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Contents

Protocols

Protocol

Effects of a 12-Minute Smartphone-Based Mindful Breathing Task on Heart Rate Variability for Students With Clinically Relevant Chronic Pain, Depression, and Anxiety: Protocol for a Randomized Controlled Trial

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Abstract

Background: Mindfulness meditation (MM) is a commonly used psychological intervention for pain, mood, and anxiety conditions, but can be challenging to practice with severe symptoms without proper training. The Mindfulness Meditation app (MMA) is a supportive training tool specifically developed for this study to aid in the practice of mindful breathing using a smartphone.

Objective: This study aims to evaluate the psychophysiological effects of the MMA. Specifically, the study will assess parasympathetic functioning using heart rate variability (HRV; primary outcome), pain and mood symptoms, mind-wandering and present moment awareness, and breath focus in groups of undergraduate participants who self-report clinically-relevant symptoms of chronic pain (CP) and depression or anxiety (DA) and condition-free (CF) participants who do not meet either criteria. We hypothesize that use of the MMA by study groups will lead to improved HRV, pain, and mood symptoms compared with groups who do not use the app.

Methods: This study is a two-arm randomized controlled trial (RCT) recruiting through a Web-based research participation pool at York University in Toronto, Canada. We are aiming for minimum 60 participants in each of CP, DA, and CF groups. Upon arriving to the laboratory, participants will be prescreened for classification into groups of CP, DA, or CF. Groups will be randomly assigned by a 1:1 ratio to an MMA (MMA+) condition or MM condition without the app (MMA−) after a brief stress induction procedure. In MMA+, participants will practice mindful breathing with a smartphone and press breath or other buttons at the sound of audio tones if their awareness was on breathing or another experience, respectively. HRV and respiration data will be obtained during rest (5 min), stress induction (5 min), and meditation conditions (12 min). Participants will complete psychological self-report inventories before and after the stress induction and after the meditation condition. Separate linear mixed models will be used to examine HRV and self-report inventories comparing groups and treatment conditions.

Results: Recruitment for the study began in November 2017 and is expected to be completed in winter of 2019-2020. As of July 2019, 189 participants have been recruited. The study's main findings are expected to reveal a positive pattern of HRV responses in the CP, DA, and CF groups, such that a significant increase in HRV (P<.05) is detected in those randomized to the MMA+ condition in comparison with those randomized to the MMA− condition.

Conclusions: This RCT will contribute to the burgeoning health psychology literature regarding the clinical relevance of HRV in assessment and treatment of psychological and medical conditions. Furthermore, possible ways to inform designs of MM training tools delivered by apps and Web platforms for CP, depression, and anxiety conditions' treatment will be discussed.

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KEYWORDS

mindfulness; mobile apps; heart rate variability; chronic pain; depression; anxiety

Introduction

Background

Mindfulness meditation (MM) is an element of the Buddhist traditions first introduced as a clinical intervention in western medicine by Kabat-Zinn [1]. Over the past 35 years, the practice has received significant interest in clinical and health psychology and, more recently, in neuro- and psychophysiology. A family of meditative practices based on mindfulness is commonly used as a psychological approach to mental illness and chronic pain (CP) management. Mindful breathing is central to the mindfulness practices and places an emphasis on paying nonjudgmental attention to one's cognitive, emotional, and physical experiences while reorienting focus on breathing sensations to cultivate cognitive and emotion regulation and progressively relaxed states [2]. Mindfulness-based treatments have been shown to be effective in reducing symptoms of depression, anxiety, and chronic pain [3,4].

One proposed mechanism for mindful breathing benefits is the state relaxation effect mediated by parasympathetic vagus nerve activation because of its process of bringing awareness to breathing sensations while practicing acceptance of stressors such as worrying thoughts, negative emotions, and pain [5]. However, individuals with pain, depression, and anxiety disorders commonly share the physiological trait of a dysregulated autonomic nervous system (ANS), particularly with respect to parasympathetic stress recovery processes, which compromise vagal activation [6,7].

Rigid and inflexible types of mind wandering, such as worry and rumination, are typically seen in individuals with psychiatric illnesses [8,9] and chronic pain [10]. These stressors lead to prolonged physiological stress activation linked to health risks [6,11]. MM attempts to counteract unhealthy mind wandering by instilling present-oriented attention that is more conducive to appropriately rested and relaxed states in the absence of stressful demands [12]. Critical to the purported benefits of mindfulness is that the removal of stressful stimuli in the environment does not always coincide with a return to resting state. Physiological stress inevitably arises through pain, worry, rumination, and distressing emotions such as fear, anxiety, and anger. Patterns of worry and rumination are defined as *perseverative stressors*, as they are typically related to past or anticipated stressors [6]. Perseverative stress refers to persistent physiological stress that can linger for prolonged periods, sometimes subconsciously, creating an undertone of stress arousal and allostatic load associated with gradual and sustained withdrawal of vagal tone, quantifiable by low heart rate variability (HRV) [11]. Chronically low HRV is a sign that the ANS is *sympathetically dominant*, with persistent and excessive activation of the stress response that is less amenable to vagal-mediated parasympathetic recovery [6,11]. Mindfulness practice may be a key method to target the pathophysiological mechanism common to chronic pain, depression, and anxiety.

Mindful breathing can enhance vagal activation through state relaxation effects, as multiple studies have shown that even brief mindfulness practice after stress significantly increases HRV [13,14]. This vagal-activating effect may have stress-relieving benefits for individuals with depression-anxiety symptoms [15]. With regards to pain, reductions in self-reported pain have been demonstrated in individuals practicing HRV-based biofeedback [16], and it has been theorized that increased vagal activation is connected to several analgesic mechanisms such as lowered systemic inflammation and inhibited pain-processing brain regions [17]. Thus, the vagal-activating treatment potential of a smartphone-based mindful breathing app may have clinical utility, given the strong research evidence associating low HRV and psychological [18] and pain conditions [7].

A potentially impeding factor for client populations in practicing mindful breathing is the demand characteristics of the silent, inwardly focused exercise that may naturally make them more saliently aware of their symptoms of depression (eg, rumination), anxiety (worry), and pain (sensations). Relatedly, a qualitative study has revealed experiential challenges to MM practice that must be addressed in clinical treatment contexts, including the fact that meditation is a difficult skill to learn and practice, and participants encounter difficult thoughts and feelings amidst practice [19]. This is all the more relevant to naïve meditators with pain, depression, and anxiety symptoms, making for a potentially challenging experience that discourages further MM practice.

Supportive training tools, such as smartphone apps, are widely used to receive audio guidance on MM, and evidence is emerging for their immediate and long-term effects on altering mood states [20]. However, few studies have investigated the clinical utility and physiological changes related to meditation-based smartphone apps [21]. Furthermore, audio instructions may not be readily applicable in participants with clinical symptoms as they may be more vulnerable to their mind-wandering effects amidst meditation practice. In 1 study, a computer-based mindful breathing task provided random audio tones during the practice to prompt participants to reorient attention to breathing sensations after pressing a button on the keyboard to indicate whether they had been paying attention to breathing or other experiences at the time of the tone [22]. The results showed higher instances of breath attention were correlated with increased HRV during the practice, suggesting a positive relaxation effect of the mindful breathing task. This paradigm could be effectively applied in a clinical context for individuals who may initially struggle to practice mindful breathing, such as those with chronic pain and severe depression-anxiety symptoms. Although multiple studies have shown that MM leads to HRV increases [13,22], there are no known studies that have investigated the effects of a smartphone-based mindful breathing task on HRV in individuals with chronic pain and severe depression-anxiety symptoms.

One study provided naïve meditators training in the mindfulness technique of thought distancing using a smartphone app or traditional mindfulness practice without an app. They found significantly greater mindfulness and pleasantness and lower perceived difficulty associated with the smartphone app–based mindfulness practice compared with the nonapp conditions [23]. More investigations are needed to determine in what ways smartphone apps can be employed as an effective medium of delivering mindfulness training to vulnerable populations who are naïve to meditation.

