participate in the intervention (assessed through readiness to participate in screening), and providing informed consent were included in this study.

Workers who (1) had recent involvement in weight loss program or activity (IF, diet changes, or physical activity changes or any activities that were performed constantly to reduce weight); (2) were affected by any eating disorder; (3) were diagnosed with diabetes and hypertension (on medication) or other metabolic health disturbances such as thyroid disease, chronic kidney disease, malignancy, and polycystic ovarian syndrome; (4) were taking any medication or supplements that can affect study outcome; (5) were pregnant; and (6) had lack of capacity or language skills to independently follow the protocol were excluded from this study.

Sample Size

Sample size calculation was conducted using a power and sample size program. It followed the rules required for comparison between the 2 groups [13]. The sample size was estimated using the level of significance (α=.05) and power of the study (1-β=.80), minimum suggested difference (delta) of 5% (SD 10%) weight loss that may be achieved under this intervention, and the corresponding differences among groups. The assumption of 5% weight loss used in the sample size calculation was based on a review conducted by Ryan and Yockey [14], which stated that a minimum weight loss of 5% is needed to improve cardiometabolic risk such as hypertension, diabetes mellitus, and hyperlipidemia. The minimum sample size required for this study was 64 participants. Considering 40% attrition, the required sample size for each arm was 90 participants. A total of 180 participants were required for this study.

Dietary Protocols

The combined IFHP regimen consisted of dry fasting from dawn to dusk for 2 days a week (Mondays and Thursdays) and practice of HP for the rest of the week. During the fasting days, the participants were encouraged to have a meal before dawn. No food or drink was allowed after dawn (approximately 13 hours) until sunset. They did not need to follow an HP diet on the fasting day. Smoking and sexual activity were also forbidden during the fasting day, following the Sunnah fasting obligation. Fasting adherence records were taken as 0, 1, or 2 fasting day or days per week. For the rest of the week, they were obligated to consume meals according to the HP concept. The female participants were discouraged from fasting during menstruation.

Participants in the HP group were asked to practice the HP concept daily: division of plate portions into a quarter for protein, a quarter for complex carbohydrates, and a half for fruits and vegetables. Participants were advised to practice HP for all 3 main meals per day. However, the practice of at least one HP meal per day is considered the minimum requirement for adherence to the dietary protocol. The research assistants (Nurul Hidayah binti Mat Yusoff and Norsyuhada binti Japri) monitored the intervention through a daily record of food intake picture (one meal per day) and a weekly fasting record.

Study Phases

Recruitment Phase

The recruitment of participants for this study comprised two phases: (1) health screening and (2) readiness to participate in screening. An invitation to participate in the study was sent through Google Forms, emails, and phone calls. Volunteers were screened for inclusion and exclusion criteria by the study team. Those eligible were screened again for readiness to participate, which was conducted through face-to-face interviews. During the interviews, the participants' readiness (motivation, willingness to commit, and enthusiasm) was assessed by a trained psychologist from the Institute for Health Behavioral Research. Only participants deemed ready to commit were included in the study. Informed consent, as well as a behavioral contract, was signed by each enrolled participant after being clearly explained the purpose of each document in the research. Both researchers and participants were unblinded to the intervention.

Intervention Phase

The overall duration of the intervention phase was 6 months, with 12 weeks in the supervised phase, followed by 12 weeks in the unsupervised phase. During the supervised phase, the participants started the diet protocol according to the designated intervention group. In the IFHP group, participants were reminded to fast, through a message sent to their mobile phones on the eve of fasting days, and accomplishments were recorded twice weekly. Participants in both groups were required to send a picture of one of their meals to the research assistant. In contrast, no fasting reminder, weekly fasting records, or meal pictures were sent during the latter unsupervised phase.

Study Procedure

Quantitative Method

Data Collection

During the 6-month study duration, data collection was conducted at 3 points: baseline (before starting the supervised phase), month 3 (at the end of the supervised phase), and month

6 (at the end of the unsupervised phase). Participants were asked to answer questionnaires on social demography (during baseline only), the Food Frequency Questionnaire (FFQ), the International Physical Activity Questionnaire-Short Form (IPAQ-SF), and the Obesity and Weight-Loss Quality of Life (OWLQOL) Questionnaire. Anthropometry measurements and fasting blood samples were taken. Oral glucose tolerance test and body composition analysis were also performed.

Self-administered Questionnaire

The FFQ was used to determine the frequency of food and beverage consumption over the previous month. The questionnaire consisted of questions covering the frequency of cereals and cereal products, fast food, meat and meat products, fish and seafood, eggs, legumes and legume products, milk and milk products, vegetables, fruits, drinks, alcoholic drinks, confectionaries, bread spreads, and flavor intake. The validated Malay version of the FFQ used in this study consisted of 165 items, and the participants required approximately 30 minutes to answer the questions at each point of data collection [15]. The records were analyzed using Nutritionist Pro Nutrition Analysis Software 7.8.0 (Axxya Systems, 2021) to determine their energy and macronutrient intake.

To measure the quality of life, a validated Malay version of the OWLQOL questionnaire was used. The OWLQOL is a self-administered questionnaire that assesses participants' feelings about obesity and their efforts in weight loss [16]. The 17 OWLQOL items consist of 7-point scale responses ranging from 0 (*not at all*) to 6 (*a very great deal)*. The score for each item was reversed before the total score was obtained. Consequently, it was transformed to a scale of 0 to 100, with a higher score indicating better quality of life [17]. The Malay version of the questionnaire has been validated among 28 female health staff with overweight and obesity, with a Cronbach of .953 [18]. The participants needed approximately 10 minutes to complete the questionnaire.

The IPAQ-SF was used to measure the participants' physical activity in the past week. The questionnaire was validated for use by adults in 12 countries [19]. In this study, we used the Malay version of the IPAQ-SF, which was validated in a study using data obtained from the NHMS 2011 [20]. The participants were requested to record how many days in the past week they spent on specific activities (vigorous and moderate activities and walking) for at least 10 minutes and the amount of time (in minutes) they engaged in a particular activity on an ordinary day. Physical activity level was calculated as the energy expenditure or metabolic equivalent task (MET) minutes per week (MET-minutes per week) based on the IPAQ scoring protocol [21]. To obtain MET scores for each activity, the total minutes spent on vigorous activity, moderate-intensity activity, and walking over the last 7 days were multiplied by 8.0, 4.0, and 3.3, respectively. The total physical activity score was calculated as the sum of all the MET scores from the 3 activity groups. Physical activity can also be categorized into low, moderate, and high physical activity levels, based on the scoring protocol available in the IPAQ website guidelines [21].

Sedentary behavior was also measured in this study. The question used to measure sedentary behavior was included in the IPAQ-SF questionnaire, based on the IPAQ sitting question. Participants were asked to state the total time they spent (hours) sitting or lying down, whether in the workplace, at home, or while traveling, excluding the time spent sleeping, on a typical day. The total daily sitting time was used as an indicator of sedentary behavior.

Anthropometric Measurements

Body weight and height were measured using a seca electronic column scale (SECA GmbH and Co KG) in kilograms and centimeters to the nearest 0.1 kg and 0.1 cm, respectively. Body weight was measured in light clothing, and participants were asked to remove their outer garments and shoes. BMI was calculated by dividing weight by height squared (kg/m^2). As only participants with overweight and obesity were included, we categorized them into overweight (23.0-27.4 kg/m^2), preobese (27.5-32.4 kg/m^2), obese class I (32.5-37.4 kg/m^2), and obese class II (≥37.5 kg/m^2), based on the cutoff points for public health action for Malaysia [22].

Waist and hip circumferences were measured using a SECA measuring tape (SECA), to the nearest 0.1 cm with the participant standing. Waist circumference was measured at the midpoint between the top of the iliac crest and the lower margin of the last palpable rib, whereas hip circumference was measured at the widest diameter around the buttocks. The waist-to-hip ratio was calculated by dividing the waist measurement by the hip measurement. On the basis of the World Health Organization cutoff points, waist-to-hip ratio of 0.90 cm (men) and 0.85 cm (women) are abnormal, and the risks of metabolic complications substantially increased beyond these points [23].

Blood pressure was measured using an automated upper arm device (Omron Automated Blood Pressure Monitor; HEM 7130). Body composition parameters such as fat mass and fat-free mass were measured using a tetrapolar bioimpedance multifrequency InBody 770 analyzer (Biospace). Personal profiles (age, height, weight, and sex) were entered upon measurement reading.

For each parameter measured 2 measurements were taken, and the average of the 2 measurements was calculated to minimize the measurement error.

Biochemical Testing

Before blood collection, all participants were required to fast overnight for approximately 8 to 10 hours. Approximately 15 ml of fasting venous blood was taken from participants by the medical officers for standard biochemical tests such as fasting blood glucose, hemoglobin A_{1c}, fasting insulin, and fasting lipid profile such as triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein (LDL) cholesterol. The oral glucose tolerance test was performed by asking the participant to drink a 250-mL solution that consists of 75 g of glucose, and another 5 mL of venous blood was collected 2 hours after the oral glucose tolerance test.

Blood samples were processed within 2 hours, and aliquots of serum or plasma samples were stored at −20 °C before analysis. Excess blood samples will be stored for up to 20 years and will be used for future research, as clearly stated in the consent form.

The hemoglobin A_{1c} level was determined by cationic exchanged high-performance liquid chromatography (Adams A_{1c} HA-8160; Arkray Inc) following the National Glycohemoglobin Standardization Programme Guidelines.

Fasting plasma glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and LDL cholesterol were analyzed using an automated analyzer (Dirui CS-400) with reagents purchased from Randox Laboratories. Consent was obtained from the participant for permission to extract DNA or RNA and store the remaining samples at −80 °C for future biomarker research related to obesity.

DNA Extraction

Genomic DNA was isolated from frozen peripheral blood samples using the QIAamp Blood Mini Extraction Kit, according to the manufacturer's protocol (Qiagen). Briefly, 20 µL QIAGEN Protease will be added in 200 µL of blood sample, followed by 200 µL Buffer AL. The mixture was vortexed thoroughly and incubated at 56 °C for 10 minutes. Later, 200 µL of absolute ethanol will be added to the mixture before being transferred to a QIAamp Mini spin column and centrifuged at 8000 rpm. Next, 2 washing steps will be performed using washing buffers AW1 and AW2. Finally, 100 µL of distilled water will be added and incubated at room temperature for 1 minute followed by centrifuging at 8000 rpm for 1 minute to elute the DNA. The quality and quantity of the extracted DNA will be quantified using NanoDrop before being stored at −20 °C for future use.

Qualitative Method

The FGDs were conducted after month 6 of the study to explore the experience the participant went through, including the enablers and barriers that led to their weight loss outcomes, and obtain their insights on how to improve the intervention.

A trained psychologist from the Institute for Behavioral Research conducted the FGDs using a predetermined outlined interview guide with probes. An audio recorder was used to record conversations and for transcription. Each FGD took approximately 60 to 90 minutes to complete. In total, 4 groups were involved in the FGD, in which 2 groups consisted of participants who successfully reduced weight by at least 4% from their baseline weight, whereas the other 2 groups were among those who did not meet the requirements for weight loss as predetermined by the study parameters.

A summary of the study outcomes, based on part of the study, is listed in Table 1.

Table 1. Summary of measurements undertaken within Cardiometabolic and Anthropometric Outcomes of Intermittent Fasting study and their associated outcome variables.

Measurements[a]	Time points			Instrument	Number of measures at each time point	Outcome variables
	Baseline	Month 3	Month 6			
Quantitative part						
Demographic data	Yes	No	No	Questionnaire	Once	• Sex • Ethnicity • Age • Highest education status • Job category • Monthly salary • Smoking history • Background illness
Weight	Yes	Yes	Yes	SECA Electronic Column Scale (SECA GmbH and Co KG)	Twice in kg, to the nearest 0.1 kg	• BMI in kg/m2, categorized based on Asian population standard
Height	Yes	Yes	Yes	SECA Electronic Column Scale	Twice in cm, to the nearest 0.1 cm	• BMI in kg/m2, categorized based on Asian population standard
Waist circumference	Yes	Yes	Yes	SECA measuring tape (SECA)	Twice in cm, to the nearest 0.1 cm	• Waist-to-hip ratio based on the World Health Organization cutoff points
Hip circumference	Yes	Yes	Yes	SECA measuring tape	Twice in cm, to the nearest 0.1 cm	• Waist-to-hip ratio based on the World Health Organization cutoff points
Blood pressure	Yes	Yes	Yes	An automated upper arm device (Omron Automated Blood Pressure Monitor; HEM 7130)	Twice (third measure if error reading or if one value outside normal range)	• Systolic and diastolic blood pressure in mm Hg
Body composition	Yes	Yes	Yes	InBody 770 analyzer (Biospace)	Once	• Body fat % • Body fat mass, kg • Skeletal muscle mass, kg
Quality of life	Yes	Yes	Yes	Obesity and Weight-Loss Quality of Life Questionnaire	Once	• Self-reported quality of life in the past month
Physical activity	Yes	Yes	Yes	International Physical Activity Questionnaire-Short Form	Once	• Self-reported physical activity for the past week, in metabolic equivalent task minutes per week
Dietary intake	Yes	Yes	Yes	Food Frequency Questionnaire	Once	• Self-reported dietary intake for the past month
Biochemical testing	Yes	Yes	Yes	Liquid chromatography (Adams A_{1c} HA-8160; Arkray Inc); automated analyzer (Dirui CS-400)	Once	• Fasting blood glucose • 2-hour postprandial blood glucose • Hemoglobin A1c • Fasting lipid profile[b] • Fasting insulin
Qualitative part						
Readiness to participate in screening	Yes	No	No	Behavioral contract and informed consent	Once, during recruitment phase	• N/A[c]
Focus group discussion	No	No	Yes	Predetermined outlined interview guide with probes; an audio recorder	Once, after unsupervised intervention phase at the end of month 6	• Themes generated from codes from each category

[a]Measurements were carried out by trained research staff using standard protocols.

[b]Fasting lipid profile parameters: total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

[c]N/A: not applicable.

Training of Study Team

Before the beginning of data collection, a 3-day workshop was conducted to train the research team members on the skills needed during data collection. The training included techniques for anthropometric measurements, body composition measurements using the InBody 770 analyzer, and explanation on questionnaires used in the study. Presentation on data collection workflow, intervention supervision processes, and biochemical testing procedures was also included in the training. In addition, selected study members were trained by a psychologist from the Institute for Behavioral Research on conducting readiness to participate in screening during the recruitment phase.

Data Management

To ascertain that data collection and record keeping are conducted efficiently, a data collection booklet was developed and assigned to each participant in this study. This booklet consisted of 5 sections (sociodemographic, quality of life, physical activity, dietary record, and anthropometry measurements) sorted into 3 parts representing each point of data collection: baseline, month 3, and month 6. This booklet was used as a data-collection tool to record the responses and measurements of the participants.

The data recorded in the booklet were entered into a database at the end of the study. The data cleaning procedure was conducted by crosschecking all the entered data in the database and booklet and exploring the data to detect any significant outliers that possibly resulted from measurement errors or data entry.

Data for qualitative part were collected using an audio recorder, and each recording was transcribed verbatim by the qualitative team. Each transcript was checked by an independent member and confirmed by a transcriber and interviewer. Consent for audio recording was obtained before the interviews.

Data Analysis

Analysis was conducted using the SPSS software (version 25; IBM Corp). Data for continuous variables were presented as mean (SD) or as median (IQR) for nonnormally distributed data. For categorical variables, frequencies were calculated and are presented as percentages. Variables were compared using the independent 2-tailed *t* test or Mann-Whitney *U* test for continuous variables and the chi-square or Fisher exact ($n \leq 5$ in any cell) test for categorical variables. All statistical tests were 2-sided, and the significance level was set at $P<.05$. In further analysis, repeated measures ANOVA will be used to compare the within- and between-group changes in the outcomes, adjusted for possible confounders such as age, ethnicity, and gender.

Data from the FGDs were analyzed using thematic analysis. Interviews transcribed verbatim were independently read by a qualitative researcher (MZJ) to identify the preliminary codes. An interpretivist approach was taken to interpret and code participants' experiences for the entire study. In this way, the coding of participants' feedback was performed without assumptions or subjective interpretation by the researchers. Meaning units were reviewed, identified, and sorted into codes, before grouping them into categories. Finally, through consensus, the content of each category group was summarized and grouped into main themes. The best representative participants' quotes for each theme were chosen to support the results. Thematic analysis was used, where initial open codes were generated from the data, after which the codes were organized into larger themes.

Ethics Approval and Informed Consent

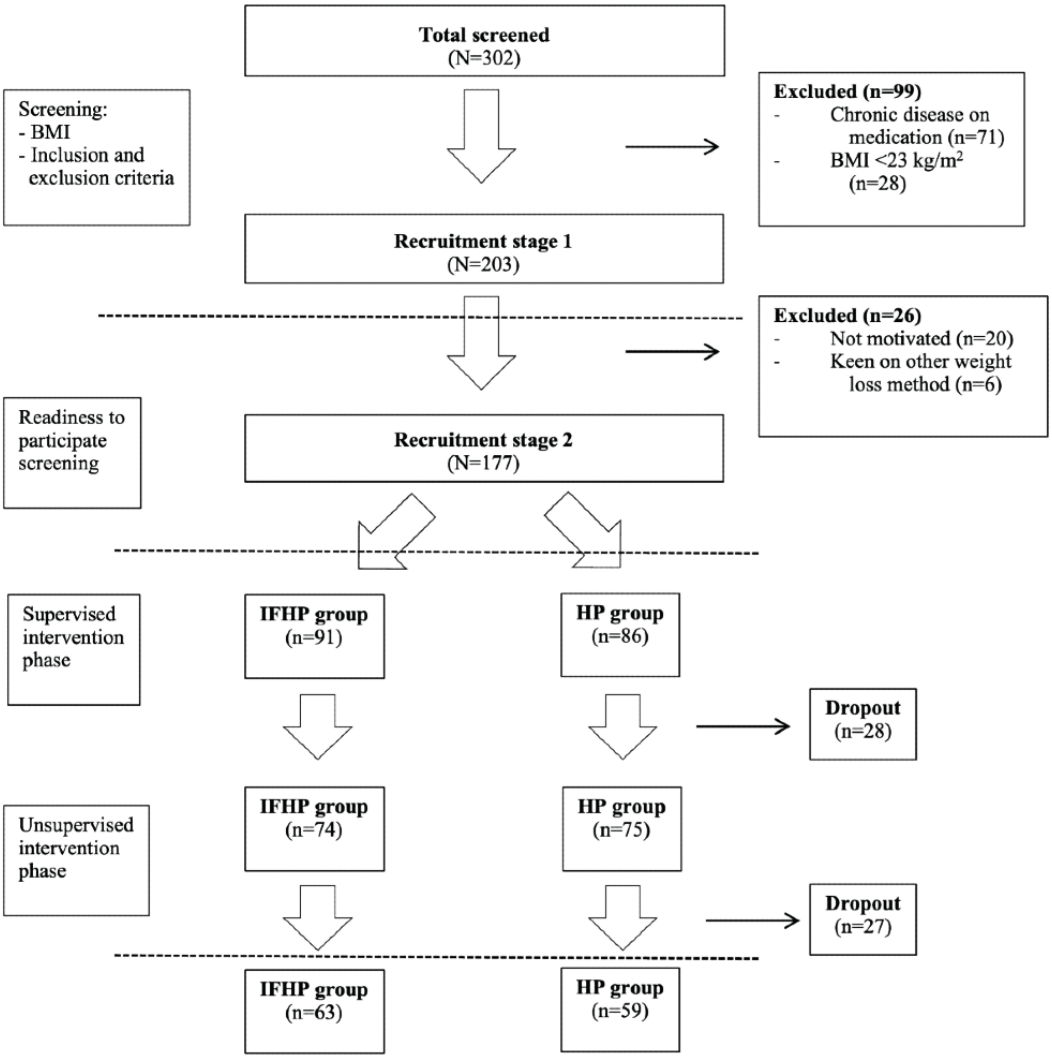
Ethics approval for this study has been obtained from the Medical Research & Ethics Committee, Ministry of Health Malaysia (NMRR-19-3261-51726). Before recruitment, written informed consent was obtained from each participant, including the storage of samples for biochemical and future DNA analyses. Participants were also informed that future research will be related to medical conditions and current interventions and that their privacy will be protected. Before enrollment, all participants were fully informed of the potential risks associated with engaging in this study. They were free to withdraw from the study at any time during their participation. This study was conducted in full conformity with the current revision of the Declaration of Helsinki and International Council for Harmonisation Guidelines for Good Clinical Practice.

Results

Study Participants

A total of 302 volunteers were interested in joining the study and underwent the screening process. After screening for BMI and eligibility during the first stage of recruitment, of 302 volunteers, only 203 (67.2%) were found eligible. Most volunteers were excluded owing to a BMI of <23 kg/m^2 or having chronic diseases on medication, such as diabetes mellitus and hypertension. During the readiness to participate in screening (stage 2 recruitment phase), 27 volunteers were excluded for various reasons but were not limited to reasons such as commitment issues, furthering education, or moving away. Hence, there were a total of 177 participants recruited in this study; 91 (51.4%) in the IFHP group and 86 (48.6%) in the HP group (Figure 1). During the supervised intervention period, 28 participants withdrew from our study in both groups (IFHP: 16/28, 57%; HP: 12/28, 43%), whereas 27 withdrew during the unsupervised period (IFHP: 12/27, 44%; HP: 15/27, 56%). The reasons for withdrawal included pregnancy (13/55, 24%), inability to commit to study intervention (24/55, 44%), transfer to a different workplace (8/55, 15%), being diagnosed with hypertension, diabetes, hypercholesterolemia on medication (5/55, 9%), and other reasons (5/55, 9%). There were 63 and 59 participants who completed the study in the IFHP and HP groups, respectively.

Figure 1. Flow chart of number of study participants throughout the study. HP: healthy plate; IFHP: intermittent fasting and healthy plate.



Sociodemographic Characteristics

Table 2 shows the sociodemographic characteristics of the study participants according to the intervention groups. Most of the participants were female (147/177, 83.1%) and had a diploma or degree with the highest education status (121/177, 68.4%). The mean age of the participants was 34.47 (SD 7.40) years. In terms of ethnicity, 79.7% (141/177) of the participants were Malay, followed by other races (20/177, 11.3%), Indian (12/177, 6.8%), and Chinese (4/177, 2.3%). Furthermore, most participants from the groups reported a monthly household income above Malaysian Ringgit 6000 (US $1422; IFHP: 35/91, 39%; HP: 41/86, 48%). Approximately 90.4% (160/177) of the participants in each group denied any history of smoking (IFHP: 82/91, 90%; HP: 80/86, 93%); of the 15 participants who had a history of smoking, only 4 (27%) participants from each group were current smokers (IFHP: 4/9, 44%; HP: 4/6, 67%). Regarding background illness history, only 5.1% (9/177) of participants reported being diagnosed with hyperlipidemia, whereas 1.1% (2/177) of participants were diagnosed with hypertension. However, all patients denied taking any medication for the illness (Table 2).

A comparison of anthropometric measurements of the study participants among the intervention groups is presented in Table 3. On the basis of the BMI category, most participants were preobese (69/177, 38.9%), followed by overweight (63/177, 35.6%), obese class I (32/177, 18.1%), and obese class II (13/177, 7.3%). Although the BMI of the participants in the IFHP group was slightly higher than that of the participants in the HP group, the difference was not statistically significant (P=.13; Table 3). Overall, no significant differences were observed in sociodemographic characteristics and anthropometric measurements between the 2 groups at baseline, except for ethnicity and job category (P<.05; Tables 2 and 3).

After 6 months after the intervention, 21 participants were interviewed for their feedback across 4 different groups: 2 being successful in their weight loss attempts and the other 2 groups that did not meet the requirements of weight loss reduction. Four main themes were constructed from the feedback given: efficacy toward the intervention, barriers and facilitators that enable or admonish weight loss attempts, support during the intervention, and perceived sustainability of the intervention. This feedback serves as a platform for researchers to improve their future interventions.

Table 2. Sociodemographic characteristics of participants in both intervention groups (N=177).

Characteristics	Participants	Intervention groups		*P* value[a]
		Intermittent fasting and healthy plate (n=91)	Healthy plate (n=86)	
Sex, n (%)				.32[b]
Male	30 (16.9)	18 (19.8)	12 (14)	
Female	147 (83.1)	73 (80.2)	74 (86)	
Ethnicity, n (%)				.02[c]
Malay	141 (79.6)	80 (87.9)	61 (70.9)	
Chinese	4 (2.3)	0 (0)	4 (4.7)	
Indian	12 (6.8)	4 (4.4)	8 (9.3)	
Others	20 (11.3)	7 (7.7)	13 (15.1)	
Age (years), mean (SD)	34.47 (7.40)	33.82 (7.50)	35.15 (7.27)	.23[d]
Highest education status, n (%)				.95[b]
Secondary school	24 (13.6)	13 (14.3)	11 (12.8)	
Diploma or degree	121 (68.4)	62 (68.1)	59 (68.6)	
Master or PhD	32 (18.1)	16 (17.6)	16 (18.6)	
Job category, n (%)				<.001[c]
Research officer	14 (7.9)	7 (7.7)	7 (8.1)	
Medical officer	8 (4.5)	5 (5.5)	3 (3.5)	
Science officer	5 (2.8)	3 (3.3)	2 (2.3)	
Medical laboratory technologist	50 (28.2)	16 (17.6)	34 (39.5)	
Assistant Research Officer	8 (4.5)	6 (6.6)	2 (2.3)	
Clerk	26 (14.7)	23 (25.3)	3 (3.5)	
Others	66 (37.3)	31 (34.1)	35 (40.7)	
Monthly household income (Malaysian Ringgit), n (%)				.63[c]
<1500 (US $357)	3 (1.7)	2 (2.2)	1 (1.2)	
1500 to <3000 (US $357 to <US $711)	34 (19.2)	20 (22.0)	14 (16.3)	
3000 to <4500 (US $711 to <US $1067)	37 (20.9)	18 (19.8)	19 (22.1)	
4500 to <6000 (US $1067 to <US $1422)	27 (15.3)	16 (17.6)	11 (12.8)	
≥6000 (≥US $1422)	76 (42.9)	35 (38.5)	41 (47.7)	
Smoking history, n (%)				.34[b]
Ever smoked	15 (8.5)	9 (9.9)	6 (7)	
Current smoker	8 (53.3)	4 (44.4)	4 (66.7)	
Ex-smoker	7 (46.7)	5 (55.6)	2 (33.3)	
Never smoked	162 (91.5)	82 (90.1)	80 (93)	
Background illness, n (%)				
Hypertension	2 (1.1)	1 (1.1)	1 (1.1)	.74[c]
Hyperlipidemia	9 (5.1)	6 (6.6)	3 (3.5)	.498[c]
Heart disease	1 (0.6)	0 (0)	1 (1.2)	.49[c]
Others	1 (0.6)	0 (0)	1 (1.2)	.49[c]

[a]*P* values of <.05 are considered statistically significant.

[b]*P* values derived from Pearson chi-square test.

[c]*P* values derived from Fisher exact test.

[d]*P* values derived from independent 2-tailed *t* test.

Table 3. Anthropometric measurements of participants in both intervention groups (N=177).

Anthropometric measurements	Value	Intervention groups		*P* value[a]
		Intermittent fasting and healthy plate (n=91)	Healthy plate (n=86)	
Systolic blood pressure (mm Hg), mean (SD)	115 (13.13)	116 (12.13)	114 (14.07)	.22[b]
Diastolic blood pressure (mm Hg), mean (SD)	80 (9.43)	80 (9.45)	79 (9.44)	.52[b]
Heart rate (beats per minute), mean (SD)	79 (10.48)	78 (8.51)	80 (12.24)	.36[b]
Waist circumference[e] (cm), mean (SD)	92.46 (10.88)	93.49 (10.70)	91.36 (11.03)	.20[b]
Hip circumference[e] (cm), mean (SD)	108.86 (8.66)	109.39 (9.02)	108.31 (8.29)	.41[b]
Weight (kg), median (IQR)	71.70 (18.70)	72.50 (18.55)	70.60 (16.28)	.13[c]
Height (cm), mean (SD)	158.36 (7.09)	158.67 (7.13)	158.04 (7.08)	.56[b]
BMI (kg/m^2), median (IQR)	28.43 (6.50)	28.48 (7.25)	28.39 (5.70)	.18[c]
BMI category, n (%)				.51[d]
Overweight	63 (35.6)	32 (35.2)	31 (36)	
Preobese	69 (39)	32 (35.2)	37 (43)	
Obese class I	32 (18.1)	20 (22)	12 (14)	
Obese class II	13 (7.3)	7 (7.6)	6 (7)	
Waist-to-hip ratio[e], mean (SD)	0.85 (0.06)	0.85 (0.06)	0.84 (0.06)	.20[b]

[a]*P* values of <.05 are considered statistically significant.

[b]*P* values derived from independent 2-tailed *t* test.

[c]*P* values derived from the Mann-Whitney *U* test (nonnormally distributed data).

[d]*P* values derived from Pearson chi-square test.

[e]Missing data: waist circumference (n=1), hip circumference (n=1), waist-to-hip ratio (n=1).

Discussion

Principal Findings

We hypothesized that there would be a significant improvement in cardiometabolic and anthropometric parameters among participants in the IFHP group following the intervention after 3 and 6 months. We expected that these changes would also be present among participants in the HP group, but the degree of change would be more prominent among participants in the IFHP group. We also believe that the effectiveness of the intervention in improving cardiometabolic and anthropometric outcomes was driven by both personal motivation and a strong support system.

The preliminary results showed no significant differences in most sociodemographic characteristics and anthropometric measurements of the participants between the 2 intervention groups. The significant difference observed in job categories is most likely because of the departmental units stationed at the Institute for Medical Research Jalan Pahang being diagnostic based; thus, there was a higher proportion of medical laboratory technologists in the HP group than in the IFHP group.

Comparison With Prior Work

On the basis of a meta-analysis by Harris et al [24], there was no significant difference in weight loss between continuous and intermittent energy restriction [24]. Thus, it can be concluded that to reduce body weight, intermittent energy restriction is an alternative method to continuous energy restriction and may be preferred because of its feasibility and practicality.

Despite robust evidence supporting the effectiveness of wet IF in reducing weight and improving cardiometabolic risks, the data on dry IF, especially 2 days per week fasting (such as fasting on Mondays and Thursdays) remain limited. Voluntary Sunnah fasting on Monday and Thursday is widely practiced by Muslims worldwide and is culturally more acceptable in Malaysia, as most Malaysians are Muslims. In 2013, Teng et al [25] compared the effect of dry fasting on Mondays and Thursdays combined with calorie restriction (fasting calorie restriction), with the control of metabolic parameters. They found that participants in the fasting calorie restriction groups showed significant interaction effects on body weight, BMI, body composition, blood pressure, total cholesterol, and LDL cholesterol compared with the participants in the control group [25]. However, as fasting was combined with calorie restriction

and compared with the control group, the sole effect of fasting was not sought. Furthermore, the study was conducted among Malay men aged 50 to 70 years, thus limiting the generalizability of the findings to the general population. Meanwhile, this study compared the combined IFHP with the use of HP method alone and involved adults (aged >18 years) of both sexes.

Strengths and Limitations

A strength of our study is that we applied both quantitative and qualitative methods. The mixed method allows us to measure the effectiveness of the intervention and explore the challenges of practicing it simultaneously. This integrated framework is crucial for a better understanding of the challenges faced during dietary intervention in obesity prevention programs so that it can be improvised in future programs to improve the outcomes and sustainability of health changes.

The main limitation of our study is the effect of the movement control order due to the COVID-19 pandemic on intervention compliance and weight management. The implementation of movement control orders and work from home for those working would limit their physical activity, expose them to unhealthy eating, reduce their motivation toward weight loss, and affect their control of food intake. Studies have shown that social lockdowns have negative consequences on weight-related behavior and weight management [26,27].

Future Directions

Adherence to dietary interventions is essential to ensure the validity of research findings and, most importantly, to ascertain the sustainability of the desired outcomes beyond the research period. As described by the World Health Organization, adherence is “the extent to which a person’s behavior-taking medication, following a diet, and executing lifestyle changes, corresponds with agreed recommendations from a health care provider” [28]. In this study, we examined the elements of adherence in both quantitative and qualitative parts. Quantitatively, we investigated adherence to intervention and sustainability of outcomes’ changes in the unsupervised intervention phase. We measured the outcomes at the end of the phase and compared them with those of the previous 2 parameters. In the qualitative part, we assessed readiness to participate in screening during the recruitment phase, in which the motivation and readiness to comply with intervention protocols were assessed. In addition, FGDs were conducted at the end of the study to explore the participants’ experiences while undergoing the intervention, including barriers and enablers that influence their adherence to the diet protocols.

We plan to disseminate the study results to collaborating institutes and organizations, study participants, and respective stakeholders. These findings will be submitted to 2 peer-reviewed journals and presented at academic conferences.

Conclusions

With the increase in the prevalence of overweight and obesity worldwide, a weight loss method that is not only effective but also practical and easy to comply with is required. Although IF has been widely practiced and studied, data on the effectiveness of dry fasting in reducing weight and cardiometabolic risk are limited. We established the Cardiometabolic and Anthropometric Outcomes of Intermittent Fasting study to determine the effectiveness of a combined IFHP and HP in improving anthropometric and cardiometabolic outcomes among civil servants with overweight and obesity. The mixed methods study was designed to measure the changes quantitatively, reflect the participants’ points of view, and ensure that the study findings are grounded in their experiences. The study findings and their in-depth explanation may contribute to the development of more effective and feasible obesity prevention methods, improve current health policies, and provide new insights that will stimulate new research questions in the future.

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Authors' Contributions

SRA, NHA, RMWMZ, NSS, NMK, RJMSMJ, and MFMN conceptualized the study. MZJ, NSS, and NHA constructed the qualitative components of this study. SRA drafted the first version of the manuscript. All authors contributed to the design and implementation of the research, analyses of the results, and reviewing and editing of the subsequent manuscript drafts. All the authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

FFQ: Food Frequency Questionnaire
FGD: focus group discussion
HP: healthy plate
IF: intermittent fasting
IFHP: intermittent fasting and healthy plate
IPAQ-SF: International Physical Activity Questionnaire-Short Form
LDL: low-density lipoprotein
MET: metabolic equivalent task
NHMS: National Health and Morbidity Survey
OWLQOL: Obesity and Weight-Loss Quality of Life

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Protocol

Trends in the Prevalence of Chronic Medication Use Among Children in Israel Between 2010 and 2019: Protocol for a Retrospective Cohort Study

Yair Sadaka[1,2*], MSH, MD, PhD; Dana Horwitz[1*], MD; Leor Wolff[3], BA; Tomer Sela[3], BA, MBA; Joseph Meyerovitch[4,5,6], MD; Assaf Peleg[7], BSc; Eitan Bachmat[7], PhD; Arriel Benis[8,9*], PhD

[1]Neuro-Developmental Research Centre, Beer Sheva Mental Health Centre, Ministry of Health, Beer Sheva, Israel

[2]Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Shevs, Israel

[3]Online and IT Division, Clalit Health Services, Tel-Aviv, Israel

[4]Community Division, Clalit Health Services, Tel-Aviv, Israel

[5]Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

[6]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[7]Department of Computer Science, Ben-Gurion University of the Negev, Beer Sheva, Israel

[8]Faculty of Industrial Engineering and Technology Management, Holon Institute of Technology, Holon, Israel

[9]Faculty of Digital Technologies in Medicine, Holon Institute of Technology, Holon, Israel

[*]these authors contributed equally

Corresponding Author:
Yair Sadaka, MSH, MD, PhD
Neuro-Developmental Research Centre
Beer Sheva Mental Health Centre
Ministry of Health
Hatzadik Meyerushalim 2
Beer Sheva, 8461144
Israel
Phone: 972 587800404
Email: yair.sadaka@moh.healh.gov.il

Abstract

Background: Prescription of psychostimulants has significantly increased in most countries worldwide for both preschool and school-aged children. Understanding the trends of chronic medication use among children in different age groups and from different sociodemographic backgrounds is essential. It is essential to distinguish between selected therapy areas to help decision-makers evaluate not only the relevant expected medication costs but also the specific services related to these areas.

Objective: This study will analyze differences in trends regarding medications considered psychobehavioral treatments and medications considered nonpsychobehavioral treatments and will identify risk factors and predictors for chronic medication use among children.

Methods: This is a retrospective study. Data will be extracted from the Clalit Health Services data warehouse. For each year between 2010 and 2019, there are approximately 1,500,000 children aged 0-18 years. All medication classes will be identified using the Anatomical Therapeutic Chemical code. A time-trend analysis will be performed to investigate if there is a significant difference between the trends of children's psychobehavioral and nonpsychobehavioral medication prescriptions. A logistic regression combined with machine learning models will be developed to identify variables that may increase the risk for specific chronic medication types and identify children likely to get such treatment.

Results: The project was funded in 2019. Data analysis is currently underway, and the results are expected to be submitted for publication in 2022. Understanding trends regarding medications considered psychobehavioral treatments and medications considered nonpsychobehavioral treatments will support the identification of risk factors and predictors for chronic medication use among children.

Conclusions: Analyzing the response of the patient (and their parents or caregivers) population over time will hopefully help improve policies for prescriptions and follow-up of chronic treatments in children.

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KEYWORDS

psychotropic drugs; central nervous system stimulants; mental health; medication therapy management; drug prescriptions; attention deficit hyperactivity disorder; ADHD, Israel; children; data mining; machine learning; electronic medical records; pediatrics; chronic disease; epidemiology

Introduction

Background

The rising health expenditure on medications, especially chronic medications, accounts for a large share of total health care spending and is a major financial issue. US prescription drug spending as a share of health expenditures was estimated to be between 9.8% and 16.8% by different estimators in 2016 [1]. Over the last decade, there has been a growth in the amounts of chronic medications used by patients with chronic diseases in the United States. When evaluating dispensed prescriptions in different therapy areas in the United States, the most significant growth between 2012 and 2017 is observed in medications prescribed for mental health conditions [2]. Similarly, in Israel, health care–related expenditures are also increasing over time, mainly involving private financing such as private insurance [3]. For example, looking at mental health conditions, the incidence of first prescription of stimulant medication for attention-deficit/hyperactivity disorder (ADHD) is growing among children in Israel year-over-year [4,5].

Understanding medication use among patients with chronic diseases is critical to evaluate health care costs better and allocate funds more effectively. Due to the global lack of data in the literature, and more particularly related to Israel in recent years, there is a need to study these issues, with a specific focus on children [6]. Although children more often have acute, short-term illnesses including upper respiratory tract and ear infections, gastroenteritis, and injury-related complaints, a growing body of literature has identified an increased risk for chronic conditions such as obesity [7], asthma [8], type 1 and type 2 diabetes mellitus [9], and ADHD and other psychiatric conditions [10-12].

One challenge to children and youth health is the wide use of psychobehavioral treatments for disruptive behavior disorders [13-16]. Indeed, there is an increasing trend of prescribing psychotropic medications in the pediatric population [17-19]. These psychobehavioral treatments are psycholeptics and psychoanaleptics, which are classified in the Anatomical Therapeutic Chemical (ATC) classification system as codes N05 and N06, respectively [20]. One of the main indications for prescribing psychotropic medications in children is the psychostimulant treatment for ADHD [4,5,21]. Prescription of psychostimulants has significantly increased in most countries worldwide for both preschool and school-aged children [22,23], as well as in Israel, where up to 10% of children have been prescribed psychostimulants [4,5,21,22].

Aims and Objectives

Studying trends in chronic medication use among children in different age groups and from varying sociodemographic backgrounds and distinguishing selected therapy areas may help decision-makers evaluate the relevant expected medication costs and the specific services related to these areas. This study aims to analyze trends in chronic medication use and identify risk factors for such treatments.

Methods

Data Acquisition

This is a retrospective cohort study. The analysis will be done on data extracted from the Clalit Health Services (Clalit) data warehouse. Clalit, the largest health care management organization in Israel, insures 52% of the Israeli population (approximately 4.6 million members), operates 14 hospitals, and manages over 1300 primary care clinics with a network of pharmacies and dental clinics.

The electronic medical records of approximately 1,500,000 children aged 0-18 years old whom Clalit insured each year between 2010-2019 will be analyzed. It is important to highlight that children are those aged between 0 and 18 years according to the current Israeli regulation and the national medical services provided in Israel and thus the same applies to the “pediatric” databases we have access to for our study.

The Clalit data warehouse stores sociodemographic data (date and country of birth, immigration status, gender, marital status of parents, clinic location–based socioeconomic status, and ethnicity) and medical data. Clinical data are collected from continuous real-time inputs from physicians and health service providers from the community and hospital settings and include medical diagnoses, laboratory data, prescription renewal, medications dispensed, clinic and emergency room visits, and consultation appointments with specialists. All relevant information includes a patient identifier, which allows compiling all data relevant to a specific patient into a single record.

In Israel, like in much of the world, a prescription can be valid for a few months (3-12 generally), but the prescription can only be filled by the pharmacist one month (28-30 days) at a time. If a patient purchases a treatment for one month or less, they cannot be defined as a patient with chronic treatment; rather, chronic medical treatment can be defined as a documented purchased prescription for 60 days or more within a year, denoted as “purchased chronic medication” for that year. This definition is valid for adults but, to our knowledge, no definition exists for children. Thus, we will consider it relevant for our study and use the same definition [24,25]. Therefore, it seems

preferable to look at recurrent delivery of medications rather than diagnosis, even though the latter may be available in the Clalit data warehouse. Indeed, it is well known that finding and characterizing diseases can be accomplished by integrating different parameters such as biological tests, clinical diagnoses, and medication prescriptions and purchases [26]. However, as this research aims to highlight the prevalence of chronic medication, the diagnosis itself is less critical than the use of medication over time. Additionally, it is essential to point out that the Israeli health system regulation changed in 2015—only since then have non–mental health professionals been able to get diagnosis and medication prescription information about a patient [27]. Thus, medication purchase is the better option for following chronic medication trends.

The chronic medications will be classified using the ATC code [20]. We will further analyze different classes of medications with specific attention to psychobehavioral treatment if classified by the ATC as N05 (psycholeptics) or N06 (psychoanaleptics).

We will further collect, according to the updated approval of the data extraction and ethics committees, sociodemographic variables (ie, date of birth, gender, immigration status, ethnicity, socioeconomic status, geographical region of residency, health care management organization–specific insurance type) and clinical variables (ie, diagnosed medical conditions such as comorbid diagnoses, health services consumption, and lab test results when relevant) for further analysis.

Ethics Approval

Ethics approval was granted by the ethical committee of the Soroka Medical Center of Clalit (0011-18-MHC; February 3, 2019).

Data Inclusion and Exclusion Criteria

Children are members of Clalit with at least one of their parents. Clalit members between January 2010 and December 2019 aged 0-18 years during that period will be included in the study. However, individuals who were Clalit members for less than one year between January 2010 and December 2019 will be excluded. Members that joined (not newborns) between January 2010 and December 2019 were included, with their related data from the date they joined if they were members for more than one year. Members that left (for any reason) between January 2010 and December 2019 were included if they were members for more than one year.

Data Preprocessing

Several studies will be conducted based on the data that will be retrieved.

Analysis

Descriptive Analysis and Trend Analysis

We will calculate the incidence and prevalence of prescribed and purchased medications for different ATC groups between 2010 and 2019. Trend estimation is a statistical technique to aid the interpretation of data [28]. When a series of measurements of a process is treated as a time series, trend estimation can be used to make and justify statements about tendencies in the data by relating the measurements to the times at which they occurred. These models can then be used to describe the behavior of the observed data without explaining it. Once data are available, an appropriate trend analysis will be conducted for the prevalence and incidence of psychobehavioral and nonpsychobehavioral medication prescriptions. We will further evaluate whether there is a significant difference between psychobehavioral and nonpsychobehavioral medication prescription trends.

Logistic Regression Models

We will compare demographic characteristics between the study groups (children who received different classes of medications for chronic diseases vs children who did not receive such medications) using *t* tests and Fisher exact χ^2 tests for categorical variables based on the normal distribution and variable characteristics. Categorical data will be shown in counts and percentages. Data on continuous variables with normal distribution will be presented as the mean and 95% confidence interval. We will use multivariable logistic regression and a lasso regression [29] to identify variables that may increase the risk for specific types of chronic medication treatment using all available sociodemographic and clinical attributes for disentangling the effects of moderately correlated variables. Moreover, if we detect some medications with too few children treated, we will deal with this issue by considering using a zero-inflated Poisson regression model. It is used to model count data that has an excess of zero counts, or in the context of this study, medication treatments that are not prescribed and delivered to many children (regarding the different attributes defining them).

Hierarchical Clustering Analysis

In addition to the "classical" statistical analysis described above, further data analysis will combine the previous methods with a data mining approach and machine learning algorithms.

We will mainly focus on hierarchical clustering and information visualization (ie, heatmaps) [5,30]. This will facilitate the analysis of the incidence and prevalence trends of prescriptions and the purchase of the different investigated medications, with regard to the collected attributes and their predefined categories (eg, age groups, socioeconomic status). In other words, the clustering analysis and its visualization as heatmaps give snapshots of medication prescriptions and purchases (as a proxy of consumption).

The incidence and the prevalence will be normalized for each ATC class.

We will compute a Euclidean distance matrix between the values of each of the normalized epidemiological measures (ie, incidence, prevalence) for the sociodemographic and clinical attributes categories. For example, we will compute a distance matrix of the normalized incidence for the prescribed medications (ie, cells of the matrix), each of the sociodemographic categories, diagnosed medical conditions, and health services consumption-related attributes (ie, rows and columns of the matrix).

Then, the heatmap will consist of a set of ordered columns according to the similarity of the attributes computed by

hierarchical clustering. The heatmap's rows will consist of the values (ie, reformulated as a color gradient) of the incidence of the prescription or the purchase over the years.

We will build the following heatmaps of the overall medications over time:

- the overall prescriptions
- the overall purchases
- the psycholeptics and psychoanaleptics (prescriptions as a whole and purchases as a whole)
- the psycholeptics (prescriptions as a whole and purchases as a whole)
- the psychoanaleptics (prescriptions as a whole and purchases as a whole)

The use of the hierarchical clustering approach for drawing heatmaps for each epidemiological metric (ie, incidence, prevalence) and for each step of the medication consumption (ie, prescription, purchase) allows showing similarities and changes over time of the different attributes (ie, sociodemographics and clinical data) related to the patients of the analyzed population.

Results

This project was funded in 2019, and the research project is scheduled to be completed in 2022.

A preliminary analysis has been performed on data from 2010 and 2015 that included 1,297,535 children aged 0-18 years in 2010 and 1,472,190 in 2015. Overall, we found that chronic medication prescription and purchase are more prevalent for children aged 0-1 years and 16-18 years. Additionally, we observed an increase in purchased prescriptions of chronic medications for children aged 11-15 years and for older children aged 16-18 years.

Additional analyses are underway and will investigate the data more deeply by looking at the differences between girls and boys from different groups (eg, secular Jews, Orthodox Jews, and Arabs) as defined by the Israeli Central Bureau of Statistics. Moreover, logistic regression models and hierarchical clustering will be processed like their interpretation during the second quadrimester (April to August) of 2022.

Discussion

Overview

This research protocol deals with understanding trends regarding medications considered psychobehavioral treatments and medications considered nonpsychobehavioral treatments. This will support the identification of risk factors and predictors for chronic medication use among children. This knowledge will help the health care system evaluate the expected medication costs and allocate funds more effectively. The study hypothesis is that there will be a gradual increase in chronic medication use over the years. This trend will be more significant for psychobehavioral treatments.

Expected Results and Future Directions

In Israel, an analysis of chronic medication use among children between 2010 and 2019 can reveal long-term prescription and treatment adherence patterns. Over time, analyzing the response of the patient (their parents or caregivers) population will hopefully help improve the policies for the prescriptions and the follow-up of chronic treatments in children.

Strengths and Limitations

Recent chronic medication purchase trends were not extensively studied in the Israeli pediatric population.

Moreover, Clalit insured and provided medical services to approximately 4.7 million patients in 2021 and is the largest health care provider in Israel with one of the world's largest medical data warehouses. The data available span all treatment providers, including hospitals and emergency units.

Nevertheless, this study is limited to Israel, and the overall ethnic distribution of the Clalit population does not fully reflect the overall Israeli demographic composition. The Clalit members comprise, in comparison with the general Israeli population, a higher proportion of Arabs, a lower proportion of ultra-Orthodox members, and globally a higher proportion of members having a low socioeconomic status [30].

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to local regulation.

Authors' Contributions

YS and AB conceptualized and designed the study, designed the data collection instruments, and were major contributors to writing this manuscript. DH drafted the initial manuscript and reviewed the literature. AB, LW, and YS coordinated and supervised data collection. AB, TS, AP, and EB designed the data collection and will perform the statistical analysis and data mining. All authors critically reviewed the manuscript for important intellectual content.

Conflicts of Interest

None declared.

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
ATC: Anatomical Therapeutic Chemical

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Protocol

The Effect of Particulate Matter Exposure During Pregnancy on Pregnancy and Child Health Outcomes in South Asia: Protocol for an Instrumental Variable Analysis

Fabian Reitzug[1], MSc; Stephen P Luby[2], MD; Hemant K Pullabhotla[3], PhD; Pascal Geldsetzer[4,5], MD, MPH, PhD

[1]Big Data Institute, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

[2]Woods Institute for the Environment, Stanford University, Palo Alto, CA, United States

[3]Center on Food Security and the Environment, Stanford University, Palo Alto, CA, United States

[4]Division of Primary Care and Population Health, Department of Medicine, Stanford University, Palo Alto, CA, United States

[5]Chan Zuckerberg Biohub, San Francisco, CA, United States

Corresponding Author:
Fabian Reitzug, MSc
Big Data Institute
Nuffield Department of Population Health
University of Oxford
Old Road Campus
Oxford, OX3 7LF
United Kingdom
Phone: 44 7414818688
Email: fabian.reitzug@web.de

Abstract

Background: Determining the longer-term health effects of air pollution has been difficult owing to the multitude of potential confounding variables in the relationship between air pollution and health. Air pollution in many areas of South Asia is seasonal, with large spikes in particulate matter (PM) concentration occurring in the winter months. This study exploits this seasonal variation in PM concentration through a natural experiment.

Objective: This project aims to determine the causal effect of PM exposure during pregnancy on pregnancy and child health outcomes.

Methods: We will use an instrumental variable (IV) design whereby the estimated month of conception is our instrument for exposure to PM with a diameter less than 2.5 μm (PM2.5) during pregnancy. We will assess the plausibility of our assumption that timing of conception is exogenous with regard to our outcomes of interest and will adjust for date of monsoon onset to control for confounding variables related to harvest timing. Our outcomes are 1) birth weight, 2) pregnancy termination resulting in miscarriage, abortion, or still birth, 3) neonatal death, 4) infant death, and 5) child death. We will use data from the Demographic and Health Surveys (DHS) conducted in relevant regions of Bangladesh, India, Nepal, and Pakistan, along with monthly gridded data on PM2.5 concentration (0.1°×0.1° spatial resolution), precipitation data (0.5°×0.5° resolution), temperature data (0.5°×0.5°), and agricultural land use data (0.1°×0.1° resolution).

Results: Data access to relevant DHSs was granted on June 6, 2021 for India, Nepal, Bangladesh, August 24, 2021 for Pakistan, and June 19 2022 for the latest DHS from India.

Conclusions: If the assumptions for a causal interpretation of our instrumental variable analysis are met, this analysis will provide important causal evidence on the maternal and child health effects of PM2.5 exposure during pregnancy. This evidence is important to inform personal behavior and interventions, such as the adoption of indoor air filtration during pregnancy as well as environmental and health policy.

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KEYWORDS

PM2.5; air pollution; fine particulate matter; birth weight; still birth; child and maternal health; Indo-Gangetic Plain; India; Pakistan; Bangladesh; Nepal

Introduction

South Asia is experiencing some of the highest levels of ambient air pollution globally. In cross-country comparisons of fine particulate matter with a diameter less than 2.5 μm (PM2.5), Bangladesh has emerged as the country with the highest population-weighted levels, Pakistan has the second highest levels, India has the third highest levels, and Nepal has the 12th highest levels [1]. The elevated levels of air pollution and the large number of exposed people result in significant air pollution–related mortality and morbidity in South Asia. Overall, 26.2% of all disease-adjusted life years lost to air pollution globally are estimated to occur in India alone [2]. In 2019, a total of 980,000 deaths in India, 114,000 deaths in Pakistan, 74,000 deaths in Bangladesh, and 18,000 deaths in Nepal were attributable to air pollution [3].