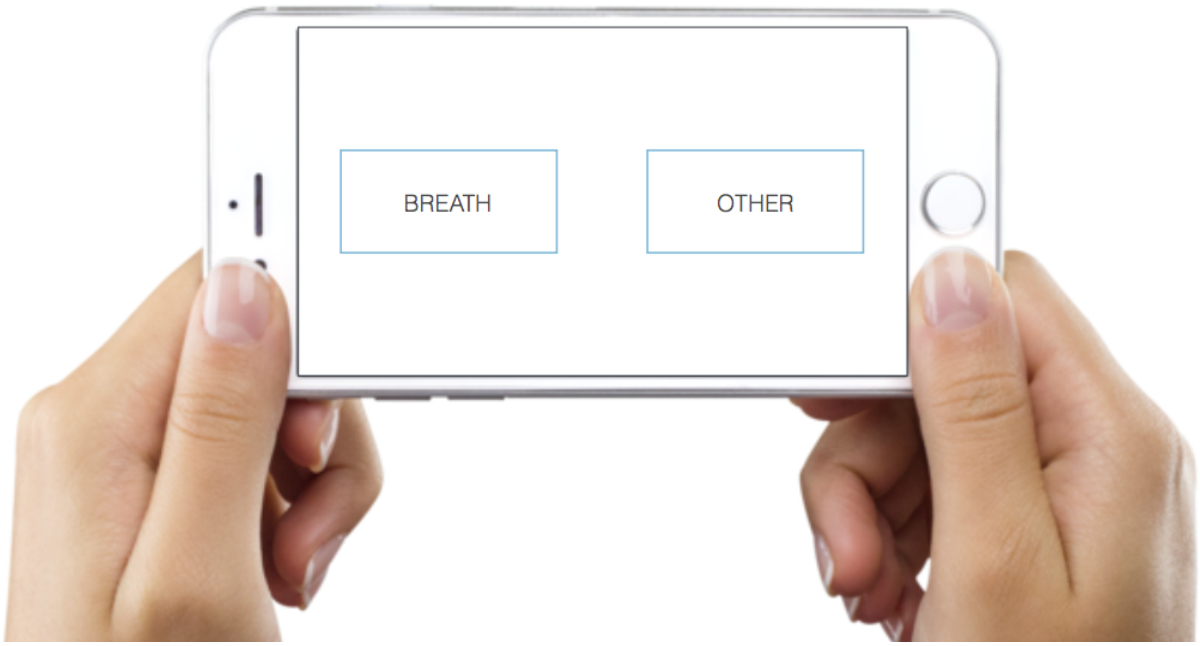
A recent systematic review of mindfulness-related apps found over 500 apps in the marketplace, but only 23 were designed to provide mindfulness training, and they were largely focused on providing audiovisual guidance, timers, and reminders to practice [21]. The review revealed that only 1 randomized controlled trial (RCT) for a mindfulness app was underway at the time [24] and that, generally, there is limited evidence available for the efficacy of apps in increasing mindfulness [21]. Furthermore, the literature on existing mobile apps marketed for chronic pain reveals that, with few exceptions [25], they rarely adhere to scientific guidelines and that health care professionals are rarely involved in their development [26-29].

The aim of this study is to overcome some of the aforementioned limitations by designing an app with input from clinical researchers and empirically testing the app's effectiveness in a sample of young adults with CP, anxiety, and depression. To cultivate mindfulness, a mobile-based Mindfulness Meditation app (MMA) was developed based on Burg et al's [22] mindful breathing exercise that "assesses the participants' ability to mindfully stay in contact with the bodily sense of the breath during an exercise aligned with breathing meditation" [22]. In lieu of verbal meditation instructions amidst practice, the task provides audio tones at random intervals to which practitioners respond by pressing keys to indicate *breath* (if they were attending to their breathing at the sound of the tone) or *other* (if they were attending to an experience other than the breath at the sound of the tone). This simplified task may be more suitable to beginner meditators and particularly those with various psychiatric and pain symptoms that make meditation practice more difficult [19]. In a previous pilot study of the MMA (VV Latman, MA, unpublished data, June 2017), participants with chronic pain and severe depression-anxiety symptoms randomized to the 12-min MMA task exhibited significant reductions in mood states of anxiety, anger, and overall distress.

This study will evaluate the psychophysiological effects of a smartphone-based MMA (12 min; Figure 1) for individuals with clinically significant symptoms of major depression or anxiety (DA) or chronic pain. Specifically, the study aims to examine parasympathetic activity using HRV (primary outcome) in groups of participants who self-report clinically significant symptoms of DA and CP and condition-free (CF) participants who do not meet our criteria for either. In addition, given the linkages between HRV and the following psychological processes within psychological and medical conditions, the study will also assess mind wandering and present moment awareness, mood symptoms, and breath focus before and after the intervention. All study groups will be randomized to an MMA (MMA+) condition or a MM condition without the app (MMA−) after a brief stress induction procedure.

Overall, 3 major hypotheses (1a, 1b, 2a, 2b, and 3) will be tested.

Figure 1. The Mindfulness Meditation App.



Primary End Point

Hypothesis 1a

HRV change scores during MM will be significantly higher in the CP and DA groups receiving MMA+ compared with corresponding CP and DA groups receiving MMA−, and will not differ between CF groups receiving MMA+ or MMA−.

Hypothesis 1b

HRV will significantly increase from the stress to MM phases in CP and DA participants receiving MMA+ compared with corresponding CP and DA groups receiving MMA−, and will not differ between CF groups receiving MMA+ or MMA.

Secondary End Points

Hypothesis 2a

CP and DA participants randomized to MMA+ will report significant pre-post increases in levels of present moment awareness and state mindfulness compared with participants randomized to MMA−, and present moment awareness and state mindfulness will not differ between CF groups receiving MMA+ or MMA.

Hypothesis 2b

CP, DA, and CF participants receiving MMA+ will report significantly lower mind wandering than corresponding participants receiving MMA−, reflecting the potential for MMA+ to make participants more able to recover their attention from mind-wandering contents and processes during MM.

Hypothesis 3

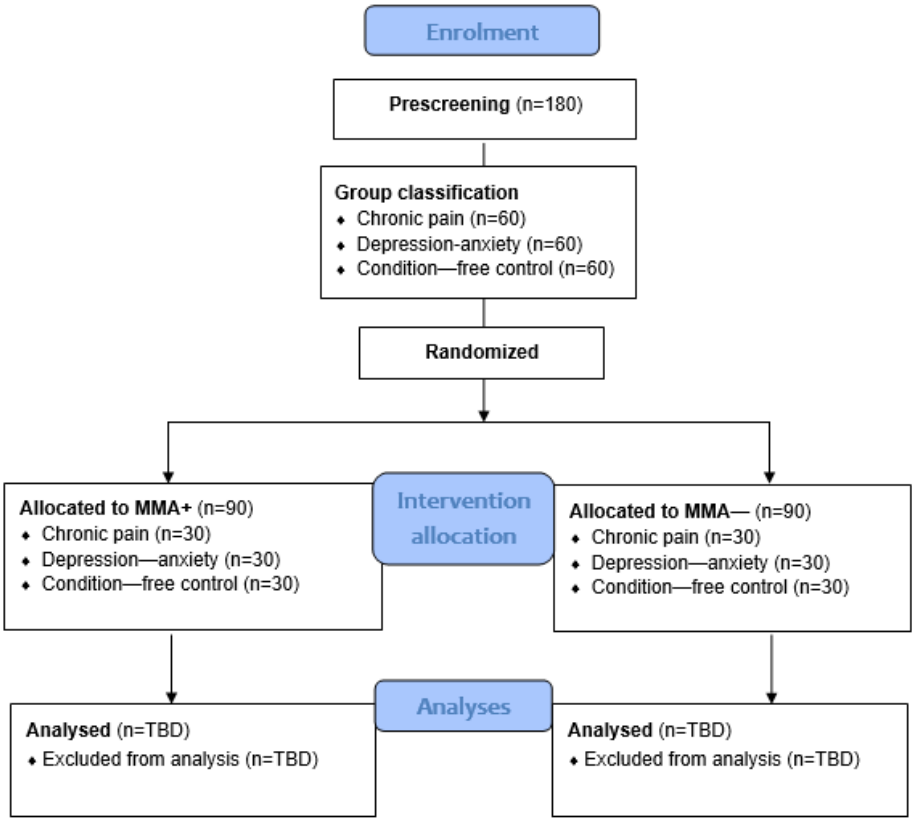
CP and DA participants randomized to the MMA+ condition will demonstrate significant reductions in mood symptoms (state depression and anxiety) after the MM task compared with CP and DA participants randomized to the MMA− condition, reflecting the potential for MMA+ to facilitate the emotion regulation effects of MM for clinical populations.

Methods

Design

This RCT study was designed according to the 2010 Consolidated Standards of Reporting Trials statement (Multimedia Appendix 1) [30], reviewed and approved by the York University research ethics board (Human Participants Review Committee protocol number e2017-303), and registered with ClinicalTrials.gov (NCT03296007) on September 22, 2017, before the recruitment of the first participant. A total of 180 male and female participants will be recruited from the Web-based York Undergraduate Research Participant Pool, based on voluntary participation, and classified into 3 groups of approximately 60 participants each (and randomized into MMA+ or MMA−) based on their prescreening questionnaires: CP (n=30 MMA+ and n=30 MMA−), depression-anxiety (n=30 MMA+ and n=30 MMA−), and CF participants (n=30 MMA+ and n=30 MMA−; Figure 2).

Figure 2. Consolidated Standards of Reporting Trials 2010 flow diagram showing anticipated participant flow for enrolment, group classification, randomization to intervention, and analyses. MMA−: mindful breathing practice without using the Mindfulness Meditation app; MMA+: mindful breathing practice using the Mindfulness Meditation app; TBD: to be determined.



Sample Size Estimation

Sample size estimate for a repeated-measures linear mixed-effects analysis of variance (ANOVA) with 3 groups (CP, DA, and CF), 2 conditions (MMA+, MMA−), and 3 phases (baseline, stress induction, and MM) indicates that a total of 141 participants are needed to detect small-to-medium effect size (f=0.15) HRV changes with a type I error rate (alpha) of .05, a power of 0.95, and a 0.50 correlation between repeated measures (G*Power; Heinrich Heine University Düsseldorf). The small-to-medium effect size corresponds to previously published studies of HRV increases during brief mindfulness practice [13,14]. Recruitment of more than 180 participants will allow for an attrition rate of approximately 20% because of withdrawals, dropouts, technical failures, and missing data. On the basis of prescreening and recruitment numbers in our past pilot study (VV Latman, MA, unpublished data, June 2017), we found the percentage of participants reporting diagnosed CP, severe depression, or anxiety symptoms to be 27%, 33%, and 41%, respectively. Accordingly, the combined number of students expected to be prescreened for eligibility to enroll 60 participants per group will be approximately N=550.

Inclusion and Exclusion Criteria

Participants will be eligible for the study if they are enrolled in a course at York University that provides course participation credit via study enrolment through the Undergraduate Research Participant Pool website. On the recruitment website as well as on the consent form, we have explained that the study may require use of a smartphone-based task. Participants with self-reported cardiac conditions (eg, cardiac arrhythmias, coronary artery disease, and pacemaker) will be excluded as they contravene the interpretation of vagal-mediated HRV [31]. Participants in this study will have no prior relationship with the researchers, including participation in classes by faculty members on the research team.

Procedures

Group Classification and Randomization

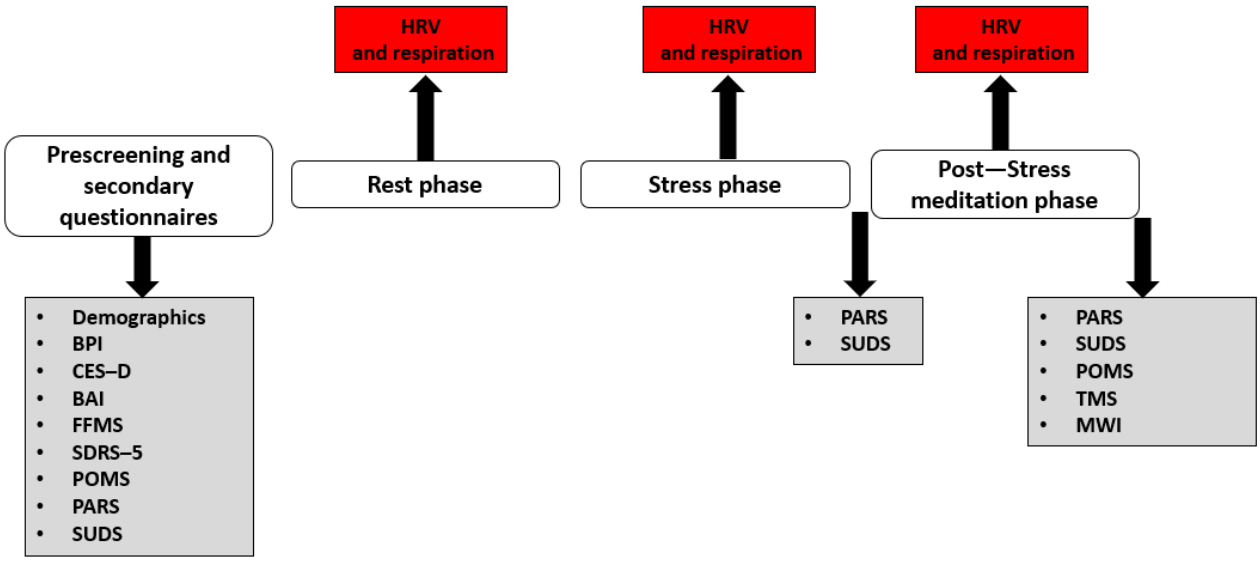
Upon signing up for the study, participants will be instructed to arrive to the Human Pain Mechanisms Lab at York University, where the study procedures will be explained, and informed consent will be obtained from all participants. Participants will complete prescreening questionnaires for CP, depression, or anxiety symptoms. A research assistant will score the questionnaire once completed and check to see if the participant meets *severe* criteria for depression symptoms (≥21 on the Centre for Epidemiological Studies Depression Scale) [32] or anxiety symptoms (≥36 on the Beck Anxiety Inventory) [33]. If they meet such criteria, they will be classified into the depression-anxiety group and randomized to the MMA (MMA+) or no app (MMA−) condition. If the participant reports having a CP condition (>3 months of pain on the Brief Pain Inventory) [34], they will be classified into the CP group and randomized to MMA+ or MMA−. Participants who do not meet the criteria for CP or severe depression-anxiety symptoms will be classified into the CF group and randomized to MMA+ or MMA−.

A 3-block randomization schedule (CP, depression-anxiety, and condition free) with 2 treatment arm allocations (MMA+ and MMA−) was created by the study coinvestigator (study author MAA) using a randomization sequence generator [35]. The randomization schedule uses a 1:1 ratio with blocks of 10. Treatment allocation will be determined by study coordinators and staff members after participants complete their prescreening questionnaires to determine their group classification (Figure 2). Study research assistants review prescreening questionnaires and assign the grouped participants to their corresponding treatment arm using a randomization schedule column concealed in a computer spreadsheet using the *highlight* (black) function. Upon entering participants into the spreadsheet, research assistants unhighlight the next available cell in the corresponding column to reveal their treatment assignment.

Experimental Session

Participants will undergo a 3-phase (baseline, stress induction, and MM) assessment during which electrocardiogram (ECG) and respiration rate data will be collected for later HRV analysis (Figure 3). A mobile cardiogram system by MindWare (MindWare Technologies, LTD) will be used, requiring placement of 3 adhesive electrodes on the right clavicle and left and right hipbones and a respiratory belt secured around the participant's waist.

Figure 3. Study procedures. Physiological assessments are in red boxes, and questionnaire assessments are in gray boxes. BAI: Beck Anxiety Inventory; BPI: Brief Pain Inventory; CES-D: Center for Epidemiology Depression Scale; FFMS: Five-Factor Mindfulness Scale; HRV: heart rate variability; MWI: Mind-Wandering Inventory; PARS: Present Moment Awareness Rating Scale; POMS: Profile of Mood States; SDRS-5: Social Desirability Rating Scale-5; SUDS: Subjective Units of Distress Scale. TMS: Toronto Mindfulness Scale.



Rest Phase

The first phase will comprise a 5-min baseline period during which participants will rest quietly with their eyes closed and not speak or make sudden movements.

Stress Induction Phase

Following the baseline phase, a 5-min stress induction procedure will be performed whereby the participant engages in a set of mental arithmetic tasks, with the instruction to work as quickly as possible for maximal performance. Mental arithmetic was chosen as a stressor task because of its superior properties in eliciting sympathetic responses compared with other laboratory-based stressors [36].

Post-Stress Meditation Phase

After the stress induction phase, a post-stress MM phase will involve either the MMA+ or MMA− task according to the randomization schedule.

After completing the prestudy set of questionnaires, participants will be randomized to either the smartphone-based MMA+ or a mindful breathing practice without use of a mobile app (MMA−). Mindful breathing instructions will involve paying attention to breathing sensations while seated with eyes closed for 12 min and reorienting attention back to breathing once aware of mind wandering [2]. Research assistants remain in the room during the intervention phase, for both intervention conditions, to ensure there are no technical or practical issues with the interventions. There are no adverse events expected during the study, and participants are free to withdraw their participation at any time during the study with no penalty to their research credit or any other costs.

Intervention Arm: Mindfulness Meditation With the App

The MMA was developed using JavaScript and installed on an iPhone 4s. As the app was designed with young adults in mind, the leading thought was to keep the intervention brief and the design simple and easy to use. Participants are asked to hover their thumbs on 2 buttons, *breath* and *other*, presented on a white screen for the duration of the task (Figure 1). The MMA is a 12-min breath awareness task that involves a total of 24 silent phases comprising 6 different durations (5 seconds, 15 seconds, 25 seconds, 35 seconds, 45 seconds, and 55 seconds) randomly presented 4 times each and followed by the presentation of a 1-second tone. During the silent phases, participants are to practice mindful breathing with their eyes closed by paying attention to their breathing sensations and reorienting their attention when noticing their mind wandering. At the sound of the tone, participants press *breath* if, in that moment, they were attending to their breath, or *other* if they were attending to other experiences. Participants are instructed to return their attention to mindful breathing after pressing 1 of the 2 buttons on the screen. The app was designed to record reaction time from tone onset to button press and the number of times *breath* and *other* buttons were pressed. A prototype was first tested internally, and feedback was gathered from the research team and pilot participants to ensure a smooth user experience without technical bugs. Feedback influenced decisions regarding the number of tones and interval between tones played, the size of the *breath* and *other* buttons, and the addition of a 1-min trial period before commencing the 12-min meditation task.

Participants in the MMA+ condition will use the MMA to practice mindful breathing with the following instructions: “For the duration of the task, pay attention to your breathing sensations, including (1) the feeling of the air passing through your nostrils, (2) the movement of your in-and-out breath at your chest and torso, (3) the sound of the air as you breathe in and out, (4) the temperature (coolness or warmth) of the in-and-out breath, and (5) returning your attention to your breath when you have noticed your attention has been elsewhere.” In addition, amidst mindful breathing practice, they will be asked

to press a *breath* (I am paying attention to my breath) or *other* (I am not paying attention to my breath) button on the phone screen when hearing a tone introduced at random intervals. The MMA task will involve a total of 24 silent phases of 6 different durations (5 seconds, 15 seconds, 25 seconds, 35 seconds, 45 seconds, and 55 seconds) randomly presented 4 times each and followed by the presentation of the tone. Participants are provided a 1-min practice session with the app before the intervention session. Participants will engage in smartphone-based mindful breathing for 12 min in a seated and eyes closed position.

Control Arm: Mindfulness Meditation With No App

Participants in the MMA− condition will engage in mindful breathing without use of the smartphone app for 12 min in a seated and eyes closed position.