Our study focuses on air pollution in the Indo-Gangetic Plain (IGP), which stretches across Bangladesh, Nepal, India, and Pakistan. Pollution levels in the IGP are even higher than those in the study region in general. For instance, in the Indian part of the IGP, the annual mean PM2.5 concentration is above 100 $\mu g/m^3$ [2], which is higher than that in India overall (83 $\mu g/m^3$) [4], and more than 10-fold the World Health Organization's (WHO's) recommended limit for healthy air (10 $\mu g/m^3$) [5]. High population density, agricultural and industrial activities, and dispersal of urban pollution to nearby rural areas, and vice versa, lead to air pollution being a public health problem in both urban and rural parts of the IGP. Moreover, rural areas considerably contribute to pollution levels through local wheat and rice stubble burning, municipal waste burning, forest fires, coal-fired factories, and other sources of rural emissions [3,6]. In the peak fire season, the mean relative effects of rural biomass burning are estimated at 30% of emission levels measured in Delhi [7]. Substantial mortality and morbidity occur in the IGP, and the number of air pollution–related deaths is approximately equally divided between urban and rural areas [3,8].

Annual mean PM2.5 levels disguise substantial seasonal variation in pollution in the IGP. While the winter months of October-February are characterized by high pollution reaching levels of over 150 $\mu g/m^3$, pollution during the monsoon period is mostly around 50 $\mu g/m^3$, and even heavily polluted cities such as Delhi occasionally record levels below 30 $\mu g/m^3$ [9,10].

Seasonal variation in PM2.5 levels is particularly salient for the study of effects of pollution on pregnancy outcomes. Depending on the month of conception, fetuses experience very different levels of in utero exposure, which affects birth and child health outcomes. Moreover, exploiting seasonal variation provides a potent research design for identifying the causal effects of prenatal pollution exposure.

By now, it is well established that exposure to increased PM2.5 levels during the prenatal period is associated with a range of negative child health outcomes. Air pollution has been linked to preterm birth [11-13], low birth weight [11,14-16], increased risk of pregnancy loss and stillbirth [13,17], and longer-term developmental effects such as lower height for age [18,19].

However, the associations between negative child health outcomes and particulate matter have not been consistent across the literature. A 2017 systematic review did not find clear evidence of an association with the risk of preterm birth or term low birth weight [20], while another recent systematic review found that PM2.5 levels and low birth weight were associated in 25 of 29 studies [21]. There is also disagreement regarding the most critical pregnancy period. Some studies highlight the importance of the late pregnancy period for birth weight [11,14,22,23], while other studies found no difference [16,21].

Our study furthers the understanding of PM2.5 on pregnancy and child health outcomes in South Asia. Our study aims to (1) determine whether exposure to higher PM2.5 concentrations during pregnancy reduces the birth weight of the child; (2) determine whether exposure to higher PM2.5 concentrations during pregnancy increases the risk of neonatal, infant, and child death; (3) determine whether exposure to higher PM2.5 concentrations during pregnancy increases the risk of a pregnancy terminating in a miscarriage, abortion, or still birth; and (4) understand in which trimesters of pregnancy PM2.5 exposure most strongly reduces birth weight and increases the risk of neonatal, infant, and child death.

Methods

Data

The primary data set for this observational study is the Demographic and Health Surveys (DHSs) conducted in Bangladesh, India, Nepal, and Pakistan [24]. The DHSs are large, representative, cross-sectional household surveys, which include questions on topics related to health, nutrition, and demographics. Households are sampled using probability sampling based on existing sampling frames, such as a census. For each of the countries, we include all DHS waves that collected survey cluster GPS coordinates. This includes the DHS waves, which took place in Bangladesh in 2004, 2007, 2011, and 2017 to 2018; in India in 2015 to 2016 and 2019 to 2021; in Nepal in 2001, 2006, 2011, and 2016; and in Pakistan in 2006 to 2007 and 2017 to 2018. We use the women's module, which contains information on child births, birth outcomes, maternal health, and infant mortality. We will match the DHS data (using the GPS coordinates of the survey cluster locations) to PM2.5 data to obtain our measure of prenatal pollution exposure. We will use monthly PM2.5 emissions data from the Atmospheric Composition Analysis Group at Washington University, St. Louis, Missouri, United States [25]. Monthly precipitation and temperature data are obtained from the Climate Research Unit gridded Time Series monthly high-resolution gridded multivariate climate data set with a 0.5°×0.5°–gridded resolution, published by the University of East Anglia's Climatic Research Unit, Norwich, United Kingdom. Daily precipitation

data at 0.5°×0.5°–gridded resolution is provided by the National Oceanic and Atmospheric Administration/Oceanic and Atmospheric Research/Earth System Research Laboratories Physical Sciences Laboratory, Boulder, Colorado, United States [26]. Crop data at 0.1°×0.1°–gridded resolution are obtained from the Spatial Production Allocation Model, developed by the International Food Policy Research Institute, Washington, DC, United States [27]. We assessed pregnancies having taking place between January 1998 and December 2019 since this is the period where gridded monthly air pollution data are available.

Data Access

Access to the DHS is public but needs to be requested. We obtained access to the DHS data on June 6, 2021 for India, Nepal, and Bangladesh and on August 24 for Pakistan.

Ethical Considerations

This research is a secondary data analysis of fully anonymized data and does not require ethics approval, as per University of Oxford institutional research ethics policy [28].

Codebook

The DHS codebook (recode manual) provides details on the file structure, computation of additional variables, and in-depth descriptions of all variables contained in the data sets [29].

Variables

Creating the Date of Conception and PM2.5 Exposure Variables

We impute the date of conception for all births within the last 5 years by subtracting the duration of an average pregnancy (40 weeks) from the date of birth reported in the DHS. The instrumental variable we construct is month of conception, a factor variable (1-12) indicating the calendar month when the pregnancy began. We also generate similar variables for each trimester of the pregnancy, using analogous procedures and assuming a length of 12.33 weeks (ie, one-third of 40 weeks) for each trimester.

Prenatal PM2.5 exposure will be computed by matching the respondents' cluster's GPS locations with gridded pollution data to obtain location-specific estimates of ambient PM2.5 exposure during each pregnancy. The computed measures include the following:

- Mean PM2.5 exposure during the pregnancy, measured in units of 10 μg/m^3 (weighted)
- Median PM2.5 exposure during the pregnancy, measured in units of 10 μg/m^3 (including also partial months)
- 10th, 25th and 75th, and 90th percentile monthly PM2.5 exposure during pregnancy, measured in units of 10 μg/m^3 (including also partial months)
- Maximum monthly PM2.5 exposure during pregnancy, measured in units of 10 μg/m^3 (including also partial months)
- Cumulative PM2.5 exposure over the whole pregnancy period, measured in units of 10 μg/m^3 (weighted)
- Number of high or low PM2.5 exposure months over the whole pregnancy period (number of months above or below mean PM2.5 levels at the respondent's location, including partial months)
- Mean PM2.5 exposure over the whole pregnancy period relative to the annual location-specific average, measured in units of 10 μg/m^3 (weighted)

All exposures with "weighted" in brackets are weighted by the fraction of the month that the pregnancy covers (between 0 and 1). For median, percentiles, minimum, and maximum exposure partial months are included.

For each trimester of the pregnancy, the following measures are computed:

- Mean PM2.5 exposure during each trimester of the pregnancy, measured in units of 10 μg/m^3 (weighted)
- Cumulative PM2.5 exposure over each trimester of the pregnancy, measured in units of 10 μg/m^3 (weighted)
- Number of high or low PM2.5 exposure months over the whole pregnancy period (number of months above or below mean PM2.5 levels at the respondent's location, including partial months)
- Mean PM2.5 exposure over the whole pregnancy period relative to the annual location-specific average, measured in units of 10 μg/m^3 (weighted)

Creating the Environmental Covariates

Using gridded temperature and precipitation data, we compute the mean temperature and precipitation for each trimester of the pregnancy, the mean over the whole pregnancy, and the mean over the neonatal period, infancy, and childhood.

We generate a variable for monsoon onset to account for spatiotemporal variation in weather patterns that could influence the timing of conception, pollution, and harvest. Using daily precipitation data and a previously validated method [30], we generate a year-specific variable (taking values from 1-365 or 1-366 in a leap year), which indicates the date of local monsoon onset in the year of conception.

Outcome Variables

Birth Weight

The following outcome variables will be considered:

1. Birth weight (in g, m19; primary outcome)
2. Low birth weight (<2500 g, m19; secondary outcome)
3. Very low birth weight (<1500 g, m19; secondary outcome)
4. Extremely low birth weight (<1000 g, m19; secondary outcome)

Birth weight (in g) is a continuous variable, and the additional aforementioned birth weight variables (2)-(4) are binary variables derived from the continuous variable. We generate binary variables for *low*, *very low*, or *extremely* in the following way: low birth weight is defined as weight<2500 g, very low birth weight as weight<1500 g, and extremely low birth weight as weight<1000 g (according to the WHO' definition [31]).

Note that all variables referenced by the short variable name (m19, etc) are directly from the DHS data set. All other variables are imputed or are obtained from additional non-DHS data sets.

Miscarriage, Abortion, or Still Birth

The rate of pregnancy termination resulting in miscarriage, abortion, or still birth per 1000 pregnancies (based on v229, v230, and v233) is the primary outcome.

Pregnancy termination will be calculated as a rate per 1000 pregnancies (and PM2.5 exposure of these pregnancies will be computed from the imputed conception date to the point of pregnancy termination).

Neonatal, Infant, and Child Mortality

The following outcome variables will be considered:

1. Neonatal death rate per 1000 children (age 28 days, b5; primary outcome)
2. Infant death rate per 1000 children (age 1, b5; primary outcome)
3. Child death rate per 1000 children (age 5, b5; primary outcome)

Explanatory Variables and Covariates

Explanatory Variables (PM2.5 Concentration)

The following explanatory variables will be considered:

1. Mean PM2.5 exposure during the pregnancy (weighted)
2. Median PM2.5 exposure during the pregnancy (including also partial months)
3. 10th, 25th and 75th, and 90th percentile monthly PM2.5 exposure during pregnancy (including also partial months)
4. Maximum monthly PM2.5 exposure during pregnancy (including also partial months)
5. Cumulative PM2.5 exposure over the whole pregnancy period (weighted)
6. Number of high or low PM2.5 exposure months over the whole pregnancy period, including partial months
7. Mean PM2.5 exposure over the whole pregnancy period relative to the annual location-specific average (weighted)
8. All of the above PM2.5 variables, but computed separately for each trimester of the pregnancy

PM2.5 exposure is a continuous variable (our instrument) that is created by using the month of conception to instrument for the exposure during each trimester or the whole pregnancy (and controlling for additional covariates described in the analysis section).

Covariates for the Main Models

Following are the covariates for the main models:

1. Preceding birth interval
2. Birth order (hwidx)
3. Maternal age at birth of the child
4. Sex of the child (b4)
5. Twin birth
6. Mean temperature during the pregnancy or for each trimester
7. Mean precipitation during the pregnancy or for each trimester
8. Monsoon onset
9. Percentage of land used for rice cultivation

Preceding birth interval is an unordered factor variable that indicates the time difference in months between the current and the previous birth (categories: ≤12 months, >12 and ≤24 months, >24 and ≤36 months, and >36 months). Birth order is a factor variable where 1 indicates the most recent birth. Maternal age provides the age (in years) of the respondent at each of child birth in the data set. Sex of the child is a binary variable. Twin birth is a binary variable. Mean temperature and precipitation are derived from gridded monthly values at the respondent's location and averaged over the pregnancy period. Monsoon onset is a discrete variable (1-365/366) indicating the day of the year when the monsoon starts. Rice fraction is a continuous variable (0-1) for the percentage of land used for rice cultivation at the respondent's location.

Additional Covariates for Some of the Robustness Checks

The following are additional covariates for robustness checks:

1. Respondent's education level (v106/v133)
2. Wealth index (v190/v191)
3. Respondent's age (v012)
4. Respondent's height (v438)
5. Altitude (v040)
6. Religion (v130)
7. Ethnicity or caste (v131)
8. Marital status (v501)
9. Region and primary sampling unit (DHSREGNA, DHSCLUST)
10. Type of cooking fuel used in the household (v161)
11. Total number of children ever born (v201)
12. Antenatal care visit in the first trimester (m13)
13. Received toxoid injections during pregnancy (m1)
14. Took iron tablets or syrup during pregnancy (m45)
15. Took antimalarial drugs (SP/Fansidar or Chloroquine, m49a-m49b)
16. Husband's occupation (v705)
17. Smoking (v464)

Education and the wealth indicators are available both as categorical and continuous variables, age, height (in cm), and altitude (in m) are continuous. Religion and ethnicity or caste are factor variables with country-specific levels. Marital status is a factor variable. Region and primary sampling unit are factor variables, and cooking fuel is a proxy for indoor air pollution and is a factor variable indicating the type of fuel used for cooking inside the house. Number of births is continuous. Antenatal care visit is a binary variable indicating whether a care visit took place in the first trimester. The variables for toxicoid injections, antimalarial drugs, and iron tablets or syrups are binary variables indicating whether the respondent received these medicines during pregnancy. Husband's occupation is a factor variable with standardized categories across countries. Smoking is a continuous variable indicating the number of cigarettes smoked in the last 24 hours by the respondent.

Unit of Analysis

We have restricted our sample to mothers who have children born within the last 5 years (v208). This is because day of birth

(hw16) is only recorded for these children, which gives us more precision for our exposure estimates (we also exclude all births where the date of birth was missing, except for all children who died after birth where the date of birth was not recorded). We further restrict the sample to all mothers with at least 2 births within the last 5 years to exploit variation in timing of multiple births from the same mothers. This allows us to control for observed and unobserved individual differences between mothers. We also exclude all respondents where de facto and de jure regions of residency differed.

Statistical Analyses

Data Exclusion

DHS surveys are cleaned by a professional team, and we do not expect many outliers. In some questions, implausible values are already flagged in the data; for instance, if the recorded age of death is a time point after the date of the interview, the value is flagged in B13. In such instances, we will not include these data points in our analysis.

Power

We have not assessed statistical power to detect our minimum effect sizes. We will conclude that the analysis supports our hypotheses if both the effect sizes are larger than the minimum effects specified under "effect sizes" below, and the respective *P* values are <.05.

Statistical Models

The following is an overview of our analytic strategy:

1. The sample will be restricted to respondents with multiple births, who reside in the IGP.
2. The IVs (joint estimation of the first and second stage) will be run: use of the month of conception to instrument for PM2.5 exposure during pregnancy; use of instrument and covariates to predict pregnancy and child health outcomes
3. Robustness checks: is the exclusion restriction plausible, that, after adjusting for all time-invariant confounders at the level of the mother (through mother-level fixed effects) as well as temperature and precipitation during the pregnancy period, the month of conception affects birth outcomes through no channel other than PM2.5 exposure?

Details of the analysis steps are as follows:

1. We include all respondents in Bangladesh, Nepal, Pakistan, and India whose survey cluster GPS coordinates fall within the boundaries of the IGP. The boundaries of the IGP were obtained from a previous study [32]. We also have restricted the sample to mothers with multiple births. By exploiting within-mother variation in the timing of births and using mother–fixed effects, we can more plausibly account for (un)observable mother-level factors that may otherwise confound our estimates.
2. We will estimate our models with an instrumental variables (IV) estimator using the R package fixest. We will use interactions of month of conception indicators with regional fixed effects to instrument for location-specific effects of month of conception on PM2.5 exposure during pregnancy (and alternatively each semester of the pregnancy). Modeling location-specific effects of month of conception on PM 2.5 exposure is important to satisfy the monotonicity assumption required of the IV estimator. We have defined regions on the basis of level 2 administrative boundaries, and we will check for robustness using other definitions of regions. We will also control for the date of the monsoon onset in the year of conception (as well as the interaction between monsoon onset and the share of rice grown at the respondents' location). The second stage of the IV estimation uses the predicted PM 2.5 values from the first stage to estimate the effect of PM 2.5 exposure on our outcomes. Our regression model includes mother fixed effects, which account for any time-invariant mother-specific unobservable factors. To account for aggregate time-varying factors, we will include birth year fixed effects. Our specification controls for temperature and precipitation, which are observable factors that may be correlated with both the month of conception and birth weight. We also have included birth-level covariates that correlate with birth outcomes, including preceding birth interval, birth order, maternal age at the birth of each child, twin birth, and sex of the child. We have 3 sets of outcomes:
   - Birth weight: a continuous variable (primary outcome) and binary outcomes low, very low, or extremely low birth weight (secondary outcome).
   - Miscarriage, abortion, or still birth: pregnancies terminating in the first, second, and third trimesters (we restricted the sample to all women who reported a pregnancy ending in miscarriage, abortion, or still birth). These are provided as rates per 1000 births.
   - Neonatal, infant, and child mortality: outcomes for neonatal, infant, and child death. These are provided as rates per 1000 children.
3. We will use multiple tests to assess the robustness of our estimates and the plausibility of the exclusion restriction. To test for differences between subgroups, we will rerun the main models as follows: (1) by including only urban or rural respondents (since urban respondents may be less affected by seasonality, whereas rural respondents' lifestyle and nutrition may depend more on agriculture, weather conditions, etc., v102), (2) by including only households working in agricultural or nonagricultural professions (since rural households working in agriculture may experience more seasonality in their lifestyles than nonagricultural households, v716), (3) including only wanted or unwanted pregnancies (v367) since desired and undesired pregnancies may have different seasonal patterns. We will also run the models without restricting ourselves to mothers with multiple births but including all mothers and controlling for the covariates described above (since we cannot use mother-level fixed effects in this case). Finally, we also assess how our estimates change when we use the month of birth instead of the month of conception as the instrument.

Variables that violate the assumption of homoscedasticity or of normality (as determined by a Kolmogorov-Smirnov test) will be transformed (for instance, using log-transformation).

Effect Size

A recent meta-analysis reported that increased pollution is associated with an 11% increase in median risk for low birth weight (mainly from US studies) [21]; thus, we would expect an effect at least as large (since exposure in India is much higher than that reported in the studies included in the meta-analysis). For low birth weight, we have not identified such a clear minimum expected value from previous studies, but we expect significant reductions in birth weight. For infant mortality, a summary of studies from developed and developing countries reports increases in mortality ranging from 10%-35% per 10 $\mu g/m^3$ increase in PM2.5 concentration [12]. The lower bound of their confidence interval is 5%, which is the minimum effect size of interest for us.

Reliability and Robustness Testing

We will use different PM2.5 concentration measures described above to assess robustness of our findings. Since the incidence of preterm births is positively associated with pollution (but we do not know which births are preterm), we can assess the reliability of our results to assuming a more conservative, imputed pregnancy duration of <40 weeks for all pregnancies. We will draw upon regional statistics on gestational length when doing so. We may also include different constructs for measuring pollution—for example, fire counts from satellite data—to evaluate the robustness to an alternative way of capturing pollution exposure.

Results

Data cleaning and processing have been completed. This study has also been preregistered in the Open Science Foundation registries (registration digital object identifier 10.17605/OSF.IO/TBQFH). Data analysis began in August 2021.

Discussion

Principal Findings

Our study will test the hypothesis that exposure to higher concentrations of PM2.5 during pregnancy reduces the birth weight of the child, and that exposure to high concentrations during pregnancy increases the risk of neonatal, infant, and child death as well as the risk of a pregnancy terminating in a miscarriage, abortion, or still birth. We will also investigate during which trimester the negative effects of PM2.5 (if any) on pregnancy outcomes are most pronounced.

Strengths and Limitations

This study makes several contributions to the literature. First, we draw upon a novel data set with globally consistent monthly PM2.5 concentrations. The unavailability of such monthly resolved PM2.5 data sets for the IGP has thus far been an impediment to the study of health effects over the entire area. Second, while other studies have investigated effects of more short-term exposures, such as wildfires [14,33] whose duration is often in the order of days, high seasonal pollution levels in the IGP enable us to study a population with high exposures over multiple months. Third, if we can show that timing of birth affects pregnancy and child health outcomes through no channel other than PM2.5 exposure (after controlling for observable factors that could intervene in this relationship), we can interpret our findings as having causal meaning. To make this assumption plausible, we account for individual-level confounders by focusing our analysis on within-mother variation in the timing of birth and by comparing the outcomes of children born to the same mother but in different months of the year. We also account for time-varying, seasonal factors such as temperature, precipitation, and local monsoon onset.

We are aware of several factors that may limit the validity of our results. First, while we can carefully control for individual-level factors and time-varying seasonal factors we cannot exclude with certainty that our instrument (month of conception) does not influence our outcome variables through channels other than PM2.5 exposure. Second, PM2.5 exposure is variable across small geographic scales, which we cannot capture. Besides ambient air pollution, respondents may also experience indoor air pollution, which is a second important pollution source, which we cannot directly measure. However, we control for household-level factors to account for unobserved household-level confounders. Exposure measurement in our study is thus limited both by the scale of the PM2.5 data as well as the systematic random displacement of GPS coordinates in the DHS survey (used to deidentify respondent's locations). Third, we infer the month of conception based on the duration of an average pregnancy (40 weeks). However, we do not know the actual length of the pregnancy periods of our respondents, which may lead to incorrect estimation of PM2.5 exposure of the individual pregnancies. Since pollution is associated with shorter gestational period, our estimates of PM2.5 exposure are likely to be upward biased and may misclassify the trimester during which the exposure occurred. We seek to address this bias by making more conservative assumptions for an average pregnancy duration. Fourth, we cannot distinguish between preterm and term births owing to unknown length of the gestational period. Thus, we are unable to disentangle the mechanism underlying low birth weight. Low birth weight at term could be the result of PM2.5 exposure. Alternatively, PM2.5 may increase the risk of premature birth, which, on average, results in lower birth weight [34].

Practical Significance

Air pollution is a major contributor to the global disease burden. While deaths due to indoor air pollution have been declining [35], ambient air pollution has become the fifth leading global cause of death in 2015. It is the second leading cause in India, fourth leading cause in Pakistan, and fifth leading cause in Bangladesh [36]. In the countries included in our study, population-weighted pollution levels have increased in recent years, which indicates a need to address this growing public health problem. Studies on the effects of postnatal PM2.5 exposure may not account for the fact that the same populations often already experience prenatal exposure. Our study contributes to the understanding of negative health effects of prenatal exposure and is able to disentangle the effects of prenatal exposure from the effects of postnatal exposure. By doing so, the study seeks to draw attention specifically to the

effects of pollution during pregnancy and to raise awareness of potential negative pregnancy and child health outcomes.

Future Directions

Future work should expand this study's approach and investigate the effect of PM2.5 on pregnancy outcomes in regions other than South Asia. The use of natural experiments, such as seasonal variation in PM2.5 or discontinuities in exposure on small spatial scales, could allow researchers to provide evidence on the causal effects of PM2.5 during pregnancy in different contexts, countries, and regions. In addition, future work would benefit from the availability of more reliable measures of gestational length to obtain precise measures of length of exposure. Finally, remotely sensed PM2.5 data, which are spatially and temporally more granular and incorporate high-resolution ground measurements or measurements from wearable sensors, could provide more accurate data on respondents' actual exposure.

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Conflicts of Interest

None declared.

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Abbreviations

DHS: Demographic and Health Surveys
IGP: Indo-Gangetic Plain
IV: instrumental variable
PM: particulate matter
PM2.5: particulate matter with a diameter less than 2.5 μm
WHO: World Health Organization

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Protocol

Implementation of a Health Promotion Practice Using Individually Targeted Lifestyle Interventions in Primary Health Care: Protocol for the “Act in Time” Mixed Methods Process Evaluation Study

Emma Nilsing Strid[1*], PhD; Lars Wallin[2*], PhD; Ylva Nilsagård[1*], PhD

[1]University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

[2]Department of Health and Welfare, Dalarna University, Falun, Sweden

[*]all authors contributed equally

Corresponding Author:
Emma Nilsing Strid, PhD
University Health Care Research Center
Faculty of Medicine and Health
Örebro University
Örebro, 701 85
Sweden
Phone: 46 721411696
Email: emma.nilsing-strid@regionorebrolan.se

Abstract

Background: There is growing evidence that noncommunicable diseases (NCDs) can be attributable to unhealthy lifestyle habits. However, there has been little application of this knowledge in primary health care (PHC).

Objective: This study aims to evaluate the process and outcomes of a multifaceted implementation strategy for a healthy lifestyle-promoting practice in a PHC setting. This practice is based on national guidelines targeting unhealthy lifestyle habits with a potential risk for NCDs.

Methods: A pre-post implementation study design with a control group is used in a PHC setting in central Sweden. The Medical Research Council guidelines for process evaluation of complex interventions will be applied. The implementation process and outcomes will be assessed using a mix of qualitative and quantitative methods. A strategic sample of up to 6 PHC centers will be included as intervention centers, which will receive a 12-month multifaceted implementation strategy. Up to 6 matched PHC centers will serve as controls. Core components in the implementation strategy are external and internal facilitators in line with the integrated-Promoting Action on Research Implementation in Health Services (i-PARIHS) framework and the Astrakan change leadership model. Data will be collected at baseline, during the implementation phase, and 4-6 months after the implementation strategy. Questionnaires will be sent to roughly 500 patients in every PHC center and 200 health care professionals (HCPs) before and after implementation. In addition, purposeful sampling will be used for interviews and focus group discussions with managers, HCPs, patient representatives, and internal and external facilitators. Use of data from medical records and activity logs will be an additional data source.

Results: Recruitment of PHC centers began in March 2021 and ended in Spring 2022. Based on the planned timeline with the 12-month implementation strategy and 4-6-month follow-up, we expect to collect the final data in Summer 2023.

Conclusions: This study will explain implementation process and outcomes using a multifaceted implementation strategy for a healthy lifestyle-promoting practice in a real-world PHC context. The study is expected to provide new knowledge about the role of facilitators and their contribution to implementation outcomes. These findings can guide policy makers, managers, and PHC staff to integrate health promotion and disease prevention in PHC and provide methodological support to facilitators.

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KEYWORDS

implementation science; facilitation; practice guideline; lifestyle; health promotion; primary health care; health personnel; qualitative research; quality improvement

Introduction

Lifestyle Habits

The leading cause of prolonged disability and premature death worldwide are noncommunicable diseases (NCDs), such as cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes [1-3]. NCDs account for almost two-thirds of deaths globally [2]. This global chronic disease burden is attributed to population demographics (eg, aging, health disparities, and certain risk factors) [3,4]. The major risk factors for NCDs are tobacco use, harmful use of alcohol, low physical activity, and poor nutrition [1,5]. These behavioral risk factors often occur in a cluster, creating a synergetic effect that increases the risk [6]. Individuals with only one of these unhealthy habits die on average 6 years earlier than their counterparts [7]. Recently, the effect of lifestyle interventions targeting these risk factors was shown to be half to almost equal to that of pharmacological treatment for cardiovascular risk factors [8]. Research has shown the importance of adopting a healthy lifestyle through health care interventions [9-11]. Health care systems are encouraged to use prevention and early detection services and improve population health [3], also among children and adolescents [4]. Primary health care (PHC) is a natural arena for this health promotion. As proposed by the World Health Organization, a proactive PHC approach has a crucial role in promoting healthier lifestyles through public contact. PHC professionals should "make every contact count"; that is, making healthy living a priority [12]. Swedish PHC has roughly 40 million visits each year in a population of about 10 million individuals. This large number of visits is an opportunity to promote proactive lifestyle habits. Behavioral and highly modifiable risk factors are well known, and clinical practice guidelines regarding their management have been established [13,14]. Despite the available evidence of the association between risk factors and NCDs, applying this knowledge in a preventive PHC still represents a huge challenge for PHC professionals [15-19].

In 2011 (updated 2018), national clinical practice guidelines for health promotion and disease prevention were published in Sweden, targeting the following unhealthy lifestyle habits: tobacco use, harmful use of alcohol, low physical activity, and poor nutrition [13]. However, the uptake and use of the Swedish guidelines have been low [20]. These guidelines should be considered a complex intervention [21]. They include several lifestyle habits, target managers and diverse health care professionals (HCPs), require expertise and skills in behavior change techniques, and demand a change in routine practice. These Swedish guidelines will be implemented in this study. The guidelines include the following: encouraging patients to fill in a screening form for health behaviors, invite patients with unhealthy lifestyle habits to visits, and discuss and provide individually targeted lifestyle advice, follow-up, and documentation in the patients' medical record. Further investigations into the implementation process and the professionals' uptake and use of these guidelines are warranted if we hope to ultimately improve health promotion in the prevention of NCDs.

Implementation Strategies

Implementation science studies methods to promote the integration of research, such as translating clinical guidelines into routine practice [22]. A theoretical springboard is desirable to understand and explain how and why implementation succeeds or fails, identifies influencing factors, and develops strategies to implement clinical interventions successfully [22]. Many theoretical implementation models and frameworks have been published in recent decades. Today, there is a call to study how such frameworks contribute to more effective implementation [23].

Implementation of clinical interventions (eg, guideline recommendations) implies a change in clinical practice, where the context in which the change takes place, plays an important role [17,24-26]. Implementation strategies, defined as techniques used to enhance the adoption, implementation, and sustainability of a clinical intervention, constitute the "how-to" component of changing health care practice [27]. Common implementation strategies targeting professional behavior change are educational meetings, audit and feedback, printed educational material, local opinion leaders, and tailored implementation strategies [28-30]. The complexity of implementation strategies can vary widely, from a single (discrete) strategy to a combination of strategies creating a multifaceted strategy [27,31,32]. Some authors suggest that implementation strategies should be chosen and tailored to address the context of a given change effort. However, there is little guidance on how to conduct such strategies [30,33]. In a systematic review of methods for designing interventions to change HCPs' behavior, approaches that identify and prioritize barriers and link strategies to overcome them were proposed, using theory and engaging end users [34]. Moreover, changes in clinical practice were found to be more likely to occur when the HCPs initiated the changes themselves, when the changes featured their active input, and when the changes were seen as well founded and properly communicated [35].

An increasingly used implementation strategy is facilitation, defined as "a process of interactive problem solving and support that occurs in a context of a recognized need for improvement and a supportive interpersonal relationship" [31]. The authors of the integrated-Promoting Action on Research Implementation in Health Services (i-PARIHS) framework describe facilitation as the active ingredient of implementation, implying a dynamic and deliberate process to support implementation [36]. The facilitator role involves assessing and responding to the characteristics of the clinical intervention and the recipients of the intervention in their work context. Facilitators can be external or internal to where implementation occurs, and a combination of the two is frequently reported [37]. They can operate at different organizational levels, from a clinical team

to a higher level of the health system. The key is that they (ie, the facilitators) meet the requirements of the role, in terms of their personal attributes, knowledge, and skills [38,39]. Facilitation is judged as a promising strategy [38-41], but there is a need for further research on the role of facilitators and their contribution to implementation outcomes.

This study will follow the recommendation of using frameworks to guide the implementation [42]. The Consolidated Framework for Implementation Research (CFIR) [26] will be used to explore and analyze determinants for the implementation of a healthy lifestyle-promoting practice in PHC based on the Swedish national guidelines for health promotion and disease prevention [13]. Core components in the implementation strategy are internal and external facilitation [36] and steps in a change leadership model [43,44]. The implementation strategies will be prioritized and adapted through discussions with the involved stakeholders [42]. The Medical Research Council (MRC) guidelines for process evaluations of complex interventions will be used in this study for evaluation of the implementation process [45].

Aims

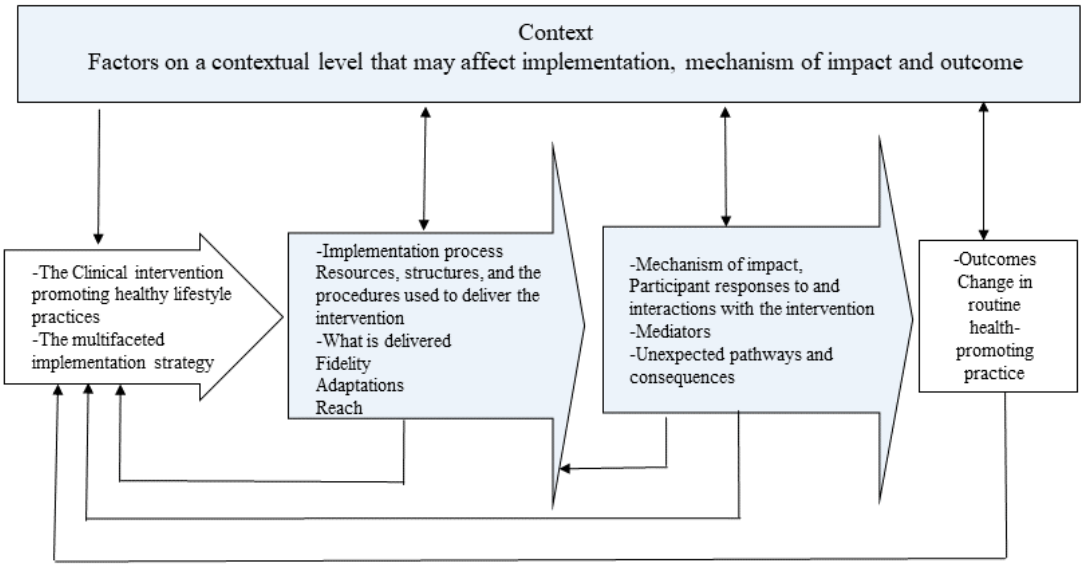
The overall aim of the Act in Time study is to evaluate the process and outcomes of an implementation strategy for a healthy lifestyle-promoting practice using individually targeted lifestyle interventions in a PHC setting. The specific aims are as follows: (1) to explore what managers, internal facilitators, HCPs, and patient representatives experience as barriers and facilitators when using individually targeted lifestyle interventions in routine health promotion practice; (2) to evaluate the outcomes achieved from implementing the new routine health-promoting practice using medical record data and stakeholders' perspectives (patients, HCPs, internal and external facilitators, and PHC managers); and (3) to explore the implementation process and the mechanisms of impact.

Methods

Design

This study incorporates a pre-post implementation design with a control group [46]. The MRC guidelines for process evaluations of complex interventions are used [45]. The implementation process and outcomes (ie, a change in routine health-promoting practice) will be evaluated using a combination of qualitative and quantitative methods as described in the MRC guidelines. The guidelines highlight the relationships among implementation, mechanisms of impact, and context (Figure 1). All 3 key components need to be evaluated to understand how change is created [45]. This study follows the Standards for Reporting Implementation Studies (StaRI) [47,48].

Figure 1. Critical functions of process evaluation and their relations (blue boxes are key components of a process evaluation). Adapted from Moore et al [45] and modified for process evaluation of the Act in Time study.



Setting and Recruitment

We will conduct the study in a PHC setting in Region Örebro County. The region, located in central Sweden, has 300,000 inhabitants. Region Örebro County has 30 PHC centers, of which 26 are publicly financed and 4 have entrepreneurship contracts with the region. During the project's initiation in March 2021, the research team informed all PHC managers about the project by email and a presentation at a manager meeting. PHC centers showing their interest in the study are provided with more information. We will use a strategic sampling strategy to achieve variation among PHC centers with respect to size, socioeconomic status, and geographic and rural/urban location. A sample of PHC centers will be contacted by a second invitation email. The first centers willing to participate will be included as intervention centers. Up to 6 centers will be included and up to 6 other centers matched by the factors mentioned above (size, socioeconomic status, and geographic and rural/urban location), will serve as control centers. The control centers will not be offered implementation support. All HCPs employed at the PHC intervention centers will be briefed by their managers and the research group about the study. HCPs (general practitioners, physiotherapists, psychologists, social workers, district nurses, registered nurses, and assistant nurses) having patient visits will be invited to participate in anonymous web surveys. A purposeful sample

procedure will be applied for interviews and focus group discussions (FGDs) with HCPs. The theoretical framework (CFIR) will guide the qualitative data collection and analysis [26]. The CFIR provides a structure for approaching complex, interacting, and multilevel implementation processes. The CFIR consists of 5 major domains: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the implementation process. Each domain contains several constructs [26,49]. The interview guides will be based on the constructs of the CFIR [26,50] and focus on the HCPs' perceptions of barriers and opportunities to integrate a healthy lifestyle-promoting practice at their PHC centers. A modified person-centered process mapping will describe the patients' perspective on the health promotion practice [51]. A purposeful sample of approximately 8 patients will be recruited from the PHC centers for individual interviews. This interview guide will cover several steps: the process of prevention, contact, investigation, decisions on action/treatment, and follow-up. In each of these steps, the questions will target the patient's needs and experiences [51]. The research team will discuss the general findings from the interviews and FGDs with the external facilitators and adapt the implementation activities in accordance with these findings. The qualitative data will also be analyzed and results presented in a scientific paper.

The Clinical Intervention: a Healthy Lifestyle-Promoting Practice

In this study, managers and HCPs will be supported in implementing a healthy lifestyle–promoting practice. In the new routine, HCPs will be expected to encourage patients to fill in a screening form for health behaviors, invite patients with unhealthy lifestyle habits to visits, and discuss and provide individually targeted lifestyle advice, provide follow-ups, and document this in the patients' medical record. This routine health promotion practice is based on the Swedish national guideline for health promotion and disease prevention, targeting unhealthy lifestyle habits: tobacco use, harmful use of alcohol, low physical activity, and poor nutrition [13]. Before the visit, patients with planned visits to a PHC will be encouraged to fill in a screening form in health care guide 1177 (Swedish: Vårdguiden 1177), a national hub for information and services within health care in Sweden. When unhealthy habits are reported in the screening form, both the patient and the HCP can be prepared and have an opportunity to discuss the information. According to evidence-based recommendations [13], measures should be offered to those with one or more unhealthy lifestyle habits. The recommendations should be recorded in the patient's medical record using the Swedish classification of health intervention codes. The classification codes are divided into qualified advice, advice, and simple advice for lifestyle habits [13]. Prescribed physical activity and completed screening forms should also be recorded in the patients' medical record.

The Multifaceted Implementation Strategy

Overview

The implementation strategy is aimed to support the implementation of a health promotion practice at the PHC intervention centers. To accomplish this goal, we will follow a systematic and theory-based approach in 2 steps to select and tailor strategies in accordance with contextual conditions and the HCPs' needs [26,49]. The multifaceted strategy to support the implementation is based on previous research [30,31] and includes the involvement of target groups, information and interactive educational activities, use of internal and external facilitators, audit and feedback, dialogue, and networking. A change leadership model will also be used to achieve sustained organizational and individual behavior change [43,44].

The implementation strategy will take place over a 12-month period. In the strategy, the managers' responsibility will be emphasized and an organization will be built to support PHC centers in the application of all steps of the change leadership model [43,44]. External and internal facilitators are central components in the implementation strategy, in line with the i-PARIHS framework [36,37]. In addition, the HCPs' motivation to participate in the change toward a health promotion practice will be facilitated by focusing on mastery/competence, autonomy, and relatedness. These 3 psychological needs are important for intrinsic motivation [52]. The 4 factors that enhance intrinsic motivation for change will be considered: (1) understanding the purpose for change, (2) opportunity to impact the change, (3) competence to perform the new behavior, and (4) feeling of belonging. The strategies will be supported by structures, including organizational and hands-on tools, quick reference guides, or functional IT systems [44]. An overview of the implementation strategy including actions, actors, target groups, etc, as recommended by Proctor et al [27], is provided in Table 1.

Table 1. Specification of Act in Time implementation strategies.

Implementation strategy	External facilitator (EF)	Internal facilitator (IF)	Mandate change	Audit and feedback
Actor	• Four organizational developers • Competence in quality improvement, implementation, and process management • Trained in the change leadership model • Experience in working with evidence-based guidelines, knowledge support, and health promotion	• 2 health care professionals (HCPs) at each primary health care (PHC) center • Interest in health promotion and disease prevention • Acknowledged as a trustworthy coworker • Given priority in the region's lifestyle education	• PHC managers • Advisory board members (mangers at the highest management levels in the PHCs' region)	• External facilitators
Actions	• Provide context-specific implementation support following the steps outlined in the model of leading change: insight, analyses, planning, and implementing • Support the clinical intervention • Arrange meetings with managers and IFs at the PHC centers to discuss roles, work structure, strategies, and steps leading to change • Distribute educational materials • Support change process and provide IFs access to structures, templates, etc • Act as a soundboard for IFs • Offer IFs individual support and guidance in supporting change, quality improvement, lifestyle habits, and motivational interviewing • Offer network opportunities to managers and IFs for peer-learning and reflections • Document activities in an activity log	• Learning through interacting with EFs • Support the implementation of change at their respective PHC center together with the manager, in close collaboration with EFs • Support and guide colleagues in change, lifestyle habits, and motivational interviewing • Document activities and organizational changes in an activity log	• PHC managers mainly responsible for the implementation at their center • The advisory board supports managers at the PHC intervention centers and participates in manager networks offered by EFs	• Provide feedback based on data from each PHC center's medical records on the classification of health intervention codes, prescribed physical activity, and numbers of filled screening forms • Communicate with IFs and managers and facilitate their reflections on areas in which they have performed well and areas that can be improved to reinforce their health-promotion practice in accordance with their goals
Action target	• IFs and managers at the PHC centers	• HCPs/colleagues at their PHC center	• Managers and HCPs at the PHC centers	• IFs and managers at the PHC centers
Temporality	• Twelve-month support, more intense in the beginning and decreasing over time	• Act as IF during the 12-month implementation period	• Planning phase and during the 12-month implementation period	• Feedback will be provided monthly and before meetings with IFs during the implementation period

Implementation strategy	External facilitator (EF)	Internal facilitator (IF)	Mandate change	Audit and feedback
Dose	• Based on the needs of IFs and managers, about 1 meeting a week (2 hours) at each PHC center • IF Network every second month (2 hours) • Manager Network every third month (2 hours)	• Implementation dedicated as a work assignment, approximately 10% of working hours	• Continuous manager support • Participate in Manager Network every third month (2 hours)	• Feedback will be provided monthly and before meetings with IFs
Implementation outcomes affected	• Change in routine health-promoting practice and sustainability	• Change in routine health-promoting practice and sustainability	• Feasibility and acceptability	• Change in routine health-promoting practice and sustainability
Justification	• Facilitation [36-38,53,54] • Activity log [55]	• Facilitation [38] • Activity log [55]	• Change leadership model [43,44]	• Audit and feedback [56]

External Facilitators

Four organizational developers at the development unit in the Örebro region are contracted as external facilitators to provide context-specific implementation support at the PHC intervention centers. During spring 2021, they were provided further education by a certified change leader in accordance with the Astrakan change leadership model [44]. In this advanced education, the change leadership model was discussed on the basis of the characteristics and challenges in the proposed research project. The external facilitators (n=4) work in pairs to support the internal facilitators and managers at the PHC centers. They will work systematically with the PHC centers to accomplish a shared vision, intrinsic motivation, adequate competence, resources to support the change, and an anchored plan for change [53]. The experiences of external facilitators of the implementation and their thoughts from meetings with managers and internal facilitators will be discussed bimonthly by members of the research group (YN and ENS). The discussions at these meetings enable a context-specific and interactive process concerning planning, coordination, learning, and tailoring implementation strategies for the specific PHC intervention centers at the micro level. The sessions are important because of the fluid nature of facilitation over time, aiming to develop the external facilitators' skills and improve the implementation of the intervention [39,53]. The external facilitators will regularly document their performed activities, intent, duration, and individuals involved, as well as perceived barriers and facilitating factors in an activity log [55].

Internal Facilitators

Managers at each PHC intervention center will appoint 2 HCPs as internal facilitators. They will receive support from the external facilitators [54] regarding the clinical intervention and in supporting each step of the change process. Every week, they will report all performed activities and organizational changes in an activity log related to the implementation at their respective PHC intervention centers [55].

Mandate Change

According to the change leadership model [43,44], the managers at the PHC intervention centers need to accept responsibility for change as they are accountable for the transition into a more health promotion practice at their centers. An advisory board anchors the project at the highest management levels in the PHCs' region.

Audit and Feedback

Data from each PHC center's medical records will be used in communication with managers and internal facilitators at the PHC intervention centers.

Data Collection

For rigorous process evaluations, data will be collected before, during, and after accomplishing the implementation strategy [45,57]. An overview of the data collection process is provided in Figure 2, and a more detailed overview including the timeline is provided in Figure 3.

Figure 2. Overview of the Act in Time study's process evaluation components, research questions, and data sources. EF: external facilitator; IF: internal facilitator; PHC: primary health care. Adapted from Saarijärvi et al [58].

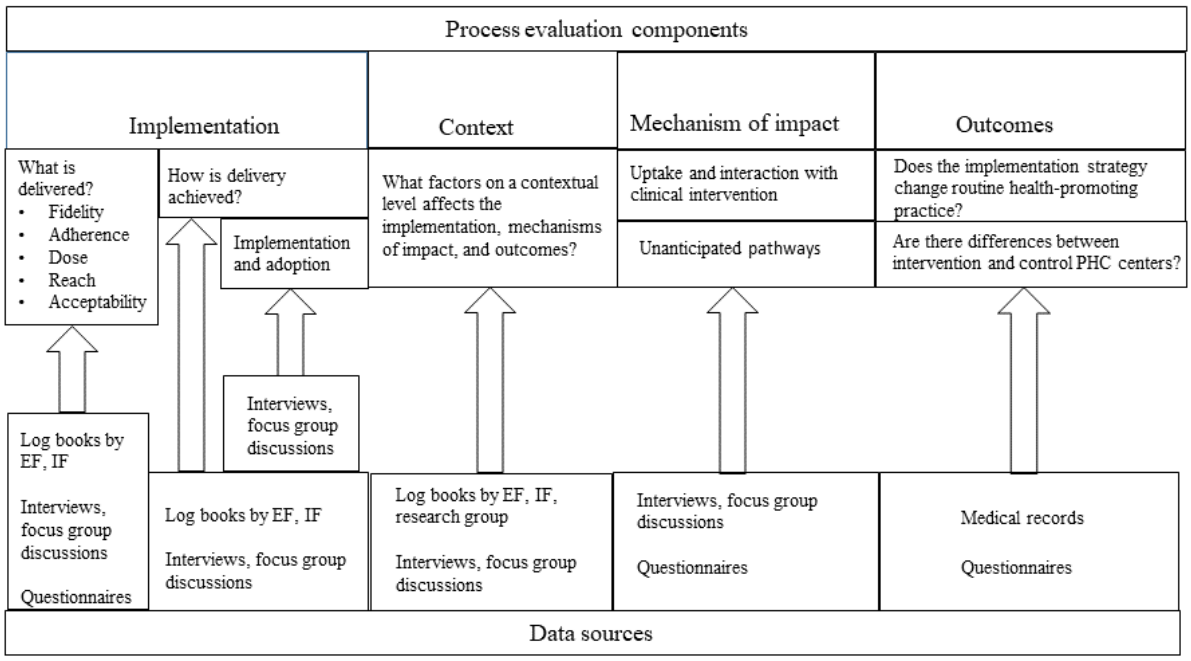
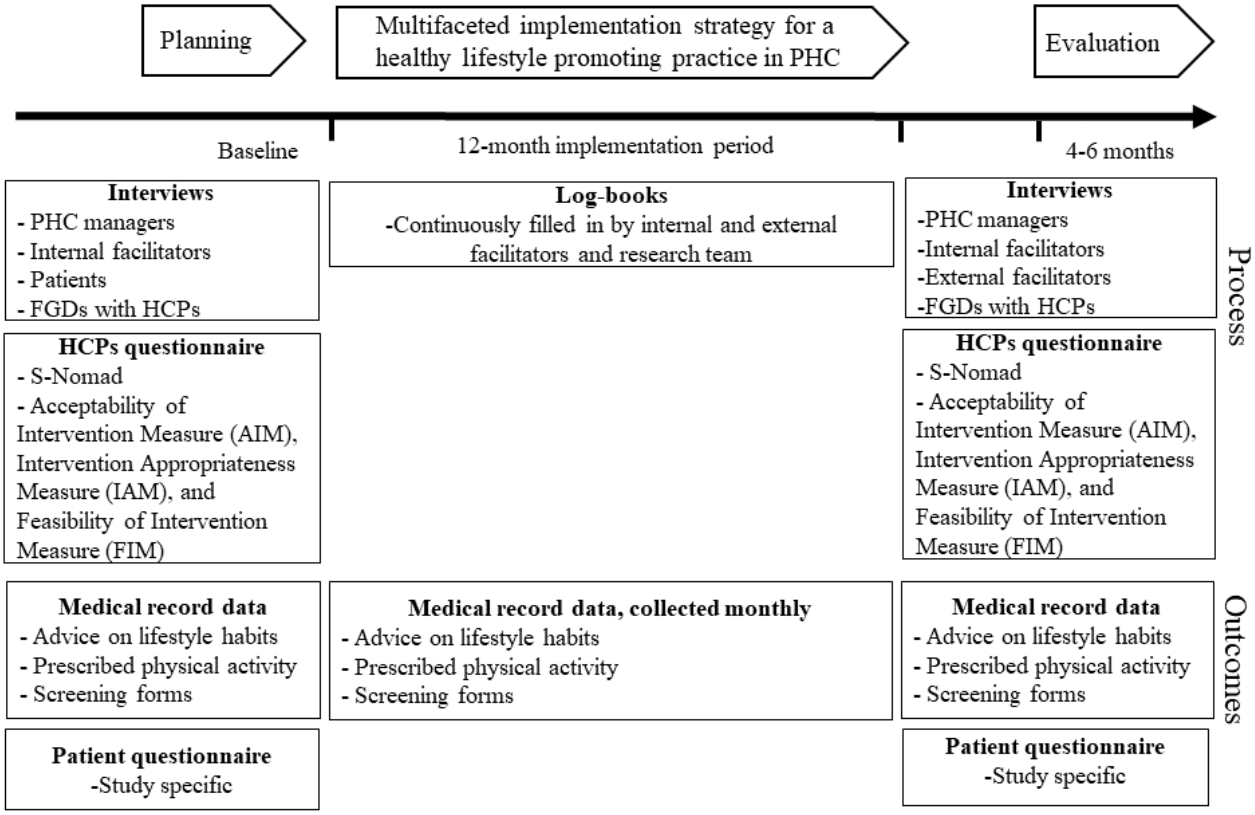


Figure 3. An overview of data collection including the timeline, target group, and methodology. FGD: focus group discussion; HCP: health care professional; PHC: primary health care.



Implementation Outcome Evaluation

To evaluate changes in HCP health promotion routine, data will be collected from both intervention and control PHC centers as follows:

1. Registered medical record data concerning the frequency of individually targeted lifestyle interventions by HCPs, as shown in the administrative registration of clinical interventions including simple or qualified lifestyle advice and prescriptions for physical activity. Data will be collected monthly.
2. Registered medical record data for screening forms on lifestyle habits will be completed by patients before visiting the PHC center. Data will be collected monthly.

3. A subset of patients visiting a PHC center for approximately 1 week will receive a questionnaire through text message (SMS) or post asking whether they had been encouraged to fill in the screening form before their visit. They will be asked whether lifestyle habits were discussed and whether advice was given. The survey will be provided in 8 languages to reach those who did not speak Swedish. The survey will be distributed to up to 3000 patients at baseline and follow-up (approximately 500 patients per PHC center). Finally, 2 reminders will be sent to all participating patients.

With regard to the aforementioned data collected (points 1-3), we will only retrieve medical records data from patients aged ≥18 years.

Implementation Process Evaluation

The following will occur at the PHC intervention centers:

1. We will query HCPs whether they perceive the health promotion practice as acceptable, appropriate, and feasible, using a validated and short questionnaire [59,60] distributed by email with a link to the questionnaire. Two reminders will be sent. Data will be collected from approximately 200 HCPs.
2. We will evaluate how HCPs have integrated the health promotion practice to their daily work using the validated questionnaire S-Nomad [61-63]. This survey will be distributed with the short questionnaire described above (in point 1).
3. We will perform individual interviews with PHC managers (n=10-12) and internal facilitators (n=10-12) and FGDs with HCPs on capturing their experiences of the implementation process. Up to 6 FGDs will be moderated with a purposeful sample of 5-7 HCPs at each intervention center.
4. We will ask internal and external facilitators to write structured activity logs during the implementation strategy to assess the fidelity, dose, and reach of the implementation intervention.
5. We will conduct individual interviews with the 4 external facilitators once the implementation strategy is completed at all PHC intervention centers. An independent researcher—not involved in the study design, the implementation strategy, or its evaluation—will conduct these interviews.