Measures

Heart Rate Variability

There are several metrics that quantify HRV, the majority of which are either time based or frequency based. With the beat-to-beat interval series (also referred to as the R-R series), one can estimate the square root of the mean of squared successive differences between interbeat intervals (IBI), which has been found to be strongly correlated with respiration-based heart rate (HR) changes) [37]. It is important to note that both the IBI and the standard deviation of IBI's are subject to increases with longer ECG recordings (influenced by slower, long-range fluctuations in HR independent of respiration-induced beat-to-beat changes). Thus, the Task Force [38] has recommended 5 min as a standardized length of HRV assessment in clinical and psychophysiological research. Using the frequency domain measure, one can examine the extent to which the HR varies within specific frequency ranges. The Fourier transform method deconstructs the time domain representation of the R-R series and computes a measure of *power* in several frequency bands in units of milliseconds squared (ms^2). These bands include ultralow frequency (<0.04 Hz), low frequency (0.04-0.15 Hz), and high frequency (HF; 0.15-0.4 Hz). Typically, the frequency band of interest for the purposes of HRV interpretation is the HF band, as this is where the respiratory-linked beat-to-beat changes are reflected [37,39]. Although this is not intended to be an exhaustive account of HRV metrics, the aforementioned measures are the most commonly used in studies of vagal influence on cardiac chronotropy. On the basis of the recommendations by the 2 international committees [38,40], this study focuses on the frequency measure as the primary measure to interpret changes in vagal-mediated HRV across different conditions.

ECG recordings will be collected using MindWare Impedance Cardiograph acquisition system and used to analyze HF-HRV as the primary HRV measure. The MindWare system utilizes 3 adhesive electrodes applied to the right collarbone (negative lead) and the lower left and right ribs (positive lead and ground lead) or alternatively the wrists (positive and negative leads) and ankle (ground lead) if necessary. MindWare BioLab and HRV software will be used to calculate time- and frequency-based HRV metrics. Patients will be measured during phases of (1) rest in a seated position with eyes closed (5 min), (2) a stress induction task requiring rapid completion of arithmetic problems (5 min), and (3) meditation conditions of MMA+ or MMA−.

Respiration Rate

A MindWare respiratory belt (below the sternum) will be used to monitor respiration rate during rest, stress induction, and meditation. Respiration is a potential confounding variable for HRV interpretation and will be used as a covariate in HRV analyses if it is found to differ between assessment phases or study groups [31].

Breath Focus and Reaction Time

Using data collected with the MMA+, breath focus will be measured using the ratio of *breath* and *other* responses during the MMA+ task. Reaction time measures will also be collected pertaining to mean (seconds) in pressing *breath* and *other* buttons during the MMA+ task.

Prescreening Questionnaires

The following prescreening questionnaires will be administered to students to determine group classification by assessing for clinical CP (The Brief Pain Inventory), depression (The Center for Epidemiological Studies-Depression Scale), and anxiety symptoms (Beck Anxiety Inventory).

Brief Pain Inventory—Short Form

The Brief Pain Inventory is a 16-item, self-report questionnaire that measures pain intensity and pain interference. The test has good internal consistency (alpha=.85) and high test-retest reliability [41].

Center for Epidemiological Studies Depression Scale

The Center for Epidemiological Studies Depression Scale (CES-D) is a screening test for depressive symptoms with good sensitivity and specificity and high internal consistency [32]. The CES-D has been found acceptable and reliable in adolescent and young adult populations [42].

Beck Anxiety Inventory

The Beck Anxiety Inventory is a 21-question multiple-choice self-report questionnaire that is used for measuring anxiety severity. Internal consistency (Cronbach alpha) ranges from .92 to .94 for adults and test-retest (1-week interval) reliability is 0.75 [33].

Secondary Outcomes and Trait Questionnaires

Participants will also be asked to complete the following questionnaires to assess mood (Profile of Mood States [POMS]), present moment awareness (Present Moment Awareness Ratings Scale [PMARS]), mind-wandering (Mind-Wandering Inventory [MWI]), state mindfulness (Toronto Mindfulness Scale [TMS]), trait mindfulness (Five Factor Mindfulness Scale), social desirability (Social Desirability Response Set 5-Item Survey), and subjective stress (Subjective Units of Distress Scale [SUDS]).

Profile of Mood States

The POMS is a 37-item questionnaire designed to assess global distress as well as 6 mood states: fatigue, vigor-activity,

tension-anxiety, depression, anger-hostility, and confusion-bewilderment. Participants are asked to indicate the degree to which they have experienced different mood states in the past week. The scale has good internal consistency (alpha=.91) and test-retest reliability (r=0.74). The POMS has been validated for use in adolescents and adults [43]. Higher total scores represent greater total mood disturbance [44].

Present Moment Awareness Ratings Scale

The PMARS is a 5-item questionnaire developed specifically for use in this study. Participants will be asked to rate their level of awareness of different aspects of present moment experiences. The PMARS was used in a previous pilot study (VV Latman, MA, unpublished data, June 2017), and statistical analyses of its psychometric properties is underway [45].

Mind-Wandering Inventory

The MWI is a 5-point Likert-based questionnaire developed by the authors with items retroactively assessing the frequency of different types of mind-wandering events the respondent experienced during the mindful breathing task. The MWI was used in a previous pilot study (VV Latman, MA, unpublished data, June 2017), and statistical analyses of its psychometric properties is underway [46].

Toronto Mindfulness Scale

The TMS is a state measure of mindfulness with 2 factors: curiosity and decentering. The TMS defines curiosity as an awareness of present moment experience with a curious attitude. Decentering is defined as an awareness qualified by distance and separation from current experience. The TMS has good internal consistency of alpha=.95. Current research demonstrates that the TMS is a reliable and valid measure of mindfulness that accurately measures curiosity and decentering [47].

Five-Factor Mindfulness Scale

The Five-Factor Mindfulness Scale (FFMS) is a 39-item Likert-based scale that assesses 5 aspects of mindfulness: nonreactivity to inner experience, acting with awareness, describing, nonjudging of inner experience, and observing. Research has demonstrated the FFMS to be valid in community and student samples with an internal consistency of alpha greater than .90 [48].

Socially Desirable Response Set 5-Item Survey

The Socially Desirable Response Set 5-Item Survey (SDRS-5) is a self-report measure designed to assess the tendency for individuals to provide socially desirable responses to self-reports of attitudes, behaviors, and feelings. Alpha reliability estimates for this instrument have been found to be between .66 and .68 [49].

Subjective Units of Distress Scale

The SUDS is a means of rating the severity of current distress (or anxiety), allowing for the monitoring of changes over time, where 0 is feeling perfectly relaxed and 100 is the worst anxiety and stress imaginable [50]. Participants will be asked to provide 0 to 100 SUDS ratings at baseline, post-stress induction, and after the post-stress meditation phases. The SUDS ratings will be used to do a manipulation check with respect to the mental arithmetic stressor and to monitor changes in stress over time.

Statistical Analyses of Outcomes

This study has 2 coprimary hypotheses based on published recommendations for HRV analyses [31,39]. Generally, within-subject designs and analyses are preferred considering the high interindividual variations observed in HRV measures. To analyze differences in HRV with respect to MMA+ and MMA− between groups, change scores from stress to MM will be computed by subtracting stress-HRV from MM-HRV and used as the dependent variable in hypothesis 1a. In addition, within-subject changes in HRV according to the MM conditions and groups will be examined in hypothesis 1b. Results will be interpreted using significance values, confidence intervals, and effect sizes [51]. Intention-to-treat methodology will be the guiding principle of analyses. A complete case analysis approach will be used in anticipation of missing or unusable data.

Hypothesis 1a

To analyze HRV change in groups between the stress and MM phases, a linear mixed model will be used with group (CP, DA, and C) and condition (MMA+ and MMA−), with HRV change scores from stress to MM phases as the dependent variable. Planned comparisons will be computed comparing the MMA+ and MMA− conditions for each group (CP, DA, and C).

Hypothesis 1b

To analyze HRV differences between groups and across phases, a 3-way linear mixed-effects ANOVA will be used with group (CP, DA, and C), phase (baseline, stress, and MM), and condition (MMA− and MMA+), with HRV as the dependent variable. Significant interactions will be followed up with simple effects analyses comparing the stress and MM phases for each group (CP, DA, C) within the 2 conditions (MMA+ and MMA−).

Hypotheses 2a and 2b

To analyze pre-post increases in levels of present moment awareness, state mindfulness, and mind wandering, separate 3-way repeated-measures ANOVA with group (CP, DA, and C), time (pre and post), and condition (MMA− and MMA+) will be used with simple main effects to examine significant interactions.

Hypothesis 3

To analyze pre-post changes in mood, a 3-way ANOVA with group (CP, DA, and C), time (pre and post), and condition (MMA− and MMA+) will be used with simple main effects to examine significant interactions.

Exploratory Analyses

Associations between HRV and psychometric measures will be explored with Pearson correlations and linear regression models using the following constructs: present moment awareness (PMARS), mind wandering (MWI), anxiety symptoms (Anxiety Sensitivity Index), depressive symptoms (CES-D), state mindfulness (TMS), and mindfulness skills (FFMS). Breath focus and reaction time will be examined for group differences (CP, DA, and C) using 1-way ANOVA. Given potential response biases in self-reported outcomes, we will examine group differences in socially desirable responding (SDRS-5)

using 1-way ANOVA and use it as a control variable in applicable outcome analyses.

Results

Recruitment for the study began in November 2017 and is expected to be completed in winter of 2019-2020. Data collection is currently underway. As of July 2019, we have recruited 189 total participants (C*P*=41, DA=55, and CF=93). Data analysis, manuscript writing, and additional publications are expected to be completed in the fall and winter of 2019.

Discussion

Principal Findings

The main findings of the study are expected to reveal a positive pattern of HRV responses across the different study groups, CP, DA, and C, such that they exhibit significantly increased HRV ($P<.05$) in the treatment condition, MMA+, in comparison with the control condition, MMA−. On the basis of previous research published by our team, HRV is expected to increase during MM when practiced after stressor tasks [13,14]. However, a pattern of *inflexible* HRV responses has been noted in previous studies involving participants with clinical characteristics. For instance, a randomized experimental study of students high on perfectionistic traits and nonperfectionist students was conducted with measurement of HRV at baseline, stress, and during subsequent audio-guided MM or a rest condition with an audio lecture. Only the nonperfectionist group exhibited significantly increased HRV in the mindfulness condition, whereas the perfectionists did not, reflecting an inflexible state of sympathetic dominance [13]. A follow-up study was conducted with headache and headache-free participants where both groups showed increased HRV during post-stress mindfulness. However, during post-stress rest, the headache group exhibited significantly lower HRV compared with headache-free participants, reflecting impaired ability for cardio-vagal recovery [14]. This pattern of results is consistent with literature indicating low and inflexible HRV patterns in individuals with clinical characteristics of depression, anxiety, and chronic pain [52-54].

The MMA is designed as a supportive training tool to aid clinical populations with mindful breathing practice. Accordingly, our primary hypothesis is that HRV will increase from the stress to MM phases in DA and CP participants randomized to MMA+ compared with MMA−. Specifically, mindful breathing practice with the aid of the MMA is expected to yield additional relaxation effects for participants, by way of respiratory sinus arrhythmia, to be reflected in increased HRV measures. Examination of secondary hypotheses will help to further contextualize the role of key psychological processes, including present moment awareness, state mindfulness, mind wandering, and mood, as mediators and outcomes of mindfulness-based treatments.

Limitations

A potential limitation of this study is the lack of blinding of research assistants with respect to group screening and treatment allocation procedures. Research assistants are required to remain in the room to address any technical or practical issues with the intervention, negating the possibility of blinding research assistants to treatment. However, both MMA+ and MMA− conditions entail app- or self-guided mindful breathing practice with no active involvement of research assistants; thus, risk of bias in intervention delivery is low. Another limitation is that the use of the MMA presents a demand characteristic requiring participants to reliably report *breath* or *other* responses. Any accidental responses by participants that do not correspond to their attentional states (eg, pressing *breath* when the intention was to press *other*) cannot be corrected during the MMA task, and may momentarily distract participants during the task. In addition, participants will only be provided 1 session of the MMA task, which is a limited duration of exposure that prevents examination of dose-response effects. In future longitudinal studies, we hope to test repeated practice with the app and its effects on HRV, pain, mood, and other outcomes. In terms of study groups, classification criteria did not exclude individuals who reported mild-to-moderate levels of depressive-anxiety symptoms or pain for less than 3 months, instead classifying subcriteria participants as condition free. The presence of symptoms in the CF group has the potential to impact results. With regard to study outcomes, it must be noted that the MWI and present moment awareness rating scales are awaiting psychometric validation and will undergo factor analyses based upon the data gathered in this and other studies. One procedural limitation is that the MMA− condition is not structurally identical to the MMA+ condition as it foregoes the use of a smartphone app during the practice of mindful breathing. To preserve task similarity, it may be useful in future studies of the MMA to provide participants with a *control app* that does not provide random-interval tones as they practice mindful breathing. Finally, the study is based on undergraduate student populations, limiting generalizability until future studies are conducted with community and clinical populations.

Conclusions

This RCT will contribute to the burgeoning health psychology literature about the clinical relevance of HRV measures in the assessment and treatment of psychiatric and health conditions. The findings may also contribute to the growing use of HRV as a biomarker and biofeedback tool within clinical and health psychology. Furthermore, there is an evolving need for an evidence basis related to supportive mindfulness training tools for the self-management of symptoms related to depression, anxiety, and chronic pain. The innovation of incorporating mindful breathing practice into a scalable app provides valuable information to allow for future iterative development of an app involving novel techniques for teaching mindfulness to clinical populations.

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Conflicts of Interest

The authors are the developers of the smartphone app examined in this study.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 2274 KB - resprot_v8i12e14119_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
ANS: autonomic nervous system
CF: condition-free
CES-D: Center for Epidemiological Studies Depression Scale
CP: chronic pain
DA: depression or anxiety
ECG: electrocardiogram
FFMS: Five-Factor Mindfulness Scale
HF: high frequency
HR: heart rate
HRV: heart rate variability
IBI: interbeat intervals
MM: mindfulness meditation
MMA: Mindfulness Meditation app
MMA−: mindful breathing practice without using the Mindfulness Meditation app
MMA+: mindful breathing practice using the Mindfulness Meditation app
MWI: Mind-Wandering Inventory
PMARS: Present Moment Awareness Ratings Scale
POMS: Profile of Mood States
RCT: randomized controlled trial
SDRS-5: Socially Desirable Response Set 5-Item Survey
SUDS: Subjective Units of Distress Scale
TMS: Toronto Mindfulness Scale

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Protocol

An App-Delivered Self-Management Program for People With Low Back Pain: Protocol for the selfBACK Randomized Controlled Trial

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Abstract

Background: Low back pain (LBP) is prevalent across all social classes, in all age groups, and across industrialized and developing countries. From a global perspective, LBP is considered the leading cause of disability and negatively impacts everyday life and well-being. Self-management is a recommended first-line treatment, and mobile apps are a promising platform to support self-management of conditions like LBP. In the selfBACK project, we have developed a digital decision support system made available for the user via an app intended to support tailored self-management of nonspecific LBP.

Objective: The trial aims to evaluate the effectiveness of using the selfBACK app to support self-management in addition to usual care (intervention group) versus usual care only (control group) in people with nonspecific LBP.

Methods: This is a single-blinded, randomized controlled trial (RCT) with two parallel arms. The selfBACK app provides tailored self-management plans consisting of advice on physical activity, physical exercises, and educational content. Tailoring of plans is achieved by using case-based reasoning (CBR) methodology, which is a branch of artificial intelligence. The core of the CBR methodology is to use data about the current case (participant) along with knowledge about previous and similar cases to tailor the self-management plan to the current case. This enables a person-centered intervention based on what has and has not been successful in previous cases. Participants in the RCT are people with LBP who consulted a health care professional in primary care within the preceding 8 weeks. Participants are randomized to using the selfBACK app in addition to usual care versus usual care only. We aim to include a total of 350 participants (175 participants in each arm). Outcomes are collected at baseline, 6 weeks, and 3, 6, and 9 months. The primary end point is difference in pain-related disability between the intervention group and the control group assessed by the Roland-Morris Disability Questionnaire at 3 months.

Results: The trial opened for recruitment in February 2019. Data collection is expected to be complete by fall 2020, and the results for the primary outcome are expected to be published in fall 2020.

Conclusions: This RCT will provide insights regarding the benefits of supporting tailored self-management of LBP through an app available at times convenient for the user. If successful, the intervention has the potential to become a model for the provision of tailored self-management support to people with nonspecific LBP and inform future interventions for other painful musculoskeletal conditions.

Trial Registration: ClinicalTrial.gov NCT03798288; https://clinicaltrials.gov/ct2/show/NCT03798288

International Registered Report Identifier (IRRID): DERR1-10.2196/14720

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KEYWORDS

low back pain; self-management; case-based reasoning; eHealth; mHealth; app; decision support system

Introduction

Low back pain (LBP) is a leading contributor to years lived with disability [1,2]. The economic costs associated with health care, sickness absence, lost ability to work, and treatment costs of nonspecific LBP are a major societal burden [3-5].

Clinical guidelines recommend education, exercise therapy, multidisciplinary treatments, and combined physical and psychological interventions for the management of LBP [6-10]. Self-management programs including elements of such recommended components are suggested as options for conditions like nonspecific LBP [11]. Self-management is commonly defined as active engagement and care for one's own health by managing symptoms, physical and psychological problems, and their impact [11,12]. Although self-management is a recommended LBP treatment, the effectiveness of self-management for LBP has been reported in systematic reviews to be moderate for pain and small to moderate for pain-related disability [13,14]. These results may be explained by the large variation in the content of self-management programs [13] and the poor adherence commonly observed in relation to such programs [14,15]. Adherence is influenced by several factors such as tailoring of the program to the individual and support to persist with self-management [16].

Digital solutions such as mobile apps can be used as platforms for supporting self-management [17,18] and may solve some of the problems outlined above. First, some evidence indicates that tailoring of self-management advice to people with LBP may be more effective than nontailoring to improve pain and function [19]. Second, tailored digital health solutions may help to increase engagement and adherence [20]. During recent years, a vast number of apps that target self-management of LBP have been introduced to the commercial market. A systematic review identified 61 available apps on Google Play and the App Store and concluded that the apps were of poor quality and included poor-quality information from questionable sources and none of the apps had been tested for effectiveness [21]. A systematic review that synthesized and critically appraised the published evidence concerning the use of interactive digital interventions to support self-management of LBP found the literature to be heterogeneous and many studies to be poorly described [22]. Thus, the benefits and utility of digital interventions for self-management of LBP for the population at large remains unclear, presenting an important knowledge gap.

In the selfBACK project, we have developed an evidence-based and data-driven decision support system (DSS) delivered via a smartphone app to facilitate, improve, and reinforce self-management of nonspecific LBP. The design and implementation of the selfBACK DSS have been described elsewhere [23]. The selfBACK trial is designed as an international multicenter randomized controlled trial (RCT) with two parallel arms testing the effectiveness of the selfBACK DSS in addition to usual care (intervention group) versus usual care only (control group) for participants with nonspecific LBP. We hypothesize that participants randomized to the intervention group will have reduced pain-related disability at 3 months, measured by the Roland-Morris Disability Questionnaire (RMDQ), compared with participants randomized to the control group.