With regard to the aforementioned points 1-3, we will collect data approximately 1 week before starting and 4-6 months after ending the implementation strategy.

Data Analysis

Separate teams will analyze outcome and process evaluations [45].

Quantitative Data

Quantitative data will be analyzed using SPSS Statistics for Windows (version 27.0, IBM Corp). Data from patients' questionnaires and medical records and HCPs' questionnaires will be analyzed using generalized linear mixed models [64]. Specifically, Poisson and logistic models will be used for count and proportion outcomes, respectively. Parameters will be estimated using maximum likelihood estimation. Fixed effects will include intervention, month, and sex, whereas random effects will include nested patients at PHC intervention centers. Model checking will involve the inspection of residual and autocorrelation plots. To quantify the magnitude and direction of intervention effects, we will use the incidence rate ratio (IRR) from the Poisson model and odds ratio (OR) from the logistic model. To determine statistical significance, a P value of <.05 will be considered. CIs will be adjusted for simultaneous inference where several contrasts are presented.

Qualitative Data

All interviews and FGDs will be digitally audio recorded and transcribed verbatim. The transcribed texts will be imported into NVivo (version 12; QSR International) to manage and code data. Qualitative content analysis will be used to analyze the data from the interviews and FGDs [65]. A deductive approach will be used for the data collected at baseline, where the constructs in the implementation framework CFIR will guide the analysis [49,50]. An inductive analysis will be used to describe the HCPs' and managers' perceptions of the health promotion practice concerning the CFIR constructs. Information from process mapping with patients and data from activity logs will be compiled and processed qualitatively and quantitatively. The process and outcome evaluation data will be integrated to determine whether implementing the health promotion practice succeeded [45,66].

Ethical Considerations

The Act in Time study was approved by the Swedish Ethical Review Authority (DNRs 2020-06956, 2021-00912 and 2021-05825-02). Participation is voluntary, all data will be handled confidentially, and only authorized personnel will have access to the data. The managers, HCPs, and internal and external facilitators participating in the interviews and FGDs will be prompted to provide written informed consent. The audio files and transcripts will be coded and saved on a password-protected server. The code key and other relevant material will be stored in a safe locker. The data gathered from medical records will be anonymized and protected. We will check the lists of patients visiting the PHC intervention centers and not send questionnaires to deceased individuals. Patients and PHC staff will fill out questionnaires anonymously. The study will comply with the tenets of the Helsinki declaration [67] and the recommendation in the StaRI checklist [47,48]. The COREQ (COnsolidated criteria for REporting Qualitative research) checklist will be used when reporting findings from the qualitative studies [68].

Results

Recruitment of PHC centers began in March 2021 and ended in Spring 2022. As of June 2022, five PHC centers have been recruited and baseline data collection is completed. Based on the planned timeline with the 12-month implementation strategy and up to 4-6–month follow-up, we expect to collect data until Summer 2023. Data collected from interviews and FGDs at baseline will be analyzed during spring 2022, and these results are expected to be published in Autumn 2022. Results from the

evaluation of process and outcomes of the implementation strategy are expected to be published between 2024 and 2025.

Discussion

Expected Findings

The results of the Act in Time study can help to better understand the implementation process and what may be effective (or ineffective) in influencing HCPs and organizational change toward a more proactive and health promotion practice in PHC. Insight into potential paths to improvement to inform broader implementation strategies and scale up implementation may also be derived from our study [23,69].

Strong evidence has been found showing a link between behavioral risk factors and NCDs [1,5-7]. National health promotion and disease prevention guidelines have been established to combat these risk factors [13,14]. Nevertheless, applying these recommendations is still a challenge for PHC professionals [15-19]. In a systematic review Wändell et al [15] identified several barriers and facilitators that PHC professionals face in preventing NCDs. Lack of time, reimbursement, education, and counseling skills were the most common obstacles. Positive attitudes toward prevention and awareness of the effectiveness of health checks were the most commonly reported facilitators [15]. This study will identify barriers and facilitators and adapt the implementation strategy in accordance with these determinants, the local context, and the stakeholders' needs, as previously proposed [30-32,34]. The engagement of stakeholder groups [34,35] (ie, managers and HCPs) is considered crucial throughout the implementation strategy and may enable change in HCPs' behavior [34]. The study is supported by regional political and higher manager levels, which, together with creating an advisory board, will strengthen the opportunities to implement the project. The role of leadership has previously been acknowledged as necessary in the implementation and sustainment of evidence-based practice in health care [70,71]. It is crucial to have acceptance and support from the leadership at different levels [42]. Facilitation is a core component of the implementation strategy. External facilitators will reinforce the strategy and support internal facilitators and managers in changing practice [38-40]. This study will contribute to important knowledge on the role of external and internal facilitators in changing the routine health promotion practice.

Strengths and Limitations

The proposed study has several strengths. A novelty of this study is the combination of implementation science [23,26] and a change leadership model [43,44]. Such an approach seeks to achieve tangible and sustained individual and organizational change. Moreover, we will use medical record data as feedback to the PHC intervention centers during the implementation period. The medical record data serve as a formative evaluation of the implementation strategy aiming to adapt and strengthen it. In addition, the discussions among external facilitators and the research group might enable beneficial adjustment of the implementation strategy [42]. This kind of refinement of the implementation strategy in response to accumulated data, operating as an adaptive and variable response to context, is considered a desirable feature of implementation research [66].

We will perform a comprehensive evaluation of the process and outcomes of a multifaceted implementation strategy for implementing a healthy lifestyle–promoting practice in a PHC setting using qualitative and quantitative methods in accordance with MRC guidelines [45]. We will use a pre-post design, which helps examine the impact of a complex implementation strategy in a real-world setting when a randomized controlled trial is not suitable or when assessing the adoption and adherence to guideline recommendations by HCPs [46,72]. However, the design may mean less control over confounding factors. Instead of power calculation, we apply a strategic sampling method to achieve maximum variation in PHC centers and thus strengthen the external validity and generalization of our findings. The external validity is dependent on the study design but also the social, economic, political, and organizational context in which the study is performed, which must be considered when translating the findings into a different context. Data will be collected before, during, and after implementation, allowing a more rigorous assessment of the implementation process [57]. A strength is the use of validated questionnaires and registered medical record data. The separate process and evaluation teams are other study strengths [45].

This study faces challenges due to the ongoing COVID-19 pandemic and organizational changes in the region. These challenges have led to staff shortages and a heavy workload, which may affect the ability of PHC centers to participate in the study and for HCPs to answer questionnaires. We will send questionnaires to approximately 500 patients per PHC center on 2 occasions. However, we expect a relatively low response rate as patients may be reluctant to click on the link to the questionnaire in the text message. Thus, reminders will also be sent by post.

Conclusions

This study will contribute to the implementation processes and outcomes of a multifaceted implementation strategy for a health promotion practice in a real-life PHC setting. More specifically, we expect to enhance knowledge and understanding of the role and contribution of internal and external facilitators for implementation outcomes when changing the routine practice and contributing to the development of facilitators' training and role in future work. Our findings could help to guide policy makers, managers, and HCPs in integrating health promotion and disease prevention into PHC practice.

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Data Availability

The data sets generated and analyzed during the current study are not publicly available because they contained information that could compromise the integrity of research participants but are available from the corresponding author on reasonable request.

Authors' Contributions

YN is the principal investigator responsible for conceptualizing and designing this study. ENS will conduct the interviews, led the focus group discussions (FGDs), and drafted this manuscript. LW and YN played important roles in revising and improving the manuscript. All authors have approved the final version of this manuscripts and agree to be personally accountable for their contributions.

Conflicts of Interest

None declared.

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
COREQ: COnsolidated criteria for REporting Qualitative research
FGD: focus group discussion
HCP: health care professional
i-PARIHS: integrated-Promoting Action on Research Implementation in Health Services MRC, the Medical Research Council
MRC: Medical Research Council
NCD: noncommunicable disease

PHC: primary health care
StaRI: Standards for Reporting Implementation Studies

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Protocol

Assessing the Clinical and Socioeconomic Burden of Respiratory Syncytial Virus in Children Aged Under 5 Years in Primary Care: Protocol for a Prospective Cohort Study in England and Report on the Adaptations of the Study to the COVID-19 Pandemic

Uy Hoang[1], MD, MPH; Elizabeth Button[1], BA, MSc; Miguel Armstrong[2]; Cecilia Okusi[1], BSc, MSc; Joanna Ellis[3], PhD; Maria Zambon[3], MD, PhD; Sneha Anand[1], PhD, MSc, BSc; Gayathri Delanerolle[1], PhD; F D Richard Hobbs[1], MD; Jojanneke van Summeren[4], PhD; John Paget[4], MD; Simon de Lusignan[1], MD

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom

[2]Imperial College London, London, United Kingdom

[3]Reference Microbiology Services, United Kingdom Health Security Agency, London, United Kingdom

[4]Netherlands Institute for Health Services Research, Utrecht, Netherlands

Corresponding Author:
Simon de Lusignan, MD
Nuffield Department of Primary Care Health Sciences
University of Oxford
Eagle House, Walton Well Road
Oxford, OX2 6ED
United Kingdom
Phone: 44 01865617283
Email: simon.delusignan@phc.ox.ac.uk

Abstract

Background: Respiratory syncytial virus (RSV) commonly causes lower respiratory tract infections and hospitalization in children. In 2019-2020, the Europe-wide RSV ComNet standardized study protocol was developed to measure the clinical and socioeconomic disease burden of RSV infections among children aged <5 years in primary care. RSV has a recognized seasonality in England.

Objective: We aimed to describe (1) the adaptations of the RSV ComNet standardized study protocol for England and (2) the challenges of conducting the study during the COVID-19 pandemic.

Methods: This study was conducted by the Oxford-Royal College of General Practitioners Research and Surveillance Centre—the English national primary care sentinel network. We invited all (N=248) general practices within the network that undertook virology sampling to participate in the study by recruiting eligible patients (registered population: n=3,056,583). Children aged <5 years with the following case definition of RSV infection were included in the study: those consulting a health care practitioner in primary care with symptoms meeting the World Health Organization's definition of acute respiratory illness or influenza-like illness who have laboratory-confirmed RSV infection. The parents/guardians of these cases were asked to complete 2 previously validated questionnaires (14 and 30 days postsampling). A sample size of at least 100 RSV-positive cases is required to estimate the percentage of children that consult in primary care who need hospitalization. Assuming a swab positivity rate of 20% in children aged <5 years, we estimated that 500 swabs are required. We adapted our method for the pandemic by extending sampling planned for winter 2020-2021 to a rolling data collection, allowing verbal consent and introducing home swabbing because of increased web-based consultations during the COVID-19 pandemic.

Results: The preliminary results of the data collection between International Organization for Standardization (ISO) weeks 1-41 in 2021 are described. There was no RSV detected in the winter of 2020-2021 through the study. The first positive RSV swab collected through the sentinel network in England was collected in ISO week 17 and then every week since ISO week 25. In total, 16 (N=248, 6.5%) of the virology-sampling practices volunteered to participate; these were high-sampling practices collecting the majority of eligible swabs across the sentinel network—200 (43.8%) out of 457 swabs, of which 54 (N=200, 27%) were positive for RSV.

Conclusions: Measures to control the COVID-19 pandemic meant there was no circulating RSV last winter; however, RSV has circulated out of season, as detected by the sentinel network. The sentinel network practices have collected 40% (200/500) of the required samples, and 27% (54/200) were RSV positive. We have demonstrated the feasibility of implementing a European-standardized RSV disease burden study protocol in England during a pandemic, and we now need to recruit to this adapted protocol.

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KEYWORDS

medical records systems, computerized; respiratory syncytial virus; general practitioners; pandemics; COVID-19; general practice; primary health care; outcome assessment, health care; respiratory; children; pediatric

Introduction

"Burden of disease" refers to the human and economic costs that result from poor health [1,2]. Respiratory syncytial virus (RSV) "burden of disease" studies in young children (aged <5 years) have mostly been focused on the morbidity and mortality rates of RSV infections [3]. In the United States, most of the health care use related to RSV in children occurs in outpatient settings [4]. Common presentations of RSV including bronchiolitis, bronchitis, pneumonia, and other lower respiratory tract infections (LRTI) are managed in primary care [5]. In the United Kingdom, this pediatric primary care is provided by general practitioners (GPs) [6]. A global burden of disease study estimates that there are 33.1 million young children infected with RSV, resulting in 3.2 million hospitalizations and 59,600 in-hospital deaths [3]; although in western countries, mortality due to RSV is rare and tends to occur in those with underlying risk factors [7].

RSV epidemics occur annually in temperate climates during the winter months, and less consistent epidemics occur in the (sub)tropics [8]. Most studies have found a positive correlation with latitude, as peak RSV activity generally occurs later in the year with increased latitude in both the northern and southern hemispheres [8-10]. One region where this is not the case is Europe, where 3 different studies have found contradictory results [11].

A study from Spain measured health care use related to RSV infections in young children in primary care and calculated the associated costs [12]. A recent literature review found only 2 further studies in primary care that have investigated the clinical and socioeconomic burden of laboratory-confirmed RSV infections in young children [1].

Further information on the clinical and socioeconomic burden of RSV is needed to support the development of clinical services and preventative care for children in the United Kingdom, including the implementation of effective preventative measures against RSV that could reduce the impact of severe LRTI for children and reduce the clinical workload in primary care [13,14].

During the winter of 2019-2020, the "RSV ComNet" team, managed by the Netherlands Institute for Health Services Research, developed a standardized study protocol and patient questionnaires to measure the clinical and socioeconomic disease burden of laboratory-confirmed RSV infections among young children (aged <5 years) in primary care. They initially tested this protocol and validated the questionnaires in Italy and the Netherlands, among 293 and 152 children, respectively, in each country, of which 119 (41%) and 32 (21%) tested positive for RSV, respectively, and 116 and 12 were included for follow-up questionnaires, respectively [1].

This paper describes our adaptations of the "RSV ComNet" standardized study protocol and its validated study questionnaires for use in England—the RSV ComNet II study. We also describe the modifications made to implement the study during the COVID-19 pandemic and evaluate the revised data collection procedures.

The RSV ComNet II study aims to describe the epidemiology of RSV in primary care in England, including the RSV incidence rates and the clinical and socioeconomic disease burden of RSV in children aged <5 years. The objective of this paper was to describe the adaptations to the RSV ComNet standardized study protocol to execute the study in England. In addition, our secondary objectives were to present preliminary results from the RSV season in 2020-2021 and the demographic and clinical characteristics of the study population included so far.

Methods

The methods are described in 4 parts: (1) the case definition of eligible participants, planned measurements, timing of follow-up questionnaires, and number of participants required; (2) adaptations of the RSV ComNet standardized study protocol in England; (3) adaptations of our approach for the COVID-19 pandemic; and (4) statistical methods and sample size calculation.

Case Definition of Eligible Patients

We used the following case definition of RSV:

- Children aged <5 years
- Consulting a GP with symptoms meeting the World Health Organization and European Centre for Disease Control's definitions of acute respiratory illness (ARI) or influenza-like illness (ILI) [15,16], see Table 1
- A reference laboratory–confirmed polymerase chain reaction diagnosis of RSV (antigen testing of swabs is not undertaken)

The following exclusion criteria were applied:

- Parents with insufficient knowledge of English

- Parents who are, for whatever reason, unable to provide informed consent
- Special personal circumstances in the family (based on the judgement of the GP; eg, a recent death in the family) and the lack of informed consent

Table 1. ARI[a] and ILI[b] case definitions used.

	ARI [17,18]	ILI [16,19,20]
Symptoms	• Acute—defined as a sudden onset of symptoms • Respiratory infection—defined as having at least one of the following: shortness of breath, cough, sore throat, and coryza • Clinician's judgement that the illness is due to an infection and that there is not a more plausible diagnosis	• An acute respiratory illness with a temperature measured, reported, or plausibly ≥38 °C and a cough, with onset within the past 10 days • ILI cases have a sudden onset, and symptoms are often suggestive of systemic upset—myalgia, fatigue, malaise, and headache, etc • ILI cases should not have another more plausible diagnosis
SNOMED[c] codes used to track symptoms	Acute bronchitis (SCTID[d]: 10509002) or acute bronchiolitis (SCTID: 5505005), according to whether the infection was judged to be in the upper or lower respiratory tract, respectively	ILI (finding; SCTID: 95891005)

[a]ARI: acute respiratory illness.

[b]ILI: influenza-like illness.

[c]SNOMED: Systematized Nomenclature of Medicine.

[d]SCTID: SNOMED Clinical Terms identifier.

Planned Measurements and Timing

We used questionnaires previously evaluated as part of the RSV ComNet study [1]. These questionnaires record the clinical and socioeconomic impact of RSV at 14 and 30 days postswab. Figure 1 shows the RSV ComNet II study schedule of events in England. A copy of the combined Day 14 questionnaire is provided in Multimedia Appendix 1.

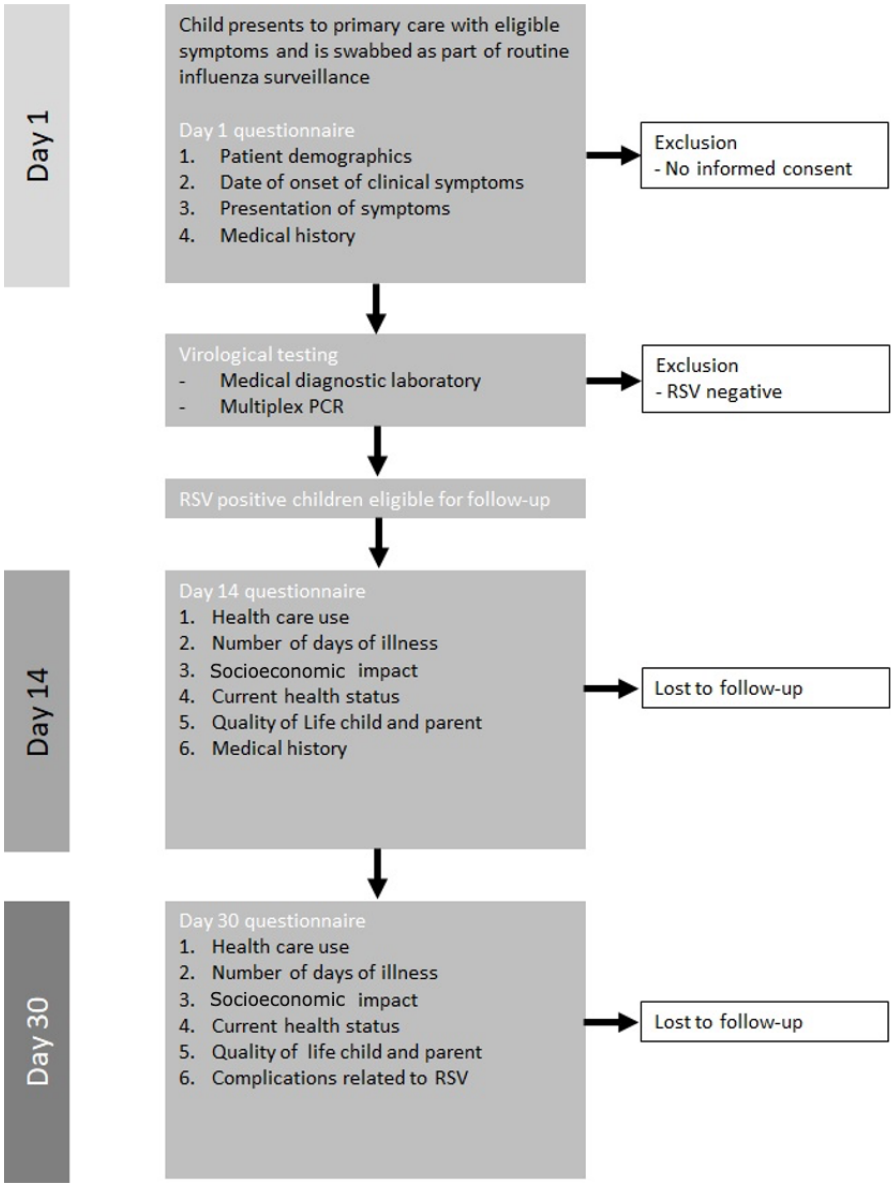
Primary care staff conducted the questionnaire follow-ups with the parents/guardians of children aged <5 years with RSV-positive swabs over the telephone, to increase the response rate, rather than sending paper questionnaires to the participants' home. Responses to the questionnaire were entered electronically by study staff through a dedicated website and stored in a secure database. Questionnaire information from this database will be linked to the computerized medical records (CMR) to analyze the final study results.

At the day of the swab (Day 1), information related to the demographics of the patient, date of symptom onset, presentation of symptoms, past medical history, and viral testing performed were extracted from the CMR and virology swabbing specimen forms of the consenting patients.

At 14 days postswab, questions relating to the health care use of the child within the past 2 weeks, number of days of illness, hospitalizations and accident and emergency department visits, current health status, quality of life, and socioeconomic impact on parents or caregivers were asked.

At 30 days postswab, the parents were asked to complete a final questionnaire similar to the Day 14 questionnaire, with an additional question regarding any complications related to the RSV infection, such as pneumonia or otitis media acute (ear infections) visits within the past month.

Figure 1. Study schedule of events for RSV ComNet II study in England. PCR: polymerase chain reaction; RSV: respiratory syncytial virus.



Sample Size Calculation

To estimate the clinical and socioeconomic disease burden of RSV with sufficient precision, it is necessary to have a sufficient sample of RSV-positive patients with a range of disease severity. To identify the optimal feasible sample size for the outcome "hospitalization rate," the RSV ComNet study team calculated the precision for this outcome, characterized by the 95% CI width, for 3 scenarios [21]. Scenarios were calculated for a sample size of 100, 150, and 200 RSV-positive cases and an expected RSV hospitalization rate of 6%. The corresponding 95% CIs were calculated to be from 1.3% to 10.7% (n=100), from 2.2% to 9.8% (n=150), and from 2.7% to 9.3% (n=200), and therefore, the study team decided that 100 RSV-positive cases were the minimum required feasible sample size.

Assuming a swab positivity rate of 20% in children aged <5 years, we estimated that a total of at least 500 swabs in the children aged <5 years category was required to reach the recommended sample size of 100 RSV-positive patients.

Specific Methods for Implementing the RSV ComNet II Standardized Study Protocol in England

English National Sentinel Surveillance Network

In England, the RSV ComNet II study was embedded within the English national sentinel surveillance network run by the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) [22]. Information from this network has been used to monitor respiratory infections including influenza and RSV for over 50 years [23]. Over this period, practices have had feedback about their data quality around influenza and respiratory disease.

The network consists of >1800 general practices in England, of which 248 take part in virology sampling—using swabs to monitor the spread of respiratory illnesses including COVID-19, influenza, and RSV. Since the COVID-19 pandemic started, virology sampling has taken place all year round.

Practice Recruitment for the RSV ComNet II Study in England

We invited all 248 virology-sampling practices within the sentinel surveillance network to participate in the RSV ComNet II study. Those that agree to participate in the study were given training on identifying and collecting consent from eligible patients, adding relevant study codes to the patient's CMR, and undertaking patient follow-up study questionnaires. Additional guidance was provided for swabbing children aged <5 years if requested.

Participant Recruitment for the RSV ComNet II Study in England

The opportunistic recruitment of participants took place in study practices. The parents/guardians of children presenting to their GP with symptoms meeting the study inclusion criteria were approached for consent by their GP or a trained study nurse. If written consent was obtained, then practices were asked to keep a copy of the signed consent form in the practice and record study consent directly into the CMR. Following consent, a nose and throat, or 2 nasal swabs, was taken and sent to the UK Health Security Agency reference virology laboratory for multiplex reverse transcription–polymerase chain reaction testing.

Study practices were encouraged to increase swabbing when RSV was observed to be circulating among sentinel network practices.

Oxford-RCGP Clinical Informatics Digital Hub

All participating practices that are part of the Oxford-RCGP RSC sentinel surveillance network have consented to the routine data extraction of information from the CMR into the Oxford-RCGP Clinical Informatics Digital Hub—a trusted research environment [24,25]. For virology specimens, information is collected by specific sentinel network request forms (with an electronic option), and the results are transmitted back to patient CMR through the eLab system (Emulation S.Hein).

Data about participant demographic characteristics and the clinical disease burden of RSV infection will be gathered from the Oxford-RCGP Clinical Informatics Digital Hub, including information from the virology specimens and patient questionnaires.

Adaptations to the RSV ComNet II Study in England Due to the COVID-19 Pandemic

The study was planned for winter 2020-2021 starting from January 4, 2021 (International Organization for Standardization [ISO] week 1), but the seasonality of RSV was interrupted by the use of nonpharmaceutical interventions (NPIs) such as lockdowns, school closures, social distancing, and the obligatory use of face masks during the winter of 2020-2021 as a result of the COVID-19 pandemic [26,27].

As a result of the NPIs and fewer patients coming to practices for face-to-face consultations, the Oxford-RCGP RSC also set up a parallel system to enable patients to order self-test kits that are sent to their home as part of virology surveillance, which have been shown to be reliable when compared to clinician-led sampling [28-31]. This system was incorporated into the study.

Through the sentinel network, we were able to identify which practices saw many symptomatic children, saw recent RSV-positive cases, and were regularly swabbing in the children aged <5 years category. We identified a positive correlation between the presentations of respiratory symptoms in children versus the number of swabs taken by practices.

We adjusted our practice recruitment strategy to actively target the practices with high RSV swab positivity rates. These practices were approached directly by research facilitators to inform them about the RSV positivity at their practice and invited to participate in the study.

A further adaptation to the study recruitment was to allow for initial verbal consent into the study if the patient was not seen in person.

Specific adaptations to the Day 14 questionnaire were made to facilitate data collection in England. First, all questions from the Day 1 consultation (ie, related to patient demographics, date of onset of clinical symptoms, and presenting clinical symptoms) are included in the Day 14 questionnaire. This inclusion was to ensure that all questions were asked if it was not possible during a time-limited initial consultation or information was missing from the virological swabbing specimen form. The only exception is a question on malnutrition, which the original protocol states should only be collected from the medical record. Second, additional questions on complications related to RSV infection were included in the Day 30 questionnaire, essentially creating a single combined questionnaire for situations where a Day 30 questionnaire was not possible, such as lost to follow-up cases due to pressure on parents/guardians to care for their children.

A further adaptation was made to expand the time window for completing the questionnaires to increase the response rate. If practices struggled to complete them within 14 and 30 days after the swab was taken, an allowance was given to retrospectively contact patients up to 60 days after the swab was taken using the combined Day 14 questionnaire.

Lastly, the study was originally due to end in June 2021. However, due to RSV-positive cases first appearing in April and June 2021, a decision was made to extend recruitment through to September 2021. The study was then extended to cover the winter season from October 2021 to the end of May 2022.

Statistical Methods

Our analysis describes the deviant RSV season in 2020-2021 including symptom incidence rates in the network, symptom incidence rates in the RSV study practices, swabbing rates in study practices, swab positivity rate in all the virology-swabbing practices within the network and RSV study practices in particular, bronchitis and ILI incidence rates in the network, and survey questionnaire response rates. The descriptive analysis using data collected to date are presented in this paper.

We also investigated differences in symptom incidence rates, swabbing rates, swab positivity rate, RSV incidence rates, and

survey questionnaire response rates between the RSV ComNet study practices in England and RSV rates measured in other European countries that implemented the RSV ComNet study protocol. Data are presented graphically by ISO weeks [32].

Ethics Approval

The study was approved by the English National Research Ethics Committees (Integrated Research Application System: 285025; Research Ethics Committees: 20/PR/0704). Subsequent study adaptions due to the COVID-19 pandemic described above were also granted approval by the English National Research Ethics Committees.

Results

Reported Results and Future Analyses

We present results on swabbing rates and swab positivity rates from the study practices and preliminary results from the questionnaires. The results include the demographic and clinical characteristics of young children with RSV infections in primary care. Additional analyses about the clinical and socioeconomic disease burden of RSV infections, including information obtained from the linkage of study questionnaires to the patients' electronic medical records, and the final analysis of the study are expected to be completed by June 2023.

Weekly Incidence Rates of ARI and ILI

There was no clear seasonal incidence of acute bronchitis or ILI in the 2020-2021 season. Figures 2 and 3 showed that the incidence rates of both ARI, as denoted by Systematized Nomenclature of Medicine Clinical Terms identifier (SCTID) 10509002—acute bronchitis, and ILI (SCTID: 95891005) across the network fluctuated during the course of the study, which fluctuated much more among RSV ComNet II study practices.

Figure 2. Acute bronchitis (SCTID: 10509002) incidence rate in RCGP RSC network compared with RSV ComNet II study practices. RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre; RSV: respiratory syncytial virus; SCTID: Systematized Nomenclature of Medicine Clinical Terms identifier.

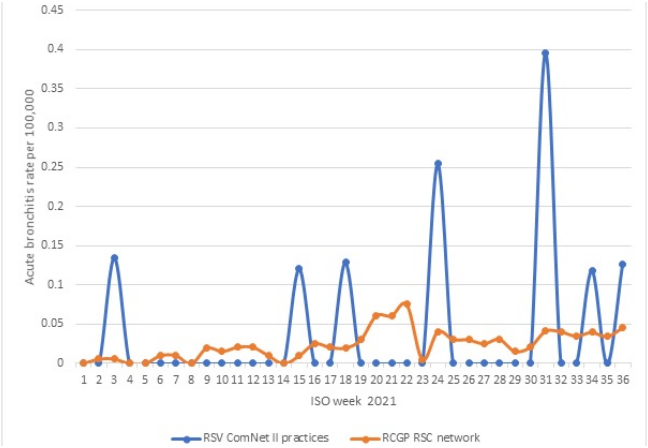
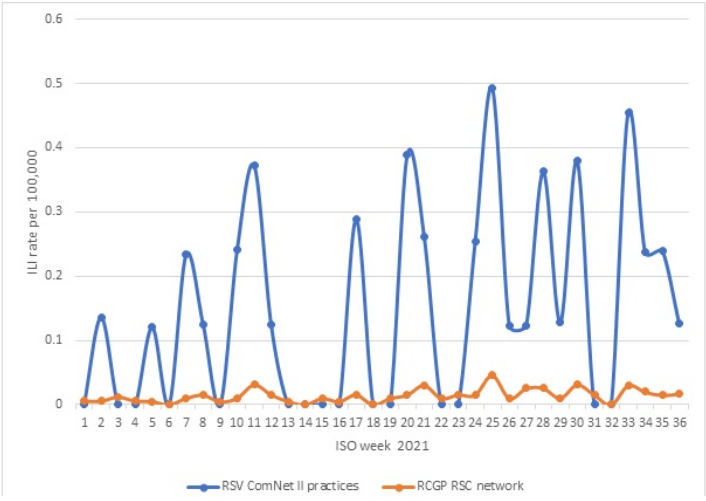


Figure 3. ILI (SCTID: 95891005) incidence rate in RCGP RSC network compared with RSV ComNet II study practices. ILI: influenza-like illness; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre; RSV: respiratory syncytial virus; SCTID: Systematized Nomenclature of Medicine Clinical Terms identifier.



RSV ComNet II Study Practice Recruitment in England

We recruited 16 practices into the study, with a registered population of 250,333 patients as of ISO week 41, 2021, which equates to 6.5% (16/248) of all virology-sampling practices within the RSC sentinel surveillance network. Figure 4 shows the recruitment of practices to the RSV ComNet II study by week. Figure 5 shows a map of the study practice locations. Between ISO weeks 18 and 19, there was a drop in the number of participating practices, which was due to on-going capacity issues resulting from the pandemic.

Figure 4. Number of practices recruited to the RSV ComNet II by week. ISO: International Organization for Standardization; RSV: respiratory syncytial virus.

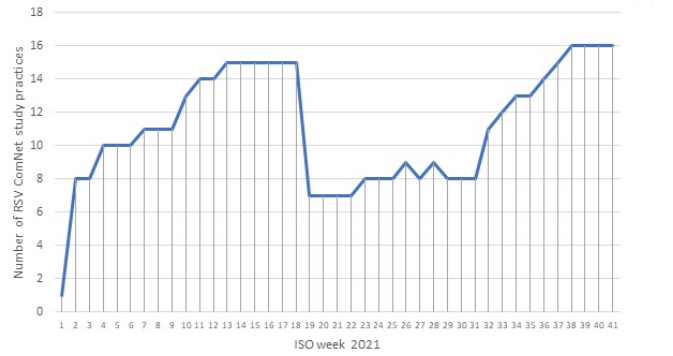


Figure 5. Map of study practice locations.

Virology-Sampling Rates and RSV Positivity

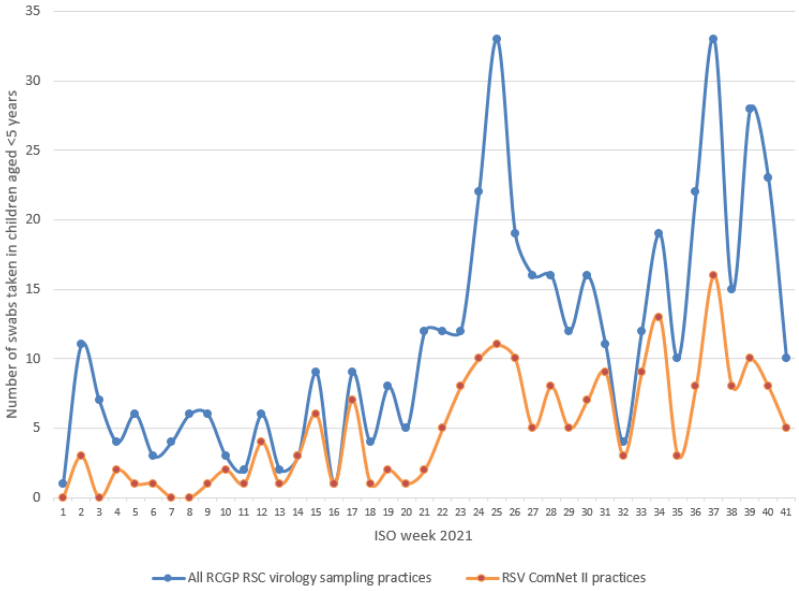
In total, 457 swabs in children aged <5 years were collected across all 248 virology-sampling practices in the sentinel surveillance network since January 4, 2021, up to ISO week 41, 2021, of which 100 swabs had been collected across the sentinel surveillance network in the winter season of 2020-2021 between ISO weeks 1-20, 2021.

Of the 457 swabs, 200 (43.8%) were collected among children aged <5 years in the RSV study practices by the 16 practices recruited into the RSV ComNet II study thus far (see Figure 6) up to ISO week 41, 2021; of these 200 swabs, 37 were collected

by RSV ComNet II study practices in the winter of 2020-2021 between ISO weeks 1-20, 2021.

The RSV swab positivity rate among children aged <5 years was 21.8% (100/457) across the entire RCGP RSC virology surveillance network, whereas an RSV swab positivity rate of 27% (54/200) was seen in the practices recruited for the study.

Figure 6. Number of swabs collected by all RCGP RSC virology sampling practices and RSV ComNet II study practices. RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre; RSV: respiratory syncytial virus.



Preliminary Characteristics of the Study Population From the Patient Questionnaires

Preliminary results on the demographic characteristics and clinical symptom presentation of the included study population so far are presented in Tables 2 and 3 up to ISO week 41, 2021.

These results do not include data linked to the medical record. There were 45 Day 14 questionnaires in this preliminary analysis, one of which was completed using the Day 30 questionnaire and thus contained incomplete information for certain entries. There were 24 Day 30 questionnaires, one of which was completed using the Day 14 questionnaire.

Table 2. Demographic characteristics of patients with respiratory syncytial virus (RSV)–positive swabs.

Characteristic	Children (N=45)
Age (months), median (IQR)	20 (26)
Age group (months), n (%)	
1-12	14 (31)
13-24	12 (27)
25-60	19 (42)
Gender, male, n (%)	22 (49)
Prematurity, n (%)	8 (18)
Presence of chronic condition, n (%)	
Respiratory disease	1 (2)
Malnutrition	Information not available for preliminary results
Immunocompromised	0 (0)
Others	3 (7)
Previous RSV infection in this season, n (%)	2 (4)
RSV typing, n (%)	
RSV A	18 (40)
RSV B	27 (60)
Coinfection with at least one other virus, n (%)	7 (16)

Table 3. Clinical symptoms of patients with respiratory syncytial virus (RSV)–positive swabs at Day 14 and Day 30.

Clinical symptoms	Day 14	Day 30	Combined
Shortness of breath, n/N[a] (%)	18/44 (41)	1/24 (4)	N/A[b]
Cough, n/N (%)	42/44 (95)	8/24 (33)	N/A
Sore throat, n/N (%)	5/44 (11)	1/24 (4)	N/A
Coryza at Day 14 or nose complaints at Day 30, n/N (%)	20/44 (45)	8/24 (33)	N/A
Fever, n/N (%)	30/44 (68)	2/24 (8)	N/A
At least 1 persisting symptom, n/N (%)	20/45 (44)	12/24 (50)	N/A
Returned to normal daily activities, n/N (%)	42/45 (93)	20/24 (83)	N/A
Duration of illness[c], median (IQR)	N/A	N/A	14 (13)

[a]N indicates the number of respondents from which the data are available. n indicates the number of patients with the specified symptom.

[b]N/A: not applicable.

[c]Calculated over a period of 60 days (the upper limit of Day 30 questionnaire).

Discussion

Principal Findings

Our results demonstrate that it is feasible to implement a standardized RSV burden of disease protocol in England during the COVID-19 pandemic. Although the pandemic has restricted access to primary health care, with more remote management of patients with respiratory symptoms and differences in the epidemiology of respiratory infections, the RCGP RSC sentinel network has acted as an adaptive platform and implemented the ComNet standardized protocol.

Of the 457 swabs among children aged <5 years, 200 (43.8%) were collected by the 16 practices participating in the RSV ComNet study up to ISO week 41, 2021; 100 were collected between ISO weeks 1-20, compared to the 382 collected in children aged <5 years between ISO weeks 1-25 in the last winter season 2019-20 and the 116 collected in children aged <5 years between ISO weeks 1-20 in the prepandemic year, 2018-19. Thus, the swabbing rate in children aged <5 year across the whole network was approximately 26% the equivalent rates for 2019-20 and 86% of equivalent rates for 2018-19.

As of ISO week 41, 2021, we were able to collect 54% (54/100) of the RSV-positive samples from children aged <5 years from an existing sentinel surveillance network in England for the RSV ComNet II study.

We noticed early in our implementation that the RSV swab positivity rate was concentrated in a small number of virology-swabbing practices across the sentinel surveillance network. This finding is similar to those in New York that show patchy RSV incidence during the COVID-19 pandemic [33]. This result has meant that recruiting practices for the study has focused on actively targeting practices that have seen recent RSV cases, which may not be generalizable to other years when the burden of RSV is more evenly spread across the network.

Strengths and Weaknesses of Our Study

A strength of this study is that it was nested in a large sentinel network that has been undertaking primary care surveillance of respiratory illness for over 50 years [22,23].

The scientific methodology developed for this study uses integrated medical record systems to obtain virological swabbing codes that allow researchers to carry forth a comprehensive analysis. Practices within the network are regularly involved in clinical and epidemiological research, and there are high levels of research engagement across the network. Thus, practices within the network are familiar with undertaking research surveys and able to explain clinical contexts to potential research participants, which allows the study to gather high-quality virological samples that reduce false positive and negative rates commonly observed in many parts of the world.

Undertaking the study during the COVID-19 pandemic has raised the awareness of cocirculating viruses and has encouraged many practices to participate in the virology-swabbing scheme, which was facilitated by our inclusion of verbal study consent and home swabbing. Evidence around the use of home swabbing for research studies is still limited compared to in-practice swabbing [28-31]; thus, it is important to observe if there are any biases introduced as a result of these adaptions of the study. However, recent clinical guidance [5] in the United Kingdom suggests that children aged <5 years with LRTI should be seen in person, thus encouraging the swabbing of more cases in the target age group for this study.

However, undertaking the study during the COVID-19 pandemic and COVID-19 vaccine rollout has meant that practices were under an increased workload pressure, with some practices having to pull out due to a lack of capacity. The implementation of NPIs during the COVID-19 pandemic has also changed the epidemiological pattern of RSV, and thus, our results on the clinical and socioeconomic burden of RSV may not be generalizable to other years. Restrictions on access to primary care and differences in managing patients with respiratory symptoms may have an influence on health care use for patients with RSV during the pandemic. For example, more patients may seek testing for COVID-19 only, which largely takes place outside of primary care currently and may also influence the estimates of the clinical and socioeconomic burden of RSV from this study.

RSV did not follow the usual winter pattern [34,35], and the incidence rates and uneven spread of RSV cases throughout the

network may be the result of differential swabbing practices due to differences in symptom severity or community prevalence of COVID-19; thus, the results may not be generalizable to other years.

Between ISO weeks 48-52, in December 2020, when RSV cases would normally have peaked [36-38], no cases of RSV were reported through national virology surveillance, with a similar lack of cases being reported by other European countries [27].

Comparisons With Prior Work, Unanswered Questions, and Need for Further Work

It was predicted that as NPIs and travel restrictions ease, the levels of circulating RSV would increase. It has also been hypothesized that changes in health-seeking behavior during the COVID-19 pandemic could have contributed to a reduced detection of RSV and that a return to normal health-seeking behaviors would see a subsequent rise in the detection of RSV [39,40]. Furthermore, it was suggested that RSV infections could present more severely as older children, who were not initially exposed to RSV during the start of the COVID-19 pandemic, would be at increased risk of contracting a severe RSV infection [27]. Indeed, since June 2021, there has been a noted, consistent increase in RSV-positive swabs from national virology swabbing.

Future studies could provide sufficient data for a comprehensive socioeconomic analysis in relation to disease burden among children aged <5 years across European countries, which would further attest to developing cost-effective models for future RSV interventions.

Protocol Amendments

Important protocol amendments will be referred to the English National Research Ethics Committees for ethical approval. Once approved, it will be communicated directly with the recruiting study practices. The amended protocol will be shared with all relevant parties, such as investigators and clinical research networks, in a timely manner.

Conclusions

This study aimed to demonstrate the possibility of implementing a standardized protocol to assess the clinical and socioeconomic impact of RSV within England. Although the results may not be easily generalizable to other years due to the COVID-19 pandemic, the lessons learned and adaptations made in light of this study may still serve to inform other studies recruiting patients via the national surveillance network in England.

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Data Availability

Data cannot be shared publicly because of it is owned by the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) and its participating practices. Data are available from the University of Oxford Institutional Data Access Committee (contact via ku.ca.xo.chp@nanigsuled.nomis) for researchers who meet the criteria for access to confidential data. The data underlying the results presented in the study are available from https://orchid.phc.ox.ac.uk/. Further enquiries about the RCGP RSC network and data requests can be found at https://orchid.phc.ox.ac.uk/index.php/orchid-data/ or by emailing ku.ca.xo.chp@seiriuqneecitcarp.

Authors' Contributions

UH and SdL contributed to the planning, conducting, and reporting of the work described in the paper.
JvS and JP contributed to the study design, data collection, data analysis, interpretation of the data, writing the manuscript, and in the decision to submit this paper for publication.
MA, CO, JE, MZ, SA, GD, and FH contributed to the conducting and reporting of the work described in the paper.

Conflicts of Interest

JP and JvS declares that the Netherlands Institute for Health Services Research has received unrestricted research grants from the World Health Organization, the European Union’s Innovative Medicines Initiative, Sanofi, and the Foundation for Influenza Epidemiology. SdL is the director of the Oxford- Royal College of General Practitioners Research and Surveillance Centre. SdL

has undertaken projects unrelated to RSV funded by GSK, Takeda, and Seqirus and has been a member of Global Advisory Boards for Seqirus and Sanofi.

Multimedia Appendix 1
Day 14 questionnaire.
[DOCX File , 24 KB - resprot_v11i8e38026_app1.docx]

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Abbreviations

ARI: acute respiratory illness
CMR: computerized medical records
GP: general practitioner
ILI: influenza-like illness
ISO: International Organization for Standardization
LRTI: lower respiratory tract infections
Nivel: Netherlands Institute for Health Services Research
NPI: nonpharmaceutical intervention
RCGP: Royal College of General Practitioners
RSC: Research and Surveillance Centre
RSV: respiratory syncytial virus
SCTID: Systematized Nomenclature of Medicine Clinical Terms identifier

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Protocol

Marijuana Use and Health Outcomes in Persons Living With HIV: Protocol for the Marijuana Associated Planning and Long-term Effects (MAPLE) Longitudinal Cohort Study

Angel B Algarin[1], MPH, PhD; Gabriela N Plazarte[2], BS; Kaitlin R Sovich[3], BA; Stella D Seeger[4], BS, BPH; Yancheng Li[4], MS; Ronald A Cohen[5,6], PhD; Catherine W Striley[4], MSW, MPE, PhD; Bruce A Goldberger[7], MS, PhD; Yan Wang[4], MS, PhD; Charurut Somboonwit[8], MD; Gladys E Ibañez[9], MA, PhD; Emma C Spencer[10], MPH, PhD; Robert L Cook[4], MPH, MD

[1]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, San Diego, La Jolla, CA, United States
[2]Department of Psychology, University of South Florida, Tampa, CA, United States
[3]Department of Neurology, University of Florida, Gainesville, FL, United States
[4]Department of Epidemiology, University of Florida, Gainesville, FL, United States
[5]Department of Clinical and Health Psychology, University of Florida, Gainesville, FL, United States
[6]Center for Cognitive Aging and Memory, University of Florida, Gainesville, FL, United States
[7]Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL, United States
[8]Division of Infectious Disease & International Medicine, University of South Florida, Tampa, FL, United States
[9]Department of Epidemiology, Florida International University, Miami, FL, United States
[10]Bureau of Communicable Diseases, Florida Department of Health, Tallahassee, FL, United States

Corresponding Author:
Robert L Cook, MPH, MD
Department of Epidemiology
University of Florida
2004 Mowry Rd
Gainesville, FL, 32603
United States
Phone: 1 352 273 5869
Email: cookrl@ufl.edu

Abstract

Background: Marijuana use is common in persons with HIV, but there is limited evidence of its relationship with potential health benefits or harms.

Objective: The Marijuana Associated Planning and Long-term Effects (MAPLE) study was designed to evaluate the impact of marijuana use on HIV-related health outcomes, cognitive function, and systemic inflammation.

Methods: The MAPLE study is a longitudinal cohort study of participants living with HIV who were recruited from 3 locations in Florida and were either current marijuana users or never regular marijuana users. At enrollment, participants completed questionnaires that included detailed marijuana use assessments, underwent interviewer-administered neurocognitive assessments, and provided blood and urine samples. Ongoing follow-ups included brief telephone assessments (every 3 months), detailed questionnaires (annually), repeated blood and urine samples (2 years), and linkage to medical records and statewide HIV surveillance data. Supplemental measures related to intracellular RNA, COVID-19, Alzheimer disease, and the gut microbiome were added after study initiation.

Results: The MAPLE study completed enrollment of 333 persons between 2018 and 2021. The majority of participants in the sample were ≥50 years of age (200/333, 60.1%), male (181/333, 54.4%), cisgender men (173/329, 52.6%), non-Hispanic Black (221/333, 66.4%), and self-reported marijuana users (260/333, 78.1%). Participant follow-up was completed in 2022, with annual updates to HIV surveillance data through at least 2027.

Conclusions: The MAPLE study is the largest cohort specifically designed to understand the use of marijuana and its effects on HIV-related outcomes. The study population has significant diversity across age, sex, gender, and race. The data will help

clinicians and public health officials to better understand patterns of marijuana use associated with both positive and negative health outcomes, and may inform recommendations for future clinical trials related to medical marijuana and HIV.

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KEYWORDS

people living with HIV; marijuana use; cannabis; Florida; longitudinal studies; cognition; protocol

Introduction

Marijuana use is common among the more than 1 million people living with HIV in the United States [1]. Between 14% and 56% of people living with HIV report any marijuana use in the past 6 months [2-4], and an increasing proportion of users report daily use and use for medical reasons [3,5-7]. This increase in use corresponds with changing state marijuana laws across the country [8]. In Florida, a state with high incidence and prevalence of HIV infections [1], medical marijuana became legal in 2016 for patients with 10 different health conditions, including HIV [9]. Yet, many people living with HIV continue to use marijuana obtained outside of the legal medical marijuana system, and new evidence is needed to inform health care decisions and policies related to marijuana use in people living with HIV.

The long-term effects of marijuana use on people living with HIV are not clear and could potentially vary across individuals and by variation in cannabinoid type and strength within different strains of marijuana and medical marijuana products. Δ9-tetrahydrocannabinol (THC) is the most psychoactive component of marijuana, whereas some evidence suggests that other components of cannabis, such as cannabidiol (CBD) and various terpenes, or their combinations, show more promise for medical treatments [10,11]. In some studies, marijuana use has been shown to alleviate HIV-related symptoms, such as loss of appetite, fatigue, anxiety, neuropathy, pain, nausea, systemic inflammation, neurocognitive impairment, and gastrointestinal problems, and medication side effects [5,11-19]. However, other studies have found limited, insufficient, or lacking evidence supporting marijuana-related improvements to appetite, anxiety, cognitive functioning [20-22], irritable bowel syndrome, and a variety of neurodegenerative disorders [23]. Additionally, other research highlights inconsistencies in the literature on the association between marijuana use and antiretroviral therapy (ART) use and adherence [24-29]. A Cochrane review found only a few clinical trials related to marijuana, and that “those studies that have been performed have included small numbers of participants and focused on short-term effects. Longer-term data are lacking.” [14].

The HIV National Strategic Plan for 2021-2025 in the United States emphasizes the importance of engagement in care, HIV viral load suppression, and reduction of HIV-associated comorbidities [30], but relatively little is known about the impact of different patterns or motivations related to marijuana use on these outcomes. Therefore, health care providers currently have minimal evidence-based guidance when considering whether to recommend or prescribe marijuana to their patients with HIV/AIDS. Clinicians also lack tools or evidence to help identify which persons are using “too much” marijuana, as evidenced by links to specific behavioral and biological harms or onset of a substance use disorder.

There is also inconsistent evidence regarding the impact of marijuana use on cognitive function [17,20-22]. While acute exposure to marijuana can adversely affect cognitive function, the majority of research has found no significant association of chronic use of marijuana and traditional aspects of cognitive function in older adults living with HIV [31]. Less is known about the relationship of chronic marijuana use with more novel aspects of cognitive function such as planning, prospective memory (remembering what to do in the future), and motivation [31].

Several other aspects of chronic marijuana use in people living with HIV are unknown or understudied, including its association with symptoms of pain and anxiety, problems such as cannabis use disorder, and biological responses such as chronic inflammation [32,33]. There is evidence linking marijuana use with a decreased inflammatory response [11,17,18], but no reports to date have examined this relationship using longitudinal data.

To increase knowledge about the impact of marijuana use on health outcomes among people living with HIV, the Marijuana Associated Planning and Long-term Effects (MAPLE) study was funded by the National Institute on Drug Abuse in 2016. The primary goals of the MAPLE study are to determine the association of different patterns of marijuana use with (1) HIV care engagement, viral suppression, and HIV disease progression; (2) traditional and novel aspects of cognitive function; and (3) biomarkers related to chronic inflammation. This paper describes the study design, research procedures, and modifications to the study after initiation. We also present baseline participant characteristics and discuss some of the challenges encountered during the MAPLE study.

Methods

Design/Overview

The MAPLE study is a longitudinal cohort study that aims to evaluate health outcomes in persons with HIV who were exposed or not exposed to marijuana at baseline. The study sought to enroll a diverse sample of persons with HIV, with enrollment occurring from 2018 to 2021. The Southern HIV Alcohol Research Consortium (SHARC) at the University of Florida acts as the central coordinating center. The MAPLE study employed a targeted convenience sampling methodology, with data collected via questionnaires, biological specimens, medical record abstraction, and linkage to existing state HIV

surveillance data from the Florida Department of Health (FDOH). The study was designed to have annual assessments with ongoing follow-up via the state surveillance data. Several study procedures were modified after study initiation owing to the coronavirus epidemic and the receipt of 2 funding supplements from the National Institutes of Health (NIH).

Ethics Approval

The research procedures have been approved by the Institutional Review Boards at the University of Florida (201702564), Florida International University (201702564-IAA), and the FDOH (2018-12UF-UF), and are in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Recruitment Settings and Procedures

Recruitment for the MAPLE study began in November 2018 and ended in December 2021. Recruitment was based in the following 3 diverse settings in Florida: Miami, Tampa, and Gainesville. The majority of participants were recruited by research staff based in local county health departments and community-based clinics, but at all sites, participants were also recruited by word of mouth, self-referral, and flyers. Potential participants were screened and those who met preliminary inclusion criteria provided written informed consent, contact information, and confirmation of study eligibility (proof of HIV status and urine cannabinoid test results that matched self-reported use).

Study Population

Participants were eligible for the MAPLE study if they (1) were 18 years or older; (2) were living with HIV (confirmed by medical records or an HIV medication bottle); (3) were not planning to move out of Florida in the next 12 months; (4) could communicate in English; and (5) had either confirmed marijuana use (cannabinoids urine screen positive and self-reported marijuana use ≥4 times in the past month) or no/very limited marijuana use (cannabinoids urine screen negative, no self-report marijuana use in the past 5 years, and no regular or lifetime use). The planned enrollment (prior to the COVID-19 pandemic) sought to enroll 300 marijuana users and 100 nonusers.

Baseline Data Collection

Study Questionnaire and Assessments

At the baseline visit, participants completed an interviewer-assisted study questionnaire and cognitive assessments via paper, a computer (via Research Electronic Data Capture [REDCap] and Substance Abuse Module), or an iPad, depending on the specific study assessment. The study procedures took approximately 3.5 to 4 hours to complete, and participants received US $75 compensation.

Table 1 lists the study measures, sources, and timepoints for the research questionnaires, which included items to assess demographic characteristics, HIV-related health (eg, history of diagnosis, medication adherence, and retention in care), alcohol and drug use, pain, sleep, sexual behavior, mental health symptoms, interpersonal factors (eg, social support, HIV disclosure, and HIV-related stigma), health care utilization, insurance, and previous incarceration. Additional marijuana-related questions assessed the modes of consumption, reasons for use, and perceived effectiveness. Links to the baseline study questionnaires are included on the SHARC website [34].

Table 1. Summary of key measures in the Marijuana Associated Planning and Long-term Effects cohort study.

Key variables	Timepoint			Source
	0 y	1 y	2 y	
Sociodemographics	Yes	Yes	Yes	N/A[a]
General well-being				
Health-related quality of life	Yes	Yes	Yes	Short Form-8 Health Survey [35,36]
Life goals	Yes	Yes	Yes	Abbreviated Personal Projects Analysis Inventory [37,38]
Apathy	Yes	Yes	Yes	Apathy Evaluation Scale [39]
Leisure activities	Yes	Yes	Yes	Adult Leisure Activities [40]
Hospitalizations (past 12 months)	Yes	Yes	Yes	N/A
HIV care and treatment				
Diagnosis/linkage to care	Yes	No	No	N/A
ART[b] use/adherence	Yes	Yes	Yes	Abbreviated ART adherence measure [41]
Access to care	Yes	Yes	Yes	N/A
CD4 count/viral load	Yes	Yes	Yes	Enhanced HIV/AIDS reporting system
Social support				
Perceived social support	Yes	Yes	Yes	Medical Outcomes Study – Social Support Survey [42]
HIV disclosure	Yes	No	No	N/A
Stigma	Yes	No	No	Modified Berger Stigma Scale [43,44]
Mental health				
Depression	Yes	Yes	Yes	Patient Health Questionnaire-8 [45]
Anxiety	Yes	Yes	Yes	Generalized Anxiety Disorder-7 [46]
PTSD[c]	Yes	Yes	Yes	Primary Care PTSD Screen [47]
Distress	Yes	Yes	Yes	NIH[d] Distress Thermometer [48]
Life stress	No	No	Yes	Holmes-Rahe Life Stress Inventory [49]
Neurocognitive functioning				
Premorbid intellectual function	Yes	No	No	Wechsler Test of Adult Reading [50]
Episodic verbal learning and memory	Yes	Yes[e]	Yes	NIH Toolbox Picture Sequence Memory Test [51-53] California Verbal Learning Test-II [54]
Prospective memory performance	Yes	Yes[e]	Yes	Memory for Intentions Screening Test [55]
Planning	Yes	Yes[e]	Yes	NIH Examiner Unstructured Task [56]
Cognitive, emotional, sensory, and motor functions	Yes	Yes[e]	Yes	NIH Toolbox Dimensional Change Card Sort Test [52,57,58] NIH Toolbox Pattern Comparison Processing Speed Test [52,59] NIH Toolbox Oral Symbol Digit Test [52,60]
Inhibitory control and attention	Yes	Yes[e]	Yes	NIH Toolbox Flanker Inhibitory Control and Attention Test [52,61,62]
Working memory	Yes	Yes[e]	Yes	NIH Toolbox List Sorting Working Memory Test [52,63]
Behavioral risk factors				
Substance use	Yes	Yes	Yes	Alcohol Use Disorder Identification Test [64]
Sexual behavior	Yes	Yes	Yes	Adapted Veterans Aging Cohort Study sexual risk measure [65]
Other health conditions				
Pain	Yes	Yes	Yes	Brief Pain Inventory [66] Short Form McGill Pain Questionnaire-2 [67]
Sleep	Yes	Yes	Yes	Abbreviated Pittsburgh Sleep Quality Assessment [68]

Key variables	Timepoint			Source
	0 y	1 y	2 y	
Other				
Incarceration history	Yes	Yes	Yes	N/A
Use of technology	Yes	Yes	Yes	N/A
Marijuana				
Information sources	Yes	No	No	N/A
Attitudes and beliefs	Yes	Yes	Yes	N/A
Use patterns	Yes	Yes	Yes	Timeline Followback [69,70]
Cannabis use disorder	Yes	No	No	CIDI-Substance Abuse Module [71,72]
Past 12-month use disorder	Yes	Yes	Yes	Mini International Neuropscyhiatric Interview [73], Cannabis Intervention Screener [74]
Reasons for use	Yes	Yes	Yes	N/A
Feelings and body effects	Yes	Yes	Yes	N/A
Sources of marijuana	Yes	Yes	Yes	N/A
Marijuana and driving	No	No	Yes	N/A

[a]N/A: not applicable.

[b]ART: antiretroviral therapy.

[c]PTSD: posttraumatic stress disorder.

[d]NIH: National Institutes of Health.

[e]Data from 57 participants were collected at this point owing to COVID-19 modification.

Marijuana Use Items

We developed an interviewer-administered marijuana questionnaire using several items developed in our previous research [6], including items to assess specific reasons for use (eg, to improve sleep and increase appetite); perceived effectiveness; use of prescription drugs, such as dronabinol, CBD, or synthetic marijuana; and interest/participation in a formal medical marijuana program (Table 1).

Data on marijuana quantity, frequency, and use patterns were obtained by the Timeline Followback (TLFB), a retrospective calendar-based measure initially developed for alcohol use, but previously found reliable for use with other substances (eg, cocaine, marijuana, and tobacco) [69,70]. Trained MAPLE research assistants used the TLFB to assess patterns related to the timing of doses, mode of consumption (eg, vaporized, smoked, ingested, etc), quantity (in grams of marijuana flower/weed or mg of THC), and frequency over the past 30 days. A calendar and other prompts, such as pictures of different marijuana products (to help estimate quantity), were used to assist participants. Information on the TLFB will be used to create summary variables such as frequency of use (days/month), quantity/use days, and number of heavy use days (eg, >1 gram flower/day).

Several measures were used to assess cannabis use disorder and related issues. The Substance Abuse Module [71,72], recently updated for the Diagnostic and Statistical Manual of Mental Disorders-5, includes questions about onset and recency of specific symptoms, as well as the specific withdrawal symptoms and physical, social, and psychological consequences for marijuana used by participants. It also includes the quantity and frequency of both the heaviest use and use in the past 12 months, age at first and last use, age at first and most recent symptoms, age at which substance use disorder criteria were first and most recently met, and age at remission. Most participants also completed The Standard Mini-International Neuropsychiatric Interview [73], version 7.0.2, which was adapted for use in this study and used to assess the criteria for cannabis use disorder in the past 12 months. Participants also completed the Cannabis Intervention Screener, a brief screening instrument developed for use in medical and social service settings to identify individuals using cannabis at levels that may impact their health or social functioning [74].

Participants completed a cognitive assessment battery that took approximately 75 minutes, which measured premorbid intelligence; episodic, working, and prospective memory; planning; language; and processing speed. The majority of the cognitive assessments were administered using the NIH Toolbox on a digital tablet [51,52], while other more traditional tests (eg, Wechsler Test of Adult Reading, California Verbal Learning Test, Memory for Intentions Screening Test [MIST], and NIH Examiner) were administered using paper and pencil [50,54-56]. The cognitive assessment also included some more novel assessments, including a “Life Goals Inventory” and an apathy scale (to assess motivation) [39], the NIH Examiner (to assess planning) [56], and the MIST (to assess prospective memory) [55]. More details on specific items and assessments can be found in Table 1.

Biospecimens

At baseline, participants provided blood and urine samples. Planned blood tests included HIV viral load, tests of liver

function, and tests of biomarkers related to inflammation, including cytokines/chemokines, markers of microbial translocation, and intracellular RNA (Table 2). Urine testing included an 8-drug immunoassay panel at baseline and liquid chromatography-mass spectrometry analysis of cannabinoid analytes in urine as outlined in Table 2.

Table 2. Additional data collection.

Source	Timepoint			Data
	0 y	1 y	2 y	
Medical record abstraction	Yes	Yes	Yes	Height, weight, current conditions and medications, and laboratory studies (complete blood count, metabolic panel, and hepatitis C virus [HCV] antibody and viral load)
Blood	Yes	Yes[a]	Yes	HIV viral load (baseline and follow-up) and HCV antibody and viral load; markers of systemic inflammation (sCD14, sCD163, sCD27, C-reactive protein, interleukin 6, and tumor necrosis factor alpha); markers of microbial translocation (lipopolysaccharide, lipopolysaccharide binding protein, and intestinal fatty-acid binding protein); and intracellular RNA expression
Urine	Yes	Yes[a]	Yes	Δ9-tetrahydrocannabinol, cannabidiol, cannabinol, cannabigerol, 11-hydroxy-Δ9-tetrahydrocannabinol, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol, creatinine, specific gravity, and dipstick drug screen

[a]Data from 57 participants were collected at this point owing to COVID-19 modification.

Medical Records

At the time of enrollment, participants either brought a copy of their medical records from their care provider (and received an additional US $20 compensation) or completed a Health Insurance Portability and Accountability Act authorization form authorizing access to their medical records. Medical records were abstracted from paper copies mailed from clinics, directly from clinic records, or through direct download of electronic medical record data, using privacy procedures approved by all participating institutional review boards. Using the time period as close as possible to the time of baseline survey completion, research assistants abstracted participants' current medical problems (with International Classification of Diseases [ICD] 9 or ICD-10 codes), current medications, and laboratory results, including HIV viral load, CD4+ count, hepatitis B and C antibodies and viral loads, complete blood count, and metabolic panel, including liver and kidney function.

Linkage to HIV Surveillance Data

The research team established a data use agreement with the FDOH Division of HIV Surveillance, which maintains the Enhanced HIV/AIDS Reporting System (eHARS) database in collaboration with the Centers for Disease Control and Prevention. The eHARS database includes CD4+ count, viral load, and other HIV-related information from all persons with HIV in Florida, with new data uploaded over time [1]. Using a procedure we developed for previous studies [75], the study team worked with the FDOH to confidentially link the eHARS with study participant data every 6 months to allow for ongoing follow-up surveillance. Follow-up with HIV surveillance data will continue for at least 5 years after enrollment.

Follow-up Assessments

In brief, follow-up phone surveys were attempted for each participant at 3-, 6-, and 9-month time points between each annual visit until recruitment stopped in 2021. These calls sought to improve retention and to capture changes in participants' marijuana use and health status. The study originally planned to have annual in-person assessments, but due to COVID, the 1-year follow-ups were mostly completed by telephone or videoconference. These assessments included nearly all follow-up questionnaire items and marijuana use assessments including the TLFB, but did not include several of the formal neurocognitive assessments or the collection of blood or urine samples. For the 2-year follow-ups, the majority of participants completed in-person questionnaires and cognitive assessments, and also provided follow-up blood and urine samples. Participants received US $10 incentive payments for each quarterly telephone assessment and US $75 for each annual follow-up study visit.

Modifications After Study Initiation

COVID-19

As a result of the COVID-19 pandemic, study activities were halted between March and June 2020 while the research team modified procedures to allow more remote data collection. Specifically, from June to November 2020, we adapted the 1-year follow-up survey to be collected by telephone and removed the neurocognitive assessments and biospecimen collection from the 1-year follow-up. Some participants were unaffected by this change as their data were collected prior to this time. The study resumed limited recruitment of new participants in November 2020, incorporating a hybrid virtual/in-person experience where the majority of the study questionnaires were completed by phone or video call before the participant's in-person appointment for laboratory testing, neurocognitive assessments, and the remaining questionnaire items. The study also received additional funding from an NIH-supported COVID supplement to incorporate items to assess how the COVID pandemic influenced marijuana use and overall health in this population and to test for COVID antibodies. Many of these assessments were integrated into the 3-month brief phone assessments. Qualitative interviews of a subset of participants related to their experience with COVID and changes in marijuana use were also completed.

Alzheimer Supplement

The study also received additional NIH funding to incorporate some additional items to better understand the relationship of marijuana use with cognitive decline in aging. These study activities were initiated for persons aged 60 years or older

starting in October 2019. The addition of this supplement consisted of additional neurocognitive measures that could more formally distinguish mild cognitive impairment and incorporate additional blood testing, and stool sampling was performed for microbiome assessments.

Quality Assurance and Data Management

Quality Assurance

Before study initiation, the research team underwent extensive training to ensure that all assessments were provided following the standard protocol. The central project coordinating team monitored for quality assurance by reviewing recordings of a sample of interviews from each research assistant to ensure standardized study procedures, and by conducting site visits 1 to 2 times a year. At weekly team meetings, the research staff discussed and addressed any protocol deviations and monitored for adverse events.

Data Management

The MAPLE database is maintained at the University of Florida on secure servers. REDCap is used to collect and maintain participant contact registry data, enrollment/study visit logs, questionnaire data, and scores from neurologic assessments. All data collected using paper forms have been scanned and uploaded into REDCap. Paper-based assessments were scored by study interviewers and double-checked by the site study coordinator to reduce data errors.

Planned Data Analyses

The longitudinal nature of the MAPLE study will allow for both cross-sectional and longitudinal analyses. Cross-sectional analyses will assess the factors associated with different patterns of marijuana use exposure, and the relationship of patterns of marijuana use with outcomes of interest at baseline. For longitudinal analyses, we plan to examine how outcomes of interest (eg, HIV-related outcomes, neurocognitive outcomes, and HIV-related inflammatory biomarkers) vary according to changes in marijuana use (increases or decreases). Additional analyses will consider the impact of lifetime history of marijuana use, the presence of cannabis use disorder, and outcomes related to symptoms such as pain or stress.

Power Considerations

The research team originally proposed to enroll 400 persons (300 who were current marijuana users), but the COVID-19 epidemic hit at the peak of the enrollment period, and there were significant delays in enrollment for at least 6 months. Therefore, the study co-investigators modified the targeted enrollment to 333, which slightly increased the minimal effect size that could be detected with statistical significance. Specifically, with a 3:1 exposed/nonexposed ratio, 333 participants provide 80% power to detect differences in key outcomes that produce odds ratios (ORs) ranging from 2.2 to 3.6 (whereas 400 persons could have detected ORs ranging from 1.9 to 3.1). For outcomes treated as continuous variables, the current sample can detect a shift of 0.4 SDs with 80% power (whereas 400 persons could have detected a shift of 0.35 SDs).

Results

Sample Demographics

Table 3 lists the baseline characteristics of the final sample (N=333). The majority of participants in the sample were ≥50 years of age (200/333, 60.1%), male (181/333, 54.4%), cisgender men (173/329, 52.6%), non-Hispanic Black (221/333, 66.4%), and self-reported marijuana users (260/333, 78.1%). By geographic location, the largest proportion of participants were recruited in Tampa (137/333, 41.1%), followed by Miami (111/333, 33.3%) and then Gainesville (85/333, 25.5%).

Table 3. Characteristics of the people living with HIV in the Marijuana Associated Planning and Long-term Effects cohort study at baseline (N=333).

Characteristic	Value
Age (years), mean (SD)	50 (12)
Age group (years) (N=333), n (%)	
18-29	26 (7.8)
30-39	45 (13.5)
40-49	62 (18.6)
50-54	67 (20.1)
55-59	57 (17.1)
60 or older	76 (22.8)
Sex at birth (N=333), n (%)	
Male	181 (54.4)
Female	152 (45.6)
Intersex/ambiguous	0 (0.0)
Gender identity (N=329), n (%)[a]	
Cisgender man	173 (52.6)
Cisgender woman	150 (45.6)
Transgender woman	6 (1.8)
Transgender man	0 (0.0)
Nonbinary/gender nonconforming	0 (0.0)
Race/ethnicity (N=333), n (%)	
Hispanic	44 (13.2)
Not Hispanic, White	53 (15.9)
Not Hispanic, Black	221 (66.4)
Not Hispanic, other	15 (4.5)
Education (N=333), n (%)	
Less than high school	98 (29.4)
High school or equivalent	113 (33.9)
Greater than high school	122 (36.6)
Location of recruitment (N=333), n (%)	
Miami	111 (33.3)
Tampa	137 (41.2)
Gainesville	85 (25.5)
Recruitment year (N=333), n (%)	
2018	10 (3.0)
2019	252 (75.7)
2020	41 (12.3)
2021	30 (9.0)

[a]Four responses were missing as the participants declined to respond.

Marijuana Use Patterns

The final sample at baseline included 260 of 333 (78%) persons who were current marijuana users and 73 of 333 (22.3%) nonusers confirmed with urine samples (Table 4). Among the current marijuana users, the majority (188/256, 73.4%) first used marijuana before the age of 18 years, and most of the remaining (62/256, 24.2%) first used it before the age of 25 years. Moreover, the majority (208/235, 88.5%) of participants in the study used marijuana flower only. Most obtained marijuana through an illicit (street) source (194/235, 92.1%) and in small quantities (86/194, 44.3%), and only 20 of 255

(7.8%) reported obtaining marijuana from medical dispensaries in Florida. Among those who only used flower, just over half (123/208, 58.1%) used it every day, and about a third of them (69/204, 33.8%) consumed 2 or more grams of flower per use day (Table 4).

Table 4. Marijuana use patterns among people living with HIV in the Marijuana Associated Planning and Long-term Effects cohort study at baseline (N=333).

Variable	Value
Self-reported marijuana use (N=333), n (%)	
Yes	260 (78.1)
No	73 (21.9)
Tetrahydrocannabinol urine screen results (N=327), n (%)	
Positive	254 (77.7)
Negative	73 (22.3)
Had a formal medical marijuana card at enrollment (N=255), n (%)	
Yes	20 (7.8)
No	235 (92.2)
Age (years) at first use of marijuana (N=256), n (%)	
<18 years	188 (73.4)
18-25 years	62 (24.2)
≥26 years	6 (2.3)
Type of marijuana used (N=235), n (%)	
Flower only	208 (88.5)
Any nonflower (vape, etc)	27 (11.5)
Frequency of marijuana use (among flower users only) (N=208), n (%)	
Daily	123 (58.1)
Less than daily	85 (40.9)
Quantity of marijuana flower used per use/day (among flower users only) (N=204), n (%)	
<1 gram	89 (43.6)
1-2 grams	46 (22.6)
2-3 grams	33 (16.2)
3 or more grams	36 (17.6)

Ancillary Data and Follow-up

Of the 333 baseline participants, 332 (99.7%) had blood tests and 332 (99.7%) had at least one complete neurocognitive assessment. As of the end of 2021, survey data of 320 of 327 (97.9%) participants had been linked to data from the Florida HIV surveillance system, and thus, they have ongoing longitudinal data related to their engagement in care, HIV viral load, and changes in CD4 counts over time. To date, the research team has obtained baseline medical record abstractions from 215 of 333 (64.6%) participants, and additional collection of medical record information is ongoing. Of the 333 participants who completed baseline assessments, 212 (63.7%) completed the 1-year follow-up. Of these, 53 (25.0%) had blood tests and 54 (25.5%) had at least one cognitive assessment. Moreover, of the 333 participants, 178 (53.5%) completed the 2-year follow-up, of whom 149 (83.7%) had blood tests and 168 (94.4%) had at least one cognitive assessment. Overall, 224 (67.3%) participants completed at least one follow-up visit (either the 1-year or 2-year follow-up).

Discussion

To our knowledge, the MAPLE study is the largest prospective cohort study designed to improve the understanding of the health impacts of marijuana use in people living with HIV. The study population is somewhat unique for a research study related to marijuana and health, because of the broad diversity of adults across age, race/ethnicity, sex, and gender. Overall, the sample of 333 people living with HIV is reasonably representative of people living with HIV in the Southern United States (people living with HIV in the South: 352,323/474,786, 74.2% male; 245,579/475,547, 51.6% Black) [1]. The MAPLE study participants were enrolled between 2018 and 2021, and completed all in-person assessments on or before June 2022. Follow-up for nearly all participants via the statewide HIV surveillance system is ongoing, and this will provide ongoing

outcome data related to the HIV care continuum until at least 2027.

One rationale to establish a cohort study is that cross-sectional comparisons of marijuana users and nonusers have several limitations, including issues related to temporality and confounding (pre-existing differences in marijuana users and nonusers). Other cohort studies, not focused on HIV, have examined the relationship of marijuana to health outcomes [76,77]. Moreover, while some cohort studies of persons with HIV have examined the relationship of marijuana use with health outcomes, they have very limited measures of marijuana use exposure [5,31]. The MAPLE study cohort is unique in that the study will obtain detailed measures of marijuana use over time among a diverse sample of adults living with HIV. The study is also unique in its focus on longitudinal outcomes related to the HIV care continuum, biomarkers of systemic inflammation, and novel aspects of cognition, such as planning, motivation, and prospective memory.

One of the major challenges in the study was the measurement of the quantity of marijuana used by participants. Nearly all participants in the MAPLE study reported using marijuana flower that they had obtained from nondispensary sources, and thus, the specific levels of marijuana components, such as THC and CBD, were not known. The research team met regularly to standardize assessments of the quantity and frequency of marijuana flower use. However, specific levels of corresponding cannabinoids, such as THC and CBD, were hard to estimate, and the research team could not legally obtain flower samples from participants for analysis. There are plans to validate the self-reported amounts with urine biomarkers for THC and CBD metabolites.

Participant recruitment and retention were also challenging. Persons were eligible if they were either a current marijuana user or someone who never or only rarely used marijuana in the past. However, many persons who were not current users but had used marijuana regularly in the past were excluded. Recruitment from 3 different settings helped to improve overall generalizability of the sample; yet with multiple settings, staff turnover also occasionally impacted enrollment because of the complexity of the study protocol. The study recruitment was just reaching its peak when the COVID-19 epidemic occurred and halted recruitment for a period during which study procedures were modified and institutional review board protocols were revised. Study follow-up visits during the pandemic also posed challenges. Due to clinic closures and minimal in-person services, some of the key outcome measures that required blood samples or neurocognitive assessments were only obtained in a small proportion of participants at 1 year. Nevertheless, the majority of participants completed at least one full follow-up assessment 1-2 years after enrollment, and this information will support analyses related to changes over time. Missing outcome data will affect the magnitude of the effect that can be detected with statistical significance, especially for the inflammatory and cognitive outcomes, but not for the HIV-related outcomes, which are tracked via the statewide HIV surveillance system.

The planned analyses of the MAPLE study will provide new evidence to improve our understanding of the health effects of marijuana use in persons with a chronic disease such as HIV infection, and some publications using the data are starting to emerge [37,78].

Future research studies may provide even stronger evidence by collecting data before and after the initiation of marijuana use (for persons who are current nonusers), or before and after cessation of marijuana use (for current users). Randomized clinical trials of marijuana and some of its components are also possible, but research studies that involve regular (daily) use in a clinical trial continue to be extremely challenging owing to a variety of legal and regulatory issues. For now, the MAPLE study data are available for sharing with a formal Data Use Agreement, and the process to request data is described on the SHARC website [34].

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Data Availability

Data can be requested from the Marijuana Associated Planning and Long-term Effects (MAPLE) project through a publicly accessible website hosted by the Southern HIV and Alcohol Research Consortium through their concept system at https://sharc-research.org/research/data/sharc-concepts-system/.

Conflicts of Interest

CS's institution (the University of South Florida) received funds from the sponsor to conduct the research and contributed work in this study.

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Abbreviations

CBD: cannabidiol
eHARS: Enhanced HIV/AIDS Reporting System
FDOH: Florida Department of Health
ICD: International Classification of Diseases
MAPLE: Marijuana Associated Planning and Long-term Effects
MIST: Memory for Intentions Screening Test
NIH: National Institutes of Health
OR: odds ratio
REDCap: Research Electronic Data Capture
SHARC: Southern HIV Alcohol Research Consortium
THC: tetrahydrocannabinol
TLFB: Timeline Followback

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Protocol

The Pragmatic Return to Effective Dental Infection Control Through Triage and Testing (PREDICT) Study: Protocol for a Prospective Clinical Study in the National Dental Practice–Based Research Network

Janine Fredericks-Younger[1], DMD; Daniel H Fine[1], DMD; Gayathri Subramanian[1], PhD, DMD; Modupe O Coker[1], BDS, MPH, PhD; Cyril Meyerowitz[2], MS, DDS; Patricia Ragusa[2], BFA; Veerasathpurush Allareddy[3], BDS, PhD; Mary Ann McBurnie[4], PhD; Ellen Funkhouser[5], Dr PH; Maria Laura Gennaro[6], MSc, MD; Cecile A Feldman[1], MBA, DMD

[1]School of Dental Medicine, Rutgers University, Newark, NJ, United States

[2]Eastman Institute for Oral Health, University of Rochester, Rochester, NY, United States

[3]Department of Orthodontics, College of Dentistry, University of Illinois at Chicago, Chicago, IL, United States

[4]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, United States

[5]Department of Medicine, University of Alabama, Birmingham, AL, United States

[6]Public Health Research Institute, New Jersey Medical School, Rutgers University, Newark, NJ, United States

Corresponding Author:
Janine Fredericks-Younger, DMD
School of Dental Medicine
Rutgers University
110 Bergen Street
Newark, NJ, 07103
United States
Phone: 1 973 972 1679
Fax: 1 973 972 5040
Email: frederja@sdm.rutgers.edu

Abstract

Background: Dental practice has been greatly affected by the COVID-19 pandemic. As SARS-CoV-2 infection is transmitted by respiratory fluids, dental practice techniques, which include aerosol-generating procedures, can increase the risk of transmission causing heightened safety concerns for both dental health care workers (DHCWs) and patients. These concerns have resulted in the reduction in patient volume and the available workforce within dental practices across the United States. Standardized methods for COVID-19 triage and testing may lead to increased safety and perceptions of safety for DHCWs and their patients and promote willingness to provide and access oral health care services.

Objective: This study is designed to develop procedures that test the feasibility of enhanced COVID-19 triage and testing in dental offices. It will provide preliminary data to support a larger network-wide study grant application aimed at developing protocols to address safety concerns of patients and DHCWs in a peri–COVID-19 pandemic era.

Methods: The feasibility study is being conducted in 4 private dental practices, each of which has a dentist member of the National Dental Practice–Based Research Network. Participants include the DHCWs and patients of the dental practice. Study procedures include completion of COVID-19 triage, completion of COVID-19 testing (point-of-care [POC] or laboratory-based [LAB] SARS-CoV-2 viral, antigen, and antibody tests based on office designation), and administration of perception and attitude surveys for participating DCHWs and patients of the dental practice over a defined study period. The office designation and the participant's role in the practice determines which testing protocol is executed within the office. There are 4 study groups following 4 distinct protocols: (1) POC DHCWs, (2) POC patients, (3) LAB DHCWs, and (4) LAB patients.

Results: Data collection began in December of 2021 and concluded in March 2022. Study results are expected to be published in fall 2022.

Conclusions: The results of this feasibility study will help identify the viability and functionality of COVID-19 triage and testing in dental practices and inform a larger network-wide study grant application that develops protocols that address safety concerns of patients and DHCWs in a COVID-19 environment.

Trial Registration: ClinicalTrials.gov NTC05123742; https://clinicaltrials.gov/ct2/show/NCT05123742?term=NCT05123742

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KEYWORDS

COVID-19; COVID-19 triage; COVID-19 testing; SARS-CoV-2; feasibility study; National Dental Practice–Based Research Network; PBRN; dental practice; dental health; dentist; dentistry; safety; healthcare professional safety; health care; patient safety; dental healthcare staff

Introduction

Background

The COVID-19 pandemic has had a profound impact on the delivery of dental services in both the private and public sectors. The uniqueness of dental practice can increase the risk of transmission of SARS-CoV-2 and has heightened safety concerns for both dental health care workers (DHCWs) and patients, resulting in a reduction in available workforce and causing patients to delay essential and preventative care [1,2]. Moreover, as the COVID-19 pandemic evolved and transmission became more widespread, practice guidelines, and recommendations were ever changing, fueling a heightened level of uncertainty and caution [3]. The lack of standardized mitigation strategies, coupled with varying degrees of implementation within dental offices, further compromised the willingness of dental professionals to return to their dental practices and patients to seek care [4,5]. Establishing standardized COVID-19 triage and testing strategies in dental practices may ultimately increase safety and promote the feeling of safety for DHCWs and their patients.

Uniqueness of Dental Practice

At the onset of the COVID-19 pandemic, the spread of this ubiquitous virus was first thought to be through droplets, but soon it became clear that the virus could be spread by aerosols, raising alarm for the dental community [6,7]. As many dental procedures generate significant aerosols through the use of high-speed handpieces and water coolant, the risk of aerosolized SARS-CoV-2 transmission significantly increases [8,9]. While it is certain that clinic dental personnel will be exposed to significant aerosol sprays derived from patients' oral cavities, the extent to which dentally generated aerosols linger within the clinical space has not been clearly tested, and questions of duration of exposure and transmission risk remain [10]. As we learn more about COVID-19 and viral transmission, we understand that infection and spread of the virus is due to the viral load (or dose) and the time of contact [11,12]. Additionally, unlike many procedures in medicine, dental-patient contact requires close proximity between the patient and dental professionals [13]. A dental procedure can often take as long as 1 hour, and prolonged close dentist-patient contact is inevitable. As such, the likelihood of viral transmission is elevated in the dental setting and requires enhanced mitigation efforts in the treatment spaces to minimize disease transmission [6,14,15].

Beyond clinical treatment rooms, auxiliary space, including waiting rooms, bathrooms, and passageways are additional areas within offices that can be safety concerns [15]. The airflow in confined office spaces, where patients would wait for 30 minutes or more, can be hazardous if an asymptomatic but COVID-19–infected individuals are in close proximity to a susceptible patient [16]. Patients in a dental office can be at risk for infection that can have varied presentation and severity and may be life threatening especially in patients with pre-existing conditions [17]. Amid the pandemic, some offices chose to restrict patient access and eliminate waiting rooms altogether, while other offices staggered appointments and enhanced physical distancing measures. Despite the various methods employed, adequate ventilation and disinfection remain areas of concern [18].

Solutions

One way of providing the security that dental offices are safe for both the dental professional and patient is by taking measures to reduce the possibility of anyone who harbors SARS-CoV-2 from entering the office, thereby limiting the risk of spread within the dental office. Mitigation strategies vary from office to office and often include identifying infected individuals through screening, most often through symptom questionnaires. As symptoms appear 2-14 days after infection (depending on a variety of factors including the variant), a triage questionnaire, based on symptomology, maybe only partially effective. Patient and DHCW triage are effective in identifying and isolating symptomatic individuals, though limitations exist by virtue of varying degrees and range of symptomatology [19]. The knowledge that asymptomatic and presymptomatic individuals may still transmit the virus suggests that solely triaging for symptoms may be inadequate to eliminate virus-infected patients from their offices [20]. More advanced diagnostic tools are necessary to identify infected individuals from initial onset of infection through their infectious period. Enhanced COVID-19 triage and testing could augment screenings and provide more reliable data to more accurately identify infected individuals and ultimately mitigate transmission amongst office personnel and patients.

Many aspects of testing have been highly debated in national forums, but little is known about the perceived value of COVID-19 testing in a dental practice and the willingness of

DHCWs to implement such testing in their offices [21]. Furthermore, several challenges exist to routine and comprehensive testing in a dental office setting, including cost, ease of use, and turnaround time. Maximum practical utility would perhaps be derived from a simple, rapid, accurate, inexpensive point-of-care (POC) test that is not technically demanding, but such a test has not yet been validated.

Importance of the Study

The effective use of testing and other modifications in dental practice could reduce the actual and perceived risk of COVID-19 transmission in a dental practice, facilitating dental health care providers' and patients' comfort with providing or seeking essential dental services. This protocol is designed to develop pragmatic procedures that address this serious problem and test the feasibility of COVID-19 triage and testing procedures in an active dental practice, utilizing the community of private practice researchers within National Dental Practice–Based Research Network (PBRN). The feasibility of implementing COVID-19–related testing and enhanced triage procedures in the dental setting will provide preliminary data to inform a larger network-wide study grant application that develops protocols that address safety concerns of patients and DHCWs in a COVID-19 environment.

The Pragmatic Return to Effective Dental Infection Control through Triage and Testing (PREDICT) PBRN Feasibility Study seeks to assess the following aims: (1) the willingness of DHCW and practice patients to participate in the research protocol; (2) the willingness and ability of practice patients and DHCWs to execute and follow through with triage, testing, and survey administration procedures; and (3) the ease of use of the Research Electronic Data Capture (REDCap) instruments, including interface access, survey design, and completion requirements for both the DHCW and practice patient end users. The PREDICT PBRN feasibility study will use qualitative and quantitative methods to collect outcomes measures and conduct data analysis. The ultimate goal of this research is to conduct a clinical study that assesses the impact of COVID-19 screening on dental practice including perceptions of safety and identifies the most efficient, acceptable, and effective workflow.

Methods

Ethics Approval

The study received institutional review board (IRB) approval through the Network single IRB (University of Alabama, IRB-300007026) and local context approval from Rutgers University IRB (Pro2021000968). The study was registered on ClinicalTrials.gov (NCT05123742).

Study Design

This observational study is designed to assess the feasibility of implementing COVID-19–related testing and triage procedures in dental practices and focuses on increasing safety and perceptions of safety for the DHCWs and their patients. This study is being conducted in 4 dental practices of northeast region members of the PBRN (hereafter referred to as "the Network") and participants include the DHCWs and patients of the practice [22]. Study procedures include completion of COVID-19 triage, completion of COVID-19–related testing (SARS-CoV-2 viral, antigen or antibody tests based on group designation), and administration of risk perception and attitude surveys for participating DCHWs and patients of the dental practice over a defined study period.

The office designation determines which testing protocol is executed within the office. Furthermore, a participant's role in the practice further delineates the protocol. As such, there are 4 study groups following 4 distinct protocols reflecting POC and laboratory-based (LAB) testing procedures: (1) POC DHCWs, (2) POC patients, (3) LAB DHCWs, and (4) LAB patients (Table 1).

Table 1. Protocol by study group.

Study group	Protocol	COVID-19 tests (method)	Participants, n
Point-of-care (POC)			
DHCW[a] in POC office	POC DHCW	Antigen (nasal swab) + Antibody (capillary blood)	5-10 DHCWs
Patients in POC office	POC Patient	Antigen (nasal swab)	10 patients
Laboratory-based (LAB)			
DHCW in LAB office	LAB DHCW	Viral (saliva and tongue)+Antibody (capillary blood)	5-10 DHCWs
Patients in LAB office	LAB patient	Viral (saliva)	10 patients

[a]DHWC: dental health care worker.

Office Selection and Designation

This study is being conducted at 4 private practice dental offices, each of which employs at least one Network member dentist. Dentist members of the Network are first solicited for participation in this study. The dental office is enlisted if the Network dentist member and 4-9 additional office DHCWs of the practice are willing to participate and the Network member is willing to fulfil the responsibilities of the protocol, including enrolling and completing the assessment of 10 patients. The Network dentist member of the practice is responsible for indicating preference in office designation (POC or LAB) and the execution of the research study within the dental practice.

Participants

Overview

The study population is drawn from Network dentist members, their coworkers, and patients seen in the dental office in which they work. The DHCW study population comprises dentists, hygienists, assistants, and office staff who work in an office with a Network member dentist. The patient study population is drawn from the dental practice of the Network member dentist.

Inclusion Criteria

A DHCW participant must meet the following criteria to be eligible to participate in the study: be aged 18 years or older, a Network member dentist, or work in a dental office with a Network member dentist who accepted study participation; understand the informed consent; provide a signed and dated informed consent form; have the capacity to understand all instructions for data collection instruments and be willing and able to comply with all study procedures, including COVID-19 testing; and be available for the duration of the study.

A patient participant must meet the following criteria to be eligible to participate in the study: be aged 18 years or older; be able to understand the informed consent; have access to a computer or electronic device with internet access; have the ability to complete consent and questionnaire on a computer or electronic tablet device; provide a signed and dated informed consent form; and have the capacity to understand all instructions for data collection instruments and be willing and able to comply with all study procedures, including having a COVID-19 test performed.

Exclusion Criteria

Participants are excluded if they participated in an earlier PREDICT feasibility study conducted at Rutgers University.

Recruitment

Informed consent is obtained for each study participant.

DHCW Participants

Within 4 weeks prior to study initiation, DHCWs in the participating office are contacted to discuss the study and gauge participation interest. DHCWs who indicate interest are sent an email link for electronic consent on REDCap. The consent clearly outlines participant expectations and offers the opportunity for potential participants to contact the Network Node Coordinator for more information. DHCWs who elect to participate affirm their willingness to participate by electronically signing the consent form.

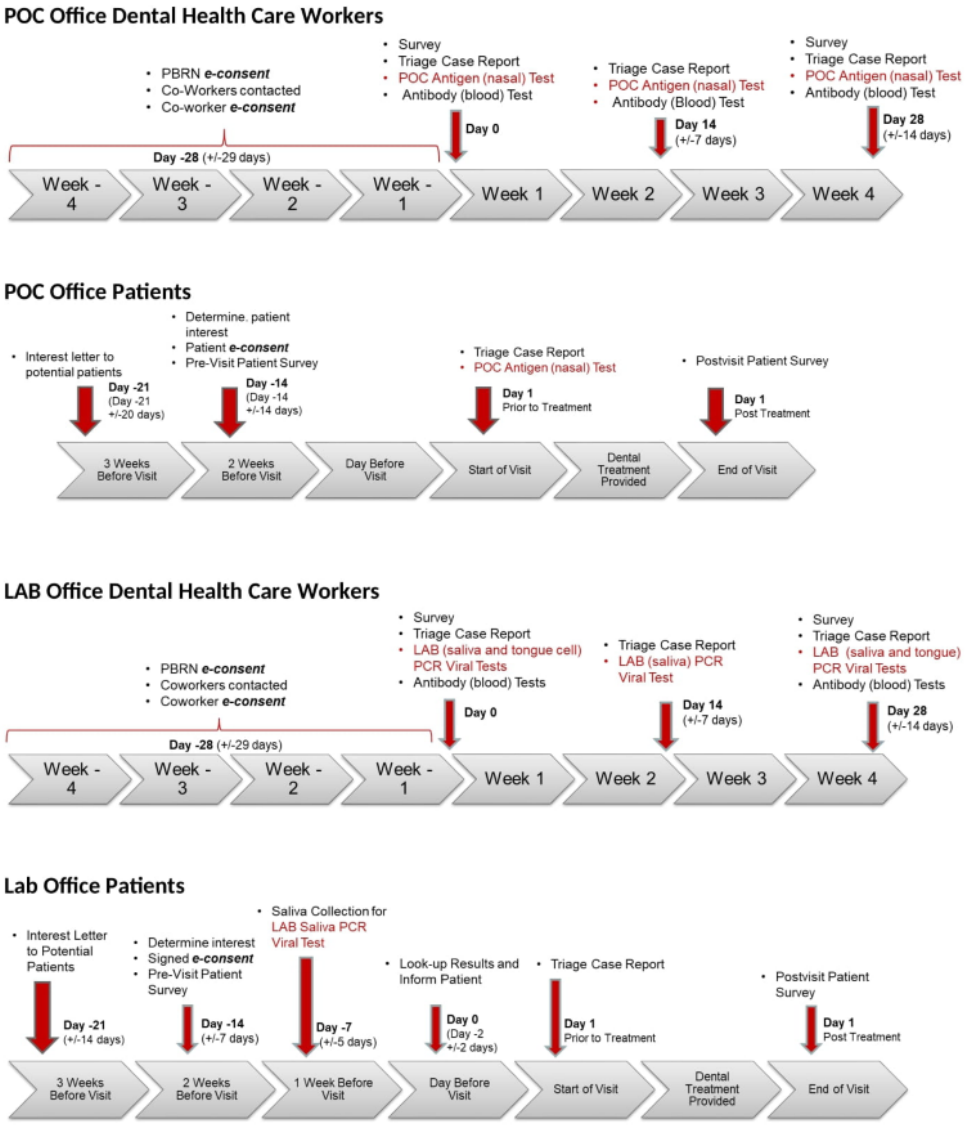
Patient Participants

Patients who have an upcoming appointment are solicited for participation. They receive an informational letter and follow-up phone call to discuss the study and determine their interest. Patients who indicate interest are sent an email link for electronic consent on REDCap. Patients who elect to participate affirm their willingness to participate by clicking the “I agree to take part in this study” button at the end of the consent form. Participation acceptance automatically triggers the Patient Pre-Visit Survey to be sent electronically to the enrolled patient.

Study Schedule

DHCWs actively engage in study procedures 3 times over a 1-month period, whereas patient participants engage in study procedures over a 2-week period prior to and at the end of their scheduled dental appointment. The 4 distinct protocols based on office designation and role in the dental practice are illustrated in Figure 1.

Figure 1. Study schedule for DHCW and patient participants in POC and LAB offices. DHCW: dental health care worker; LAB: laboratory; PBRN: National Dental Practice–Based Research Network; PCR: polymerase chain reaction; POC: point of care.



Triage

In-office COVID-19 triage screening includes a series of questions related to symptoms commonly associated with SARS-CoV-2 infection (fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle and body aches, headache, loss of taste, loss of smell, sore throat, congestion or runny nose, and nausea or vomiting), a temperature check, and an oxygen saturation measurement using a pulse oximeter. Results are documented on the triage case report. Patient participants undergo triage once the day of their appointment, whereas DHCW participants undergo triage in 3 intervals over a 1-month period.

Testing

Overview

All testing materials are labeled and packaged in distinct participant kits, with explicit testing instructions and return shipping guidelines. Test kits for sample collection are shipped directly to the residence of patients participating in the LAB protocol. All other test kits, including those packaged for DHCWs in both the LAB and POC offices, as well as for patients in the POC offices, are shipped en masse to the dental office.

SARS-CoV-2 POC Tests

The Abbott BinaxNOWTM Covid-19 antigen card used in this study is specific for SARS-CoV-2 nucleocapsid protein antigen and used to determine SAR-CoV-2 infection. As part of both the DHCW and Patient POC office study protocols, participants will undergo a SARS-CoV-2 POC test in the dental office. A nasal swab is swept inside the participant's nose (not beyond the nares) to collect the specimen for the POC test. The office staff processes the specimen and reads the results within 15 minutes.

PCR Viral Tests

The polymerase chain reaction (PCR) test is a molecular test that analyzes specimens from a subject's nose or mouth to detect the RNA of SARS-CoV-2—the virus that causes COVID-19. This test is used as an indicator of COVID-19 infection. Patient

participants following the LAB protocol are asked to provide a saliva sample using the saliva collection kit and mail it to the laboratory for processing 1 week prior to the scheduled dental visit. DHCW participants are required to provide a similar saliva sample 3 times during their month-long participation. In addition, DHCWs are asked to provide tongue specimens, collected using a cytology brush and collection medium, twice during their participation. Both saliva and tongue samples are mailed to Rutgers University laboratories for processing.

Specifically, RNA extraction will be performed and the total RNA concentrations for saliva, tongue, and nasal samples will be determined using a Nanodrop One machine (Thermo Scientific).

Enzyme-Linked Immunosorbent Assay Antibody Tests

This antibody test utilizes peripheral blood to detect immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against the SARS-CoV-2 antigen, which indicates a history of SARS-CoV-2 infection. All DHCWs in either the POC or LAB protocol undergo an enzyme-linked immunosorbent assay (ELISA) antibody test at 2 intervals during the study. Following finger puncture with a lancet device, peripheral blood is collected utilizing a volumetric absorptive microsampler (Mitra Collection Kit, Neoteryx). The microsamplers are packaged by the DHCW following the manufacturer's instructions and placed in the practice collection box for shipment to the testing laboratory. Prior to ELISA, fluid is eluted from the microsamplers. Detection of IgM and IgG antibodies directed against the receptor binding domain of the SARS-CoV-2 Spike protein is performed in accordance with published ELISA protocols [23].

Data Management

Study data and participant consent were collected and managed using the REDCap software [24]. REDCap is a secure, web-based software platform designed to support data capture for research studies. All data elements are being entered directly into the REDCap system, including subject survey responses, triage case reports, and testing orders and results.

Study Surveys

DHCW participants complete 3 surveys over a 1-month period: DHCW Start-of-Study Survey, DHCW End-of-Study Survey, and the Participation Survey. The DHCW Start-of-Study and DHCW End-of-Study surveys include the validated 6-question Safety Culture Evaluation Survey aimed at assessing workplace safety. Specifically, the DHCW Start-of-Study Survey administered on day 1 includes questions related to demographics, personal protective equipment (PPE) used in the office, work practice controls used in the office, importance of triage and testing, importance of PPE measures, perceptions of safety and comfort in the workplace, safety culture in the office, SARS-CoV-2 testing preferences, dentists' role in SARS-CoV-2 testing, and willingness to test in the dental office. The DHCW End-of -Study Survey administered on day 28 includes questions related to the importance of triage and testing, importance of PPE measures, perceptions of safety and comfort in the workplace, safety culture in the office, SARS-CoV-2 testing preferences, dentists' role in SARS-CoV-2 testing, willingness to test in the office, and vaccinations.

Patient participants are asked to complete 3 surveys: the Patient Pre-Visit Survey, Patient End-of-Visit Survey, and Participation Survey. Launched automatically after the completed consent approximately 2 weeks prior to their dental visit, patient participants are asked to complete the Pre-Visit Survey, which explores COVID-19 exposure and vaccination history, perceptions of safety and comfort, reasons for delaying dental care, concerns about returning to dental care, safety precautions valued, importance of triage and testing, and demographics. Following their dental treatment, patient participants will complete 2 electronic surveys. The Patient End-of-Visit Survey explores perceptions with testing preferences, PPE observed, environmental controls observed, concerns about returning to dental care, safety precautions valued, importance of triage and testing, likelihood of reporting symptoms, dentists' role in COVID-19 testing, and vaccinations.

All participants enrolled in the feasibility study are asked to complete a participation survey, which will solicit feedback related to study participation including survey and testing logistics, preferences, and testing ease.

Statistical Analysis

Sample Size Considerations

This is a feasibility study to assess viability of conducting study procedures within dental practices and refine study logistics for a larger multisite clinical trial. No sample size calculations were performed, but the results will be used for sample size calculations for future studies. As the Network attracts both solo practitioners and practitioners in multi-dentist offices, pilot sizes were set to 5-10 DHCWs. This range allows for participation of smaller offices as well as those with greater numbers of dentists and auxiliary staff. Ten patient participants were enrolled to adequately test office workflows in terms of both time and space availability within a functioning practice.

Analyses for Aim 1: Willingness to Participate

Willingness to participate is an important determinant in deciding whether dental offices, DHCWs, and patients would be willing to participate in a large-scale study. Analysis of the following outcomes measures will be conducted: (1) proportion of DHCWs who agree to participate among those who were approached for participation, (2) proportion of patients who agree to participate among those patients who were approached for participation, and (3) percentage of individuals who indicate the opportunity to ask questions during the consent process. These first 2 measures will be assessed at the time of consent, while measure number 3 data is derived from the Patient Participation Survey.

Analyses for Aim 2: Willingness or Ability to Follow Through With Triage, Testing, and Survey Administration Procedures

Determination of the willingness and ability to follow through with triage, testing and survey administration procedures are important for refining the survey procedures. Analysis of the following outcome measures for both patient and DHCW

participants will be conducted: (1) percentage of individuals who complete the study, (2) percentage of individuals who complete the surveys, (3) percentage of activities occurring within each defined window, and (4) percentage of individuals who feel complying with testing (saliva, PCR, POC, and ELISA antibody tests) procedures was easy. Compliance will include specimen collection, specimen preparation for shipping, specimen storage, timeliness of results, and reporting of results.

Analyses for Aim 3: Ease of Use With the REDCap Survey Instruments

Determination of the ease of use and completeness of the REDCap instruments should enable refinement of the system. We will conduct analysis for the following outcomes measures for both patient and DHCW participants: (1) percentage of individuals who feel surveys are easy to complete owing to the administration method, (2) percentage of individuals who feel that the survey questions are understandable, and (3) percentage of individuals who complete each of the following surveys: DHCW Start-of-Study Survey, DHCW End-of-Study Survey, Pre-Visit Patient Survey, End-of-Visit Patient Survey, and the Triage Case Report.

Results

The PREDICT study was funded in September 2020. Data collection began in December 2021 and concluded in March 2022. In total, 30 DHCW and 45 patient participants consented. Following data analysis, study results are expected to be published in fall 2022. The results from this study will also provide feasibility data to support a larger network-wide study grant application aimed at developing protocols to address safety concerns of patients and DHCWs in a peri–COVID-19 pandemic era. This project will also inform and shape responses to future pandemics.

Discussion

Expected Findings

The PREDICT study sought to develop and assess procedures for improved COVID-19 triage and testing in dental practices to increase safety and perceptions of safety of DHCWs and their patients. As testing is an effective mitigation strategy that has become commonplace in the COVID-19 era, it is anticipated that both DHCWs and patients would not only agree to participate, but also effectively carry out testing and triage procedures. With cell phones and other electronic devices used as widely accepted communication tools, it is expected that participants will engage in electronic surveys through the REDCap interface with ease.

Study Strengths and Limitations

This novel study design engages both the office personnel and patients through targeted testing and triage to synergistically enhance feelings of safety and increase willingness to return as employees and as patients. The study team recognized that in order to alter the overall perception of safety in a meaningful way, one could not focus on a single group but rather on the office collective. Typical dental practices employ a small number of office staff, who perform a myriad of functions, from delivery of care to front desk and patient billing. All roles are essential for the success of the practice. Absences related to COVID-19 could significantly hamper operations and limit patient flow, ultimately leading to decreased production, revenue, and care delivery.

As time away from chair-side dentistry can directly affect revenue, researchers considered the cost-benefit ratio of triage and testing within an office. In designing the protocol, the study team was cognizant of dental office dynamics and workflow. With rapid patient turn-over and limited physical space, triage and testing needed to be efficient and cost-effective. Efforts to maximize protocol efficiency are the focus of the unique study design. Several initial study procedures for patient participants are conducted electronically outside the dental office prior to the patient dental visit, minimizing extended in-office time. Through the REDCap interface, patients' consent is obtained at home with electronic signatures captured via REDCap. Participation acceptance triggers the automatic launch of the electronic Patient Pre-visit Survey, allowing them to complete the survey unimpeded, within the comfort of their own home. Similarly, saliva specimen collection for LAB patient testing occurs at home, significantly reducing the burden on office staff. It became clear that a feasibility study was necessary help identify viability and functionality of testing, as well as the preferred method of testing in a dynamic dental practice. In a larger-scale trial, there is a more comprehensive cost-benefit analysis planned to look at specific time requirements for testing related to diversion of staff support, productivity, and cost allocation to patients.