Methods

Participants and Setting

Inclusion and exclusion criteria are outlined in Textbox 1. The assessment of whether the criteria are considered to limit participation is performed either by the referring health care professional (HCP) or based on participant's self-report. The selfBACK intervention is tested on a general LBP population rather than a specific subgroup to reflect that the intervention targets care-seeking patients not limited to specific characteristics such as symptom duration.

Textbox 1. Selection criteria.

Inclusion criteria:

- Danish or Norwegian adults (aged 18 years and older)
- History of low back pain of any duration in patients having sought care for their low back pain within the preceding 8 weeks from primary practice (general practice, physiotherapy, or chiropractic serving as first point of contact) or a specialized outpatient hospital facility (Denmark)
- Must score mild to severe pain-related disability rated as 6 or above on the Roland-Morris Disability Questionnaire
- Must own and regularly use a smartphone with internet access
- Must have a working email address and access to a computer with internet access

Exclusion criteria:

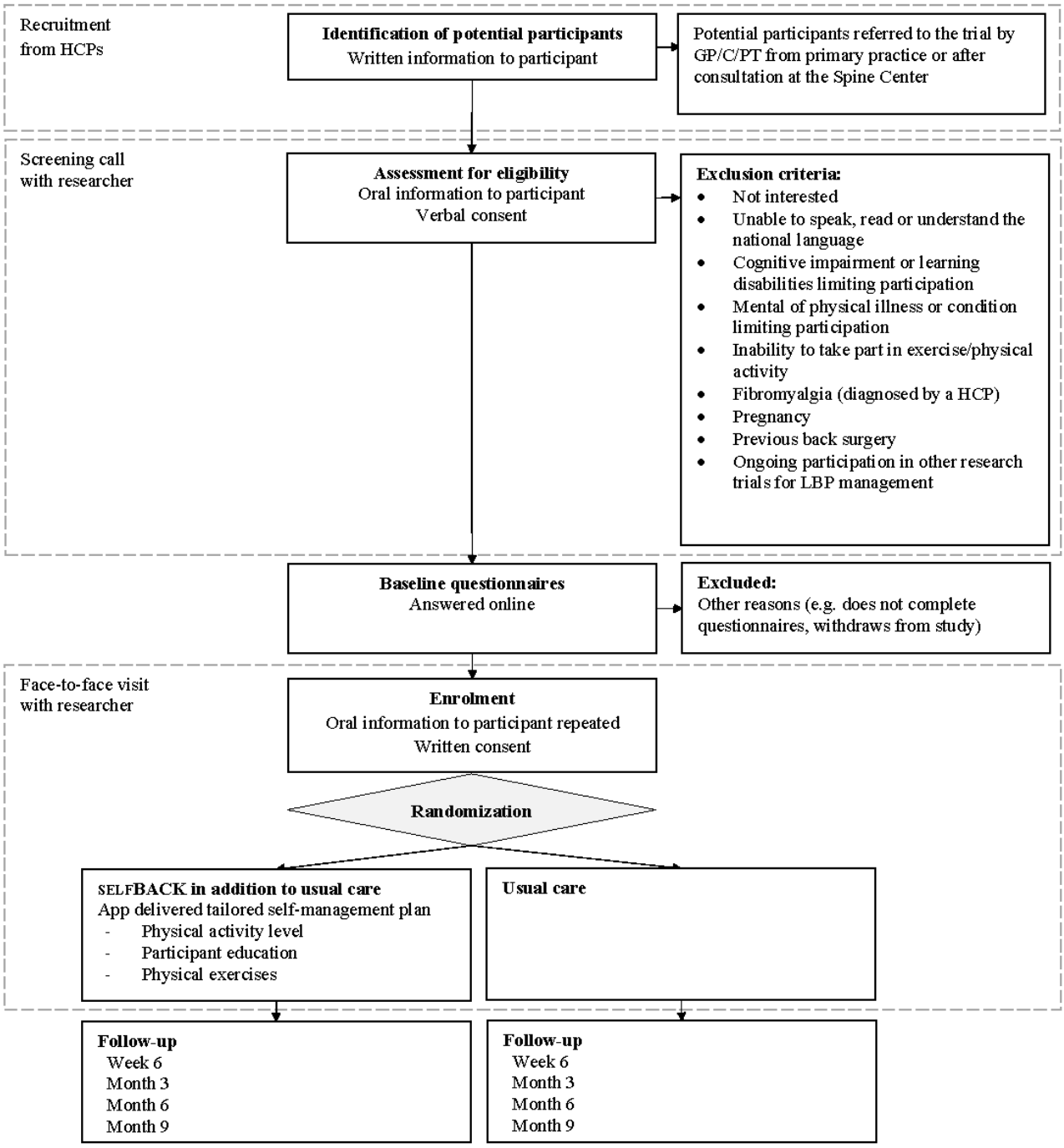
- Unable to speak, read, or understand the national language (Danish or Norwegian)
- Cognitive impairments or learning disabilities limiting participation
- Mental or physical illnesses or conditions limiting participation as assessed by the referring health care professional or the participant
- Inability to take part in exercise or physical activity
- Fibromyalgia (diagnosed by a health care professional)
- Pregnancy
- Previous back surgery
- Ongoing participation in other research trials for low back pain management

Recruitment and Screening

Recruitment is performed in Trondheim, Norway, and Odense, Denmark. The recruitment flow is described in Figure 1. A total of 350 participants are to be recruited to the RCT. Of these, 75% (262/350) will be recruited in Denmark and 25% (88/350) in Norway. Recruitment is undertaken by physiotherapists, chiropractors, and general practitioners. In Denmark, participants are additionally recruited from the Spine Centre of Southern Denmark, an outpatient hospital that provides care for people with back pain referred from primary care, either family physicians or chiropractors. The Spine Centre provides diagnostic assessment and prescribes treatment plans. For all recruitment sites, people seeking care due to nonspecific LBP may be referred to the trial by the consulting HCP based on a short description of eligibility for the trial. Final eligibility is assessed by the research team during a screening phone call. The recruitment to the selfBACK trial will not affect any planned routine diagnostic assessment or treatment (usual care).

Interested patients are screened via telephone by a member of the research team. If eligible and willing to participate, participants give their verbal consent to participate and are invited to complete the baseline questionnaire. Thereafter participants give their written consent to participate and are randomized to one of two groups.

Figure 1. Participant flow through the selfBACK trial. The dashed lines indicate who the participant interacts with during the screening process and randomization. GP: general practitioner; PT: physiotherapist; C: chiropractor; HCP: health care professional; LBP: low back pain.



Randomization and Blinding

Participants are randomized to either (1) selfBACK DSS in addition to usual care or (2) usual care only. Randomization is performed as a block randomization with permuted blocks of random size and stratified by country and care provider (ie, general practitioner, physiotherapist, chiropractor, or Spine Centre). The allocation ratio between groups is 1:1. Randomization is performed in a Web-based trial management system (Web Case Report Form [WebCRF]) developed and administered by the Unit of Applied Clinical Research, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. The WebCRF system holds a minimal dataset on all screened participants (variables include trial indentification number, participant initials, country, type of HCP recruiting participant, age, and gender). The study is single-blinded; participants are not blinded to group allocation. Analysis and interpretation of the study results will be performed by researchers blinded to group allocation.

Intervention

The trial and intervention are described following the Standard Protocol Items: Recommendations for Interventional Trials [24] and Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth (CONSORT-EHEALTH) [25] guidelines.

Usual Care

Participants receive usual care as deemed appropriate by their HCP. This includes any diagnostic procedure, treatment, or referral the HCP finds relevant considering the case history, clinical findings, and pragmatic, daily clinical practices. Participants can seek care, treatment, or help elsewhere as they find relevant. After the completion of the trial at 9 months, participants in this group are offered a wearable device like the one given to the selfBACK group.

Use of the selfBACK App in Addition to Usual Care

The selfBACK app presents participants with weekly tailored self-management plans consisting of recommendations on number of steps per day, educational material, and a program for strength and flexibility exercises. The process of tailoring the weekly self-management plan has been described elsewhere [23]. In short, a weekly self-management plan is created based on information from four different sources: (1) the baseline questionnaire; (2) a weekly question and answer session (tailoring session) where the participant via the app provides up-to-date information on their LBP, function, fear-avoidance, sleep, pain self-efficacy, perceived stress, symptoms of depression, and barriers for self-management; (3) the participant's report on accomplishing the recommended program for strength and flexibility exercises in the preceding week; and (4) number of steps in the preceding week recorded by a physical activity–detecting wristband connected to the selfBACK app. Tailoring of the self-management plans is achieved by using case-based reasoning (CBR) methodology. CBR is a branch of artificial intelligence that imitates human reasoning and tries to solve new problems by reusing solutions that were applied to past similar problems. Hence, in the selfBACK DSS, the CBR system uses data about the current participant case (from the sources described above) along with knowledge about previous and similar participant cases to tailor the self-management plan to the current individual with LBP. The intervention is not intended to replace follow-up by an HCP but to supplement the usual care, and the participant is informed accordingly. Using the CBR methodology to support self-management is relatively unexplored. A recent study showed that using the CBR methodology has the potential to improve glycemic control in type 1 diabetes [26,27]. However, we are not aware of any studies that have used CBR to support self-management of musculoskeletal disorders.