Limitations to protocol implementation were identified and primarily revolved around Network member dentist training. The complexity of the study warranted several training sessions, and practitioner availability for real-time training was limited. While training for this feasibility study was conducted contemporaneously via a digital platform, it was apparent that this method would be inefficient in a larger-scale trial. A concerted effort to ensure training efficiency would be required for a larger, nationwide clinical trial implemented in dental practices across multiple states and time zones. The use of prerecorded training modules would help alleviate the time burden placed on practitioners, enhance the understanding of the protocol, and eliminate questions through on-demand viewing capabilities.

Utilizing a multilocation practice as a designated office (POC or LAB) added a layer of complexity to the execution of this study protocol related to subject specimen kits. During this feasibility study, study kits were sent to one office location. In our larger multisite practice, these kits required to be transferred from one office to another within a practice. Similarly, after specimen collection, completed study kits needed to be collated prior to shipping them back to the laboratory for processing. In a larger-scale trial, study kits for a multi-office practice should be sent separately, reducing the time and effort burden on office staff.

Conclusions

The PREDICT PBRN feasibility study will assess the viability and workability of COVID-19 triage and testing within dental practices. Our results will influence protocols proposed for a larger network-wide study grant application that addresses safety concerns of patients and DHCWs in a COVID-19 environment. Establishing enhanced triage and testing protocols within dental offices not only has the potential to not only increase willingness of patients and staff to return to work during the COVID-19 pandemic but also may have utility in the event of another disease outbreak.

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Data Availability

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

Authors' Contributions

JFY and CAF contributed to the conception, design, drafting, and critical revision of the manuscript. DHF, GS, MOC, CM, PR, VA, MAM, EF, and MLG contributed to the conception, design, and critical revision of the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

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Abbreviations

DHCW: dental health care worker
ELISA: enzyme-linked immunosorbent assay
IgG: immunoglobulin G
IgM: immunoglobulin M
IRB: institutional review board
LAB: laboratory-based
PBRN: National Dental Practice–Based Research Network
PCR: polymerase chain reaction
POC: point of care
PPE: personal protective equipment
PREDICT: Pragmatic Return to Effective Dental Infection Control through Triage and Testing
REDCap: Research Electronic Data Capture

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Protocol

Description of the Method for Evaluating Digital Endpoints in Alzheimer Disease Study: Protocol for an Exploratory, Cross-sectional Study

Jelena Curcic[1], PhD; Vanessa Vallejo[1], PhD; Jennifer Sorinas[1], PhD; Oleksandr Sverdlov[2], PhD; Jens Praestgaard[3], PhD; Mateusz Piksa[1], MSc; Mark Deurinck[1], DVM, Dr med vet; Gul Erdemli[3], MD, PhD; Maximilian Bügler[4], PhD; Ioannis Tarnanas[4,5], PhD; Nick Taptiklis[6], PhD; Francesca Cormack[6], PhD; Rebekka Anker[7], MSc; Fabien Massé[7], PhD; William Souillard-Mandar[8,9], PhD; Nathan Intrator[10], PhD; Lior Molcho[10], PhD; Erica Madero[11], PhD; Nicholas Bott[12], PhD; Mieko Chambers[13], PhD; Josef Tamory[13], BS, COA, OSC; Matias Shulz[14], PhD; Gerardo Fernandez[14], PhD; William Simpson[15], PhD; Jessica Robin[15], PhD; Jón G Snædal[16], MD; Jang-Ho Cha[3], MD, PhD; Kristin Hannesdottir[3], PhD

[1]Novartis Institutes for Biomedical Research, Basel, Switzerland
[2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States
[3]Novartis Institutes for Biomedical Research, Cambridge, MA, United States
[4]Altoida Inc, Washington, DC, United States
[5]Global Brain Health Institute, Trinity College, Dublin, Ireland
[6]Cambridge Cognition Ltd, Cambridge, United Kingdom
[7]MindMaze SA, Lausanne, Switzerland
[8]Linus Health, Boston, MA, United States
[9]Massachusetts Institute of Technology, Cambridge, MA, United States
[10]Neurosteer Inc, New York, NY, United States
[11]Neurotrack Technologies Inc, Redwood City, CA, United States
[12]Department of Medicine, School of Medicine, Stanford University, Stanford, CA, United States
[13]Neurovision Imaging Inc, Sacramento, CA, United States
[14]ViewMind Inc, New York, NY, United States
[15]Winterlight Labs, Toronto, ON, Canada
[16]Memory Clinic, Landspitali, Reykjavik, Iceland

Corresponding Author:
Jelena Curcic, PhD
Novartis Institutes for Biomedical Research
Fabrikstrasse 2 Novartis Campus
Basel, 4056
Switzerland
Phone: 41 795003648
Email: jelena.curcic@novartis.com

Abstract

Background: More sensitive and less burdensome efficacy end points are urgently needed to improve the effectiveness of clinical drug development for Alzheimer disease (AD). Although conventional end points lack sensitivity, digital technologies hold promise for amplifying the detection of treatment signals and capturing cognitive anomalies at earlier disease stages. Using digital technologies and combining several test modalities allow for the collection of richer information about cognitive and functional status, which is not ascertainable via conventional paper-and-pencil tests.

Objective: This study aimed to assess the psychometric properties, operational feasibility, and patient acceptance of 10 promising technologies that are to be used as efficacy end points to measure cognition in future clinical drug trials.

Methods: The Method for Evaluating Digital Endpoints in Alzheimer Disease study is an exploratory, cross-sectional, noninterventional study that will evaluate 10 digital technologies' ability to accurately classify participants into 4 cohorts according

to the severity of cognitive impairment and dementia. Moreover, this study will assess the psychometric properties of each of the tested digital technologies, including the acceptable range to assess ceiling and floor effects, concurrent validity to correlate digital outcome measures to traditional paper-and-pencil tests in AD, reliability to compare test and retest, and responsiveness to evaluate the sensitivity to change in a mild cognitive challenge model. This study included 50 eligible male and female participants (aged between 60 and 80 years), of whom 13 (26%) were amyloid-negative, cognitively healthy participants (controls); 12 (24%) were amyloid-positive, cognitively healthy participants (presymptomatic); 13 (26%) had mild cognitive impairment (predementia); and 12 (24%) had mild AD (mild dementia). This study involved 4 in-clinic visits. During the initial visit, all participants completed all conventional paper-and-pencil assessments. During the following 3 visits, the participants underwent a series of novel digital assessments.

Results: Participant recruitment and data collection began in June 2020 and continued until June 2021. Hence, the data collection occurred during the COVID-19 pandemic (SARS-CoV-2 virus pandemic). Data were successfully collected from all digital technologies to evaluate statistical and operational performance and patient acceptance. This paper reports the baseline demographics and characteristics of the population studied as well as the study's progress during the pandemic.

Conclusions: This study was designed to generate feasibility insights and validation data to help advance novel digital technologies in clinical drug development. The learnings from this study will help guide future methods for assessing novel digital technologies and inform clinical drug trials in early AD, aiming to enhance clinical end point strategies with digital technologies.

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KEYWORDS

digital endpoints; cognition; Alzheimer disease; brain amyloid; methodology study; clinical trial design; mobile phone

Introduction

Background

Alzheimer disease (AD) is a progressive and terminal illness and the most common form of dementia, with a rapidly growing societal and economic burden [1]. Patients with AD present with gradual and wide-ranging cognitive and functional impairments, as well as loss of motivation, social withdrawal, and other neuropsychiatric challenges [2,3]. The standard of care for AD is based on providing patients with symptomatic relief; however, these therapies are unsatisfactory and provide limited efficacy [4]. In recent years, drug development has largely focused on disease-modifying treatments to stop, slow, or prevent disease progression. However, because of the high clinical trial failure rate, AD remains the illness with the highest unmet medical need in neuroscience [5]. This high failure rate might be because of the multifactorial etiology of AD and the large diversity of the clinical manifestations in each patient. However, these failures may also be partially because of weak efficacy end points that cannot reliably and accurately demonstrate drug treatment effects across heterogeneous patient populations.

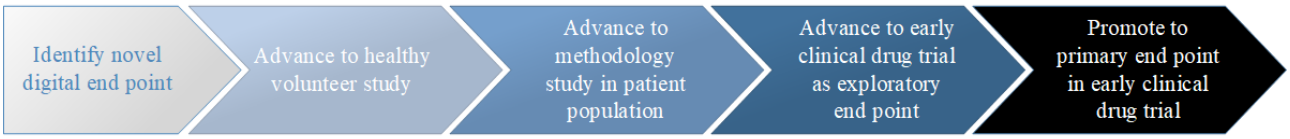
Currently, the standard method for assessing cognition in clinical drug trials is modeled on traditional neuropsychological paper-and-pencil assessments that tend not to be optimal for frequent monitoring of drug treatment effects, primarily because of practice effects, high variability and burden, single–time point administrations, and poor psychometric properties such as ceiling and floor effects. Ceiling and floor effects pose critical risks to the accurate monitoring of immediate symptomatic drug treatment enhancements of cognition and longitudinal disease-modifying effects on disease progression. Moreover, the information obtained from traditional clinical trial end points is often reduced to a single total score, thereby potentially losing important clinical insights into drug treatment effects. In reality, as with most cognitive functions required in daily life, solving these tests involves the orchestration of several cognitive domains operating together. In clinical trial settings, single–time point paper-and-pencil tests often provide limited and inaccurate information about central nervous system functioning and have poor sensitivity to drug treatment effects. For someone who is not a trained expert, the paper-and-pencil tests can be burdensome and complex to administer, often resulting in rater errors, high variability, and small drug treatment effect sizes. Poor sensitivity to changes and limitations of conventional end points often leads to large, lengthy, and costly trials. Finally, many of these paper-and-pencil tests are quite subjective and, as a result, may not reflect the reality of the symptoms, for example, because of expectations of drug treatment effects and anosognosia [6]. Taken together, poor efficacy end points pose serious risks to neuroscience drug development.

There is an urgent need for improved clinical trial efficacy end points, and new assessments using novel digital technologies are rapidly emerging. For instance, using sensor technology to collect physiological data during cognitive assessments allows for a richer evaluation of central nervous system functioning that cannot be obtained by means of conventional paper-and-pencil administration only. The combination of several sensors measuring motion, voice, and brain activity within different test modalities allows for a high resolution of patient symptoms. Gamification via augmented reality (AR) technology is a novel and promising approach that could offer ecological validity to cognitive and functional assessments [7]. Moreover, digital technologies allow for the implementation of an adaptive level of difficulty to avoid ceiling and floor effects [8], which are important psychometric limitations of many conventional paper-and-pencil tests. Although novel sensor technologies hold promise for improved clinical trials in AD, it remains unclear how best to evaluate these technologies or

how to use them to derive efficacy end points that can more effectively detect drug treatment effects. With regard to the development of improved assessment tools, the technology, operational feasibility, and usability need to be carefully considered to suit the perceptual and interaction needs of clinical trial participants with cognitive impairments.

Hannesdottir et al [9] previously proposed a road map to advance novel digital end points within the early drug development process (Figure 1).

Figure 1. A road map to advance digital end points within the drug development process.



The initial step once a promising digital end point has been identified involves technical verification in healthy controls to determine whether the digital end point is ready for testing in the target patient population. The next step of the road map involves running a digital end point methodology study to provide technology and operational feasibility, psychometric properties, and patient acceptance in the target population. Digital technologies that successfully meet predefined success criteria based on a previously developed scoring system [9] can then be advanced to the next step, which involves studying the digital technology in a phase 2 clinical drug trial as an exploratory end point. In the phase 2 trial, the sensitivity of the digital end point to drug treatment effects can be compared head to head with conventional paper-and-pencil end points. If the digital end point is considered clinically meaningful and produces less variability and greater drug signal detection than the conventional end points, the digital end point may eventually advance to the final step of the road map and be used as a primary end point to run smaller and shorter phase 2 trials in the same target population.

Objectives

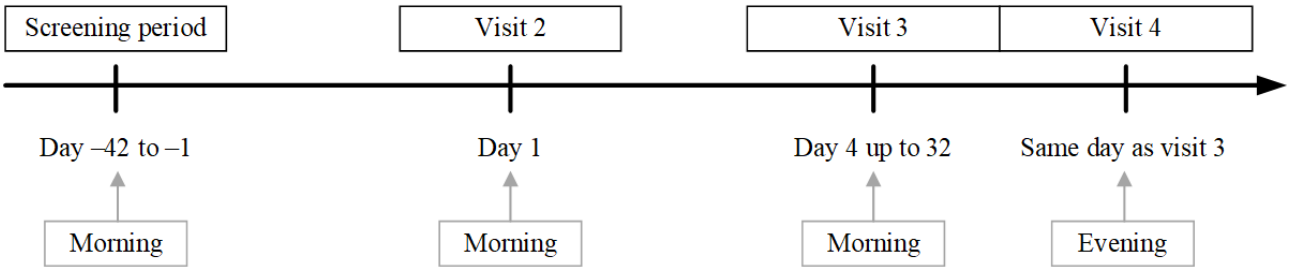
In light of the urgent need for improved efficacy end points for clinical drug trials and the rapid surge of promising digital technologies, the aim of the Method for Evaluating Digital Endpoints in Alzheimer Disease (MEDIA) study is to assess the psychometric properties, operational feasibility, and patient acceptance of 10 promising technologies for measuring cognition to be used as efficacy end points in future clinical drug trials. Each of the novel digital technologies will be compared against established paper-and-pencil end points in their ability to accurately classify participants into 4 cohorts of cognitive impairment and dementia severity. This paper describes the MEDIA study protocol and participant demographics, the role this study plays in the drug development process, and some of the limitations of the study.

Methods

Study Design

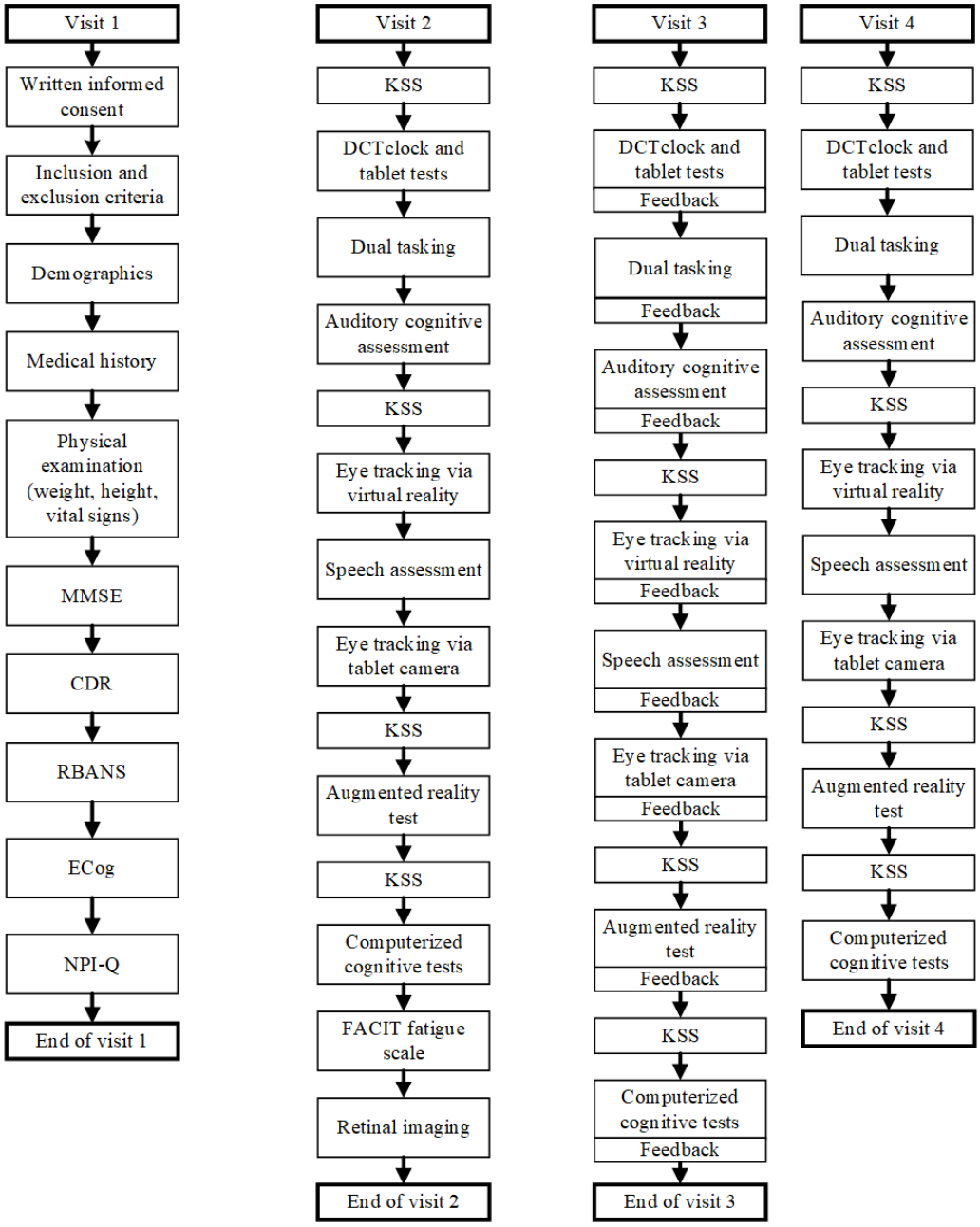
This is a cross-sectional, noninterventional study conducted at the Memory Clinic at Landspítali University Hospital in Iceland. The total study duration (including a screening period of up to 42 days) was a maximum of 74 days, allowing for scheduling flexibility but avoiding the effects of disease progression [10]. Assessments were completed at visit 1 (ie, screening visit, occurring 1-42 days before day 1), visit 2 (day 1), visit 3 (day 4 to day 32, morning), and visit 4 (evening of the same day as visit 3; Figure 2).

Figure 2. Method for Evaluating Digital Endpoints in Alzheimer Disease study design.



At visits 1, 2, and 3, assessments were conducted in the morning to avoid the effect of circadian fluctuation in AD [11]. At visit 4, a benign cognitive challenge model was implemented to assess the sensitivity of digital end points to change. Fatigue and sleep deprivation have been shown to affect performance across a wide range of cognitive domains [12,13]. To produce cognitive fatigue, all assessments during visit 4 were conducted in the evening. No napping was allowed before the evening assessments, and no caffeine or other stimulants were allowed after noon. The order of assessments at each visit was predefined, as illustrated in Figure 3.

Figure 3. Order of assessments at each visit of the MEDIA study. CDR: Clinical Dementia Rating scale; ECog: Everyday Cognition scale; FACIT: Functional Assessment of Chronic Illness Therapy; KSS: Karolinska Sleepiness Scale; MEDIA: Method for Evaluating Digital Endpoints in Alzheimer Disease; MMSE: Mini-Mental State Examination; NPI-Q: Neuropsychiatric Inventory–Questionnaire; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.



Participants

The study was conducted at an academic Memory Clinic in the Geriatric Department of Landspítali University Hospital in Reykjavik, Iceland. Participants were grouped into 4 cohorts derived from 2 sources. The 2 cohorts comprised cognitively healthy amyloid-negative (controls; cohort 1) and cognitively healthy amyloid-positive (presymptomatic; cohort 2) male and female participants. These participants had been investigated using either cerebrospinal fluid (CSF) analysis or amyloid positron emission tomography (PET) up to 2 years earlier. The other 2 cohorts comprised male and female individuals who had been referred to the Memory Clinic by their primary health care physician and had either been diagnosed with mild cognitive impairment (MCI; predementia; cohort 3) or mild AD (mild dementia; cohort 4) at the Memory Clinic. The participants were aged between 60 and 80 years. The clinical diagnosis of MCI and mild AD was made according to the National Institute on Aging and Alzheimer Association criteria [14]. A total of 53 participants were enrolled in the study, of whom 3 (6%) failed the screening criteria (because of the Mini-Mental State Examination score being <20), resulting in a total of 50 (94%) participants who were included in the study: 13 (26%) were controls, 12 (24%) were presymptomatic, 13 (26%) were predementia, and 12 (24%) had mild dementia. Of the 50 participants, 4 (8%) discontinued the study after finalizing visit 2; hence, 46 (92%) participants completed all study visits: 12 (26%) were controls, 12 (26%) were presymptomatic, 11 (24%) were predementia, and 11 (24%) had mild dementia. The data of all 50 participants were used for further analysis where

applicable; that is, for all analyses performed on the data up to visit 3. The detailed inclusion and exclusion criteria are listed in Multimedia Appendix 1, and protocol deviations are listed in Multimedia Appendix 2.

Ethics Approval

Written informed consent was obtained from all participants. The study was approved by the National Bioethics Committee (reference number VSN-20-022) in Reykjavik, Iceland, and conducted in accordance with the National Bioethics Committee's ethical standards and the latest version of the Declaration of Helsinki.

Conventional Paper-and-Pencil End Points

The Repeatable Battery for the Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [15] is a clinical tool specifically designed for both diagnostic purposes and for tracking changes in neurocognitive status over time. The RBANS was selected for the MEDIA study as this battery was designed to detect and characterize the earliest neurocognitive changes associated with dementia. RBANS scores have been reported to be correlated with cerebral amyloid in both cognitively normal individuals [16] and patients with MCI because of AD [17]. The RBANS takes 30 to 40 minutes to administer and generates age-adjusted index scores for 5 neurocognitive domains that are used to calculate a total scale index score (total possible range 40-160; a higher score indicates better cognitive function). It comprises the following domains with associated subtests used for index scores: (1) Immediate Memory (List Learning and Story Memory), (2) Visuospatial and Constructional (Figure Copy and Line Orientation), (3) Language (Picture Naming and Semantic Fluency), (4) Attention (Digit Span and Coding), and (5) Delayed Memory (List Recall, List Recognition, Story Memory, and Figure Recall).

Mini-Mental State Examination

The Mini-Mental State Examination is a brief, practical, clinician-reported outcome that examines cognitive status [18]. It evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and the ability to create a sentence and copy 2 intersecting pentagons. The test comprises 5 sections (orientation, registration, attention, recall, and language), with a total score ranging from 0 to 30. Higher scores indicate better cognitive function.

Clinical Dementia Rating Scale

The Clinical Dementia Rating scale (CDR) is a global measure of cognitive and functional performance and is widely used in clinical research on AD [19]. The scale assesses 6 domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. Each domain is assigned a score that can be summed to obtain the sum of boxes (CDR Sum of Boxes [CDR-SOB]) score. The necessary information for assessment is obtained through a semistructured interview with the participant and a reliable informant or collateral source (ie, study partner). Descriptive anchors are provided for each score, which guides the clinician in making appropriate ratings based on interview data and clinical judgment to evaluate the staging severity of dementia. Global CDR scores and CDR-SOB scores were also collected. Global CDR scores range from 0 to 3, with greater scores indicating greater disease severity. CDR-SOB scores range from 0 to 18, with greater scores indicating greater disease severity.

Neuropsychiatric Inventory–Questionnaire

The Neuropsychiatric Inventory (NPI) assesses a wide range of behaviors encountered in patients with dementia. The NPI-Questionnaire (NPI-Q) is a questionnaire (adapted from the NPI [20] and omitting the frequency rating) that is well-suited for use in general clinical practice settings [21]. In the NPI-Q, the study partner (informant) is asked whether the participant has experienced a variety of neuropsychiatric symptoms in the past month, which are then assessed in terms of severity on the same 3-point scale as in the original NPI (1=mild, 2=moderate, and 3=severe) using similar anchor points. The total NPI-Q severity score represents the sum of the individual symptom scores and ranges from 0 to 36. The total NPI-Q severity score and the individual symptom scores were recorded. Informant distress scores were not collected in this study.

Everyday Cognition Scale

The Everyday Cognition scale (ECog) measures cognitively relevant everyday abilities and comprises 39 items covering 6 cognitively relevant domains: Everyday Memory, Everyday Language, Everyday Visuospatial Abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention [22]. The questionnaire is a self-reported measure completed by both the participant (ECog-participant) and their study partner (ECog-informant). Within each domain, the ability to perform a specific task is rated on a 5-point scale ranging from (1) no difficulty, (2) mild difficulty, (3) moderate difficulty, (4) severe difficulty, or (5) unable to do. The total score for the 39 items ranges from 39 to 195, with greater scores indicating worse daily function. The 39-item data and total scores were collected. Details on study partner characteristics (relationship and frequency of interaction) are also captured on the ECog-informant.

The Functional Assessment of Chronic Illness Therapy–Fatigue scale

The Functional Assessment of Chronic Illness Therapy–Fatigue Scale is a short 13-item questionnaire that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a 4-point Likert scale ranging from 0 (very much fatigued) to 4 (not at all fatigued) [23].

Karolinska Sleepiness Scale

Participants completed the Karolinska Sleepiness Scale before starting the testing at each study visit to assess their level of sleepiness [24]. This scale was completed at 4 different time points during the testing at each study visit to assess the change in the sleepiness of each participant over the time they were tested. The Karolinska Sleepiness Scale is a 1-question scale that measures the level of sleepiness or alertness in 9 steps: *extremely alert*; *very alert*; *alert*; *rather alert*; *neither alert nor*

sleepy; *some signs of sleepiness*; *sleepy, but no effort to keep awake*; *sleepy, some effort to keep awake*; and *very sleepy, great effort to keep awake, fighting sleep.*

Digital End Points

Overview

Owing to the rapidly evolving field of digital technologies, it was considered beyond the scope of this study to ensure an exhaustive review and evaluation of all emerging digital end points and technology providers. Before starting the study, JC and KH reviewed and evaluated >100 companies to identify digital technologies that (1) augment conventional clinical assessments (using sensor technologies and machine learning), (2) allow direct physiological assessments of cognition (in particular, gait, eye movements, and brain activity), and (3) provide gamified cognitive assessments (such as AR, virtual reality, and computerized cognitive tests). Several potential technologies were identified in each category. Technology providers were prioritized if they had already demonstrated promising findings in the targeted patient population, showed promise during beta testing, or healthy volunteer testing. Figure 4 shows an overview of all digital end points selected for the MEDIA study.

Figure 4. All technologies included in the MEDIA study. EEG: electroencephalogram; MEDIA: Method for Evaluating Digital Endpoints in Alzheimer Disease; VR: virtual reality.

Technology	Description	Technology	Description
Digital clock drawing and short cognitive tablet-based tests 	DCTclock a digitalized version of the standard paper-and-pencil neuropsychological clock drawing test and short cognitive tablet-based tests to evaluate executive function, spatial reasoning, memory, and motor control	Tablet-based speech assessment 	Picture description task to evaluate speech, language, and cognition by applying speech analysis to short samples of naturalistic speech
Dual task paradigm testing 	Participants are asked to perform a series of motor and cognitive tasks in isolation (single task) and concurrently (dual task) while gait, voice, and brain activity are measured	Augmented reality test 	Augmented reality-assisted activity battery on a tablet to assess motor function, spatial and prospective memory, among other neurocognitive domains
Auditory cognitive assessment during EEG recording 	Noninvasive, single-channel, frontal EEG recording while participants are performing interactive auditory battery to assess cognitive function using multiple cognitive tasks at different difficulty levels	Computerized cognitive tests 	A tablet based battery of non-invasive neuropsychological assessments that load onto a specific cognitive domain or neural network
Eye-tracking and pupil dilation VR-based test 	Using a virtual reality eye tracker device, eye movements, pupil diameter, and response behavior were measured while participants were performing cognitive tests assessing memory, attention, and executive function	Retinal imaging 	Using an adapted ophthalmoscope imager, confocal images of the retina were acquired to measure autofluorescent spots on the retina which may correlate to positive brain amyloid pathology
Eye-tracking technology 	Eye-tracking technology that captures eye movements through web camera within a tablet to assess memory and response behavior	Emotional bias test 	The emotional bias test is an assessment that measures whether people can perceive facial emotions in others

AR, Spatial Navigation, and Memory Test (Digital Neuro Signature by Altoida)

Using Altoida's technology, participants were asked to complete a battery of AR and motor activities on a tablet. First-time users can complete a brief training session to familiarize themselves with the activities and digital interface and ensure that they can successfully complete the different activity types. The testing session comprises the following activities: (1) motor activities where participants are asked to accurately trace colored paths on the screen with their index finger and to rapidly and accurately tap circles on the screen as they become highlighted; (2) an AR activity titled *Back in Time*, which primarily exercises spatial memory by asking the participant to place 3 AR objects in their environment and then locate the objects again in a similar fashion; and (3) an AR activity titled *Day Out*, which primarily measures prospective memory by asking the participant to learn a specific order of AR actions in an evacuation scenario. While performing 1 of the 2 AR activities described previously, the participants were asked to tap an on-screen icon when they hear a sound signal. The participant needs to discriminate between the high- and low-pitched sounds.

This is a dual-task condition in which psychomotor processing speed is primarily assessed.

The data used for analysis is gathered by the sensors on the selected smart device (accelerometer and gyroscope) to determine parameters such as motion agility, speed, and smoothness of motion, as well as behavioral parameters such as recalled items placed in real space and the correct number of taps. These comprehensive parameters were used to calculate a Digital Neuro Signature score that can be used to predict an individual's conversion from MCI to AD.

Computerized Cognitive Tests (Cambridge Neuropsychological Test Automated Battery by Cambridge Cognition)

The Cambridge Neuropsychological Test Automated Battery is a tablet-based battery of neuropsychological assessments, which load onto specific cognitive domains. The following test battery was chosen for this study: (1) Motor Screening Task, (2) Paired Associates Learning, and (3) Emotional Bias Task. The Motor Screening Task provides a general assay of whether sensorimotor or comprehension difficulties limit the collection of valid data from participants. Participants must touch the flashing cross, which is shown at different locations on the screen. The key outcome measure for this task is median latency. In Paired Associates Learning, which is a measure of episodic memory [25], boxes are opened on the screen to reveal a number of patterns. The participants are instructed to try to remember the location of each pattern. Each pattern is shown in the center of the screen in a randomized order, and the participant touches the box in which the pattern was located. The key outcome measures for this task are adjusted total errors and first attempt memory score. The Emotional Bias Task is an assessment of how people perceive facial emotions in others. The participant is required to view images of faces morphed between happy and sad emotions of varying intensities. They must then indicate whether they perceive the face shown on the screen as happy or sad. The key outcome measure for the Emotional Bias Task is the bias point, which is the proportion of trials selected as happy compared with the alternative emotion, adjusted to a scale of 0 to 15.

Instrumented Motor-Cognitive Dual Tasking (Physilog by GaitUp, NeuroVocalix by Cambridge Cognition, and Portable Electroencephalogram by Neurosteer)

The participants were asked to perform a series of motor and cognitive tasks in isolation (single task) and concurrently (dual task). The motor task comprised walking at a self-selected pace for 1 minute. The cognitive task comprises counting backward in 2 difficulty levels (in steps of 1 and 3). The sequence and duration of the tasks are presented in Figure 5. To measure motor performance, 2 wearable inertial sensors (Physilog 5 by GaitUp) measuring acceleration (accelerometer; sampling frequency 128 Hz) and angular velocity (gyroscope; sampling frequency 128 Hz) were attached to participants' feet. Using GaitUp's algorithm, which has been validated in several patient populations [26-28], gait parameters such as but not limited to gait speed, step and stride length, step and stride time, and step and stride variability were extracted. To measure cognitive performance, a small microphone (Wireless GO; RØDE) was attached to participants' clothes, which recorded the counting. Voice recordings were streamed to the NeuroVocalix web-based platform by Cambridge Cognition. The voice recordings will be analyzed for counting rate, number of errors, and correct counts, as well as vocal features during counting such as the length of pauses between numbers, energy, and pitch as features of the frequency spectrum. In addition, a wearable, single-channel electroencephalogram by Neurosteer was placed on the participants' foreheads to measure brain function. The single- and dual-task phases will be used to compare the frontal brain activity between tasks and correlate to measures of cognitive load such as frequency-band power and Neurosteer's brain activity biomarkers [29].

Figure 5. Task flow during dual tasking paradigm testing.

Test number	1	2	3	4	5	6	7	8
Cognitive	Rest	Rest	– 1	– 3	– 3	– 1	Rest	Rest
Motor	Stand	Walk	Sit	Walk	Sit	Walk	Walk	Sit
Duration	1 minute	1 minute	1 minute	1 minute	1 minute	1 minute	1 minute	1 minute

Neurosteer Auditory Cognitive Assessment

This test is a cognitive assessment based on auditory stimuli used to probe cognitive functionality. The testing includes auditory detection, n-back, auditory memory tasks, and resting state tasks. The detection and n-back tasks introduce different sequences of musical instrument melodies, eliciting participant responses. The detection task is used to test attention, inhibition response, and accuracy, whereas the n-back measures working memory. The memory tasks include statement recollection, mental clock imagery, and word recall. These are meant to test semantic memory, working memory, and memory consolidation and retrieval. Participants performed a 10-minute assessment while being recorded with a single-channel, medical-grade electroencephalogram. A total of 3 cognitive load levels (high, low, and rest) were used during the tasks and were correlated with behavioral performance and brain activity. The biomarkers extracted by the system were calculated using harmonic analysis and machine learning methods.

Winterlight Speech Assessment

Winterlight Speech Assessment was developed to record and analyze naturalistic speech using a tablet app. For the MEDIA study, each assessment included 2 picture description tasks in which participants were prompted to describe drawings of scenes presented on the tablet's screen. Tasks of this type have been shown to be good proxies for spontaneous discourse and have been shown to be sensitive to speech changes in AD in previous studies [30-34]. The participant's speech was recorded through the device's microphone and analyzed via an automated speech analysis pipeline, generating variables reflecting different acoustic and linguistic properties of speech.

The Short-term Memory-Binding Test and Reading Task (by ViewMind)

Participants were asked to perform 2 cognitive tests, a short-term memory-binding test (STMBT) and a reading task while wearing a virtual reality headset with eye tracking (sampling rate of 120 Hz).

During the STMBT [35-37], participants were presented with a set of either 2- or 3-colored geometric shapes (Figure 2), depending on the cohort assignment at screening. The STMBT assesses the ability to temporarily hold bicolored objects whose colors have to be remembered either as individual features (baseline) or integrated within unified representations (binding).

The sentence corpus of the reading task comprised 40 regular sentences in Icelandic, which is the native language of all participants (eg, "Leifur heimsótti ættingja frá Evrópu í síðasta mánuði"; see the study by Fernández et al [38] for a description of a complete sentence corpus). The sentences comprised a well-balanced number of content and function words and had similar grammatical structure. Single sentences were presented at the centerline of the screen. The data used for analysis will be the x and y coordinates of eye movements together with time stamps and eye pupil diameter.

Retinal Imaging (Retia by NeuroVision)

Using an adapted ophthalmoscope (ophthalmoscope specification tailored for blue-light confocal autofluorescent imaging, with excitation illumination at 450 nm using a single flash light-emitting diode, emissions capture at ≥500 nm, and pixel resolution equivalent to 9 µm on the retina), confocal images of the retina were acquired at visit 2. After the administration of drops for eye pupil dilation (tropicamide 1% weight/volume) to the participant's eyes to dilate the pupil to at least 3.5 mm in diameter, a series of autofluorescent images of the retina were acquired—nominally 18 images per eye. The entire noninvasive imaging procedure takes approximately 15 to 30 minutes. The participants' raw image stack is processed by the automated software analysis package to assess the presence, size, position, shape, and other attributes of retinal autofluorescent spots. As the number of autofluorescent spots on the retina was correlated with the larger retinal amyloid burden in participants with AD versus controls [39,40], the likelihood of positive brain amyloid pathology, as determined by CSF sampling or amyloid PET imaging, will be calculated.

Digital Clock-Drawing and Cognitive Tablet-Based Drawing Tests (DCTclock by Linus Health)

DCTclock

DCTclock [41,42] is a digitized version of the standard rapid and noninvasive pen-and-paper neuropsychological clock-drawing test. The test involves participants drawing 2 clock faces on a piece of paper with a digital pen that precisely tracks and records the drawing behavior. The time-stamped positional data (x and y coordinates and time stamps) generated during this assessment are analyzed using proprietary machine learning algorithms that evaluate hundreds of features captured by the drawing process and the final output. By comparing test results with normative data, the system then determines whether the test is within normal limits and provides a detailed breakdown of performance on the various cognitive tasks evaluated during the test.

Cognitive Tablet-Based Drawing Tests

Participants were asked to complete a pretest assessment to familiarize themselves with the tablet and five short tablet-based drawing tests: (1) pretest, (2) pathfinding test, (3) symbol test, (4) trails test, and (5) tracing test. The pretest exercise involves copying waves. It was administered before completing the other tablet tests with the only goal of making the participant comfortable with drawing using the Apple Pencil and the iPad. In the pathfinding test, participants were asked to complete a series of mazes of increasing difficulty as quickly and accurately as possible. The symbol test comprises a key of 9 symbol-digit pairs followed by empty boxes with symbols on the top. Under each symbol, the participants must write down the corresponding symbol as fast as possible. In the trails test, the participant was instructed to connect a set of circles as quickly as possible, with the first part connecting numbers only and the second part connecting alternating numbers and letters. In the tracing test, the participant was prompted to trace a series of spirals and circles, first with their dominant hand and then with their nondominant hand. Expected features for further analysis are the time to finish a task, total strokes needed, and efficiency of drawing.

Imprint Assessment With Paired Recognition (Visual Paired Comparison by Neurotrack)

A tablet-integrated camera was used to record a video of the participant's face while they were seated comfortably in a quiet, well-lit room in front of a tablet computer. Participants were shown a series of paired images during a familiarization phase and were then exposed to novel images. A second learning and test phase assessed paired associate learning and memory. Trial-level multimodal cognitive data (saccades, oscillations, gaze duration, and blinks), keystroke latency, performance accuracy, and discriminability for every participant on their digital multimodal cognitive tasks were collected. From these measures, measures of visual episodic memory, visual working memory, processing speed, executive function, and recognition discriminability will be derived.

Participant Feedback Survey

A brief participant feedback survey was adapted from the Subject Usability Scale [43] and National Aeronautics and Space

Administration Task Load Index [44] and was used in the MEDIA study to evaluate the participants' experience and acceptance of the digital tools and assessments. The survey included 7 statements: "The device was easy to use"; "I needed to learn many things before I could get going with this device"; "This assessment was mentally demanding"; "This assessment was physically demanding"; "I enjoyed this assessment"; "I was insecure and/or frustrated during this assessment"; and "This assessment felt meaningful and relevant to difficulties I have in my daily life." For these statements, participants indicated their degree of agreement or disagreement on a 6-point Likert scale ranging from 0 (strongly disagree) to 5 (strongly agree). There was an open question—"Is there anything else you would like to add?"—for open comments from the participants on the assessments.

Statistical Analysis

As this is an exploratory study, the sample size was chosen pragmatically to balance statistical and feasibility considerations. Data from 12 participants per cohort were considered to provide sufficient information for the study objectives [45].

Descriptive statistics (ie, mean, median, range, and SD) of the total score from each conventional end point and questionnaire will be reported by the cohort. Estimates of the between-cohort standardized differences in the corresponding total scores will be provided.

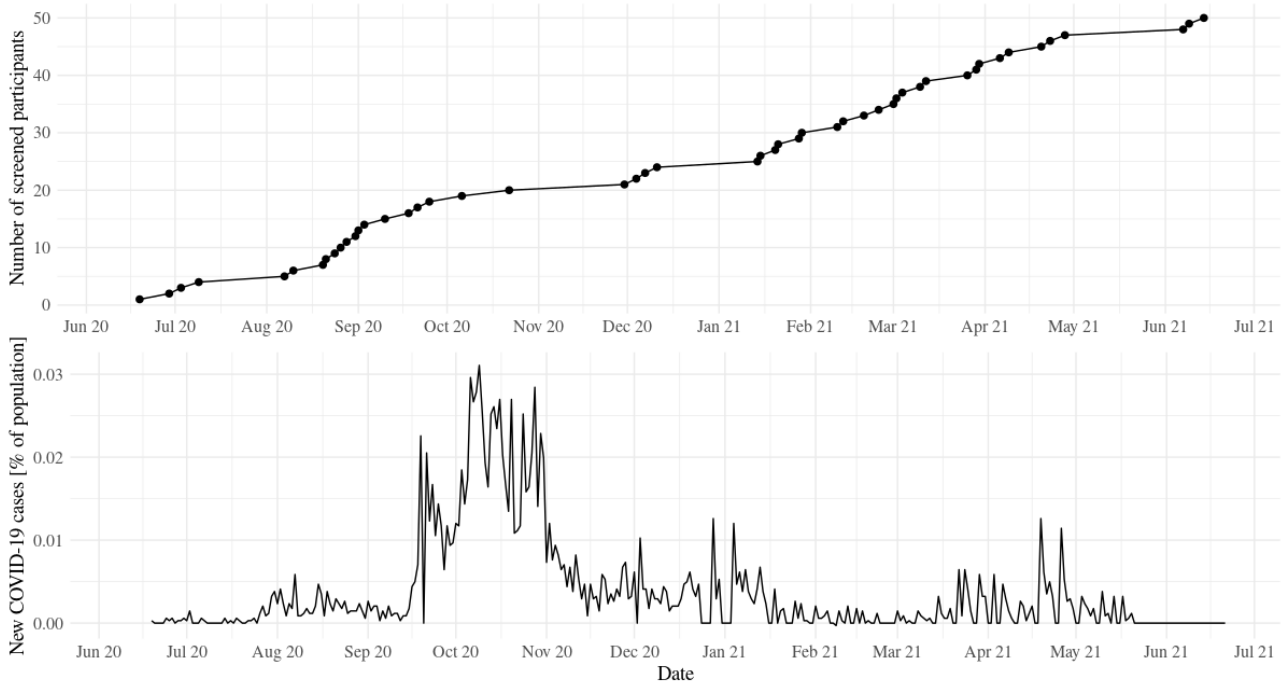
Digital technologies will produce ≥1 outcome variable (features) for each participant and assessment time. On the basis of these features, psychometric properties will be assessed: acceptable range (ceiling and floor effects), reliability (test-retest variability), validity (correlation to conventional end points), and responsiveness (change from test and retest to challenge) as appropriate. Various statistical rules for classifying participants into cohorts will be explored. The goodness of these rules will be assessed by calculating the sensitivity, specificity, positive predictive value, and negative predictive value. Receiver operating characteristics curves will be constructed to determine cutoff points with the best trade-off between sensitivity and specificity. Data from the participant feedback survey will be summarized descriptively.

Results

Trial Status

Participant recruitment and data collection ran from June 2020 to June 2021. This study was fully conducted during the COVID-19 pandemic. Figure 6 shows the recruitment of the study participants together with daily new COVID-19 cases as a percentage of the population in Iceland (data from the study by Ritchie et al [46]).

Figure 6. Study progress in Iceland during the worldwide COVID-19 pandemic.



Trial Participants

The approximate average duration of all assessments at each study visit was as follows: visit 1, 1.48 (SD 0.25; range 1.10-2.17) hours; visit 2, 2.70 (SD 0.40; range 0.88-3.38) hours; visit 3, 2.17 (SD 0.33; range 1.47-2.90) hours; and visit 4, 1.63 (SD 0.28; range 0.83-2.18) hours. Table 1 shows demographic and conventional end point data. Medical history and comorbidities are listed in Multimedia Appendix 3.

Table 1. Demographics and baseline characteristics of the study population (N=50).

Demographics	Cohort 1: controls (n=13)	Cohort 2: presymptomatic (n=12)	Cohort 3: predementia (n=13)	Cohort 4: mild dementia (n=12)
Age (years)				
Values, mean (SD)	68.1 (3.7)	72.4 (4.3)	70.6 (4.1)	69.3 (6.5)
Values, median (range)	68 (63-73)	71 (65-78)	71 (62-78)	68 (61-80)
Sex, n (%)				
Male	9 (69)	7 (58)	9 (69)	8 (67)
Female	4 (31)	5 (42)	4 (31)	4 (33)
Education, n (%)				
Higher education	9 (69)	4 (33)	4 (31)	3 (25)
Upper secondary education	4 (31)	6 (50)	5 (39)	6 (50)
Compulsory education	0 (0)	2 (17)	4 (31)	3 (25)
BMI (kg/m^2)				
Values, mean (SD)	26.7 (2.7)	25.3 (3.9)	26.6 (4.3)	26.7 (3.4)
Values, median (range)	27.2 (22.5-31.4)	24.4 (20.5-34.1)	25 (21.1-33.5)	25.9 (23-35.4)
MMSE[a]				
Values, mean (SD)	29.5 (1.1)	29.7 (0.7)	27.4 (2.2)	21.8 (1.5)
Values, median (range)	30 (26-30)	30 (28-30)	28 (24-30)	22 (20-25)
RBANS[b]				
Values, mean (SD)	101 (7)	98.4 (8.8)	75.7 (12.2)	66.3 (8.8)
Values, median (range)	101 (88-115)	97 (84-118)	74 (49-95)	65 (55-83)
CDR[c] global				
Values, mean (SD)	0.04 (0.1)	0 (0)	0.5 (0)	0.7 (0.2)
Values, median (range)	0 (0-0.5)	0 (0)	0.5 (0.5-0.5)	0.5 (0.5-1)
CDR-SOB[d]				
Values, mean (SD)	0.1 (0.2)	0 (0)	1.7 (0.9)	3.5 (1.1)
Values, median (range)	0 (0-0.5)	0 (0)	1.5 (0.5-3)	3.5 (1.5-5)
ECog[e] patient				
n-Nan[f]	1	0	1	0
Values, mean (SD)	44.4 (4.7)	44.5 (4.5)	68.3 (28.5)	64.4 (10.2)
Values, median (range)	44 (39-57)	44.5 (39-54)	56.5 (46-140)	67.5 (49-80)
ECog caregiver				
Values, mean (SD)	45.5 (6.2)	47.5 (9.3)	67.6 (12.3)	88.7 (28.8)
Values, median (range)	42 (39-56)	43 (39-65)	70 (53-91)	83 (53-137)
NPI-Q[g]				
Values, mean (SD)	0.23 (0.6)	1.1 (2.2)	5.6 (5.3)	5.3 (6.9)
Values, median (range)	0 (0-2)	0 (0-7)	4 (0-13)	3 (0-22)
FACIT[h]				
n-Nan	0	0	1	1
Values, mean (SD)	10 (2.3)	9.3 (3.7)	14.4 (7.8)	13.2 (5.4)
Values, median (range)	11 (6.5-13)	8.75 (6-20)	11.2 (7-33)	11 (5.5-22)

[a]MMSE: Mini-Mental State Examination.

[b]RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

[c]CDR: Clinical Dementia Rating scale.

[d]CDR-SOB: CDR Sum of Boxes.

[e]ECog: Everyday Cognition.

[f]This is the number of missing values (eg, 1 study participant with a missing result for Everyday Cognition in cohort 1).

[g]NPI-Q: Neuropsychiatric Inventory–Questionnaire.

[h]FACIT: Functional Assessment of Chronic Illness Therapy.

Discussion

Expected Findings

The expected main findings of this study are as follows: (1) the accuracy of each of the 10 technologies in classifying participants into 4 cohorts according to the severity of cognitive impairment and dementia; (2) the psychometric properties of each of the digital technologies tested, including acceptable range (ceiling and floor effects), concurrent validity (correlation of ≥1 outcome measure of each of the technologies to traditional paper-and-pencil tests in AD), reliability (concordance of test and retest), and responsiveness (the sensitivity to change in a mild cognitive challenge model); and (3) feasibility of applying these technologies in drug trials based on study participant feedback.

Digital technologies hold promise in amending psychometric limitations associated with many conventional paper-and-pencil end points and transforming the way drug treatment effects are measured in clinical trials. For example, the digital pen used in this study to augment standard cognitive tests may reduce subjectivity and variability of well-established paper-and-pencil tests such as the clock-drawing test, trail-making test, or digit-symbol substitution test [42]; computerized testing implemented on tablets or smartphones with short cognitive test batteries may allow more frequent monitoring of cognition in the real world, thereby reducing variability and bias [47-49]; eye tracking while reading and voice analytics of conventional picture description tests may provide direct physiological assessments of cognition, which may increase sensitivity [30-37]; and AR or virtual reality testing may introduce more real-life assessments in a clinical setting [50,51]. More accurate and reliable efficacy end points could potentially reduce the number of failed or inconclusive trials and allow for more efficient drug development through shorter, smaller, less costly, and less burdensome drug trials, ultimately allowing more drugs to be studied and medicines to reach patients faster. However, it remains unclear how to best evaluate a wide range of novel and promising technologies, how to use them to derive efficacy end points, and how to advance them through early drug development processes.

The MEDIA study is an effort to establish a method for efficiently evaluating a range of technologies in a single study. Within the drug development framework, it is important to collect validation data and better understand operational feasibility before attempting to implement novel digital technologies in clinical drug trials. Clinical trials of drug interventions are highly complex and effortful undertakings and typically do not offer a good opportunity to study multiple novel digital end points. Often, these trials are already quite onerous for both participants and clinical sites, and the introduction of additional end points risks overburdening and jeopardizing the integrity of the primary objective of the study. Hence, carefully designed methodology studies such as the MEDIA study derisk drug intervention trials and offer valuable insights into the ceiling and floor effects, concurrent validity, reliability, and responsiveness of novel end points, as well as information about implementation, patient acceptance, and any operational complexity that a novel end point might add to a drug intervention trial.

A previous noninterventional study of 8 digital technologies for characterizing unipolar depression [52] successfully identified promising digital end points to advance as exploratory end points in numerous early phase clinical drug trials. However, this study lacked a challenge model and hence did not provide insights into sensitivity to change. A benign cognitive challenge model was implemented in the current MEDIA study, and the results will demonstrate if this is a feasible approach to study sensitivity to change in future methodological studies. The digital technologies included in the MEDIA study are in various stages of development. Some are already well established, with considerable validation data and clinical trial experience, whereas other technologies are still in early development. This will be taken into account when evaluating their performance.

Health authorities have published guidelines on the data required for a novel end point to be considered validated or qualified from a regulatory perspective [53-56]. Among the important qualities that an end point needs to meet are good psychometric properties (eg, lack of ceiling and floor effects), assay sensitivity (ie, sensitivity to drug treatment effects or disease progression), sufficient reliability and validity (eg, test-retest reliability and concurrent validity), and clinical meaningfulness. There are many ways of establishing clinical meaningfulness. This study used a participant feedback survey to understand patient acceptance of the end points and whether they considered the assessments meaningful to the problems they faced in their daily lives. Moreover, the outcomes of the novel digital end points will be correlated with the outcomes of conventional paper-and-pencil assessments of function, offering another method for assessing clinical meaningfulness. The topic of regulatory qualification of novel clinical end points is beyond the scope of this paper and will be addressed in a future publication.

Good concurrent validity occurs when a new end point demonstrates an appropriate correlation with an established gold standard. This is an important psychometric feature of sound clinical trial end points. However, as conventional

neuroscience end points often display poor psychometric properties in various stages of AD (eg, ceiling effects in early predementia stages and floor effects in overt dementia), as well as rater errors and cultural bias, one might start to question the appropriateness of some of these conventional end points in establishing the concurrent validity of novel end points. Moreover, conventional end points are rarely pure measures of a single cognitive domain. For example, performing a memory task comprising a word list learning task relies not only on intact memory processes but also on attention, language comprehension, working memory, and executive function. Hence, it may be difficult to accurately interpret any potential lack of correlation between the conventional and novel cognitive end points. This dilemma will likely continue to challenge the development and validation of novel digital end points.

This study was conducted during the COVID-19 pandemic (SARS-CoV-2 virus pandemic). The full impact of the pandemic on this study is not clear [57]. First, the study was delayed at the beginning because of the implementation of preventive measures, and the overall duration of the project was prolonged because of various measures such as phases of lockdowns and quarantine. Originally, the planned duration of the study was approximately 6 months; however, this was prolonged to 1 year. Second, social distancing and infection control measures may have affected the digital assessments. For example, the use of face masks may have affected the quality of voice recordings and gait assessments. Finally, restrictions on social gatherings and regarding lockdown of commercial activities may have contributed to feelings of lethargy, anxiety, social isolation, disorientation to time, and a feeling of *every day is the same*. The psychological impact of the pandemic is yet to be further elucidated; however, it is clear that responses to questions about activities of daily living and neuropsychiatric symptoms during such unprecedented times are likely to be affected [58].

Limitations

This exploratory methodology study has several limitations. Most notably, the small sample size necessitates findings to be confirmed in larger trials. Second, as this is a noninterventional study, it is difficult to establish sensitivity to change. One of the greatest risks that conventional end points pose to clinical drug development in neuroscience is the lack of sensitivity to changes and the possibility of missing important drug treatment effects. Hence, it is of utmost importance to demonstrate good assay sensitivity when studying novel digital end points to be implemented as efficacy measures in clinical trials. In this study, a benign cognitive challenge model was used in an attempt to assess the sensitivity to change of each digital end point. However, it is difficult to determine what challenge will be sufficient to reliably produce cognitive impairment in a cross-sectional study such as this one. Moreover, producing fatigue through late-night testing may not affect all cognitive domains to the same extent. Hence, the challenge model may affect participant performance on the various digital end points differently. In addition, as participants had no expectations of treatment benefits in this noninterventional study, it is possible that the digital end points would show different sensitivities to change in a clinical drug trial. Sensitivity to drug treatment effects cannot be fully evaluated until the digital end point is studied in a drug intervention trial. This is often the key validation data that novel digital end points are missing and is the most challenging data to acquire. This was a single-site study that provided limited information on how scalable the digital technologies are to multisite global trials and to what extent culture and language may be confounding factors. Finally, although the study included more men (33/50, 66%) than women (17/50, 34%), the proportions of men and women were, overall, similar across the 4 cohorts. It should also be noted that the education level was not evenly distributed across the cohorts; there was a greater number (and percentage) of participants with higher education in cohort 1 (9/13, 69%) than in cohort 2 (4/12, 33%), cohort 3 (4/13, 31%), and cohort 4 (3/12, 25%). As the education level may potentially be an important confounder, statistical analysis will be adjusted for it, as appropriate. Owing to the invasive procedures and sensitive biomarker information, there were no prospective CSF samples or PET imaging conducted in this noninterventional methodology study. Amyloid status was based on historical investigations that had to be aged <2 years. Historical reports were based on both CSF analysis (48/50, 96%) and PET imaging (2/50, 4%), and this study was not able to confirm any potential changes that may have occurred in amyloid status. Moreover, this study could not confirm any potential discrepancies between the 2 amyloid assessment procedures.

The findings of this study are planned to be disseminated in peer-reviewed journals and at key scientific conferences in 2022 and 2023.

Conclusions

Although the surge of novel technologies is revolutionizing the way we approach cognitive testing, the challenge of systematically evaluating the performance of these digital end points remains. The MEDIA study delivers technology feasibility evaluations of 10 novel in-clinic digital end points and determines whether these tools provide tolerable and reliable measures of cognition, with improved psychometric properties and greater sensitivity and specificity than conventional clinical trial assessments. The MEDIA study psychometrically evaluates multiple digital cognitive end points head to head with conventional end points, as well as in a mild cognitive challenge model. Digital end point methodology studies such as the MEDIA study can efficiently avoid costly failures of improper digital end point implementation in clinical drug trials. Moreover, the MEDIA study may identify more sensitive screening tools for the earlier detection of AD, as well as potentially superior efficacy readouts for use in clinical drug development. A noninterventional study such as this is an important step toward establishing reliable and valid digital technologies ready to be used as efficacy end points in future clinical drug trials.

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Conflicts of Interest

JC, VV, JS, OS, JP, MP, MD, GE, J-HC, and KH are employees of Novartis. MB and IT are employees of Altoida Inc, NT and FC are employees of Cambridge Cognition, RA and FM are employees of MindMaze SA, WS-M is an advisor for Linus Health Inc, NI and LM are employees of Neurosteer Inc, EM is an employee of Neurotrack Technologies Inc, NB was an employee of Neurotrack Technologies Inc, MC and JT are employees of NeuroVision Imaging Inc, MS and GF are employees of ViewMind Inc, and BS and JR are employees of Winterlight Labs.

Multimedia Appendix 1
Inclusion and exclusion criteria.
[PDF File (Adobe PDF File), 234 KB - resprot_v11i8e35442_app1.pdf]

Multimedia Appendix 2
Protocol deviations.
[PDF File (Adobe PDF File), 102 KB - resprot_v11i8e35442_app2.pdf]

Multimedia Appendix 3
Medical history data.
[PDF File (Adobe PDF File), 109 KB - resprot_v11i8e35442_app3.pdf]

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Abbreviations

AD: Alzheimer disease
AR: augmented reality
CDR: Clinical Dementia Rating scale
CDR-SOB: Clinical Dementia Rating scale Sum of Boxes
CSF: cerebrospinal fluid
ECog: Everyday Cognition scale
MCI: mild cognitive impairment
MEDIA: Method for Evaluating Digital Endpoints in Alzheimer Disease
NPI: Neuropsychiatric Inventory
NPI-Q: Neuropsychiatric Inventory–Questionnaire
PET: positron emission tomography
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
STMBT: short-term memory-binding test

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Protocol

The Variations in Care and Real-world Outcomes in Individuals With Rectal Cancer: Protocol for the Ontario Rectal Cancer Cohort

Sunil Patel[1]; Chad McClintock[1], MSc; Christopher Booth[1]; Shaila Merchant[1], MD, MSc; Carl Heneghan[2], DPhil, MD; Clare Bankhead[2], DPhil

[1]Department of Surgery, Queen's University, Kingston, ON, Canada

[2]Centre for Evidence Medicine, University of Oxford, Oxford, United Kingdom

Corresponding Author:
Sunil Patel
Department of Surgery
Queen's University
76 Stuart Street
Kingston, ON, K7L 2V7
Canada
Phone: 1 613 549 6666 ext 7995
Email: sunil.patel@kingstonhsc.ca

Abstract

Background: Individuals with rectal cancer require a number of pretreatment investigations, often require multidisciplinary treatment, and require ongoing follow-ups after treatment is completed. Due to the complexity of treatments, large variations in practice patterns and outcomes have been identified. At present, few comprehensive, population-level data sets are available for assessing interventions and outcomes in this group.

Objective: Our study aims to create a comprehensive database of individuals with rectal cancer who have been treated in a single-payer, universal health care system. This database will provide an excellent resource that investigators can use to study variations in the delivery of care to and real-world outcomes of this population.

Methods: The Ontario Rectal Cancer Cohort database will include comprehensive details about the management and outcomes of individuals with rectal cancer who have been diagnosed in Ontario, Canada (population: 14.6 million), between 2010 and 2019. Linked administrative data sets will be used to construct this comprehensive database. Individual and care provider characteristics, investigations, treatments, follow-ups, and outcomes will be derived and linked. Surgical pathology details, including the stage of disease, histopathology characteristics, and the quality of surgical excision, will be included. Ethics approval for this study was obtained through the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

Results: Approximately 20,000 individuals who meet the inclusion criteria for this study have been identified. Data analysis is ongoing, with an expected completion date of March 2023. This study was funded through the Canadian Institute of Health Research Operating Grant.

Conclusions: The Ontario Rectal Cancer Cohort will include a comprehensive data set of individuals with rectal cancer who received care within a single-payer, universal health care system. This cohort will be used to determine factors associated with regional variability and adherence to recommended care, and it will allow for an assessment of a number of understudied areas within the delivery of rectal cancer treatment.

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KEYWORDS

rectal cancer; survival; adherence to care; regional variability

Introduction

Colorectal cancer is the third most common cancer diagnosed in Ontario, Canada, with approximately 9000 cases per year [1]. Ontario (estimated population: 14.6 million) is Canada's largest province, and residents of Ontario benefit from a single-payer, universal health care system. Diagnostic tests, treatments, and follow-ups for individuals with colorectal cancer are almost exclusively provided through this single-payer system.

The real-world impact of variations in patterns of care and adherence to recommended treatments is an important aspect of determining the effectiveness of a cancer care system. Individuals with rectal cancer in Ontario have an estimated 5-year survival rate of approximately 70% [1], but substantial variations in survival have been noted between regions and hospitals. A previous publication from members of our group found up to an 8% (66.4% vs 58.4%) absolute difference in 5-year overall survival between regions, while also finding up to a 20% (72% vs 52%) absolute difference in 5-year overall survival between the best- and worst-performing hospitals [2]. These differences in outcomes are at least in part due to differences in treatment, access, and the quality of care, as the case mix was minimally different among regions.

The management of individuals with rectal cancer often requires several diagnostic tests, the use of multidisciplinary teams during the delivery of multimodality treatment, and ongoing surveillance for identifying recurrent or metastatic disease. With this level of complexity, the fragmentation of care can occur [3], and inconsistent delivery of treatments may be observed [4]. In addition, due to the nature of the treatments, patients with rectal cancer often experience high rates of short- and long-term morbidity.

There are a number of strategies for assessing the delivery and outcomes of rectal cancer care at a population level. The limitations of many of these approaches are the lack of detailed histopathology data, the inability to assess surgical quality, the discontinuity of care, and high rates of loss to follow-up. The ability to overcome these limitations would substantially improve the ability to assess the real-world effectiveness of cancer care systems and identify the impact of variations in care and/or adherence to recommended care on survival and other important outcomes.

The objective of the Ontario Rectal Cancer Cohort (OntaReCC) is to create a comprehensive clinical-pathological database of individuals who are diagnosed with rectal cancer in Ontario. This database will allow investigators to assess practice patterns, adherence to recommended care, and outcomes within this population. This protocol describes the methods used to establish this database.

Methods

Study Setting

Ontario is Canada's most populous province (estimated population of 14.6 million in 2019) and is a large and diverse region. The province includes large metropolitan areas, as well as sparsely populated rural communities. The demographics of Ontario residents include a wide range of socioeconomic backgrounds, a large number of first- and second-generation Canadians, and indigenous populations [5].

Residents of Ontario are eligible for a government-run, universal, single-payer health insurance plan (ie, the Ontario Health Insurance Plan). This plan covers the costs of physician visits, diagnostic investigations, hospital stays, surgical services, and cancer services (including radiation therapy and chemotherapy). Ontario routinely collects clinical and demographic data, as well as other health care–related data, within a number of linked administrative databases.

Study Population

Individuals who were diagnosed with rectal cancer between 2010 and 2019 were identified through the Ontario Cancer Registry (OCR) by using the *International Classification of Diseases, Tenth Revision* (ICD-10), codes for rectal cancer (ICD-10 20.9). The OCR captures incident cancer cases through mandatory reporting and is estimated to include >95% of newly diagnosed cancer cases, in which >94% of colorectal cancers were microscopically confirmed [6,7]. Individuals with a histopathology code that was consistent with the adenocarcinoma of the rectum were included. Those aged <18 years at time of diagnosis, those who died on or before the date of diagnosis, and those who were ineligible for the Ontario Health Insurance Plan were excluded. We also excluded those who were diagnosed with cancer at another site (ie, breast cancer, prostate cancer, lung cancer, etc) within the preceding 3 years.

Data Sources

The OntaReCC combines data from a number of provincially maintained administrative data sets with data from histopathology reports that are made available through the OCR. A full listing of the administrative data sets can be found in Textbox 1. These data sets include health administrative data that are generated whenever a health care service is delivered to an individual, which are utilized for billing, registration, transactions, or record keeping by health care providers. The heath administrative data sets are linked to other provincially maintained data sets that provide vital statistics, census information, and other demographic data.

These data sets provide comprehensive data on individual characteristics (ie, demographics, comorbidities, and socioeconomic status), diagnostic details (the date of diagnosis, histologic variants, and cancer sites), and treatment details. In addition, health care provider details and institution details are captured within these data sets. By using the abovementioned data sets, we will be able to derive important factors or characteristics, including the completeness of preoperative investigations; the type, extent, and completeness of treatments (including surgery, radiation, and chemotherapy); treating clinician characteristics (volumes and practice setting) and institution characteristics (volumes, the level of care, and the presence of a multidisciplinary cancer center); and cancer-related outcomes (overall and cancer-specific survival, the treatment

of metastatic disease, the use of palliative treatments, and symptom burden).

Textbox 1. Summary of sources of data to be linked within the Ontario Rectal Cancer Cohort database.

Ontario Cancer Registry

- The Ontario Cancer Registry is the provincial database of information for all Ontario residents who have been diagnosed with cancer (incidence) or have died from cancer (mortality). Data are collected from hospitals, regional cancer centers, pathology reports, and death certificates and cover the entire province of Ontario.

Cancer Activity Level Reporting database

- The data elements constitute patient-level activities within the cancer system that focus on radiation and systemic therapy services and outpatient oncology clinic visits. The data set contains clinical, patient-level data.

Canadian Institute of Health Information-Discharge Abstract Database (CIHI-DAD)

- The CIHI-DAD captures administrative, clinical, and demographic information on hospital discharges (including deaths, sign-outs, and transfers). This includes demographic, administrative, and clinical data for inpatient discharges (including surgery) and day surgery interventions.

Ontario Drug Benefit program

- The Ontario Drug Benefit program provides drug benefits for all adults aged 65 years and older and those receiving social assistance in Ontario. Pharmacists submit claims for each prescribed drug that is covered under the Ontario Drug Benefit formulary. These claims form the basis of the data set.

Symptom Management Database

- This database contains data that are used to improve symptom management and collaborative palliative care planning through the earlier identification, documentation, and communication of patient symptoms and performance status.

Registered Persons Database

- A listing of all persons who are insured under the Ontario Health Insurance Plan. The data are used to ensure that individuals in other data sources are identified correctly and to support analyses by demographic groups and geography.

Pathology Data Collection

Histopathology reports were requested from the OCR for individuals who were undergoing biopsy, local excision/polypectomy, or major surgical excision for rectal cancer during the study dates. Cancer Care and Epidemiology at the Queen's Cancer Research Institute has established processes for abstracting comprehensive details from these types of reports [8-10]. These processes allow for reliable and reproducible data abstraction. A data abstraction manual was created for abstraction. Trained histopathology data abstractors were utilized for data abstraction. Regular meetings for reviewing inconsistencies within and between reports were completed to ensure the validity and reliability of the pathology data abstraction. The data elements are summarized in Textbox 2.

Textbox 2. Histopathology data to be included in the Ontario Rectal Cancer Cohort database.

Quality of reporting

- Synoptic report
- Completeness of reporting

Quality of excision

- Intactness of the mesorectum (complete, near complete, or incomplete)
- Margin status (proximal, distal, or circumferential)
- Nodal harvest (≥12)

Histology

- Adenocarcinoma and its variants
- Degree of differentiation
- Lymphovascular invasion and perineural invasion

Stage of disease

- Tumor stage, nodal stage, and metastatic disease (if applicable)

Neoadjuvant treatment response

- Complete response, partial response, or no response (if applicable)

Mutations and immunohistochemistry

- *BRAF* and *KRAS* gene status
- Microsatellite instability and mismatch repair proteins

Exposures and Outcomes

The proposed cohort will contain a number of exposure and outcome variables that are pertinent to a wide range of research questions. Potential exposures include those related to individuals, the circumstances of the cancer diagnosis, health care providers, the institutions where care was delivered, the regions, and the nature and extent of treatments, as summarized in Table 1. A number of outcomes will also be examined and will include the intent and extent of treatments, adherence to recommended care, and short- and long-term outcomes. In addition, symptom burden will be examined, which is a unique feature of the proposed database.

Table 1. Summary of the exposures and outcomes that are contained within the Ontario Rectal Cancer Cohort database.

Exposures and outcomes	Variables
Exposures	
Patient characteristics	Age, sex, comorbidities, social economic status, rurality, and geographic region
Cancer characteristics	Method of diagnosis, symptoms, stage at diagnosis, and histopathologic features
Treatment	Surgical excision, chemotherapy, and radiation therapy
Health care providers	Practice setting, specialization, and volume
Treating institution/hospital	Setting, type, and presence of multidisciplinary care
Outcomes	
Diagnostic and surveillance investigations	Endoscopic, local-regional, and metastatic disease assessments and tumor markers
Completeness and quality of treatments	Quality of surgical excision, completeness of neoadjuvant and adjuvant therapies, and interruptions in treatments
Timeliness of care	Diagnosis to investigations, investigations to first treatment, time between treatments, and appropriate timing of surveillance
Adherence to standard or recommended care	Adherence to staging and treatment and surveillance recommendations based on the stage of disease
Fragmentation of the delivery of care	Consistent versus inconsistent site of the delivery of surgery, radiation, or chemotherapy
Utilization of treatments for metastatic disease	Utilization of surgical resection, radiation, and chemotherapy
Symptom burden	Patient-reported symptoms in various domains and symptom trajectory over time
Survival	Overall survival and cancer-specific survival

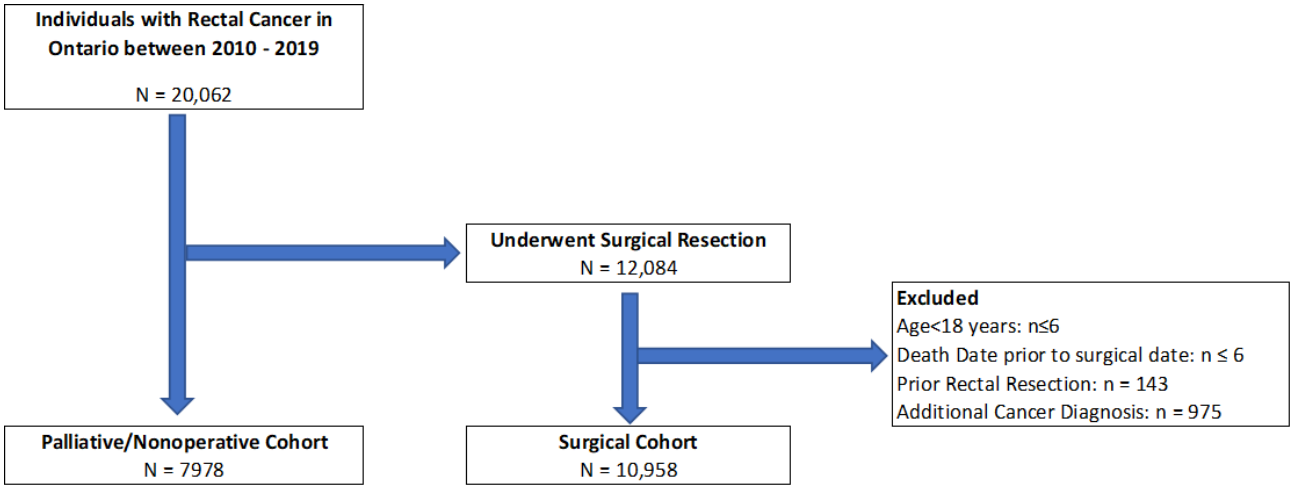
Ethics Approval

Ethics approval for this research was obtained through the Queen's University Health Research Ethics Board (approved on October 20, 2020; reference number: 6019418). A number of potential issues were addressed, including how personal health information will be used, the necessity for the linkage of personal health information with other information, and how the linkage would be completed. In addition, we identified potential harms and how they would be mitigated by using previously developed data confidentiality and privacy protocols, via appropriate data handling and curating, via the use of encryption, and via storage on a restricted server behind a firewall. The study will take place at the Queen's Cancer Research Institute – Cancer Care Epidemiology, which has undergone previous external audits pertaining to data curation and security.

Results

We identified approximately 20,062 individuals with a new diagnosis of rectal cancer during the study period. After exclusions, 10,957 unique individuals underwent curative intent surgical resection, while 7980 did not (Figure 1). The average age at the time of diagnosis was 64.9 (SD 12.6) years, with men accounting for 62.8% (6887/10,957) of those included in the surgical cohort. Individuals from a rural setting accounted for 19.3% (2116/10,957), while there was an equal distribution of individuals among income quintiles (lowest quintile: 2193/10,957, 20%; quintile 2: 2248/10,957, 20.5%; quintile 3: 2138/10,957, 19.5%; quintile 4: 2167/10,957, 19.8%; highest quintile: 2148/10,957, 19.6%). Treatment occurred most commonly at a regional cancer center (5914/10,957, 54%), followed by an affiliated cancer center (3626/10,957, 33.1%) and a satellite or nondesignated cancer center (1401/10,957, 12.8%). Adherence to staging investigations, including local-regional and metastatic assessments, occurred in 74.1% (8111/10,957) of individuals. Of the eligible individuals, 62.1% (4148/6681) received radiation therapy, and 58% (3877/6681) received adjuvant chemotherapy.

Figure 1. Cohort flow sheet.



Discussion

Protocol Overview

The overall objective of the OntaReCC is to provide a comprehensive data set of individuals diagnosed with rectal cancer in Ontario, and it will include details on the complete cancer journey (from diagnosis to death). This data set will allow investigators to assess the real-world, population-level outcomes of these individuals and allow for an assessment of the performance of the cancer system. A number of research themes will be explored by using the OntaReCC database, including (1) the regional variability in the delivery of care and outcomes, (2) the predictors and impact of adherence to recommended care, and (3) assessments of other understudied areas of rectal cancer care.

Regional Variability in the Delivery of Care and Outcomes

Regional variability in survival following the treatment of colorectal cancer has been reported by the Cancer System Quality Index [11]. This report demonstrated a 10% absolute difference in 5-year mortality between the best- and worst-performing regions within Ontario. Other publications identified similar themes [2], demonstrating large variations in 5-year survival between regions and between hospitals despite them having a similar case mix. Members of our group have explored the variation in the delivery of care for individuals with colon cancer. Within this population, significant variations were observed in the use of preoperative investigations [12], surgical quality and pathologic assessments [13,14], and treatment delivery to specific populations [8,9,15,16]. We anticipate similar themes for individuals with rectal cancer, and due to the increased complexity of care, we expect that the magnitude of difference will be greater. The proposed cohort will allow for the assessment of variability in the delivery of care based on geography, hospital type (ie, the presence of a multidisciplinary cancer center), and hospital volume. Importantly, we will use this comprehensive data set to identify predictors of variations in care and outcomes for potential knowledge translation and for interventions at the hospital and regional levels.

Predictors and Impact of Adherence to Recommended Care

Cancer Care Ontario has developed recommendations for the care of individuals with rectal cancer [17]. These recommendations are consistent with those proposed in other jurisdictions within Canada and elsewhere [18]. Despite the wide availability of clinical practice guidelines and recommendations, significant variability in adherence has been demonstrated in a number of studies [19-24]. The OntaReCC will be utilized to assess the predictors of adherence to recommended care. In addition, we will be able to assess the impact of guideline-adherent care on patient outcomes.

Assessment of Understudied Areas of Rectal Cancer Care

Practice patterns and outcomes of understudied aspects of rectal cancer care will be assessed, including the treatment of early rectal cancer and end-of-life care.

Practice Patterns and Outcomes in Individuals With Early-Stage Rectal Cancer

The OntaReCC will provide an opportunity to explore the practice patterns and outcomes of individuals with early-stage rectal cancer. Although major surgical resection remains the standard of care for many individuals undergoing curative-intent rectal cancer surgery, these procedures have the potential for significant morbidities and poor functional results. In addition, a number of individuals will be required to undergo a permanent colostomy as an outcome of these procedures. Consequently, there has been great interest in avoiding major resection, especially for individuals with early-stage disease. Local excision/polypectomy has been proposed as an adequate alternative for carefully selected individuals [17,25]. Some studies have questioned the safety of this approach [26] and found that careful patient selection is important in ensuring acceptable outcomes. The OntaReCC will allow for the assessment of the appropriateness of local excision (through histopathology data), the risk of local recurrence requiring surgical excision, the risk of metastatic disease, and the impact on overall survival.

End-of-Life Care

The type and delivery of care for individuals in their last month of life have been inadequately studied for those with rectal cancer. Our group has assessed potentially aggressive treatments, symptom burden, and the utilization of palliative care services for other disease sites [27-29]. These population-based studies identified the inconsistent delivery of palliative care treatments, high rates of potentially aggressive interventions, and significant symptom burden among many patients. The OntaReCC database will describe variations in end-of-life care and outcomes for this understudied population.

Strengths and Limitations

As described above, the OntaReCC database will have a near-complete capture of incident rectal cancer cases in Ontario during the study period. Unlike the Surveillance, Epidemiology, and End Results program (around 30% capture) [30] and the National Cancer Database (around 70% capture) [31], the OCR has a near-complete capture of incident colorectal cancer cases [6,7]. As treatment for colorectal cancer is almost exclusively provided through the publicly funded health care system, the linked administrative databases provide a complete description of an individual's cancer care journey. Low losses to follow-up are expected, regardless of the location or institution in which an individual receives care. By using detailed histopathology data, a comprehensive assessment can be undertaken, which is often not possible with other large population-level data sets or registries. The described cohort will also allow for an assessment of the symptoms that an individual experiences throughout their treatments and follow-ups, which is another unique aspect of the OntaReCC.

Although the proposed cohort will allow for a comprehensive assessment of individuals with rectal cancer, limitations to such population health research exist. First, the reasons behind treatment decisions and patient preferences are unknown. Nonadherence or variations in care may be partially explained by an individual refusing aspects of care or preferring nonstandard approaches, which will not be captured. Second, we will be unable to capture the reasons behind delays in treatment or care, which could be related to nonmodifiable factors. Third, we will not have access to detailed diagnostic radiology reports. This will limit our ability to assess the pretreatment stage of disease (which is primarily determined through magnetic resonance imaging) and the ability to fully capture the development of metastatic disease. Our data set will identify metastatic disease that is either treated (ie, via resection or other local therapies) or documented within applicable linked data sets. Finally, a number of potentially pertinent patient characteristics are not captured well within the available data sets, including individuals' level of education, employment status, race/ethnicity, obesity, and alcohol or cigarette use.

Conclusions

The OntaReCC will provide a comprehensive and complete assessment of the care and outcomes of individuals diagnosed with rectal cancer in Ontario. The data set will be an important resource in evaluating the real-world management and outcomes of individuals with rectal cancer. In doing so, we will be able to identify opportunities for improving the delivery of cancer care to this group of individuals.

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Authors' Contributions

SP, C Booth, SJM, CH, and C Bankhead were responsible for study conception. All authors were responsible for the study design. SP drafted the manuscript, and all authors revised the manuscript. CM was responsible for data acquisition. All authors have given their final approval of the manuscript and are accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Canadian Institutes of Health Research / Instituts de recherche en santé du canada (CIHR/IRSC).
[PDF File (Adobe PDF File), 106 KB - resprot_v11i8e38874_app1.pdf]

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Abbreviations

ICD-10: *International Classification of Diseases, Tenth Revision*
OCR: Ontario Cancer Registry
OntaReCC: Ontario Rectal Cancer Cohort

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Protocol

Utilizing Real-time Technology to Assess the Impact of Home Environmental Exposures on Asthma Symptoms: Protocol for an Observational Pilot Study

Sharmilee Nyenhuis[1], MD; Emily Cramer[2,3], PhD; Matthew Grande[4], BSc; Luz Huntington-Moskos[5], RN, CPN, PhD; Kathryn Krueger[6], CPH, MPH; Olivia Bimbi[7], BSN, RN; Barbara Polivka[6], RN, PhD; Kamal Eldeirawi[7], RN, PhD

[1]Section of Allergy and Immunology, Department of Pediatrics, University of Chicago, Chicago, IL, United States

[2]Biostatistics & Epidemiology Core, Health Services & Outcomes Research, Children's Mercy Research Institute, Kansas City, MO, United States

[3]School of Medicine, University of Missouri-Kansas City, Kansas City, IL, United States

[4]College of Medicine, University of Illinois Chicago, Chicago, IL, United States

[5]School of Nursing, University of Louisville, Louisville, KY, United States

[6]School of Nursing, University of Kansas, Kansas City, KS, United States

[7]College of Nursing, University of Illinois Chicago, Chicago, IL, United States

Corresponding Author:
Sharmilee Nyenhuis, MD
Section of Allergy and Immunology
Department of Pediatrics
University of Chicago
5841 S. Maryland Ave.
MC 5042
Chicago, IL, 60637
United States
Phone: 1 773 834 7121
Email: snyenhuis@bsd.uchicago.edu

Abstract

Background: It is estimated that over 60% of adults with asthma have uncontrolled symptoms, representing a substantial health and economic impact. The effects of the home environment and exposure to volatile organic compounds (VOCs) and fine particulate matter ($PM_{2.5}$) on adults with asthma remain unknown. In addition, methods currently used to assess the home environment do not capture real-time data on potentially modifiable environmental exposures or their effect on asthma symptoms.

Objective: The aims of this study are to (1) determine the feasibility and usability of ecological momentary assessment (EMA) to assess self-report residential environmental exposures and asthma symptoms, home monitoring of objective environmental exposures (total VOCs and $PM_{2.5}$), and lung function in terms of forced expiratory volume in 1 second (FEV_1%); (2) assess the frequency and level of residential environmental exposures (eg, disinfectants/cleaners, secondhand smoke) via self-reported data and home monitoring objective measures; (3) assess the level of asthma control as indicated by self-reported asthma symptoms and lung function; and (4) explore associations of self-reported and objective measures of residential environmental exposures with self-reported and objective measures of asthma control.

Methods: We will recruit 50 adults with asthma who have completed our online Global COVID-19 Asthma Study, indicated willingness to be contacted for future studies, reported high use of disinfectant/cleaning products, and have asthma that is not well controlled. Participants will receive an indoor air quality monitor and a home spirometer to measure VOCs, $PM_{2.5}$, and FEV_1%, respectively. EMA data will be collected using a personal smartphone and EMA software platform. Participants will be sent scheduled and random EMA notifications to assess asthma symptoms, environmental exposures, lung function, and mitigation strategies. After the 14-day data collection period, participants will respond to survey items related to acceptability, appropriateness, and feasibility.

Results: This study was funded in March 2021. We pilot tested our procedures and began recruitment in April 2022. The anticipated completion of the study is 2023.

Conclusions: Findings from this feasibility study will support a powered study to address the impact of home environmental exposures on asthma symptoms and develop tailored, home-based asthma interventions that are responsive to the changing home environment and home routines.

Trial Registration: ClinicalTrials.gov NCT05224076; https://clinicaltrials.gov/ct2/show/NCT05224076

International Registered Report Identifier (IRRID): DERR1-10.2196/39887

(JMIR Res Protoc 2022;11(8):e39887) doi:10.2196/39887

KEYWORDS

asthma; home environment; ecologic momentary assessment; air quality; spirometry

Introduction

Background

Asthma is a disease of chronic airway inflammation that affects 1 in 12 adults in the United States [1]. Despite effective treatments for asthma, it is estimated that over 60% of adults with asthma have uncontrolled symptoms [2]. Poorly controlled asthma increases the risk of severe asthma exacerbations, which may result in missed workdays, emergency room visits, and hospitalizations [3].

Adults usually spend the majority of their day indoors (~15 hours/day) [4,5], and during the COVID-19 pandemic, the number of hours spent at home increased due to lockdown orders and personal precautions. Environmental triggers of asthma identified in residential settings include aeroallergens (eg, dust mites, animal dander), moisture, tobacco smoke, particulate matter (PM), volatile organic compounds (VOCs), and nitrogen dioxide [3,6,7]. In adults with asthma, indoor residential air quality has been associated with decreased general health, airway inflammation, asthma exacerbation, and decreased lung function [8-12]. In particular, there is strong evidence suggesting that indoor VOCs, especially aromatic and aliphatic compounds, are associated with increased asthma symptoms [12].

VOCs are widely used as ingredients in household products, including cleaning, disinfecting, cosmetic, degreasing, and hobby products. Early in the pandemic, it was recommended to disinfect surfaces with a US Environmental Protection Agency (EPA)–registered household disinfectant [13]. While the effects of disinfectants on adults with asthma have been widely explored in occupational settings, less is known about their impact in the home environment. Our team examined disinfectant use by adults with asthma using an online global survey between May and October 2020. We found a dramatic increase in household disinfectant use during the pandemic, and this correlated with poorer asthma control [14]. What is not known is the extent to which adults with asthma routinely engage in these types of practices, how often they clean/disinfect, and what impact these practices have on their asthma. In addition, data on how these environmental exposures impact asthma symptoms in real time are not available.

PM are small particles or liquid droplets that include acids, organic chemicals, metals, soils, dust, and allergens [15]. Common indoor sources of particulates include vacuum cleaner bags, printers, cooking, secondhand smoke, wood combustion in fireplaces or stoves, dust, pet hair, mold, candles, and outside and biological sources [10,16]. A study found that concentrations of fine particulates less than 2.5 micrometers ($PM_{2.5}$) were highest indoors in homes (versus outdoors or in offices) on weekends when participants wearing personal air quality monitors were at home for longer periods [17], thus supporting the increased potential exposure to particulates during the COVID-19 pandemic. $PM_{2.5}$ have been shown to affect cardiovascular health, anxiety, cognitive function, and respiratory health [16]. However, the effects of indoor $PM_{2.5}$ on asthma are still unclear [12]. Increased frequency and severity of asthma exacerbations, symptoms, hospitalizations, and mortality were associated with increased ambient $PM_{2.5}$ [18-21]. Existing research on VOCs and particulate matter provides a strong scientific premise for further exploration of these exposures in the home. We aim to extend the existing research to develop innovative intervention strategies for those with asthma, thereby addressing the impact of changes in environmental exposures related but not limited to COVID-19 and enhancing our preparedness for future infectious disease outbreaks.

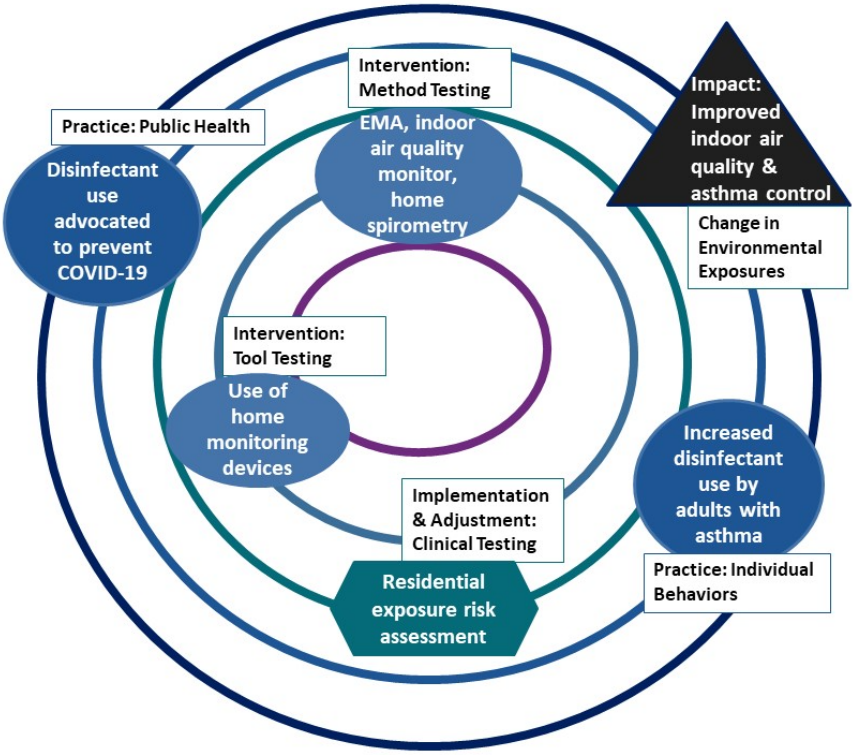
Collecting home air quality data and asthma symptoms typically rely on subjective patient report, which is impacted by recall bias and resource-intensive methods, such as collection of environmental samples from homes. These methods have made it difficult to fully assess the impact of potentially modifiable home environmental exposures on asthma symptoms in real time or provide practical and timely interventions to reduce exposures and disease burden. Ecological momentary assessment (EMA) allows for the collection of time-dependent, real-time data on self-report measures. Thus, EMA reduces potential biases and enhances ecological validity by taking measurements in real time in the settings where they occur, providing high-quality longitudinal data. EMA has been increasingly applied to diseases impacted by lifestyle and outdoor environmental exposures, including studies of asthma-related exposures [3-5]. Yet, there is limited research utilizing EMA to capture in real-time the impact of home environmental exposures on asthma symptoms. To complement EMA-captured subjective data on symptoms, recently developed commercial home environment sensors, such as the Awair system, have been increasingly used to efficiently collect objective and continuous data on multiple measures of home air quality (eg, VOCs, $PM_{2.5}$). These validated sensors and EMA provide real-time environmental exposure data; however, they have yet to be used to examine the home air quality of adults with asthma and its associations with symptoms in real time [22-25].

Accordingly, this study aims to assess the feasibility and usability of EMA to capture the context of real-time behaviors and environmental exposures that impact indoor environments. In addition, this study assesses the feasibility and usability of providing participants with an indoor air quality monitor (Awair Omni) to continuously capture total VOCs and $PM_{2.5}$. This design will allow us to alert participants of high levels of VOCs and $PM_{2.5}$ and collect real-time data on exposure and asthma symptoms. Daily and exposure-related lung function will be measured with a low-cost home spirometer. Finally, we will examine the effect of residential environmental exposures that may be related to time spent at home and the associations between these exposures and asthma control. In this paper, we will describe the study protocol and outline how multiple commercially available technologies that measure air quality, lung function, and EMA were harmoniously blended and refined prior to pilot testing.

Conceptual Framework

Research efforts that focus on indoor home environments are essential to elucidate the possible extent of exposures that can impact asthma outcomes and further exacerbate the risk of hospitalization in a time when home and health care resources continue to be strained. We illustrate the goals of our feasibility study and the impacts we intend to accomplish using the Translational Research Framework [26,27]. This feasibility study will assess residential exposures of disinfectants and particulates with the goal of reducing exposures and improving asthma outcomes (Figure 1).

Figure 1. Application of the National Institute of Environmental Health Sciences (NIEHS) Translational Research Framework. EMA: ecological momentary assessment.



Objectives

The aims of this study are to (1) determine the feasibility and usability of EMA to assess self-report residential environmental exposures and asthma symptoms, home monitoring of objective environmental exposures (total VOCs and PM2.5), and lung function in terms of forced expiratory volume in 1 second (FEV_1%); (2) assess the frequency and level of residential environmental exposures (eg, disinfectants/cleaners, secondhand smoke) via self-reported data and home monitoring objective measures; (3) assess the level of asthma control as indicated by self-reported asthma symptoms and lung function; and (4) explore associations of self-reported and objective measures of residential environmental exposures with self-reported and objective measures of asthma control.

Methods

Project Overview

We will recruit 50 adults with asthma who completed our online Global COVID-19 Asthma Study (GCAS), indicated willingness to be contacted for future research, reported high use of disinfectant/cleaning products, and have suboptimally controlled asthma [14]. Participants will receive an indoor air quality monitor and a home spirometer to measure VOCs, $PM_{2.5}$, and forced expiratory volume in 1 second (FEV_1%), respectively. EMA survey data will be collected using a personal smartphone and the PiLR Health software platform [28]. Participants will be sent scheduled and random EMA notifications to assess asthma symptoms, environmental exposures, lung function, and mitigation strategies. After the 14-day data collection period, participants will respond to survey items related to acceptability,

appropriateness, and feasibility. In addition, a random sample of 20 participants will be interviewed to provide further insights.

Ethics Approval

All studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and approved by the relevant institutional review boards at the University of Kansas (STUDY00145830), University of Louisville (21.0466), University of Illinois Chicago (2020-0851), and University of Chicago (22-0767).

Study Components

Figure 2 shows the study components. The Awair Omni Indoor Air Quality Monitor continuously monitors about 1000 square feet of indoor air for 7 air quality indicators: total VOC, $PM_{2.5}$, temperature, humidity, carbon dioxide, ambient light, and ambient noise [29]. This feasibility study will only focus on VOCs and $PM_{2.5}$ levels (Table 1). The Awair Omni device measures about 4 × 4 × 1.3 inches, is Wi-Fi and Bluetooth–enabled, plugs into a standard alternating current (AC) outlet, and includes an 8-hour battery backup. An air quality reading will be taken every 10 seconds and real-time data uploaded to a dashboard accessed only by research personnel. The Awair Omni proprietary dashboard provides secure communication between the Awair Omni and its dashboard. Data will be exported from the dashboard as a .CSV file [30-34].

Figure 2. Study components. EMA: ecological momentary assessment; $PM_{2.5}$: fine particulate matter; VOC: volatile organic compound.

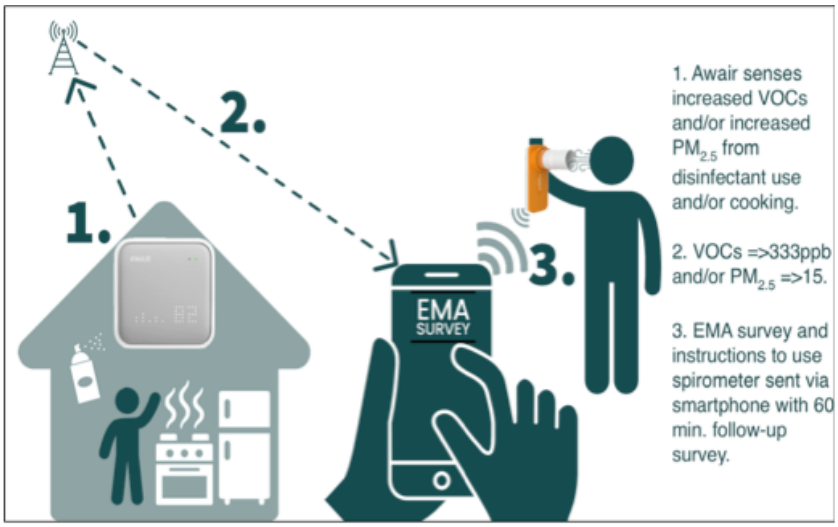


Table 1. Type and range of air quality measures.

Exposure	Sensor	Detectable range/ accuracy	Optimal range
VOCs[a]	Multipixel metal oxide semiconductor gas sensor	0-60,000 ppb/±10%	<333 ppb
$PM_{2.5}$[b]	Laser-based light scattering particle sensor	0-1000 μg/m^3/±15 μg/m^3 or 15%	<15 μg/m^3

[a]VOC: volatile organic compound.

[b]$PM_{2.5}$: fine particulate matter.

EMA is a survey approach that uses repeated assessment of participants to capture behaviors and experiences in a real-time context. This methodological approach maintains the ecological validity of reported behaviors and decreases the impact of recall bias because surveys are sent periodically to participants through electronic devices [35]. EMA is particularly useful when trying to understand the context of symptoms or behaviors. Available literature that combines the EMA methodology with asthma research focuses primarily on asthma-related outcomes such as symptoms, control, quality of life, history, and medication adherence and their relationship with stress (ie, perceived stress, mood, hassles, and social support) [36-38]. The ability to time stamp behaviors, events, and experiences and determine whether they present a positive or negative health impact is valuable when seeking to understand the complexity of multiple risk factors and multiple environmental and behavioral interactions. EMA data will be collected electronically using the PiLR EMA software platform, which can be installed on a personal smartphone (iOS or Android) [28]. Data captured will be transmitted to the PiLR EMA platform and stored in a secure database in the cloud. Participants will receive prescheduled notifications asking them to complete small surveys. In addition, we collaborated with PiLR staff to configure the EMA platform to send EMA notifications based on certain logics and triggers (ie, VOC and $PM_{2.5}$ readings exceeding the optimal ranges outlined in Table 1). Researchers can access the PiLR dashboard to monitor participants' use of the EMA app and review their data.

The ZEPHYRx Spirometer system allows for laboratory-quality pulmonary function tests (PFTs) at home, such as forced vital

capacity (FVC), FEV_1, FEV_1/FVC, and flow-volume loop [39]. The system consists of a Food and Drug Administration (FDA)–approved handheld Bluetooth spirometer (MIR Spirobank Smart), and a mobile application that works on a smartphone or tablet device. The spirometer measures 49 × 109 × 21 mm and weighs 60.7 grams. Participants will share PFT results through the ZEPHYRx app, and the research team members will access a Health Insurance Portability and Accountability Act (HIPAA)–compliant portal to view participants' PFT results in real time. An in-app video coaching feature guides the participant through the PFT maneuver. Each maneuver conducted by the participant creates a time and date–stamped American Thoracic Society standard PFT report accessible through the portal. Deidentified data will be exported from the dashboard as a .CSV file.

Participants and Recruitment

Participants

This study builds on data collected from the GCAS, a cross-sectional online survey we conducted in 2020 to examine how the COVID-19 pandemic affected the prevalence of disinfectant use among adults with asthma and to assess the association between the frequency of disinfectant use and asthma control as measured by the Asthma Control Test (ACT) [14]. Over 1300 individuals responded. Of those, 93.4% (n=934) indicated they are based in the United States, 78.5% (n=783) are female, about 23% (n=225) indicated a minority race/ethnicity, and 741 agreed to be contacted for follow-up research. About 57% (n=422) used disinfectant/cleaning products ≥5 times per week.

Inclusion/Exclusion Criteria

Eligibility criteria include GCAS participants who (1) indicated willingness to be contacted for future research and provided an email address or phone number and (2) reported high use of disinfectant/cleaning products since COVID-19 (≥5 per week) and current ACT ≤19 or ≥2 asthma exacerbations in the past 12 months. The commonly used and validated ACT includes 5 items addressing asthma symptoms, use of rescue medications, and effect of asthma on daily functioning. Responses are summed for total ACT score with scores ≤19 indicating asthma that is not well controlled [40,41]. Non-US residents and non-English speakers are excluded. We will strive to have at least 20% of the sample represent ethnic/racial minority populations.

Recruitment

A total of 50 individuals with at least 20%-40% of the sample representing individuals who self-identify as being of a minority race/ethnicity (Hispanic, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Arab, multiracial, or other race) who meet the eligibility criteria will be randomly selected and invited to participate in this study via email or phone. Invites will be sent to selected individuals on a staggered timeline based on response rate and positive participation interest. Participants will be randomized within their participant category (ie, White or minority race/ethnicity). Participants within each category will be randomly assigned an order number using a random number generator in Excel (Microsoft). Participants will be recruited in the order of their random assignment until we have recruited a total of 50.

Using the randomized order assignment, invitations will be sent to 2 to 5 individuals from each group at a time, with the intent of enrolling initially up to 5 participants at any 1 time. If fewer than 5 consent to participate in any wave of invitations, invitations will be sent to the next potential participants in the randomized order assignment. We will scale up to 10 to 15 enrolled participants once we have passed the initial start-up period. The staggered recruitment process will be repeated until 50 individuals including at least 20%-40% minorities have completed study participation. Recruitment will focus on equal numbers from each participant category (ie, 25 each). However, given the smaller initial pool, if we are unable to recruit 25 minority participants, additional participants will be recruited from the White participant pool until a total of 50 participants are enrolled.

Interested individuals will be directed to a Research Electronic Data Capture (REDCap) survey link to confirm willingness to participate, verify eligibility, and provide current contact information. REDCap will be formatted to automatically send 2 additional email invitations 1 week apart if no response is received. If no response is received after the second email invitation and a phone number is provided, a phone call contact will be attempted. If no phone number is provided, a third follow-up email will be sent. A total of 3 contact attempts over a 3-week period with 1 week between each contact will be made to each invited individual. We will randomly select replacements if no response is received after 3 contact attempts, lack of interest is indicated, or inclusion/exclusion criteria are not met.

Development and Testing of EMA

Four types of EMA surveys will be sent to participants: a daily morning survey (ie, Daily Survey) inquiring whether participants had asthma symptoms and requesting participants use their ZEPHYRx spirometer; 2 daily random surveys (ie, Random Surveys) to assess disinfectant use and asthma symptoms and remind those with asthma symptoms to use their spirometer; and 2 triggered surveys based on elevated VOCs and/or $PM_{2.5}$ levels as captured by Awair Omni. The first triggered survey (ie, Air Quality Event Survey) will be sent to participants as soon as elevated levels of VOCs or $PM_{2.5}$ levels are detected to assess behaviors or environmental changes that may have caused elevation, ask participants to report any asthma symptoms they are experiencing, and remind them to use their spirometer. The second triggered survey (ie, Air Quality Follow-up Survey) will follow 1 hour after the trigger event (ie, elevated VOC or $PM_{2.5}$) and will assess interventions by participants to improve the indoor air quality or reduce their exposure (eg, open a window, leave the room) and any ongoing asthma symptoms. All these surveys were built on the PiLR dashboard by study team members after receiving orientation by PiLR staff. After creating the surveys, research team members were added as "participants" to allow for rigorous testing of the surveys, prompts, skip logics, and so on. Sending EMA surveys triggered by Awair Omni readings required significant programming conducted by PiLR staff. Primary considerations for scheduling

the triggered surveys were timing of the survey prompt relative to the event (ie, prompt sent as close to the event as possible) while reducing burden on participant for the number of prompts received (ie, VOC/$PM_{2.5}$ levels may "bounce" above and below the threshold several times within a small interval of time). Real-time data resulted in frequent prompts to respond to the same event, whereas 5-minute averages could result in delay of a few minutes between actual event and the deployment of the survey prompt. Several team members received Awair Omni devices and used them to assess the functionality and potential burden on participants and test the link between Awair Omni readings and EMA triggered surveys to ensure that the proper link is established and real-time data on VOCs and $PM_{2.5}$ are captured that will trigger EMA surveys.

Development of Participant Guides for Research Tools

How-to guides were developed to describe the set-up and use of each research tool. The goal was to create a seamless guide with step-by-step pictures so a participant could easily follow and pinpoint any missteps. The currently available user guides from the specific companies (ZEPHYRx, Awair Omni, and PiLR EMA) were used as templates, with additional specificity added as needed. For each device, research team members downloaded the app, set up the device, took screenshots of the processes, and wrote step-by-step instructions of the set-up. Issues faced while developing the guides included variations between phone types (eg, iPhone, Android) and software updates that occurred during testing requiring adjustments in the guides. An asthma-focused community advisory board hosted and led by the Chicago Asthma Consortium was utilized to review the guides and provide feedback. This feedback was incorporated into each guide. Suggestions included having study team contact information readily available in case of any issues and using highlighted boxes to relay important information.

Baseline Measures

Measures that will be administered at baseline via REDCap are outlined in Textbox 1.

Textbox 1. Measures to be administered at baseline via Research Electronic Data Capture (REDCap).

1. Adult Asthma History includes 5 items adapted from the Behavioral Risk Factor Surveillance System Survey [42] and 3 items from the Airborne Exposures PROMIS (Patient-Reported Outcomes Measurement Information System) Pool V1.0 Dyspnea Airborne Exposure. Four items address participants' recent contact with health care professionals for asthma. A fifth item addresses changes in routine work/activities due to asthma. An additional 3 items address airborne allergens, pollutants, and living in an area with extreme temperature changes using yes/no response options.
2. Adult Asthma Adherence Questionnaire includes 5 items on following a prescribed asthma medication plan and barriers to following that plan [43].
3. Health Behaviors includes items addressing exercise, use of alcohol, vaping products, marijuana, and cigarettes.
4. Home Environmental Exposure data include time typically spent at home, exposure to residential secondhand smoke, use of hand sanitizer, disinfectants, room where most time is spent in the home, potential asthma triggers in that room (carpeting, vacuuming, flooring), potential asthma triggers in the room participants sleep in, and cleaning products used in the shower/tub, kitchen, and on furniture. Additional data will include frequency of cleaning these areas, exposure to fragrances in the home, use of dryer sheets, presence of plants in the home, use of allergy control covers for pillows and mattress, pets in the home, heating, ventilation, use of a humidifier, having an attached garage, and use of pesticides in the home [44,45].
5. Demographics include where participants live, education level, occupation, ZIP code, health insurance, rent/own home, type of home, number of people in the home, number of bedrooms, 8 items addressing feelings of worry/tiredness/anxiety, self-rated physical health, comorbidities, height/weight, COVID-19 exposure/infection status, COVID-19 vaccine status, face mask, impact of COVID-19 on finances/employment, and an open-ended question to address any additional concerns.
6. In terms of emotional support the PROMIS_SF_V2 Short Form 4A measures perceived feelings of support, being cared for, and valued (4 items) [46]. Higher scores indicate higher perceived emotional support.
7. Perceived Stress Scale includes 4 items measuring the degree to which situations in one's life are appraised as stressful. Higher scores indicate an increased level of perceived stress [47].

Subsequent Measures

Seven-Day Check-in

Open-ended questions will be asked to identify any troubleshooting areas, determine if adjustments need to be made, and assess ease of use of the app/devices. Participants will be asked how things went with each of the study tools (Awair Omni indoor air quality monitor, ZEPHYRx spirometer, and EMA). Additional things to be asked include feedback on the set-up materials provided prior to data collection, interactions with research staff, queries if a participant is nonresponsive to EMA prompts, and an open-ended general item about how the study is going. Interactions will be recorded and reviewed by the research team to identify patterns as well as any adjustments that are needed.