The content for the app was developed using an intervention mapping process [28]. Full details of the process will be reported separately. During the intervention mapping, the content of the app was reviewed and assessed by patients and clinicians and the app was then tested in two separate feasibility and one pilot study before the RCT version of the app was finalized. The results from these studies will be reported separately. Participant experiences using the app and entering the studies were captured in interviews and informed the conduct of this RCT. Overall, the app was very well received among the pilot users, and feedback from participants gave us areas for improvement for the RCT (eg, explanation text in the app and during installations). The self-management plans are built from three types of content: (1) a bank of educational material, (2) a bank of strength and flexibility exercises, and (3) physical activity level (ie, step count). An overview of the available content is presented in Table 1. The educational material is structured under 14 main categories. Short messages are about 140 characters long. Some messages may include links to longer, more explanatory texts (maximum 500 characters) or tools that can be used to help the self-management of LBP. Some short messages are rewritten into quizzes, where the educational content is rephrased into yes or no questions.

The bank of physical exercises holds 56 strength and flexibility exercises organized in 5 targets and 14 pain-relief exercises (Table 1). Exercises are presented as a short video accompanied by a written instruction. The default recommendation is to perform exercises in 3 to 5 sessions per week of 15 minutes duration (eg, 3 exercises with an estimated duration of 5 minutes per exercise, Table 1). The number of exercises is adjusted by the participant's indication of time available. The participant reports on completed number of sets and repetitions per exercise. The progression and regression of exercise difficulty is based on the reported completion level. If the participant reports a flare-up of LBP in the weekly tailoring session, a set of pain-relief exercises is recommended instead of strength and flexibility exercises.

Physical activity is tracked using a wearable device (Mi Band 3, Xiaomi). The wristband shows the achieved step count per day. Educational messages and notifications aimed to motivate more physical activity are pushed to the participant through the app based on the step count data.

Table 1. Overview of the content of self-management plans.

Data available	Physical activity	Physical exercise	Education
Information from preceding week	Achievement of preceding week's step goal	Completion of exercise sessions	Completion of educational messages and quizzes
Content available	Physical activity registration: • Step count registration by wristband • Individualized feedback for daily, weekly, and monthly step count • Advice to stay active • Motivational messages to increase physical activity	Exercise targets: • Abdominals • Back extensors • Core stability • Gluteal and hip muscles • Flexibility • Pain relief Default program: Three exercises (1 abdominal + 1 back extensor OR 1 core stability exercise). Remaining exercises chosen randomly from the other groups.	Message themes: • Information about LBP[a] • Understanding mind-body connection • Self-management for LBP • Thoughts, behavior, attitude, and feelings • Fitting in self-management in a busy life • First aid when your back hurts • LBP and comorbidities • Goal-setting and action planning • Pacing and progression • Problem-solving • Relaxation • Sleep and LBP • Social support • Overcoming barriers for self-management Educational tools: • Sleep reminder and sleep hygiene • Mindfulness • Goal-setting

[a]LBP: low back pain.

Outcomes

The primary outcome is pain-related disability at 3-month follow-up assessed using the RMDQ [29]. The questionnaire includes 24 items asking participants to indicate if they experience functional impairments by answering yes or no to a series of descriptions of functional abilities. Higher scores indicate higher level of disability [30]. For the selfBACK trial, we aim to identify a 2-point difference in RMDQ between the intervention and control group at 3-month follow-up. The rationale for selecting this cutoff was based on several considerations. First, self-management through selfBACK is included as an add-on to usual care in this trial. Although the magnitude of effect for this novel intervention is difficult to predict, a small beneficial effect above that of usual care could be important for this group of patients. Second, the suggested minimal clinically important difference in RMDQ may vary according to the disability level in the population under study [31]. Even though a 5-point difference has been reported as clinically important [32], others have suggested a 1- to 2-point difference to be clinically important if the disability level is low [33].

Descriptive variables include age, gender, height, weight, and report of any comorbidities (comorbidities were registered using an existing questionnaire (HUNT3) from the Norwegian HUNT study [34]). Demographic variables including family relations, ethnicity, educational status, employment, and work characteristics if employed are collected at baseline (Table 2).

A range of secondary and exploratory outcomes is included in the trial, and participants randomized to use the selfBACK app in addition to usual care are asked a set of tailoring questions weekly to individualize their self-management plan (Table 2). App use data such as number of visits, duration spent using the app, achievement scores, and number of days with visits are registered (Matomo software).

Table 2. Overview of the information collected at baseline, during the weekly tailoring sessions, and at follow-ups at 6 weeks and 3, 6, and 9 months.

Characteristics	Baseline	Weekly tailoring	Follow-ups
Descriptive variables			
Participant characteristics	x		
Sociodemographics	x		
Primary outcome			
Roland-Morris Disability Questionnaire [29,32]	x		x
Secondary and exploratory outcomes			
Average pain intensity past week	x	x	x
Worst pain intensity past week	x		x
Duration of current episode with low back pain	x		x
Pain medication frequency past week	x		x
Fear-Avoidance Belief Questionnaire [35]	x	x[a]	x
Pain Self-Efficacy Questionnaire [36]	x	x[b]	x
Activity limitation, work and leisure	x		x
Work ability index (single-item) [37]	x	x	x
Saltin-Grimby Physical Activity Level [38]	x		x
Patient Specific Function Scale [39]	x		x
Sleep problems [40]	x	x[b]	x
Perceived Stress Scale [41]	x	x[b]	x
Quality of life: EuroQoL 5-Dimension [42]	x		x
Brief Illness Perception Questionnaire [43]	x		x
Patient Health Questionnaire–8 [44]	x	x[b]	x
Global Perceived Effect			x
Patient Acceptable Symptom State			x
Perceived barriers		x	
Pain-related function		x[c]	

[a]Fear-avoidance assessed with single-item Tampa scale [45].

[b]Reduced number of items or single items.

[c]Function assessed with single items from Chronic Pain Grade Scale [46].

Data Collection, Storage, and Protection

Outcome measures are collected at baseline, 6 weeks and 3, 6, and 9 months. Data collection is Web-based, and all data are entered directly into the selfBACK database by the participants. To maximize response rate, reminder emails are sent after 3 days and again after 6 days if no response to the first email. If still no answer, a researcher will contact the participant and ask if they are willing to answer the RMDQ questionnaire over the phone at follow-ups.

All outcome and other data are stored on secure servers at NTNU, the servers are firewall protected, and back-up is performed daily. Data storage is consistent with national (Denmark and Norway) and European regulations on data protection. Also, all data transferring processes are protected using https and Secure Sockets Layer as well as sending the data in encrypted format.

Sample Size

The sample size calculations have been performed in two ways. First, we performed a calculation assuming only one follow-up measure and a standard deviation of the RMDQ score of 6 points. The expected standard deviation was informed by previous high-quality studies in Denmark and United Kingdom investigating similar LBP populations [47-50]. Based on this calculation, we estimated that a sample size of 382 (191 in each group) was necessary to detect a 2-point difference with 90% power and a 2-sided alpha level of .05.

Second, we performed a simulation using 1000 repetitions of a mixed-model regression for repeated measures assuming (1) 3 data points per participant (ie, baseline, 6 weeks, and 3 months), (2) a 2-point difference between groups on RMDQ at 3 months, (3) a standard deviation of 6 points, and (4) a correlation between repeated measures of 0.4. The latter was based on

information from previous trials with repeated measures for the RMDQ in similar LBP populations [51,52]. Based on these assumptions and an alpha level of .05, sample size calculations show that 250 participants (ie, 125 participants in each group) result in a power of 92% (95% CI 90%-93%) to detect a 2-point difference in RMDQ between the intervention group and control group at 3 months. Furthermore, simulations assuming a 2-point difference between groups observed at both follow-up time points (6 weeks and 3 months) indicated that a sample size of 180 (90 in each group) will result in a power of 94% (95% CI 92%-95%). These sample size calculations indicate that a sample size of approximately 250 persons (125 in each group) is adequate when using the repeated measure design. A recent systematic review showed that attrition rates ranged between 4% to 94% for digital self-management interventions lasting between 2 weeks and 12 months in LBP populations [22]. To allow for a 30% dropout rate at 3-month follow-up, we aim to include a total of 350 participants in the trial (175 participants in each arm).

Statistics

The primary analysis will estimate mean group difference with 95% confidence interval of the RMDQ score over the first 3 months. Analyses will be conducted according to the intention-to-treat principle using a linear mixed model for repeated measures. This model includes all available data for all participants at each time point (ie, baseline, 6 weeks, and 3 months). In the regression model, individual participants will be specified as a random effect, accounting for the within-subject covariance structure. The effect of group and time will be specified as fixed effects using a joint variable of intervention and time. The analysis will investigate the effect of the intervention as constant over time, as well as an interaction between time and group allocation. Here, baseline levels are pooled over the two study groups assuming that any baseline differences are due to chance [53]. All effects will be estimated both crude and adjusted for the two variables used for stratification in the randomization (ie, country and care provider) [54]. Any missing values are inherently accounted for in the mixed-model approach [55].

To increase transparency, a statistical analysis plan will be agreed upon and made publicly available before ending the collection of the primary outcome. To reduce the risk of biased interpretation of results, the following procedure will be undertaken: two interpretations will be drafted based on a review of the primary outcome data with groups arbitrarily labeled A and B [56]. One interpretation assumes that A is the intervention group and B the control group, the other interpretation assumes the reverse. After agreeing on both interpretations, the randomization code is broken and the correct interpretation chosen.