Participant Feasibility Assessment

At the end of the 14-day data collection period, participants will be asked to respond to a short REDCap survey assessing usability of the Awair Omni indoor air quality monitor (10 items), PiLR EMA Health app (10 items), and the ZEPHYRx home spirometer (10 items), with response ranging from 1 (strongly agree) to 5 (strongly disagree). After each section, there will be an open-ended item for participants to comment on what they liked or did not like about each study tool (Awair Omni air quality monitor, EMA, ZEPHYRx home spirometer). A random sample of 20 participants will be interviewed to further explore these factors using 4 open-ended questions: (1) "How did the study work for you?" (2) "Tell us what you liked/didn't like about the indoor air quality monitor." (3) "How did you feel about the integration of the various tools

(Awair Omni, ZEPHYRx, and EMA) in the study?" (4) "Is there anything else you'd like to tell us?"

Data Analysis Plan

Each day of observation will be divided into 4 periods between 6 AM and 10 AM that will be 4 hours each. Data from event-contingent prompts as well as fixed (ie, daily morning and 2 random) prompts will be analyzed. Multiple event–contingent prompts may occur within the same 4-hour window, in which case data will be averaged across all event-contingent prompts during that period. The daily morning survey is scheduled so that it will always occur within the first 4-hour window of the day, and the random prompts are scheduled so only 1 will occur within any of the 4-hour windows.

To address the first aim of this study, we will assess compliance in 4 areas: survey response, spirometry use, interventions to reduce exposure, and air quality monitoring. Survey response compliances will be measured using EMA prompts and defined by the total number of completed prompts of each type out of the number of EMA prompts of each type received. Behavioral compliance to use of the spirometer will be assessed as the number of times the participant used the spirometer out of the number of times the participant was prompted to use it. Compliance to completing interventions to reduce exposure following an air quality event will be assessed using completed follow-up surveys as the number of times the participant reported taking action to reduce exposure out of the number of event-contingent surveys where the participant indicated they were in the home at the time of the event. Air quality monitoring compliance will be assessed as the duration the indoor air quality monitor is used by each participant out of the total study time. Compliance in all 4 areas will be assessed for the entire study period as well as within the 4-hour daily windows.

The quantitative participant assessment of acceptability, appropriateness, and feasibility will be analyzed descriptively. Differences in use and acceptance by participant demographics will be examined to identify factors (eg, age, asthma symptoms, overall health, education) that may make participants more or less likely to use the monitors or respond to prompts. Qualitative interview data will be transcribed and uploaded to Dedoose qualitative analysis software (SocioCultural Research Consultants) for content analysis.

To address the second aim of this study, we will analyze baseline data on the current use and frequency of disinfectants/cleaners and exposure to environmental triggers (eg, secondhand smoke). Real-time self-reported data on disinfectant use throughout the study period obtained through the EMA studies will be analyzed for total use during the study period as well as trends within and across the daily time intervals (eg, levels reporting in morning versus evening survey windows). We will determine the prevalence of disinfectant use and frequency (percent of EMA prompts at which disinfectant use is reported). We will also obtain data from the Awair Omni dashboard to determine the number of times VOC and $PM_{2.5}$ levels exceed optimal levels, average daily levels, average levels per time, and fluctuations in VOC and $PM_{2.5}$. We will identify possible environmental triggers that contribute to high levels of VOCs and $PM_{2.5}$ and event-contingent prompts.

To address the third aim of this study, we will determine the baseline level of asthma control as reported by the ACT. We will use EMA to determine the level of asthma control over the study period as indicated by (A) asthma symptoms reported at each prompt and over the 14 days, (B) number of time periods in which participants report asthma symptoms, and (C) lung function as measured by FEV_1% predicted within 30 minutes of each event-contingent prompt. Asthma control will also be evaluated using EMA by exploring differences in variability in lung function.

We will use the data collected using the EMA approach to evaluate the fourth aim of this study. EMA data are multilevel, with time windows (level 1) nested in individual participant information (level 2). The exposure variables will include (1) baseline person-level variables such as self-reported use and frequency of disinfectant/cleaner use and $PM_{2.5}$ exposure, (2) time-level exposure frequency variables defined by the number of times VOC and $PM_{2.5}$ levels reach or exceed the threshold for the optimal readings per week, (3) time-level exposure level variables defined by the average scores of VOC and $PM_{2.5}$ levels in the time windows considered in the analysis, and (4) time-level exposure duration variables defined by the total time within the time windows that the VOC and $PM_{2.5}$ levels were elevated. The outcome variables that we will consider include occurrence of any asthma symptoms, inhaler use, and FEV_1% predicted within 30 minutes from the event-contingent prompt.

We will use multilevel binary logistic regression to examine the associations between the exposure variables and binary outcome variables. We will also use multilevel linear regression to examine associations between the exposure variables and predicted FEV_1%. We will control for both level 1 variables (time of day, day of week) and level 2 variables (baseline asthma symptoms, demographic characteristics). Using available time stamps from the indoor air quality monitor, EMA, and the spirometer, we will also explore average lag time between an event-contingent prompt and self-reported asthma symptoms using multilevel survival analyses.

Results

This project received funding in March 2021. The first year of this project has been spent focusing on determining the feasibility and usability of using an EMA to assess self-report of residential environmental exposures, home monitoring or environmental exposures, and lung function. This has involved creating participant research materials and developing and coordinating 4 diverse software platforms: REDCAp surveys, ZEPHYRx spirometer, Awair Omni home air quality monitor, and PiLR EMA. We pilot tested our procedures and began recruitment in March 2022. We anticipate study completion in 2023.

Discussion

Summary

This study contributes to our knowledge of the real-time impact of VOCs and $PM_{2.5}$ in the home environment on asthma in several ways. First, it addresses how increased cleaning and disinfecting practices could impact asthma control in people with asthma. This consideration is particularly relevant considering the COVID-19 pandemic, during which people have dramatically increased their use of disinfectants. This study also addresses the methodological shortcomings of previous studies of the home environment of adults with asthma, as we uniquely use real-time collection of symptoms data with EMA to examine the effects of environmental triggers on adult asthma symptoms, real-time objective residential exposure data (VOCs, $PM_{2.5}$), and we collect an objective measure of asthma control with the measurement of lung function.

Strengths

This study has several strengths. First, it builds on an ongoing study and will be conducted with individuals who have agreed to be recruited for future studies and thus facilitate enrollment. Second, participants will be drawn from a wide geographic area in the United States, which increases broad representation of participants. We will gather real-time environmental exposure data and indicators of asthma control in unregulated indoor home spaces without actual in-person contact. Findings from this study have the potential to impact recommendations for indoor use of disinfectants/cleaners for those with asthma and guide further research.

Anticipated Challenges and Limitations

There are a number of challenges we anticipate as we launch this feasibility study. First is the presence of the digital divide and the extent to which we may encounter it. The concept of the digital divide acknowledges that communities across nations have differing levels of access to technology, including smartphones, internet, and broadband infrastructure, which may be related to geography (rural versus urban), generational differences, comfort level with technology, and finances. As part of the feasibility design, we will document the impact of this differing access to better address challenges of the digital divide and promote inclusion of varied communities in future studies involving the indoor home environment and technology platforms.

Along with documenting the extent of the digital divide encountered in this study, our team is interested in addressing any ethical concerns that arise with using multiple technology platforms in the indoor home environment. Real-time data collected by Wi-Fi and Bluetooth–enabled devices may bring about unique ethical concerns that must be addressed to ensure privacy and confidentiality. Our team will address any ethical concerns in real time with the guidance of our institutional review board, and we will strive to share best practice when bringing such technology into homes with our research participants as partners in this process. The feasibility design of this study will allow us to purposefully address any challenges that may arise in a larger, powered study.

Conclusions

Findings from this study will provide preliminary data for a powered study to develop innovative intervention strategies for people with asthma and address the impact of changes in environmental exposures related to COVID-19, thereby enhancing our preparedness for future infectious disease outbreaks. This has implications for risk reduction in people with asthma to help improve asthma self-management using personal monitors and sensors for individually tailored exposure profiles.

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Conflicts of Interest

SN, KE, BP, LHZ, and EC receive funding from the National Institute of Environmental Health Sciences (NIEHS).

Multimedia Appendix 1
External peer-review report from the National Institute of Environmental Health Sciences Special Emphasis Panel - Emerging Research Opportunities in Environmental Health Sciences - Population-based Studies (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 136 KB - resprot_v11i8e39887_app1.pdf]

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Abbreviations

AC: alternating current
ACT: Asthma Control Test
EMA: ecological momentary assessment
EPA: Environmental Protection Agency
FEV_1%: forced expiratory volume in 1 second
FVC: forced vital capacity
GCAS: Global COVID-19 Asthma Study
HIPAA: Health Insurance Portability and Accountability Act
NIEHS: National Institute of Environmental Health Sciences
NIH: National Institutes of Health
PFT: pulmonary function test
PM: particulate matter
$PM_{2.5}$: fine particulate matter
PROMIS: patient-reported outcomes measurement information system
REDCap: Research Electronic Data Capture
VOC: volatile organic compound

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Protocol

Risk and Resilience Pathways, Community Adversity, Decision-making, and Alcohol Use Among Appalachian Adolescents: Protocol for the Longitudinal Young Mountaineer Health Study Cohort

Alfgeir L Kristjansson[1], PhD; Annette M Santilli[2], MA; Rosalina Mills[1], BA; Hannah M Layman[1], MPH; Megan L Smith[3], PhD; Michael J Mann[3], PhD; James MacKillop[4,5], PhD; Jack E James[6], PhD; Christa L Lilly[7], PhD; Steven M Kogan[8], PhD

[1]Department of Social and Behavioral Sciences, School of Public Health, West Virginia University, Morgantown, WV, United States
[2]School of Public Health, West Virginia University, Morgantown, WV, United States
[3]School of Public and Population Health, Boise State University, Boise, ID, United States
[4]Peter Boris Centre for Addictions Research, McMaster University, Hamilton, ON, Canada
[5]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada
[6]Department of Psychology, Reykjavik University, Reykjavik, Iceland
[7]Department of Epidemiology and Biostatistics, School of Public Health, West Virginia University, Morgantown, WV, United States
[8]Department of Human Development and Family Science, University of Georgia, Athens, GA, United States

Corresponding Author:
Alfgeir L Kristjansson, PhD
Department of Social and Behavioral Sciences
School of Public Health
West Virginia University
64 Medical Center Drive
Morgantown, WV, 26506
United States
Phone: 1 3042933129
Fax: 1 3042936685
Email: alkristjansson@hsc.wvu.edu

Abstract

Background: Alcohol use impairs psychosocial and neurocognitive development and increases the vulnerability of youth to academic failure, substance use disorders, and other mental health problems. The early onset of alcohol use in adolescents is of particular concern, forecasting substance abuse in later adolescence and adulthood. To date, evidence suggests that youth in rural areas are especially vulnerable to contextual and community factors that contribute to the early onset of alcohol use.

Objective: The objective of the Young Mountaineer Health Study is to investigate the influence of contextual and health behavior variables on the early onset of alcohol use among middle school–aged youth in resource-poor Appalachian rural communities.

Methods: This is a program of prospective cohort studies of approximately 2200 middle school youth from a range of 20 rural, small town, and small city (population <30,000) public schools in West Virginia. Students are participating in 6 waves of data collection (2 per year) over the course of middle school (sixth to eighth grades; fall and spring) from 2020 to 2023. On the basis of an organizational arrangement, which includes a team of local data collection leaders, supervising contact agents in schools, and an *honest broker* system to deidentify data linked via school IDs, we are able to collect novel forms of data (self-reported data, teacher-reported data, census-linked area data, and archival school records) while ensuring high rates of participation by a large majority of youth in each participating school.

Results: In the spring of 2021, 3 waves of student survey data, 2 waves of data from teachers, and a selection of archival school records were collected. Student survey wave 1 comprised 1349 (response rate 80.7%) participants, wave 2 comprised 1649 (response rate 87%) participants, and wave 3 comprised 1909 (response rate 83.1%) participants. The COVID-19 pandemic has had a negative impact on the sampling frame size, resulting in a reduced number of eligible students, particularly during the fall

of 2020. Nevertheless, our team structure and incentive system have proven vitally important in mitigating the potentially far greater negative impact of the pandemic on our data collection processes.

Conclusions: The Young Mountaineer Health Study will use a large data set to test pathways linking rural community disadvantage to alcohol misuse among early adolescents. Furthermore, the program will test hypotheses regarding contextual factors (eg, parenting practices and neighborhood collective efficacy) that protect youth from community disadvantage and explore alcohol antecedents in the onset of nicotine, marijuana, and other drug use. Data collection efforts have been successful despite interruptions caused by the COVID-19 pandemic in 2020 and 2021.

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KEYWORDS

adolescence; middle school; Appalachia; caffeine; alcohol use; Young Mountaineer Health Study; prevention

Introduction

Underage youth drink 11% of the total alcohol consumed in the United States [1]. The personal and social consequences of underage drinking are staggering; each year, approximately 5000 deaths of minors can be attributed to alcohol use [2]. Alcohol use impairs psychosocial and neurocognitive development and increases the vulnerability of youth to drug abuse, academic failure, high-risk sexual behavior, and mental health problems [1]. The onset of alcohol use during middle school years is particularly problematic, forecasting problems with alcohol and other substances during adolescence [3] and chronic substance use problems in adulthood [4].

The Young Mountaineer Health Study (YMHS) is a prospective school-based investigation of the development of alcohol use vulnerability among Appalachian youth in West Virginia (WV). WV, the only US state located entirely within the Appalachian region, has among the highest poverty rates in the United States [5]. The region's coal mining areas, in particular, evince low economic diversification, low employment in professional services, and low rates of educational attainment, which have contributed to pervasive health disparities [6,7] and epidemic levels of opioid abuse and mortality [8]. Historically, residing in rural communities in general, including Appalachian communities, has protected youth from many of the risk factors for early onset alcohol use encountered in urban settings. However, recent epidemiological research underscores the prevalence of alcohol use in adolescents and adult alcoholism in the resource-poor Appalachian environments [9-12]. Of particular concern, early onset alcohol use among rural Appalachian youth places them at risk for future substance use, including the nonmedical use of prescription drugs [13-15].

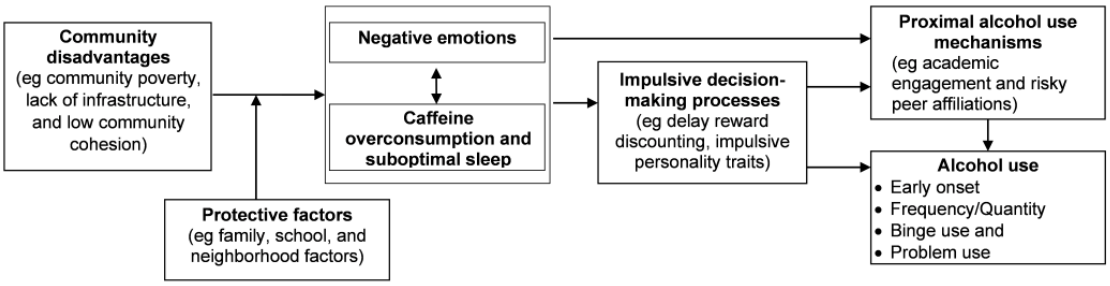
Current etiological models of the development of alcohol use vulnerability in the Appalachian region emphasize the proliferation of risk factors in resource-poor communities [16]. Poverty, isolation, and unemployment affect neighborhood, school, and family contexts. This, in turn, undermines academic engagement and increases the likelihood of alcohol use and affiliation with peers who support it [16]. Appalachian youth may be exposed to rearing environments that are generally more alcohol-friendly than those experienced by their urban peers [17]. Alcohol is readily available as surveillance of service to minors in alcohol retail outlets is less stringent in rural areas [2]. Investigations of unique stressors in Appalachian and other rural contexts have yielded considerable progress, informing an initial generation of prevention programs [18] and policy-related initiatives designed to reduce exposure of youth to key contextual risk factors. Nevertheless, emerging research on the influence of lifestyle factors on alcohol use vulnerability suggests that these models may omit important risk mechanisms, undermining the effectiveness of the programs they inform. In particular, this study considers the influence of caffeine use and sleep health in the etiology of early onset alcohol use.

Figure 1 presents the conceptual model guiding the study. It specifies the risk and protective pathways linking residence in disadvantaged community environments to the development of alcohol use vulnerability among Appalachian youth. As shown in Figure 1, disadvantaged community environments promote negative affect and problems concerning the regulation of emotions. Studies have documented elevated levels of depressive symptoms, anger, and anxiety in resource-poor Appalachian communities [19]. Similar links with emotion regulation, including emotional awareness and the ability to modulate distressing emotions, have emerged [20,21]. We hypothesize that negative emotionality, caffeine use, and sleep problems form a system of mutually reinforcing behaviors. The stimulant effects of caffeine tend to be short lived and followed by increased irritability and reductions in the quality [22] and quantity [23] of adolescents' sleep. Youth often increase their caffeine consumption to combat irritability and drowsiness, thus forming a cycle of reinforcement. Sleep may also be disrupted as a consequence of neighborhood disadvantage. Specifically, youth from resource-poor communities report more disruptions in sleep and greater negative consequences in school achievement because of sleep disruptions [23]. Thus, youth from resource-poor Appalachian environments may be expected to report heightened problems with negative emotions, caffeine use, and sleep problems.

We hypothesize that problems with sleep, caffeine, and negative emotionality carry forward to affect alcohol use through proximal alcohol use mechanisms, including youth self-regulation, youth academic engagement, and youths' affiliations with risk-taking peers. Negative affectivity promotes impulsive decision-making, which reduces the extent to which youth consider the consequences of alcohol use when faced with an opportunity to drink [24]. Cycles of irritability and negative emotionality reinforced by caffeine use and

sleep-related problems are expected to undermine academic achievement and school engagement. Reductions in academic engagement in middle school are robust antecedents of early onset alcohol use and alcohol misuse in high school [25]. Youth who experience negative emotions and impulsive decision-making, as well as those with low attachment to school, tend to select friends with similar characteristics who are likely to provide opportunities and reinforcement for using substances [26].

Figure 1. Risk and protective pathways linking community disadvantage to early adolescent alcohol use.



Despite exposure to community disadvantage, most young people avoid problems with alcohol use. Resilience models focus on the sources of this protection. As shown in Figure 1, we hypothesize that protective factors in the family, school, and local community contexts will attenuate the influence of community disadvantage on caffeine use and poor sleep, negative emotionality, and decision-making. The proximity, reliability, and durability of family relationships represent the focal points of life in Appalachian communities [27]. Multiple studies in other populations attest to the power of effective parenting practices to shield youth from the effects of poverty [28]. Protective parenting styles include high levels of youth monitoring, consistent discipline and family routines, and the expression of support and affection [29,30]. In studies of minority youth living in disadvantaged rural communities, these parenting styles attenuated the influence of poverty on a range of outcomes, including internalizing and externalizing problems and affiliation with deviant peers [31,32]. For youth residing in challenging communities, parental regulation and family routines foster self-regulation and emotion regulation, thus allowing them to stay focused on school and avoid risky peers and dangers in the community [33]. However, these factors have not yet been investigated in Appalachia.

For youth residing in disadvantaged communities, effective schools can be a refuge that supports social, emotional, and cognitive development [34]. In many central Appalachian communities, schools play a vital role in providing students with a life structure, a consistent supply of meals, and access to physical resources in a secure environment, which are not commonly available to students at home [35]. Students are more likely to engage in healthy behaviors and succeed academically when they feel strong connections with school [36]. The protective aspects of effective schools include classroom dynamics (high demand, high warmth teachers, and classroom consistency), school-wide climate (safety and positive affect), and opportunities to engage with extracurricular activities [37]. In Appalachia, geographic dispersion and a lack of municipal areas and infrastructure can create a strong sense of interdependence, trust, and cohesion among local community members [27]. Community systems have the potential to affect adolescent development, particularly when neighbors intervene to assist vulnerable families struggling with economic distress or substance-related problems [38]. Studies of disadvantaged communities have underscored the influence of collective efficacy in shielding adolescent development [39]. Collective efficacy includes collective socialization, neighbors taking responsibility for the care and monitoring of others' children, social cohesion, and a sense of trust in local community relationships. To our knowledge, prospective studies of the buffering influence of these factors on youth development in Appalachian communities have not been conducted.

In a sample of early adolescents in Appalachia, our three specific aims are as follows.

- To test the pathways linking community disadvantage to alcohol misuse; we expect community disadvantage to forecast slower growth in decision-making processes directly and indirectly via negative emotionality, which is reinforced by the use of caffeine and attendant problems with sleep; in turn, we expect negative emotionality and decision-making trajectories to forecast alcohol misuse directly and indirectly via proximal vulnerability factors (affiliation with risky peers and academic disengagement)
- To test hypotheses regarding contextual factors (eg, parenting practices and neighborhood collective efficacy) that protect youth from community disadvantage; we expect contextual protective factors to attenuate the influence of community disadvantage on negative emotionality, caffeine use and sleep problems, and decision-making trajectories
- To explore the aforementioned alcohol antecedents in the onset of nicotine, marijuana, and other drug use

Methods

Methodological Overview, Design Considerations, and the "Honest Broker" System

We proposed to test the hypotheses presented in Figure 1 in a prospective study of middle school youth from a range of rural, small town, and small city (population <30,000) public schools (N=20) in WV. Students will participate in 6 waves of data collection (2 per year) over the course of middle school (sixth to eighth grade). Drawing on our school partnerships and "honest broker" system described in the following paragraphs, we will be able to collect multimethod data (self-reported data,

teacher-reported data, school records, and census-linked area data) and ensure high rates of participation by most youth in each school. This design allows us to investigate growth and changes in alcohol use vulnerability factors across the transition to adolescence. This study was funded by the National Institute on Alcohol Abuse and Alcoholism, with an official start date of October 9, 2019 (Multimedia Appendix 1).

The YMHS uses a novel data collection system to gather prospective multimethod assessments and ensure high rates of participation by most youth in each school. At the same time, it should be acknowledged that prospective multimethod research through school systems poses unique challenges. The most significant involves obtaining sufficient percentages of youth whose parents consent to their participation. In resource-poor rural areas, the youth from whom data collection is most urgent may have disordered living situations that may prevent the obtaining of parental or caregiver consent for many young individuals. Over the past 8 years, our team has collaborated with school officials, parents, and the institutional review board (IRB) of the university to develop a system that addresses the needs and rights of youth and parents; the responsibilities of researchers, IRBs, and school officials; and the critical need for data on youth exposed to Appalachian poverty. In accordance with the Family Education Rights and Privacy Act guidelines, schools may collect data for evaluation purposes, and these data may be shared with researchers if deidentified to the investigative team. Thus, we developed a system of school contact agents and school-based officials who collect self-reported and school record data, which are deidentified before being accessed by study investigators and analysts via an "honest broker" system. The honest broker creates a research ID for each individual respondent and secures a key linking school ID numbers to the nonidentifiable research IDs. This deidentifies the data to the research team while allowing the collection of survey data, census-linked zip code information, and school record–based data for research purposes. Parents passively consent (by way of an opt-out letter sent to the home), and the youth provide informed assent for their participation. This facilitates the collection of prospective data from most students for research purposes. Importantly, researchers provide reports back to the schools, which allows them to identify the risk factors and needs for planning interventions and seeking funds for extracurricular and intervention-based activities within the school system. We pilot-tested this system by collecting 3 waves of data on an annual basis (2015-2018) from 16 middle schools in WV [40,41].

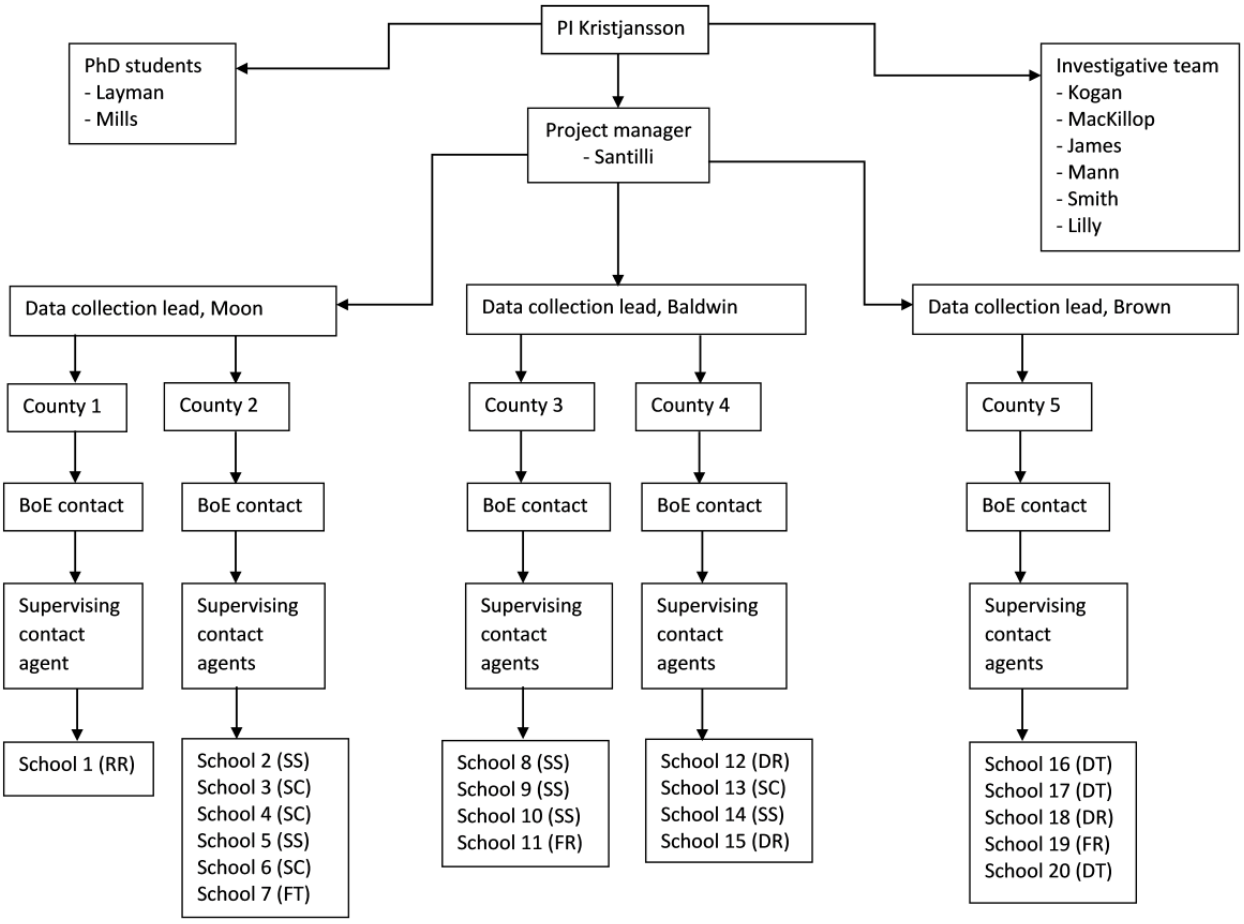
Recruitment Strategy

The baseline sampling frame included all sixth-grade students from 20 middle schools in 5 counties in WV (approximately 2200). Securing the recruitment of participants required the involvement of many parties. Given our preliminary data and previous data collection efforts in WV [41,42], it appeared logical to seek continued collaboration with public schools. The first step in securing their collaboration was to pursue approval from the highest level of educational authority at the local level, which, in WV, are the County Superintendents and the Boards of Education (BoEs). Counties were selected based on prior collaborations and their potential to contribute to a maximally diverse sample. Schools within the counties were included from communities designated as remote rural, distant rural, fringe rural, distant town, fringe town, small suburb, and small city [43]. To begin communication and outreach to counties and schools, the investigative team developed a Memorandum of Understanding (MoU), which described the project, its aims, school involvement, and school-based incentives. The MoU was then submitted and reviewed by the superintendents or their designees, which was subsequently followed by in-person meetings between the principal investigators and superintendents and a mutual signing of the MoUs. In some cases, this process required several meetings and involved other associated parties such as members of the BoEs, school principals, or their designees. The next step in this process was to engage in individual meetings with individual school principals. During this process, one county decided not to participate in the project, and another with a similar demographic profile was recruited in their place. Once principals had approved their schools to participate in the study, they were asked to nominate a supervising contact agent (SCA) for their school. The SCA is an individual in each school with whom the investigative team collaborated most closely regarding all aspects of the data collection, such as finding suitable dates and times and location of survey administration delivery. The SCA is often the principal, assistant principal, or guidance counselor. Acknowledging that schools are busy places with a different mission than that of collecting data for researchers, having access to a single individual in each school has proven very important for data collection quality and the securing of high response rates.

Organizational Chart

Figure 2 presents the organizational chart for the project, including the investigative team, students, and staff. Once funding was secured, we proceeded to complete the organization of the planned data collection procedures, which included the training and hiring of relevant personnel. A full-time project director and 3 data collection leaders were hired. In line with the principles of community-engaged research [44], an important prerequisite for hiring data collection leaders was their understanding and experience with local schools. The 3 data collection leaders were all either retired teachers or close to retirement teachers from the local communities of the schools. The fact that our data collection leaders are experienced teachers from the localities under investigation has proved vitally important in the mitigation of various challenges that have come up during data collection, including issues associated with the COVID-19 pandemic.

Figure 2. Young Mountaineer Health Study organizational chart. BoE: Board of Education; DR: distant rural (approximately 10 miles from town); DT: distant town (approximately 20 miles from city); FR: fringe rural (approximately 5 miles from town); FT: fringe town (approximately 5 miles from city; small suburban area within a city); PI: principal investigator; RR: remote rural (>25 miles from town); SC: small city.



Data Collection Methods and Measures

Data collection protocols include a student report survey, a teacher report survey, and archival data from the BoEs and schools. The student survey includes close to 300 variables and requires 1 full class period (approximately 45 minutes) to complete. Teacher survey data were collected from teachers for each participant. It includes 37 questions on three constructs: self-control [45], peer affiliations and social acceptance by peers [46], and problem behavior [47]. Finally, archival data are collected from the BoEs and schools and include zip codes, grades, free or reduced lunch status, and disciplinary actions. These data are collected routinely by schools, and zip codes are linked to area data from the American Community Survey to provide contextual information on community affluence.

Table 1 lists the constructs included in the data collection, their source, and relevant references.

Table 1. Measurement concepts in the Young Mountaineer Health Study.

Construct	Source	Reference
Family affluence	Student survey	Health Behavior in School-aged Children study [48]
School climate	Student survey	Resnick et al [36]
School as a protective factor	Student survey	Mann, MJ, unpublished data, May 2022
Peer delinquency	Student survey	Heimer and Matsueda [49]
Peer ATOD[a] use	Student survey	Kristjansson et al [50]
Perceived peer respect for ATOD use	Student survey	Kristjansson et al [50]
Perceived parental reactions to ATOD use	Student survey	Kristjansson et al [50]
Daytime sleepiness	Student survey	Meltzer et al [51]
Sleep disturbance	Student survey	Meltzer et al [51]
Caffeine consumption	Student survey	James et al [52]
ATOD use	Student survey	Monitoring the Future, ESPAD[b] [53,54]
Anxiety	Student survey	Derogatis et al [55]
Depressed mood	Student survey	Derogatis et al [55]
Anger	Student survey	Derogatis et al [55]
Conduct disorder	Student survey	Lewinsohn et al [56]
Family management	Student survey	Communities that Care [57]
Parental monitoring	Student survey	Sigfúsdóttir et al [58]
Social capital	Student survey	Sigfúsdóttir et al [58]
Dysfunctional parenting	Student survey	Arnold et al [59]
Caregiver support	Student survey	Schaefer [60]
Impulsive personality traits	Student survey	Watts et al [61]
Delayed reward discounting	Student survey	Kirby et al [62]
Community safety	Student survey	Echeverria et al [63]
Perceived access to drugs	Student survey	Cochran et al [64]
Neighborhood ties	Student survey	Bernburg et al [65]
Collective efficacy	Student survey	Sampson et al [39]
Organized leisure time activities	Student survey	Kristjansson et al [66]
Pubertal development	Student survey	Carskadon and Acebo [67]
Life satisfaction	Student survey	Seligson et al [68]
COVID-19 exposure and impact	Student survey	N/A[c]
Problem behavior	Teacher survey	Piper et al [47]
Peer affiliations and social acceptance	Teacher survey	Dishion et al [46]
Self-control	Teacher survey	Humphrey [45]
Zip codes	Schools/BoE[d]	N/A
Census tracks	Am Com survey	N/A
Grades	Schools/BoE	N/A
Free or reduced lunch status	Schools/BoE	N/A
Disciplinary actions	Schools/BoE	N/A

[a]ATOD: alcohol, tobacco, and other drugs.

[b]ESPAD: European School Survey Project on Alcohol and Other Drugs.

[c]N/A: not applicable.

[d]BoE: Board of Education.

Pilot Study

During the summer of 2020, the student survey was pilot-tested with a convenience sample of 15 youths (n=6, 40% boys; n=8, 53% girls; and n=1, 7% gender nonconforming) aged 11 to 12 years who lived in areas in WV that were not part of the YMHS study. The purpose of the pilot study was to assess the students' understanding of the questions and response categories and to determine the length of time required to complete the survey. Furthermore, a selection of teachers and SCAs reviewed both the study questionnaire and teacher survey. Comments from all parties were combined into a file and used to make minor adjustments to the wording and order of questions. Both the student and teacher surveys were deemed to be of appropriate length for completion in 1 full class period, and no pilot participants reported significant problems in understanding the survey items.

Data Collection Procedures

All parents or caregivers received an introductory letter 2 weeks before data collection, which described the study and permitted parents to opt out their children from participating. The letters were sent via regular mail, take-home mail with students, or email via school listservs. Many schools have used multiple ways of contacting parents or caregivers about study involvement. The youth report survey was administered via the Qualtrics platform during student attendance at the school. Qualtrics facilitates audio computer–assisted self-interviews for those who require this support. Organized by the project manager, data collection leaders, and SCAs, each school administers the survey at a predetermined date and time either inside computer laboratories or on student laptops while at school, depending on the best fitting circumstances at any given time. To date (wave 3), this process has sometimes required multiple days of data collection to acquire responses from the maximum number of participants. During the COVID-19 pandemic, added flexibility became an important feature of the study data collection procedures, as some students were only accessible while at home because of school closures or mixed or distance learning protocols. In such instances, survey data were collected from students while they were home via laptops during web-based class times and supervised by the SCA. Teacher surveys were administered using a paper-and-pencil questionnaire within schools supervised by the data collection leaders and SCAs. Informed consent was collected. On the basis of school preferences, ≥1 teacher would respond to the survey questions pertaining to each individual student linked to the database via students' school ID numbers. A project manager who is not part of the investigative team entered the data into a spreadsheet deidentified by the honest broker before cleaning and analyses. The schools and BoEs submitted zip code and grade data to the honest broker.

Compensation and Incentive Structure

To maximize buy-in and commitment from schools, study participants, and data collection personnel, an incentive system was built into all the data collection procedures. Incentives were provided after each wave of data collection, and the data collection leaders were hired part-time to oversee data collection within the schools. Schools are directly incentivized with US $1500 for their time and efforts, and the SCAs are compensated separately with US $500 to oversee the survey administration for their school. Teachers who respond to the teacher survey are compensated with US $10 for each student assessment they complete, and students are given a healthful treat (eg, Kind bar) and a pencil, pen, or other "swag" that includes the study logo as a token of appreciation for participating. Students are also enrolled in a lottery for an iPad, which is drawn at the end of each wave of data collection. During challenging times such as the COVID-19 period, this incentive system has proven vital for encouraging high levels of participation.

Data Processing, Analysis Plan, Power Analysis

Overview

The data obtained from the students, teachers, and archives were organized and cleaned following well-established quality control procedures. Item distributions and construct psychometric properties are examined, and a comprehensive codebook is created, which is updated once each new wave of data becomes available. For multivariable tests, most analyses will be run in Mplus using maximum likelihood (ML) robust estimation, a sandwich estimator that generates estimation with SEs that are robust for nonnormal data, including symmetric or platykurtic, nonsymmetric, or zero kurtotic distributions. Mplus facilitates path analysis, latent variable modeling, and estimation of latent growth curves (LGC) and growth mixture models. Mplus can provide ML estimates for a range of distributions pertinent to alcohol use and psychosocial outcomes, including binary (lifetime onset of alcohol use), zero-inflated Poisson, negative binomial (low base rate count data; eg, days using alcohol), and continuous data. Model fit will be evaluated using the criteria for chi-square, comparative fit index, and root mean square error of approximation proposed by Hu and Bentler [69]. The study team has used all of these techniques in previous research [70-74]. Our analyses routinely incorporate nested data (youth nested in schools or youth nested in zip code). When data are clustered, Mplus adjusts the SEs via the multilevel pseudo ML estimator [75]. The method is likelihood based and thus applies to multivariate outcomes from any parametric family of distributions, including generalized linear models. The default estimation of Mplus is robust to bias, with a ratio of parameters to sample size of 1:5.15. In the event that the cell sizes are smaller than expected and the software encounters convergence problems or biased estimates, we will incorporate a Bayesian methodology, which does not assume large sample sizes and, in fact, performs well with very small sample sizes, particularly with informative priors [76,77].

In addition, Mplus provides unbiased ML parameter estimates and reasonable estimates of SEs for cases in which data are missing completely at random or missing at random [78,79]. Modeling data that are missing not at random is possible with full information ML estimation using latent indicators of missingness in a mixture model context, as specified by Muthén et al [80].

Power Analysis

Power was determined using Monte Carlo simulations in Mplus (version 7.4195), with a proposal based on our conceptual model

(Figure 1) as an example. The proposal is a parallel LGC model with structural relationships with a time-invariant risk factor index and was estimated with an expected 2% to 4% attrition and ML under the assumptions of normality (although in the event of nonnormality, the proposed analytic adaptions will be made). Parameters were estimated as 0.5 for the intercept growth factors, 0.25 for the residual variance of the intercept growth factors, and 0.09 for the residual variance of the slope growth factor [81]. To determine the smallest, well-powered effects (0.80), regression coefficient values were estimated starting at 0.2 (reflecting a medium effect size) and decreasing for each subsequent test by 0.01. Tests of power for N=2200 were conducted for each model, with 1000 Monte Carlo simulations for each model. All 1000 simulations were completed successfully for each model. The following criteria were used to determine the smallest detectible effect: (1) parameters and SE biases ≤10% per parameter, (2) coverage ≥0.91, and (3) power for all main effect regression coefficient parameters had to be approximately 0.80 for sufficient power. A final model of regression coefficients equaling 0.07 was obtained with satisfactory model omnibus statistics: χ^2_{74}=74.5 (SE 11.92); root mean square error of approximation 0.003 (0.004); standardized root mean squared residual 0.013 (0.001). The 95% CI coverage for all parameters, as well as all the power estimates, was ≥0.942. We repeated this procedure for a discrete time survival mediation model using a conservative estimate of alcohol use onset from our prior research (8% in sixth grade, growing to 20% in eighth grade), a time-invariant risk index, and an LGC as mediators. All power estimates for model coefficients as small as 0.07 were ≥0.80, with satisfactory model omnibus statistics: χ^2_{55}=78.6 (25.259). The 95% CI coverage for all the parameters was ≥0.91.

Ethics Approval

All study documents, plans, and protocols were reviewed and approved by WV University IRB. This included plans for the administration of the parent or caregiver letters, student surveys, teachers' consent and surveys, incentive systems, individual-level confidentiality, data cleaning and data linking procedures, and analyses. The IRB of West Virginia University approved all the study protocols (#1903499093).

Data-Sharing Plan

The proposed research does not exceed the US $500,000 cap set by the National Institutes of Health in any project year. However, based on the importance of the data, we encourage collaborations with interested investigators. We will also make deidentified data available to appropriate external investigators within 2 years of the publication of the main findings of the study. This will occur under the auspices of a data-sharing agreement that provides for the following: (1) a commitment to use the data only for research purposes and not to identify any individual participant, (2) a commitment to secure the data using appropriate computer technology, (3) a commitment to destroy or return the data after analyses are completed, and (4) monitoring by an approved human subjects board.

Results

In 2020 and 2021, 3 waves of student data, 2 waves of teacher survey data, and zip codes for student homes via school records were collected. Table 2 shows a breakdown of the number of student surveys and adjusted response rates based on accessibility because of the COVID-19 pandemic.

The response rate of each wave exceeded 80%. Variations in sampling frame numbers are to be expected as the sampling frame encompasses all registered students in the 20 schools that participate in the study each year. Minimal changes from one semester to the next are considered normal. The inaccessible students were those who participated in the WV state curriculum during the COVID-19 pandemic and, thus, were not registered through any of the participating schools. Opt-outs are the eligible participants whose parents or caregivers or the students themselves opted to not participate in the study. Response rates are calculated based on the total number of cleaned responses (omitting double entries and empty entries) divided by the total number of eligible participants (total sampling frame minus inaccessible students). Opt-outs are included in the sampling frame when response rates are calculated.

Table 2. Breakdown of participant numbers for all study waves 2020 to 2021.

Wave	Sampling frame, N	Inaccessible (COVID-19), n (%)	Opt-outs, n (%)	Cleaned responses, n (%; percentage of sampling frame, including inaccessible)	Response rate (%; percentage of sampling frame minus inaccessible)
1 (fall 2020)	2247	576 (25.63)	79 (3.52)	1349 (60.04)	80.7
2 (spring 2021)	2320	425 (18.32)	83 (3.58)	1649 (71.08)	87
3 (fall 2021)	2374	78 (3.29)	73 (3.07)	1909 (80.41)	83.1

Discussion

Study Overview

The YMHS plans to fill a gap in the literature concerning the health and well-being of early adolescents residing in geographically isolated and often resource-scarce Appalachian communities. The proposed research focuses on alcohol use among youth in small cities, towns, and rural areas of WV, a US state entirely within the Appalachian region. Historically marginalized in American society, many Appalachian communities experience chronic poverty and epidemic levels of opioid abuse [5]. In the past, residing in rural communities protected youth from many risk factors of early onset alcohol use encountered in urban settings. However, recent research underscores the prevalence of alcohol use in adolescents and alcohol use disorders in adults in resource-poor rural communities [9]. Of particular concern, early onset alcohol use

places rural youth at risk for future substance use, including opioid abuse [13-15]. We will follow a single cohort of middle school students in 5 counties and 20 schools in WV as they progress through the middle school years from sixth to eighth grade. A total of 6 waves of data will be collected in the fall and spring each year via self-reported surveys, teacher surveys, and archival school records. To date, 3 waves of data have been collected, with a response rate of ≥80% for each wave. Data cleaning, quality checks, and preliminary analyses have been conducted.

We believe that our network of data collection personnel, relationship with county and school officials, and incentive structure have all contributed to the consistently high response rate we have achieved, despite the major challenges brought about by the COVID-19 pandemic. Through contracted agreements with county-level BoEs and superintendents, locally hired data collection leaders, and principals and SCAs in all schools, we were able to adjust and readjust our plans for data collection with many schools during the height of the COVID-19 pandemic (specifically, in the fall of 2020 and spring of 2021) and secure solid responses from most students. Currently, we have 3 manuscripts under review from the first 3 waves of the data, others in preparation or planning, and multiple ideas at the analysis stage, including those that directly test the conceptual model in the grant application.

Limitations and Strengths

During the COVID-19 pandemic, schools have been stretched thin to continue providing federal and state-mandated services to children. Despite being able to navigate many challenges that resulted from the pandemic, a noteworthy complication in our data collection efforts to date concerns issues caused by a higher than expected number of missing participants, particularly from wave 1 (at the height of the pandemic in the fall of 2020 and before vaccines became widely available) and wave 2 (in the spring of 2021 when vaccines were only recently available and not yet widely distributed). Although our response rate was >80% for waves 1 and 2, we operated with a somewhat condensed sampling frame in both instances (Table 2). During the pandemic in WV, as in most other US states, students were given three options to register for their studies: in school only, hybrid format (enrolling in school but studying from home), and via the state-operated curriculum not executed via individual schools. In addition, homeschooling remained an option. Although our sampling frame is contingent on school collaborations, and thus, the sampling frame for each wave represents all accessible students in each of the 20 participating schools, unfortunately, we missed students who participated in the WV state-operated curriculum. A challenging and persistent problem in any longitudinal study is how to deal with dropout rates that may be higher than expected via random missingness. Owing to the COVID-19 pandemic, moving forward, an important problem for the study team will be dealing with missingness that is not because of systematic error. In particular, given that participants who were included in the original sampling frame may have elected to participate in the state-operated curriculum, they may not have been randomly distributed in the sample.

Despite notable shortcomings that were predominantly brought about by the COVID-19 pandemic, our study design and data collection system have several strengths. So far, we have been able to secure 3 waves of high-quality data (complete responses) from approximately 1300 to 1900 middle school–aged youth. Our approach to data collection mimics the principles of community engagement, in which collaborations with locally knowledgeable and trusted personnel have been established to secure access to participants and their caregivers. A considerable portion of the grant funding is used to incentivize both participants and school and county personnel who assist us in our data collection efforts. In addition, each county and school receives a summary report with aggregated results regarding risk and protective factors and alcohol, tobacco, and other drug use outcomes among their youth, which they can then use to plan prevention efforts or apply for funding. This system has proved vitally important during the COVID-19 pandemic when many competing interests have been brought to the table of county and school administrators to keep our education systems functioning. The honest broker system has proven to be an important and novel approach to securing linkable longitudinal data from many participants without jeopardizing confidentiality.

Conclusions

The YMHS cohort will provide novel data for both risk and protective behaviors and social contexts among early adolescents residing in the Appalachian region of the United States. The data collection mechanisms in this study comprise a combination of self-reported student surveys, teacher surveys, and archival school data. This study is unique in that it follows a young group of adolescents through an understudied developmental period in an environment that has not received ample attention to date. Through a robust data collection structure and collaborations with county and school officials, our team has collected 3 waves of data with high response rates despite numerous challenges brought on by the COVID-19 pandemic. Data from this study will provide unique opportunities for various analyses related to early adolescent health and development, with a focus on the Appalachian environment.

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Authors' Contributions

All authors contributed to the study design. ALK conceived and drafted the first version of this manuscript. AMS supervised on-site data collection and handled communication with county and school officials. RM formatted the manuscript and provided comments on its structure and content. HLM conducted the literature searches and provided comments on the structure and literature content. MLS oversaw the formatting of the survey data platform and conducted quality checks. MJM reviewed the measures and questions and provided comments on the structure and format of the manuscript. CLL wrote portions of the measurement and analysis sections and conducted the power analyses. JM and JEJ edited multiple versions of the grant and manuscript. SMK co-wrote the grant and manuscript with ALK. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

JM is a principal in Beam Diagnostics, Inc, and a consultant for Clairvoyant Therapeutics, Inc. ALK is a consultant for Planet Youth Ltd.

Multimedia Appendix 1
Peer-review report by the Community Influences on Health Behavior Study Section - Healthcare Delivery and Methodologies Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 166 KB - resprot_v11i8e40451_app1.pdf]

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Abbreviations

BoE: Board of Education
IRB: institutional review board
LGC: latent growth curve
ML: maximum likelihood
MoU: Memorandum of Understanding
SCA: Supervising Contact Agent
WV: West Virginia
YMHS: Young Mountaineer Health Study

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Original Paper

Grocery Delivery to Support Healthy Weight Gain Among Pregnant Young Women With Low Income: Protocol for a Randomized Controlled Trial

Marika Waselewski[1], MPH; Melissa Plegue[1], MA; Kendrin Sonneville[2], ScD, RD; Ken Resnicow[2], PhD; Aisha Ghumman[1], MPH; Cara Ebbeling[3,4], MS, PhD; Elham Mahmoudi[1,5], PhD; Ananda Sen[1,6], PhD; Julia A Wolfson[2,7], MPP, PhD; Tammy Chang[1,5], MPH, MS, MD

[1]Department of Family Medicine, University of Michigan, Ann Arbor, MI, United States
[2]School of Public Health, University of Michigan, Ann Arbor, MI, United States
[3]New Balance Foundation Obesity Prevention Center, Boston Children's Hospital, Boston, MA, United States
[4]Department of Pediatrics, Harvard Medical School, Boston, MI, United States
[5]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, United States
[6]Department of Biostatistics, University of Michigan, Ann Arbor, MI, United States
[7]Bloomberg School of Public Health, Johns Hopkins, Baltimore, MD, United States

Corresponding Author:
Marika Waselewski, MPH
Department of Family Medicine
University of Michigan
1018 Fuller Street
Ann Arbor, MI, 48104
United States
Phone: 1 734 998 7120
Email: marikag@med.umich.edu

Abstract

Background: Excessive weight gain during pregnancy is associated with complications for both the mother and her infant including gestational diabetes, hypertensive disorders, operative delivery, and long-term obesity. A healthy diet during pregnancy promotes healthy gestational weight gain and determines fetal epigenetic programming in infants that impacts risk for future chronic disease.

Objective: This project will examine the impact of grocery delivery during pregnancy on the weight, diet, and health outcomes of young pregnant women and their infants.

Methods: A three-arm randomized controlled trial design will be performed. A total of 855 young pregnant women, aged 14-24 years, from across the state of Michigan will be enrolled and randomized equally into the three study arms. Participants in arm one (control) will receive usual care from the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); arm two will receive WIC plus biweekly grocery delivery; and arm three will receive WIC plus biweekly grocery and unsweetened beverage delivery. Weight will be assessed weekly during pregnancy, and total pregnancy weight gain will be categorized as above, below, or within guidelines. Additionally, dietary intake will be assessed at three time points (baseline, second trimester, and third trimester), and pregnancy outcomes will be extracted from medical records. The appropriateness of pregnancy weight gain, diet quality, and occurrence of poor outcomes will be compared between groups using standard practices for multinomial regression and confounder adjustment.

Results: This study was funded in April 2021, data collection started in December 2021, and data collection is expected to be concluded in 2026.

Conclusions: This study will test whether grocery delivery of healthy foods improves weight, diet, and pregnancy outcomes of young moms with low income. The findings will inform policies and practices that promote a healthy diet during pregnancy, which has multigenerational impacts on health.

Trial Registration: ClinicalTrials.gov NCT05000645; https://clinicaltrials.gov/ct2/show/NCT05000645

International Registered Report Identifier (IRRID): DERR1-10.2196/40568

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KEYWORDS

pregnancy; weight; diet; grocery delivery

Introduction

The United States has one of the highest adolescent pregnancy rates among high-income countries with almost 800,000 15- to 24-year-old women giving birth in 2021 [1-3]. Among youth who give birth, over half gain excessive weight during pregnancy [4-8]. Excessive weight gain during pregnancy is associated with complications for both the mother and her infant including gestational diabetes, hypertensive disorders, operative delivery, and long-term obesity [5,9-15]. Young women with low income and those from racial/ethnic minority groups have the highest rates of adolescent pregnancy and face significant barriers to healthy food and beverage consumption and physical activity during pregnancy [16-21].

A healthy diet during pregnancy promotes healthy weight gain among mothers [22] and impacts permanent fetal epigenetic programming that determines future risk for chronic disease among infants [23,24]. However, most youth consume suboptimal diets that can lead to unhealthy weight gain in pregnancy [25-28]. Sugar-sweetened beverage (SSB) consumption during pregnancy is further associated with lower diet quality and greater total energy intake among pregnant women [29].

Grocery delivery is a well-established and inexpensive service that removes logistical barriers to obtaining healthy foods and beverages. There are numerous grocery delivery services (eg, Shipt.com, Instacart, FreshDirect, Amazon Fresh, Peapod, and Google Express) that help make obtaining fresh food and groceries more convenient for those who cannot or do not shop in person. However, grocery delivery is predominantly used by affluent middle-aged women [30,31], and few efforts have yet explored online grocery ordering and delivery for young pregnant Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) beneficiaries [32], a population with significant logistical barriers to obtaining healthy foods.

To address this critical problem, we developed Special Delivery, a program that uses grocery delivery to overcome these logistical barriers to a healthy diet during pregnancy among pregnant young women with low income to prevent excessive gestational weight gain.

The aim of this randomized controlled trial is to assess whether grocery delivery of healthy foods to the homes of young women during pregnancy will promote healthy pregnancy weight gain. The study will also assess secondary outcomes of diet quality, pregnancy complications, and delivery outcomes. Our long-term goal is to identify effective interventions to support a healthy diet during pregnancy and promote healthy weight gain among pregnant young women with low income.

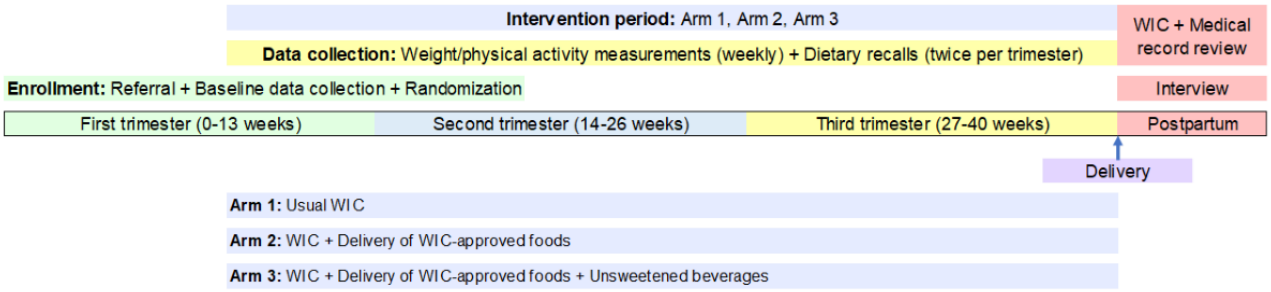
The primary hypotheses to be tested are that the home delivery of healthy foods will promote healthy weight gain during pregnancy and that the addition of unsweetened beverage delivery will promote more healthy weight gain. The findings will inform policies and practices that promote a healthy diet during pregnancy, which may have multigenerational impacts.

Methods

Study Design

This study is a three-arm randomized controlled trial with an additive parallel design. Enrollment in the study is rolling and starts as early as possible in the pregnancy (by 21 weeks' gestation). The intervention period begins at enrollment and continues to the end of pregnancy/birth (Figure 1). Data collection occurs throughout the study with surveys at baseline, the second trimester, the third trimester, and after delivery, as well as short weekly assessments. Upon enrollment in the study, participants will be randomized to one of three groups: usual WIC (arm 1; control), usual WIC + delivery of WIC-approved food (arm 2), and usual WIC + delivery of WIC-approved food plus unsweetened beverages (arm 3).

Figure 1. Participant study timeline. WIC: Special Supplemental Nutrition Program for Women, Infants, and Children.



Specifically, we will be testing the following hypotheses:

- Mothers who receive free grocery delivery of WIC-approved healthy foods will have healthier weight gain during pregnancy, higher-quality diets, and fewer perinatal complications than peers with usual WIC benefits
- Mothers who receive free grocery delivery of WIC-approved healthy foods plus unsweetened beverages will have healthier weight gain during pregnancy, higher-quality diets, and fewer perinatal complications than peers with usual WIC benefits and home delivery of WIC-approved foods only

The rationale for the study is that grocery delivery will address barriers to accessing healthy foods and will therefore facilitate a healthier diet and prevent excessive weight gain during pregnancy.

Ethics Approval

This study was approved by the University of Michigan Institutional Review Board (HUM00190614).

Participants

The study will include 855 young moms who are pregnant with their first child. Those with previous births are excluded to limit the impact of variable past pregnancy experiences and habits on the intervention. Participants will be included from across the state of Michigan based on the criteria below.

- Inclusion criteria
  - Youth (ages 14-24 years)
  - Enrolled in WIC
  - Gestational age ≤20 weeks
  - SMS text message capability
  - Healthy singleton pregnancy
  - Nulliparous
  - Consume SSBs
  - Living within delivery zone of a grocery delivery service
- Exclusion criteria
  - Non-English speaking
  - Participants who live at the same address
  - High-risk pregnancy requiring specialized care

Procedure

Participants in this study will be referred from WIC offices, online study recruitment sites, or other clinical and community organizations that serve young pregnant women across the state of Michigan. Interested women complete an online screening and enrollment survey or call the study line for assistance in completing the survey. Consent is obtained verbally or in completion of the online enrollment form and a copy of the consent form is emailed to participants.

Sample Size Determination

Based on nationally representative studies of weight gain in pregnancy [4], we anticipate 30%, 45%, and 60% of participants in arm 1 (control), arm 2 (WIC + food delivery), and arm 3 (WIC + food plus unsweetened beverage delivery), respectively, to gain weight within the Institute of Medicine guidelines [5,33]. The sample size was determined using methods for comparing independent proportions, and a conservative alpha value of .01 was set for significance to address the multiple testing of 3 comparisons. A sample size of 774 (258 per arm) after attrition will have over 80% power (2-tailed) to detect these differences as statistically significant. Accounting for an anticipated 10% attrition rate based on our preliminary study and low-burden design, we will aim to recruit 285 participants per study arm (855 total).

Randomization

Upon completion of baseline screening and assessments, 855 pregnant young women will be randomly assigned to either the control group or one of the two experimental groups. We will use county-level block randomization to assign participants in a 1:1:1 ratio to the three study arms. The treatment assignments will be created and stored in the Consulting for Statistics, Computing and Analytics Research randomization tool managed by the University of Michigan. No treatment assignments will be made until after collection of baseline data (consent, demographic survey, diet recalls, and other baseline questionnaires). At this time, the participant will be notified of their arm assignment and additional details required for grocery delivery (delivery address, day, and time) will be collected from participants in arms 2 and 3. All personnel who assess study outcomes are masked to group assignment. Participants and staff implementing the grocery delivery are not masked to group assignment.

Intervention

All groups will receive usual WIC nutritional assessment and counseling benefits, including monthly nutritional counseling sessions based on a state-approved curriculum with trained nutritionists and peer counselors [34,35]. These sessions are designed to support each woman's motivations for healthy diet in pregnancy and include education on healthy diets, portion sizes, minimizing SSB intake, cooking skills, and recipes. The intervention period will begin at study enrollment and continues until the end of pregnancy (termination or miscarriage) or infant birth.

The control group (arm 1) will receive usual WIC counseling, as described above, and food benefits loaded onto their Electronic Benefits Transfer (EBT) card to use in person at approved grocery stores. At completion of study participation, arm 1 participants will receive a 1-year prepaid subscription to a grocery delivery service of their choosing.

Participants in arm 2 (WIC counseling + food delivery) will choose WIC-approved foods from an online survey, which will be purchased and delivered to their home biweekly by the study team via a grocery delivery service at no cost to the participant. Fruit and vegetable options will be offered as well as whole grains (cereal, bread, pasta) and proteins (milk, egg, cheese) as listed in the WIC-approved foods booklet (Textbox 1) [36]. The quantities of food will follow the WIC-approved allocations for each month. Participants must text or call the study team to confirm they received the food. These deliveries are not meant to replace their normal grocery shopping or use of WIC benefits but rather to make healthy eating more convenient, and participants are not restricted in their use of WIC food benefits by participating in this program. These foods are in addition to the WIC benefits they already receive.

Textbox 1. Example grocery delivery options.

Vegetables

Baby carrots, broccoli, bell peppers, cauliflower, radishes, snap peas, green peas, avocados, tomatoes, cucumbers, celery, mushrooms, spinach, corn.

Fruits

Apples, pears, oranges, clementines, grapes, bananas, nectarines, peaches, strawberries, blueberries, raspberries, blackberries, watermelon, pineapple.

Proteins and grains

Yogurt, cheese, milk, whole grain bread, whole grain buns, whole grain tortillas, brown rice, whole grain cereal, beans, lentils, peanut butter, eggs.

Unsweetened beverages

Seltzer water, unsweetened tea, Spindrift, sparkling tea, bottled water

Participants in arm 3 (WIC counseling + food plus unsweetened beverage delivery), the home delivery of healthy foods, as described above, will be supplemented with the inclusion of participant-selected unsweetened beverages, in quantities comparable to their current SSB intake (based on self-reported consumption). Unsweetened beverages are intended to replace current SSB consumption. Because SSBs contribute to a significant number of excess calories among youth, this group includes unsweetened beverage delivery to further promote healthy weight gain. The unsweetened beverage choices will include bottled water (flavored or unflavored), unsweetened seltzer water (flavored or unflavored), and unsweetened teas. Artificially sweetened beverages and SSBs will be excluded.

Participant Retention

Our study is designed to be low burden, so participants only have to maintain minimal communication via text, phone call, or email to remain in the study. In addition, participants are incentivized with Amazon gift cards for various components of the study. Participants in all arms receive US $20 for completing the enrollment process, baseline survey, first diet recall, and medical record request form. Participants in all arms will receive US $20 for each additional diet survey completed on their own throughout the course of the study (up to 5 total). For each week participants use their study provided scale, they will receive US $1, and an additional US $10 is given for the end-of-study interview. Women in the intervention arms receive biweekly grocery deliveries during their pregnancy, while women in the control arm receive free access to 1 year of a grocery delivery service at the end of their pregnancy. The resulting maximum incentive for participation is US $160 for participants who enroll at 10 weeks' gestation, complete all study questionnaires, and remain active for the remaining 7 months of their pregnancy.

Data Collection

At baseline, interested and eligible participants will complete the consent process to participate and respond to baseline measures, described in detail below. In addition to the baseline surveys, participants will be asked to share weight, physical activity, and diet recall data at specified times throughout the study period. The complete list of outcomes, covariates, and timeline of assessments is shown in Table 1.

Table 1. Study outcomes and covariates with timeline of data collection.

Measure	Data source	Time points
Primary outcome		
Total and weekly weight gain in pregnancy: above, below, or within guidelines	• Prepregnancy weight: self-report and medical record review • Pregnancy weight gain: BodyTrace scale and medical record review	At enrollment, weekly during pregnancy
Secondary outcomes		
Diet quality: Healthy Eating Index score	• Paired ASA24[a] diet recall surveys	Twice at baseline, twice at second trimester, twice third trimester
Prenatal complications: gestational diabetes, hypertensive disorders; delivery complications: operative delivery, shoulder dystocia, postpartum hemorrhage; and birth weight: small/large for gestational age	• Medical record review	Postpartum
Process measures		
Delivery of WIC[b]-approved food and unsweetened beverages	• Online grocery delivery orders; requested monthly by participants	Biweekly deliveries
Experience with deliveries	• Phone interview	Postpartum
Medical/WIC record release	• SignNow e-signature	At enrollment
Confounders/modifiers		
Age, race, ethnicity, socioeconomic status, home environment, food insecurity	• Demographic survey	At enrollment
Physical activity	• Physical activity survey	Weekly during pregnancy
Food behaviors	• Cooking frequency, fast-food frequency, cooking confidence, eating disorder examination	At enrollment, postpartum
Body shape preference	• Pulvers body image instrument	At enrollment, postpartum
WIC nutrition visits and food benefits redeemed	• WIC record review	Postpartum

[a]ASA24: Automated Self-Administered 24-hour.

[b]WIC: Special Supplemental Nutrition Program for Women, Infants, and Children.

Sociodemographic Data

All sociodemographic data will be collected upon enrollment online or by phone with the study team. These include date of birth (to calculate age), self-reported race and ethnicity, highest level of education, free/reduced lunch status while in school (a valid measure of socioeconomic status among youth) [37], full address including zip code (for grocery delivery and delivery of BodyTrace scale), home environment (validated Home Food Environment assessment [38,39], other individuals in household, access to transportation), and a validated two-question food insecurity screen for youth to determine baseline access to food [40,41]. Participants' and household members' food allergies and cultural/religious food preferences will also be collected upon enrollment.

Weight and BMI

Prepregnancy weight and height will be obtained by self-report and verified by medical record review after birth to determine prepregnancy BMI and identify target weight gain zones. Weekly weight measurements during pregnancy will be measured via a BodyTrace scale and recorded automatically using cellular connectivity (no Wi-Fi or cellular plan required) [42]. The scale will be mailed to participants' homes upon enrollment. The BodyTrace scale provides valid weight measures and has been used by several other large-scale weight interventions [43-45].

Dietary Intake

Dietary intake will be measured with paired assessments using the Automated Self-Administered 24-hour (ASA24) dietary recall survey [46-48]. This process has been validated by comparison to in-person 24-hour recalls and has been used by other studies of pregnant youth with low income [49,50]. At enrollment, participants will complete their first recall over the phone with the study team. A second baseline ASA24 survey will then be completed, approximately 2 to 5 days after enrollment. Participants will complete four additional ASA24

surveys using the same paired system during the intervention period. Two will be completed in the second trimester and two in the third trimester. Study team members will be available, as needed, to assist participants in completing all ASA24 surveys. Paired responses will be combined and used to calculate a Healthy Eating Index (HEI) score for each time point: baseline, second trimester, and third trimester [46,51]. The output from the ASA24 includes additional data on fruit and vegetable servings as well as other macronutrient data.

Physical Activity

The American College of Obstetricians and Gynecologists recommends an exercise program of moderate intensity exercise for at least 20 to 30 minutes per day on most or all days of the week for pregnant women [52]. To measure physical activity, we will use an adaptation of the Youth Risk Behavior Survey and National Youth Physical Activity and Nutrition Study survey item that has been validated with accelerometer data [53-56]. The survey will be sent weekly via SMS text message to assess the proportion of time youth meet the guidelines, as physical activity impacts weight gain in pregnancy.

Body Size Preference

Participants will complete the validated Pulvers Body Image [57] scale at enrollment and during the phone interview after birth to assess their body size preferences. At baseline, participants will be asked to identify their prepregnancy body shape and ideal body shape from the 9 options included in the Pulvers scale. At follow-up, participants will be asked to identify their current (postpartum) body shape and ideal body shape. Participants' preference in body size may impact their weight-related behaviors and provides critical context on whether they wish to be or stay bigger after pregnancy or try to return to their prepregnancy size [58].

Food Behaviors

Participants will be prompted to complete questions adapted from the Eating Disorder Examination Questionnaire Short and Youth Eating Disorder Examination-Questionnaire at baseline and end of study to identify perceptions of loss of control of eating, binge eating, weight/shape overvaluation, and body dissatisfaction [59-61]. Additional questions drawn and adapted from the National Health and Nutrition Examination Survey focused on the frequency of home-cooked meals in the household and fast-food meals [62] will also be asked as well as participants' confidence in cooking meals [63,64]. These questions will be assessed during the baseline and end-of-study survey assessments.

Text Message Reminders

SMS text messages will be sent to participants in all arms using Textizen.com, a GovDelivery platform. Participants will receive 2 to 3 SMS text messages per week reminding them to confirm their delivery, place their order, step on their scale, and respond to physical activity questions. These SMS text messages will also prompt participants to share any updates they may have regarding their pregnancy, allowing participants an opportunity to report on infant birth, miscarriage, or any other outcomes. In addition, participants will be prompted via SMS text message to complete their diet recall surveys throughout their pregnancy.

Medical Records Data

Medical records will be requested from participants' prenatal and delivery care sites within a few weeks of delivery using the release forms completed at enrollment. Data collected will include all health care visits during pregnancy and up to 12 weeks postpartum, including prenatal visits (diagnoses and complications), nutrition visits (number and content of visits), emergency department visits, inpatient stays, WIC counseling visits (number and type: nutrition vs breastfeeding), quantity of WIC foods redeemed, laboratory results (1-hour glucose tolerance test, A1C, blood glucose levels, complete blood count, urine studies, liver/renal studies), vital signs (weight, height, blood pressure, pulse), medications prescribed, complications during prenatal care (gestational diabetes, hypertensive disorders), infant birth weight, and gestational age at delivery.

End-of-Study Interview

A phone interview will be performed after each woman gives birth to collect qualitative insights into participants' experience with grocery/beverage delivery; the impact of delivery on their diet; overall WIC experiences; and end-of-pregnancy body preference, self-reported weight gain, physical activity, any prenatal or childbirth complications, plans for breastfeeding, and food insecurity.

Data Analysis

To understand the effect of grocery delivery on pregnancy weight gain, diet quality, and health outcomes, weight will be measured weekly, dietary quality will be assessed twice per trimester, and perinatal outcomes will be assessed at the end of the pregnancy. All analyses will follow the intention-to-treat principle. Prior to analysis, assessment of missing data will be completed and appropriately imputed using multiple imputation methods [65].

Our primary outcome is appropriate weight gain in pregnancy, which is based on prepregnancy BMI and includes weekly weight gain and total weight gain recommendations. Total weight gain at birth will be categorized as above, below, or within the Institute of Medicine guidelines [5,33]. Multinomial logistic regression analysis will be used to compare the likelihood of falling above, within, or below guidelines for total weight gain in pregnancy across arms after adjusting for potential confounders such as age, race, ethnicity, socioeconomic status, and household characteristics. Confounders will be identified through significant findings in bivariate analysis comparing the three groups and by consideration of variables based on prior scientific evidence. Summary statistics of key time-dependent measures and other non–time-dependent measures will also be included as covariates. Modification of the study arm effect by key variables will be investigated through interaction terms in the regression model.

The trajectory of weight gain behavior, using each week's categorized weight gain (within guidelines vs not), will additionally be assessed as the outcome in a clustered logistic regression model fit using a generalized linear mixed model framework. The study arm is the primary between-participant factor, while time (week) is the main within-participant

covariate. The interaction term between time and arm is also a factor of interest, as it will allow us to assess changes in weight gain behaviors over time between study arms. A random participant-level intercept will account for within-participant clustering, and a random slope for time will be investigated to account for additional between-participant variability. Additional covariates and effect modifiers included in these regression models will be chosen using the same methods as before.

Our secondary outcome is diet quality as measured by the HEI score based on two ASA24 measurements at baseline and in the second and third trimesters [51,66]. A comparison of overall HEI scores between study arms will be carried out using separate linear mixed models with calculated HEI scores from each trimester as the outcome. As before, the study arm will be the primary between-participant factor; time, as measured by trimester, the within-participant covariate; and the interaction between arm and time will be assessed to measure the difference in trimester effect between the arms. Random participant-level intercepts and slopes for time will assess the deviation from the overall average and account for any within-participant clustering. Models will be adjusted for additional confounders and covariates, determined as in prior models. Fruit and vegetable intake, as well as other macronutrient details, will also be evaluated.

Prenatal complications, delivery complications, and birth weight (small/large for gestational age) are also secondary outcomes that will be assessed. Comparison of the proportion of participants with complications between study arms will be analyzed using a logistic regression model in a manner analogous to the primary outcome of appropriate weight gain in pregnancy.

The end-of-study interview transcripts will be analyzed using standard qualitative techniques [67-69]. Two investigators will review all transcripts, create memos of major concepts present, and iteratively develop a codebook. Transcripts will be coded and major themes and conclusions determined by consensus. Themes identified from these transcripts will describe participants' satisfaction or dissatisfaction with delivery, perceived impact of food delivery on their health and diet, and other challenges/barriers to healthy behaviors during pregnancy. The interviews will be used to provide context and narrative to inform findings from quantitative outcome data, and will be used in dissemination to tell the participants' perspective regarding the impact of grocery delivery.

Finally, we will conduct a cost analysis focused on costs from the payer perspective during the pregnancy period. All costs will be adjusted to current dollars and will represent average cost per participant. Our analysis will estimate the costs of delivering the intervention, including cost of grocery delivery service, increased costs for WIC due to increased redemption of food benefits [70], print and online media advertisements to maximize uptake, costs to train WIC staff on new procedures, and increased WIC visit time to allow staff to educate beneficiaries. Medical records data will also be used to identify the number and type of all medical care used by participants during pregnancy, including prenatal care visits, specialist visits and consultations, emergency department visits, inpatient care, and delivery care. The average total health care costs per participant associated with each arm of the trial will be calculated using nationally representative health care expenditure data from the most recent Medical Expenditure Panel Survey [71]. Although medical records data from their usual sources of care may not include visits to urgent care and outside facilities, this will not likely introduce bias due to randomization to study arms.

Results

This study was funded in April 2021, data collection started in December 2021, and data collection is expected to be concluded in 2026. No results are available as of manuscript preparation.

Discussion

This protocol describes a randomized controlled trial to evaluate whether grocery delivery of healthy WIC-approved foods supports healthy pregnancy weight gain for young pregnant women with low income. We will additionally evaluate if the grocery delivery impacts diet quality, pregnancy complications, and delivery outcomes. We anticipate that the young pregnant women in the two intervention groups will have better rates of appropriate pregnancy weight gain, improved diet quality, and lower rates of pregnancy and delivery complications.

Results from this study can be used to inform United States Department of Agriculture policies on online use of WIC benefits as well as to provide evidence about the cost-effectiveness of national implementation of grocery delivery for WIC beneficiaries [32]. These outcomes may additionally provide evidence to clinical practices or health systems on opportunities for the use of food delivery programs within their patient populations to address social determinants of health.

There are several key strengths to this protocol. This work uses a low-cost well-established service to enhance an existing government program which enables the results to inform policies to improve the implementation of WIC services and other programs for vulnerable populations. COVID-19 has also led to a surge in online grocery ordering, which enhances the generalizability of this study [31]. Additionally, this study uses low-burden communication and data collection methods to allow for high levels of participant retention.

Limitations of this study are that it does not perfectly emulate the real-life application of integrating grocery delivery into WIC services, as study personnel are ordering and managing the delivery process, which reduces the generalizability of the results to program-based implementation. Specifically, participants request the groceries from the study team who then place the orders and manage the deliveries. Additionally, participants are able to access and use their WIC food benefits in addition to groceries provided, and it does not directly replace this benefit.

Ultimately, this study will provide rigorous evidence regarding the impact of grocery delivery of healthy foods and unsweetened beverages among pregnant young women with low income and their infants. The findings from this study will provide

invaluable information about the potential benefits of incorporating grocery delivery in WIC and about the costs to implement, sustain, and expand such a program.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Report from the Community-Level Health Promotion (CLHP) Study Section - Healthcare Delivery and Methodologies Integrated Review Group - Center For Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 149 KB - resprot_v11i8e40568_app1.pdf]

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Abbreviations

ASA24: Automated Self-Administered 24-hour
HEI: Healthy Eating Index
SSB: sugar-sweetened beverage
WIC: Special Supplemental Nutrition Program for Women, Infants, and Children

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Protocol

The Effects of Virtual Reality Tele-exergaming on Cardiometabolic Indicators of Health Among Youth With Cerebral Palsy: Protocol for a Pilot Randomized Controlled Trial

Byron Lai[1*], PhD; Drew Davis[1*], MD; Raven Young[1*], BS; Erin Kimani-Swanson[1*], MD; Cynthia Wozow[1*], MD; Huacong Wen[2*], PhD; Yumi Kim[2*], PhD; Jereme Wilroy[2*], PhD; James Rimmer[3*], PhD

[1]Division of Pediatric Rehabilitation Medicine, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, United States
[2]Department of Physical Medicine & Rehabilitation, University of Alabama at Birmingham, Birmingham, AL, United States
[3]Dean's Office, School of Health Professions, University of Alabama at Birmingham, Birmingham, AL, United States
[*]all authors contributed equally

Corresponding Author:
Byron Lai, PhD
Division of Pediatric Rehabilitation Medicine
Department of Pediatrics
University of Alabama at Birmingham
1720 University Blvd
Birmingham, AL, 35294
United States
Phone: 1 205 638 9790 ext 8 9725
Email: blai@uabmc.edu

Abstract

Background: Youth with cerebral palsy do not have enjoyable, accessible, and scalable exercise options that can empower them to independently maintain their cardiometabolic health.

Objective: The primary aim is to examine the preliminary efficacy of a 12-week home-based virtual reality tele-exergaming intervention on several indicators of cardiometabolic health in youth with cerebral palsy compared to the wait list control. A secondary aim is to describe feasibility metrics, namely, recruitment, retention, and adherence rates; perceived enjoyment; intervention safety; and management issues. The tertiary aim is to generate a theory that reveals critical behavioral mechanisms of adherence to tele-exergaming.

Methods: In this parallel group design randomized controlled trial, 34 inactive youths with cerebral palsy are randomly allocated to one of two groups: a group that immediately receives 12 weeks of virtual reality exergaming with tele–physical education or a wait list control group that undergoes their habitual activity for 12 weeks. Participants are recruited from a Children's Hospital and community network. At baseline (week 0), week 6, and week 12, high sensitivity C-reactive protein and blood insulin, hemoglobin A_{1c}, triglycerides, cholesterol, and pressure are measured by the youth and a caregiver at home using a blood spot test kit and blood pressure cuff. They will also self-measure their lung function and body weight using a peak flow meter and bathroom scale, respectively. Collections are supervised by research staff via videoconference. Changes in outcomes are compared between and within groups using exploratory statistical analyses and descriptive statistics. At postintervention or dropout, participants will undergo semistructured interviews to identify behavioral mechanisms that underly participation.

Results: Recruitment procedures started in June 2022. All data are expected to be collected by October 2023. Full trial results are expected to be published by February 2024. Secondary analyses of data will be subsequently published.

Conclusions: This trial tests an innovative serious exergaming virtual reality program that includes a completely remote enrollment, assessment, and intervention tele-protocol. The knowledge obtained will inform the development of a larger effectiveness trial for improving the health and well-being of youth with cerebral palsy.

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KEYWORDS

disability; physical therapy; adapted physical activity; physical activity; active video gaming

Introduction

Cerebral palsy is currently estimated to be prevalent among 1 million people in the United States and 23 million people worldwide [1-4]. Cerebral palsy is defined as "a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" [5,6]. While cerebral palsy is not a progressive disorder, the youth age range of 13-24 years is a critical transitory stage to adopt exercise behavior that sets the course for positive health trajectories in adulthood [7]. The youth era captures both adolescents and the beginning years of early adulthood. At an early adult age, people with cerebral palsy have substantially increased risk of cardiovascular disease (CVD)–related conditions, metabolic syndrome [8], and a 3-fold increased risk of CVD mortality compared to the general population [7,9,10]. These conditions are believed to be associated with a lack of participation in regular moderate intensity exercise behavior during the adolescent period [7,11]. Adolescents with cerebral palsy engage in alarmingly low levels of exercise that far exceed those observed among peers without cerebral palsy [12-15], but they are two times more likely to exercise as early adults when exercising as adolescents [13]. Thus, there is a need to identify healthy aging strategies that support youth with cerebral palsy with interventions that reduce the risk of physical inactivity and early disease onset.

Conventional modalities of aerobic exercise such as cycling, running, and walking [16] are often not feasible or enjoyable for youth with cerebral palsy to maintain over prolonged periods of time. Approximately, 35% of youths with cerebral palsy will experience a decreased walking ability in adulthood, 9% will lose their ability to walk, and 27% will never have been able to walk [17,18]. Youth with cerebral palsy often use mobility devices such as wheelchairs, walkers, or orthotics. They are also highly susceptible to experiencing secondary conditions such as fatigue, impaired balance, and joint pain [18-21].

Despite over three decades of research, recent scoping reviews found that randomized controlled trials (RCTs) of exercise for people with cerebral palsy have low rates of participation and recruitment [22]. Of the 49 published RCTs on youth with cerebral palsy, the average sample size was 30 [22], and most of the study participants were ambulatory because wheelchair users were often excluded, which hinders the generalizability and transferability of the study findings [22-26]. Programs with on-site data collection or intervention procedures are difficult to recruit given the low density of youth with cerebral palsy at a single site in addition to the numerous barriers that youth with cerebral palsy may experience such as geographic (eg, distance to a fitness facility), environmental (eg, lack of accessible transportation, parks, and communities), or economic challenges (eg, cannot afford a fitness membership or one-on-one supervision by a therapist) [27,28]. Therefore, there is a need to identify innovative health-enhancing exercise interventions with strong scale-up potential for youth with cerebral palsy to confirm the effects of exercise in robust RCTs [22,23].

No RCT has demonstrated clinically meaningful improvements in cardiometabolic health in people with cerebral palsy [22,23]. Although one RCT by Slaman et al [29] reported statistical improvements in cholesterol from 6 months of loosely structured participation in local activity programs, the absolute change was small and several other blood parameters demonstrated no change. As acknowledged by the authors, these absences of changes were likely due to a suboptimal exercise dose that did not meet national and global guidelines to improve health: at least 150 minutes of moderate-to-vigorous intensity exercise per week [30,31]. Given that cardiometabolic indicators of health, including blood pressure (BP), lipids, and glucose tolerance, require gradual physiological adaptations following 1-3 months of exercise training at a moderate intensity [32-34], there is a need to identify programs that can maintain the interest of youth with cerebral palsy to participate in regular moderate intensity exercise.

Active video gaming with the latest virtual reality (VR) technology can be performed at a moderate intensity (ie, exergaming) with use of only the arms and trunk [35], making it an accessible method of improving health and function. Previous disability-related active video gaming studies primarily incorporated the Nintendo Wii and Xbox Kinect. These devices demonstrated great promise as health-enhancing exercise modalities and are still used within rehabilitation clinics nationwide, but they were discontinued by their manufacturers. In May 2019, one of the largest investments in VR gaming technology by Facebook (now referred to as Meta) led to a pivotal advancement in making VR gaming more ubiquitous for consumers: the development of the Oculus Quest. The Quest is the first VR headset of high visual quality (up to 120 frames per second) that does not require a plug-in connection to an expensive desktop gaming computer or game console. The relatively lower price of this stand-alone US $400 headset has transformed the market by allowing a wider range of people to have a fully immersive, enjoyable, and socially connected VR experience through a variety of cooperative and competitive fitness games. Moreover, true immersion within a virtual world and *built-in* internet capability, provided by the Quest, are critical elements of a potentially long-term VR gaming experience. Although the Quest may be a potentially scalable method of promoting moderate exercise among youth, simply providing them the device will likely not be sufficient to promote moderate exercise behavior over a 3-month period, as was concluded from a 3-month RCT using Nintendo Wii and Xbox Kinect technology with children [36]. Therefore, there is a need to supplement active video gaming with strategies that can promote long-term use.

Home-based telehealth programs that incorporated *virtual* behavioral coaching (telecoaching) are a desirable approach for promoting nonsupervised exercise behavior among people with disabilities who do not have convenient access to community

programs. According to the Supportive Accountability Theory [37], programs that use telehealth technology can foster strong intervention adherence by providing objectively monitored feedback and promoting strong relationships with health professionals. The addition of behavioral coaching strategies such as goal-setting, confidence-building, setting reasonable expectations, and understanding benefits, underpinned by social cognitive theory [38], have been found to enhance the likelihood of promoting exercise behavior among people with disabilities [39]. Social cognitive theory provides a targeted approach toward promoting exercise behavior through four constructs: self-efficacy (perceived control over one's behaviors), outcome expectations (anticipated physical, social, or self-evaluative outcomes from participation), sociostructural factors (facilitators and barriers), and goals (concrete plans and strategies) [38,40]. A critical advantage of incorporating social cognitive theory is that it has been tested extensively among various adult disability groups [37], this has resulted in replicable processes for increasing exercise behavior in telehealth programs. An exercise intervention that uses telehealth technology, active video gaming, and a minimal dose of behavioral coaching may promote sustainable exercise behavior among large groups of youth with cerebral palsy, as demonstrated in the largest exercise trial for youth with cerebral palsy (N=101) [41].

In a feasibility case study [35], youth wheelchair users independently maintained health-enhancing doses of moderate intensity exercise over a 1-month period at home using a VR exergaming protocol. Specifically, 2 youths with spina bifida achieved an average of 200 minutes of moderate intensity exercise per week across a 1-month period, which exceeded the recommended exercise guidelines for adults [30,31]. The 2 participants used a bundle of consumer-available equipment to exergame and objectively recorded and monitored their sessions at home. Equipment included a heart rate monitor, a mobile app, and the Quest headset installed with several active games. Participants received a low dose of weekly behavioral coaching. The youths attributed the amount of exercise they achieved to the enjoyment of the system and games, which was fostered by the immersive, "real" quality of the gameplay experience. A caregiver reported a substantial reduction in body composition for a participant after the intervention. Despite these findings, the study was only a month in duration, included youth with spina bifida, and did not measure objective health outcomes. No RCT has tested the effects of a serious telecoached exergaming program with the latest consumer-available VR equipment on cardiometabolic health among youth with cerebral palsy, particularly a trial that includes completely remote study procedures (ie, enrollment, data collection, and intervention).

The primary purpose of this study is to examine the preliminary efficacy of 12 weeks of home-based VR exercise training on several indicators of cardiometabolic health in youth with cerebral palsy compared to the wait list control (WC). The secondary purpose of this study is to explore feasibility metrics that will inform the design of a larger trial, namely, recruitment, retention, and adherence rates; perceived enjoyment; intervention safety; and management issues. The tertiary purpose of the study is to generate a theory that reveals critical behavioral mechanisms of adherence to tele-exergaming.

Methods

Study Design

This study is a pilot RCT using a 2-armed parallel group design to test the effect of a serious VR exergaming intervention on indicators of cardiometabolic health among youth with cerebral palsy compared with a WC. The project will include 34 youths with cerebral palsy, 13-24 years of age.

Ethics Approval

The protocol and informed consent and assent forms were approved by the Institutional Review Board for Human Use of the University (IRB-300007833) on March 3, 2022. Eligible participants are given the study website to review the consent and assent forms in detail prior to enrollment. During a videoconference meeting on the baseline data collection visit, a member of the research team verbally reviews the consent and assent forms with the prospective participant and their caregiver. Informed consent and assent are signed digitally by the participant and their caregiver through a secure web application for building and managing online surveys and databases: Research Electronic Data Capture (REDCap). REDCap is programmed to send them a nonsigned copy of the document to their email once they sign the digital form. Participants who prefer to sign a physical copy will have a consent and assent form mailed to them. Participants are given access to a study website that contains the consent and assent forms that they can review at least 24 hours prior to their baseline data collection. Consent and assent documents are written in English.

Eligibility Criteria

The study includes physically inactive youth with cerebral palsy who walk or use wheelchairs and mobility devices (Gross Motor Function Classification System [GMFCS] levels I-IV) [42,43].

The inclusion criteria were a medical diagnosis of cerebral palsy, being between the ages of 13-24 years to accommodate the World Health Organization definition of youth and the minimum age of 13 years specified by the Quest, and a physician's clearance to participate.

The exclusion criteria were being physically active (defined as >150 minutes per week of moderate-to-vigorous intensity exercise in a typical week); a classification of GMFCS level V, which we have found to preclude the ability to use the Oculus Quest handheld controllers; complete blindness or deafness; and having contraindications to exercise based on the American College of Sports Medicine guidelines [44].

Randomization Allocation and Other Trial Considerations

Participants are randomized into one of two groups—VR tele-exergaming or WC (n=17 per group)—with a 1:1 allocation ratio using a permuted block randomization approach. To balance the functional ability of participants between groups, the first 30 participants will be evenly stratified into VR tele-exergaming or WC based upon their GMFCS level [45,46]. The last 4 participants will intentionally not be stratified to prevent having to exclude prospective participants. GMFCS

levels I-II are indicative of an ability to walk indoors and outdoors. Levels III-IV are indicative of ambulatory with the assistance of mobility devices or nonambulatory. The randomization sequence was generated by the project statistician using a computer-generated random schedule in permuted block (SAS V.9.4; SAS Institute). Only the project statistician is aware of the randomization schedule. Data are collected and entered into REDCap by a member of the research team. This outcome assessor will be blinded to group allocation (single-blinded trial design).

Home-Based Intervention

The VR intervention includes home-based exercise using the Oculus Quest, a heart rate monitor (Polar OH1), BP cuff, and mobile app (shown in Figure 1). The Quest comes with 2 handheld controllers and 9 preinstalled active games (playable while standing or sitting). The games include rhythmic movements to music and sport/recreation activities that elicit high-energy expenditure (eg, dancing, boxing, and tennis) and were chosen based on our feasibility study [35]. The Polar OH1 is worn on the forearm and is used to measure heart rate during gameplay. The OH1 has demonstrated excellent intraclass correlation coefficients (0.99) with gold standard electrocardiography [42]. Feasibility study participants reported difficulty with equipping a chest-worn monitor. During exercise, participants monitor their heart rate and exercise time via a free mobile app (VR Health) from the Google Play or Apple Store. VR Health displays exercise intensity based on an age-predicted heart rate maximum. Regarding safety, participants are instructed to refrain from exercise and call the study team if their resting heart rate is >100 bpm or BP is ≥180/110 mmHg before exercise. After exercise, the participant or caregiver uploads their exercise data from VR Health into a secure cloud server managed by study staff. Participants are instructed to exercise for 1 hour per day, with a minimum of 5 days of exercise per week. Subprescription goals are to reach 300 minutes of total play or 150 minutes per week of moderate exercise in week 1 and maintain this volume across the 12-week intervention. To enhance the likelihood that participants achieve the prescription and subgoals, participants are provided with a "Level Up" protocol, where they can earn a new game (purchased by research staff) if they achieve the prescription and at least one subgoal. The rationale for providing alternative subgoals is to accommodate the needs of participants with medications that affect their heart rate response to exercise. Intervention participants are asked to maintain their habitual diet and eating patterns throughout the 12-week period. For WC participants, they are instructed to maintain their habitual exercise, diet, and eating patterns for 12 weeks (wait period) and then receive the intervention, but no data will be collected from them during their intervention period.

Figure 1. Demo of the exercise gaming protocol.

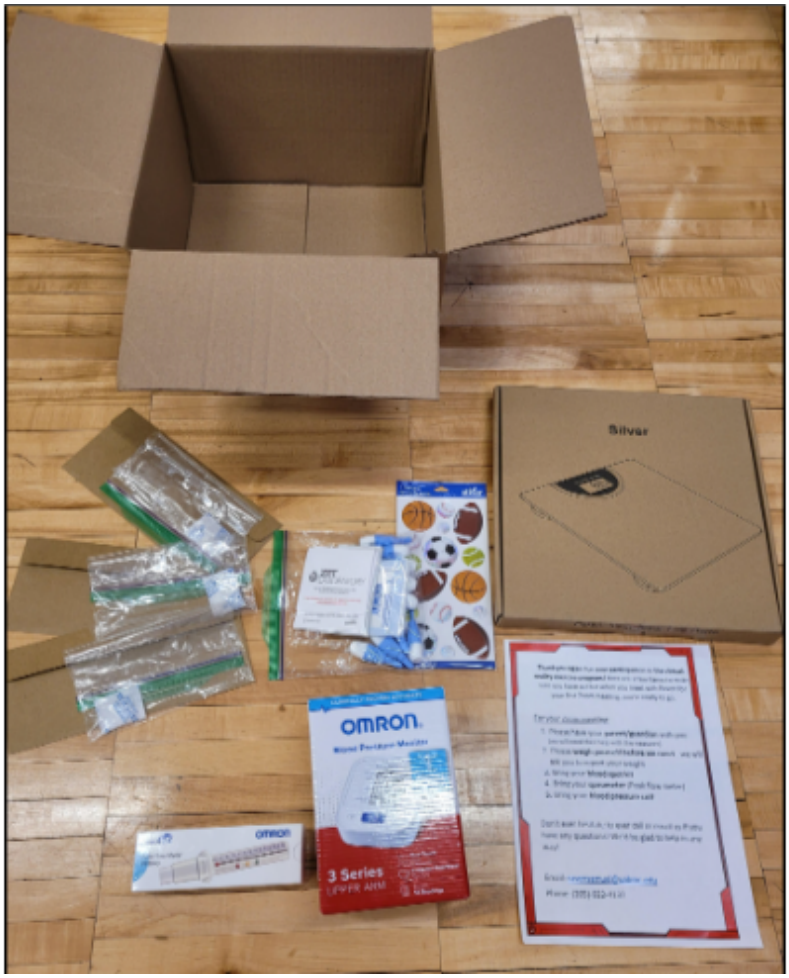
Telecoaching

The intervention includes behavioral physical education (PE) coaching through videoconference (tele-PE). Tele-PE aims to enhance adherence, provide basic exercise knowledge, monitor exercise, and increase mastery playing the games. Calls will last 15 minutes and are provided weekly in month 1, biweekly in month 2, and once at the end of month 3. Caregivers are included in the interview since caregiver knowledge and attitude are determinants of participation [43,47,48]. Tele-PE includes behavior change strategies framed within social cognitive theory [38], including planned steps toward achieving goals (earning new games via the "Level-Up" protocol), instructions on proper movement and gaming skills to increase mastery, adaptations to hardware and game settings, resolution of participation barriers, and education of the importance of exercise for health from systematic reviews. Tele-PE is delivered primarily by medical residents that are trained by the principal investigator (author BL), who has experience with adapted exercise and coaching in other telehealth trials [49-51] (NCT04264390).

Remote Study Procedures

This trial was designed so that it could be easily replicated in a future scale-up trial. All study procedures, including screening, consent, data collection, and intervention, are conducted remotely at home. Survey data are collected through a secure web-based application for managing and creating databases (REDCap). All equipment is shipped to participants (Figure 2).

Figure 2. Data collection equipment package.



Data collection equipment includes:

- Three home dried blood spot test kits (ZRT Labs)
- Three return envelopes to ship blood samples back at the three data collection time points
- Stickers to secure the blood spot test card during collection
- BP cuff (Omron 3 Series Upper Arm, OMRON, United States)
- Peak flow meter (Peak Flow Meter PF9940, OMRON, United States)
- Low-cost bathroom scale

Outcomes for aims 1 and 2 for both the virtual reality tele-exergaming and WC groups are measured through tele-assessment at baseline (week 0), midintervention (week 6), and postintervention (week 13). The participant, a caregiver, and a research assistant meet through a Health Insurance Portability and Accountability Act–protected Zoom (Zoom Video Communications) videoconference room to complete testing synchronously. Participants are asked not to consume food or drink 10-12 hours overnight before completing a blood spot and BP test in the morning. The research assistant visually and verbally guides the caregiver through the procedures. Systolic and diastolic BP will be measured after 5 minutes of seated rest and a second time after 2 minutes of rest using a sphygmomanometer with evidence to support its accuracy and reliability for home use [52]. Lung function is measured using a low-cost, clinical, and nondigital peak flow meter. Body weight is measured using an off-the-shelf bathroom scale. For a blood spot test, capillary blood drops will be taken from the finger following a finger stick with a lancet and deposited onto a blood spot card. Blood spots are dried on the filter card for at least 2 hours before closing the cover and then dried overnight before shipping to the research team. Specimens will be stored at −70 °C until they can be shipped in bulk for testing and analysis to ZRT Laboratory, Beaverton, Oregon [53]. The blood spot test kit was designed for adult home use and has been conducted with children [54]. Participants are reimbursed with US $60 per tele-assessment session (3 × US $60 = US $180). The dollar amount is loaded onto a debit card. After completing the intervention or dropping out, the participant and a caregiver will be asked to participate in a semistructured interview through a videoconference or phone call (aim 3). Interviews will last up to 30 minutes and contain 10 general questions examining barriers and facilitators to adherence, likes and dislikes with the program and equipment, and recommendations to improve the program. General questions will include follow-up questions that probe underlying behavioral mechanisms to participation. BL is the study interviewer. He has completed over 400 interviews related to disability and exercise. Participants will be reimbursed with US $25. Interviews will be audio recorded and then transcribed for analysis. The qualitative component will be published in a secondary analysis publication.

Outcomes

Baseline participant characteristics will include age, sex, ethnicity, physical activity level, and GMFCS level. Physical activity will be measured by the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [55], and GMFCS will be obtained via parent report [45,46]. The GLTEQ is a 7-day recall, 3-item self-report questionnaire, with evidence to support its use as a valid and reliable measure of physical activity among adults with disabilities [56] and adolescents [57].

Aim 1

Primary outcomes will include lung function, body weight, and blood tests, including high-sensitivity C-reactive protein (hsCRP); hemoglobin A_{1c} (HbA_{1c}); and fasting insulin, triglycerides, and cholesterol (total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]). The ZRT Lab dried blood spot test has demonstrated excellent validity with venous serum samples (eg, hsCRP, r=0.99; fasting insulin, r=0.93; fasting triglycerides, r=0.95) [53,58].

High-Sensitivity C-Reactive Protein (mg/L)

C-reactive protein is a critical marker of inflammation that contributes to proinflammatory and prothrombotic elements of CVD risk. A single hsCRP measure is a strong predictor of myocardial infarction or coronary heart disease mortality, and several other diseases of the circulatory system in people without a history of such conditions [59]. Changes in hsCRP may occur from as early as 8 weeks of exercise [33].

Hemoglobin A_{1c} (mmol/mol)

HbA_{1c} is a measure of red blood cell mean hemoglobin glycation over the previous 3 months. Exercise interventions for 1 month without a dietary component can expect a small to moderate effect on HbA_{1c} from 1 month of training [34].

Fasting Insulin (µIU/mL)

High fasting insulin indicates the presence of insulin resistance, whether or not an individual shows glucose intolerance. Exercise interventions without a dietary component can expect a small beneficial change in fasting insulin levels from 1 month of training [34].

Fasting Triglycerides (mg/dL)

A triglyceride level >150 mg/dL is largely supported as an indicator of CVD risk [60,61]. Exercise interventions without a dietary component can expect a small beneficial change in triglyceride levels following 1 month of training [34] even among people with normal triglyceride levels [62].

Fasting Cholesterol (mg/dL)

Abnormalities in the lipid profile, including high total cholesterol, high LDL cholesterol, and low HDL cholesterol, are predictors of future CVD among young and middle-aged people [63,64]. Exercise interventions without a dietary component can expect a small effect after 1 month [34].

Blood Pressure (mmHg)

Elevated BP during childhood and adolescence is associated with intermediate markers and CVD-related events in adulthood [65]. Moderate intensity exercise is negatively associated with BP [11]. Small changes in BP can occur from as little as 1 month of endurance training [66].

Aim 2

Feasibility is measured through process and management metrics [67]. Recruitment, retention, and adherence rates are recorded throughout the study and will be descriptively reported at the end of the study. Recruitment rate is described as the number of people contacted via phone call divided by the number of people enrolled in the study. Retention is defined as the average number of exergaming minutes per week completed and uploaded by participants across the intervention divided by the total number of minutes prescribed (300 minutes per week). Adherence is described as the number of data collection sessions completed divided by the total number of sessions scheduled (total of 102: 34 participants with 3 data collections per participant). At weeks 0, 6, and 13, participants complete 3 questionnaires to measure enjoyment, pain, and fatigue. Enjoyment is measured via the Physical Activity Enjoyment Scale (PACES) [68]. PACES includes 18 items that are measured on a scale from 1 to 7 and has demonstrated its usefulness as a valid measure of physical activity enjoyment among a variety of age groups [68,69]. Pain and fatigue (prevalent among youth with cerebral palsy) [18] are measured by the National Institutes of Health Neuro-QoL Pediatric Pain and Fatigue [70]. Adverse events (eg, falls or injuries) and problems are recorded and reported to the university institutional review board (IRB) as appropriate. Management issues with the remote procedures are recorded and reported.

Analyses

General Rules

As a preliminary study, the study is not powered for effectiveness. Findings will inform sample size and design considerations for an effectiveness trial. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram will be reported. Analyses will be performed in an intent-to-treat manner. Statistical tests will be conducted using SAS software 9.4 or greater, considering 2-sided tests with an alpha level of .05.

Primary Aim

Descriptive statistics and exploratory statistical procedures will be presented [71,72]. Descriptive statistics will include means/medians, SDs/IQRs, effect sizes, box and whisker plots, and 95% CIs. Statistical procedures will primarily use mixed model repeated measures analysis of covariance (ANCOVA). This will allow us to test the group, time, and group by time interaction effect simultaneously while adjusting for potential differences in blood-related health outcomes or participant characteristics at baseline. Post hoc analysis will include Tukey-Kramer multiple comparisons test. Means between groups will be compared using the 2-group t test; changes within groups will be compared using paired t tests. If the results of the ANCOVA warrant further investigation, additional analyses will be conducted.

Secondary Aim

For the feasibility metrics (ie, recruitment, retention, and adherence rates), no a priori criteria for acceptability will be established. Questionnaire results will be descriptively reported, and changes across time will be explored using general linear mixed models techniques, such as mixed models repeated measures analyses. An appropriate structure for the covariance matrix (eg, unstructured) will be selected for these models using the final data. Post hoc analyses will be performed using the Tukey-Kramer multiple comparisons test.

Tertiary Aim

The qualitative component will follow Charmaz's constructivist grounded theory framework [73], guided by the following philosophical assumptions: critical realism ontological perspective [74] and an interpretivism epistemological perspective [75]. Data will be analyzed by authors BL and YK (who is not directly involved with the intervention). Data analysis will include three phases: (1) generation of initial codes (ie, phrases that represent lines of text) and (2) focused codes (ie, phrases that represent one or more initial codes), and (3) creation of conceptual categories (ie, higher order phrases that represent focused codes) and linkages to construct a substantive theory [73]. Further details are described elsewhere [76].

Power

Given the lack of previous research, we are primarily interested in examining the effect estimates of tele-exergaming on blood outcomes in aim 1, which will inform sample size determinations for an efficacy trial. Thus, the sample size determination was based on a power *estimate* calculation using a noncentral T distribution approach that is intended for pilot RCTs [77]. Specifically, a sample size of 34 will allow relatively precise estimates of the treatment effect on aim 1 study outcomes, considering a modest effect (standardized difference 0.5), 2 tails, type I error rate of 5%, 90% power [77], two parallel arms with 1:1 allocation, and a 14% dropout rate. This sample size will surpass the recommendations for pilot feasibility trials of 30 [78] and 12 per group [79]. The effect size of 0.5 was based on the RCT by Slaman et al [29], which is the only RCT with a statistically significant benefit associated with cardiometabolic health (cholesterol) in youth with cerebral palsy.

Results

This study was approved by the university IRB in March 2022. The study was initiated in June 2022, and the first participant was enrolled on June 17, 2022. Recruitment of the last participant is anticipated in Q2 of 2023.

Discussion

Overview

Due to alarmingly low rates of exercise participation, youth with cerebral palsy are at substantially high risk for CVD-related conditions and CVD mortality as they age into adulthood. Regular participation in aerobic exercise is an effective nonpharmaceutical method for preventing CVD and metabolic syndrome, but effective modalities such as walking, running, and cycling are often not suitable for the large demographic of youth with cerebral palsy who have reduced mobility. The growing availability of internet access and acceptance of telehealth (due to the COVID-19 pandemic) create an unprecedented opportunity to engage large underserved groups of youth with cerebral palsy in exercise behavior. When combined with recent advances in consumer-available VR video game technology, telehealth programs have the potential to create accessible and fully immersive single and multiplayer active video gaming experiences at home. This enjoyable modality of exercise may enhance the likelihood that youth with cerebral palsy maintain regular participation over periods of time that are necessary to elicit changes in cardiometabolic health. Therefore, we hypothesize that 3 months of telemonitored VR exergaming with behavioral coaching will result in greater changes in key indicators of cardiometabolic health in youth with cerebral palsy compared with a WC group that maintains habitual activity. This study is being tested among a cohort of patients from the Children's Hospital of Alabama, Birmingham, Alabama.

Strengths and Limitations

In addition to the intervention, another innovative component of the study is that it incorporates remote study procedures, including tele-assessment data collections. Due to difficulties with allocating transportation and the low density of youth with cerebral palsy in one geographic area, an entirely remote study procedure creates far greater accessibility than one that requires on-site visitation. Therefore, the study has strong potential to be replicated in a scale-up effectiveness trial. Regarding limitations, the sample size determination was based on a pilot estimate; therefore, the statistical analyses may not be adequately powered. Results from this study will need to be confirmed in a larger confirmatory trial. Additionally, this study requires participants to be able to use the handheld controllers and view the screen of the head-mounted display, which may not be appropriate for some youth with cerebral palsy who have functional and visual impairments.

Conclusions

This study is testing the latest consumer-available VR gaming technology with a serious exercise prescription and behavioral telecoaching protocol on cardiometabolic indicators of health among youth with cerebral palsy. Should the results demonstrate a potential effect on outcomes, they will need to be confirmed in an efficacy and effectiveness trial.

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Authors' Contributions

BL, JR, DD, and YK contributed to the design of the study. All authors contributed to the second draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Special Emphasis Panel.
[PDF File (Adobe PDF File), 91 KB - resprot_v11i8e40708_app1.pdf]

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Abbreviations

ANCOVA: analysis of covariance
BP: blood pressure
CONSORT: Consolidated Standards of Reporting Trials
CVD: cardiovascular disease
GLTEQ: Godin Leisure-Time Exercise Questionnaire
GMFCS: Gross Motor Function Classification System

HbA_{1c}: hemoglobin A_{1c}
HDL: high-density lipoprotein
hsCRP: high-sensitivity C-reactive protein
IRB: institutional review board
LDL: low-density lipoprotein
PACES: Physical Activity Enjoyment Scale
PE: physical education
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
VR: virtual reality
WC: wait list control

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Toronto, ON, M5A 3Y5
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