Process Evaluation

A process evaluation exploring how participants use the intervention in daily life will be conducted as an integrated part of the RCT. For this we will use a mixed-methods process evaluation: gathering quantitative measures by questionnaires for participants including the Virtual Care Climate Questionnaire [57] and 3 rating questions (overall rating of the app, ease of use, recommendable to others), measures of data analytics on app use, and semistructured qualitative interviews. Normalization process theory [58], an implementation theory used extensively to identify barriers and facilitators to uptake and use of new technologies [59], will provide the conceptual underpinning to the process evaluation. The process evaluation will be guided by the RE-AIM framework and investigate all 5 elements of the framework: reach, effectiveness, adoption, implementation, and maintenance [60]. The full details on design and methods for the process evaluation will be published separately.

Ethics and Dissemination

The trial was approved by the national ethical committees in Denmark (S-20182000-24) and Norway (2017/923-6). Correspondingly, national review boards or data protection agencies have approved the trial. In Denmark, approval was granted from the Danish Data Protection Agency through application to the University of Southern Denmark's legal office (201-57-0008) and in Norway from the National Data Protection Authority or the Centre for Research Data through the ethics approval. The trial is registered with ClinicalTrials.gov [NCT03798288].

The trial results will be reported in accordance with the CONSORT 2010 reporting guideline and the 2013 CONSORT-EHEALTH checklist amendment for reporting Web-based and mobile-based RCTs [25,61].

No serious adverse events are expected for this trial. Should a participant contact the research team concerning any worsening of symptoms, the participant will be advised to seek care from their HCP as they normally would. All inquiries regarding potential adverse events will be recorded and discussed in an internal audit and reported with the study results. In addition, the selfBACK DSS is designed to react to increased pain or deterioration in symptoms, and it will adjust the self-management plans based on this information. In addition, participants are informed in the written information and during the screening call and inclusion process that this intervention is an add-on to usual care and should not replace contact with their HCP and that they should always follow the advice of the consulting HCP. Also, the app contains a Caution section describing worsening in symptoms that should be acted upon and advising participants to seek care from their consulting HCP if they experience any such symptoms.

Results

Recruitment to the trial started in early 2019 and is expected to run until the end of 2019. Data collection is expected to be complete by September 2020, and dissemination of trial results is planned thereafter. The results on the primary outcome is expected to be ready during fall 2020.

Discussion

This protocol describes the design and methods of the selfBACK trial assessing the effectiveness of the selfBACK app in addition to usual care in helping people with nonspecific LBP manage their condition. Digital solutions have been described as

promising platforms for supporting people in managing chronic conditions [17,18], and a vast number of mobile apps for managing LBP are already available on the commercial market [21]. In a recent systematic review, 9 studies were identified describing digital mHealth and eHealth self-management interventions for the LBP population [22]. Few studies reported their theoretical underpinnings for the included content, and consequently, the evidence base for digital self-management interventions for LBP remains weak [22,62]. Two recent RCTs showed improvements in participants' symptom status after 12 weeks of using apps providing a digital program of noninvasive treatment options for LBP [63,64]. Only the study by Shebib and colleagues [63] reported greater improvements for the intervention group than the control group. However, the choice of comparators in the two trials were markedly different. In the study by Shebib and colleagues [63], the control group was given a static program consisting of 3 digital educational articles whereas participants in the intervention arm had unlimited access to a personal coach. In the other RCT, no personal contact was present in the intervention arm, but the comparator was individual lessons with a physiotherapist.

The content of the selfBACK intervention was developed using an intervention mapping process and is therefore theoretically underpinned and evidence-based [23]. Also, the DSS is a data-driven system that uses CBR methodology to structure and reuse real participant information to give advice and guide the self-management process in new participant cases. Thus, over time the DSS learns from experience which results in improved self-management plans for future participant cases. In addition to the learning from participant cases, a set of carefully described rules was developed to tailor the self-management plans to different scenarios (eg, flare-up of LBP). We also used participant cases derived from existing patient cohorts to develop a set of seed cases for the case base. Additionally, the app was tested in a pilot study before the start of the RCT, and these participants cases were included in the case base. This ensures clinically meaningful cases in the case base at the start of the RCT.

It is important to recognize that the content of usual care will differ for participants both within and across study centers (countries) of this trial. This is a common problem in trials where usual care is the comparator. However, it is also a reflection of how LBP is managed in a real-life setting. Thus, the results of the trial will have a high degree of external validity. In addition, the process evaluation for the trial will address perceptions of usual care through interviews with participants from the usual care group as well as with participants using the selfBACK app.

Similarly, the content of the suggested self-management plans will vary for participants using the selfBACK app. The app presents tailored self-management plans with three components: exercise, physical activity, and educational material. However, it is very likely that some components will appeal more to some participants than others. Therefore, should the RCT show the selfBACK app in addition to usual care to be more effective than usual care only, the trial design does not allow analyses of which components of the intervention may be causal of such an effect, although the process evaluation may provide some useful insights regarding such issues.

The outcomes from this trial will provide valuable new insights into the potential of mHealth solutions to support effective self-management in relation to LBP, while the parallel process evaluation will aid understanding of barriers and facilitators to uptake, use, and wider implementation of the intervention. The effectiveness of the app will be evaluated on the primary outcome; however, a range of secondary outcomes is included to elucidate the variation in and complexity of symptoms in people with LBP.

Acknowledgments

The selfBACK project has received funding from the European Union Horizon 2020 research and innovation program under grant agreement number 689043. The funding body supervises the conduct of the overall project but is not involved in the planning, implementation, and interpretation of the RCT. NTNU is leading the development of the underlying structure for the database and DSS, Robert Gordon University (RGU) is leading the physical activity monitoring, and the private company Trade Expansion is leading the mobile app development. University of Southern Denmark (UoSD) is lead in the planning and conducting of the RCT. UoSD, National Research Centre for the Working Environment (NFA), NTNU, University of Glasgow (GLA), and RGU developed the content for the app. Participants will be recruited at NTNU and UoSD; NTNU is leading the overall project. Ownership of the data collected in the selfBACK trial is shared between the participating partners (NTNU, GLA, RGU, NFA, and UoSD). A data steering committee will be established that will be competent to decide over the use of the data. The steering committee will comprise one member from each participating partner. The selfBACK consortium supports the concept of data sharing, and inquiries from outside research partners to use the data are welcomed and will be discussed and decided upon by the steering committee.

Authors' Contributions

LFS provided the first draft of the manuscript, and PJM and KS critically scrutinized the first draft and provided comments. TILN, MJS, and JH gave specific input to sample size calculation, and KB gave specific input to the description of the data storage and DSS function. MJS, MS, KW, CNR, BN, and FSM designed the process evaluation. All authors participated in the design and content of the RCT and all authors read, commented on, and approved the final manuscript prior to submission.

Conflicts of Interest

The overall aim of the selfBACK project is to develop a digital DSS and mobile app to support participants to self-manage their LBP. The results and experiences from the pilot and RCT will inform the further development of the selfBACK system, which may be introduced into a commercial market. If the selfBACK system is introduced into a commercial market, it will be done by a separate company that will have obtained a license to take the app to market. Any profit from such a transaction will be received by the participating universities and not by individual authors. In order to secure an unbiased interpretation and dissemination of the RCT, interpretation of the results will be performed blind to group allocation. Upon publication of study results, this commercial potential in the app development will be clearly stated, and the publication will undergo peer review to ensure methodological and scientific rigor. Additionally, the overall conduct of the trial is overseen by biannual review from the European Union, which is funding the project.

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Abbreviations

CBR: case-based reasoning
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DSS: decision support system
GLA: University of Glasgow
HCP: health care professional
LBP: low back pain
NFA: National Research Centre for the Working Environment
NTNU: Norwegian University of Science and Technology
RCT: randomized controlled trial
RGU: Robert Gordon University
RMDQ: Roland-Morris Disability Questionnaire
UoSD: University of Southern Denmark
WebCRF: Web Case Report Form

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Protocol

Normothermic Insufflation to Prevent Perioperative Hypothermia and Improve Quality of Recovery in Elective Colectomy Patients: Protocol for a Randomized Controlled Trial

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Abstract

Background: Perioperative hypothermia during laparoscopy for bowel resection is a risk factor for postoperative medical complications and surgical wound infections. Despite various warming methods used during surgery, a significant number of patients experience perioperative hypothermia. Use of dry, unwarmed insufflation carbon dioxide (CO_2) during laparoscopic procedures may contribute to this problem. Evidence exists that the HumiGard device, which humidifies and heats CO_2 for insufflation, can reduce the risk of perioperative hypothermia.

Objective: The aim is to determine if insufflation with warmed, humidified CO_2 using the HumiGard device, alongside standard perioperative warming techniques, can improve patient recovery, including pain, surgical site infections, complications, and the use of analgesia compared with standard care alone.

Methods: The study is a multicenter, randomized, blinded (patient, surgeon, and assessor), sham device-controlled, parallel group-controlled trial of 232 patients. The study aims to recruit patients undergoing elective laparoscopic, segmental, or total colectomy. Patients will be randomized to receive HumiGard plus standard care or standard care alone (1:1 ratio). The primary outcome is patient-reported quality of recovery, measured by the validated QoR-40 (quality of recovery) questionnaire, from baseline to postoperative day 1. Secondary outcomes include postoperative pain, the incidence of hypothermia, and the rate of postoperative complications.

Results: The information gathered during a small-scale service evaluation at a single hospital was used to inform this study protocol. Before applying for a grant for this full randomized controlled trial, the authors will conduct a feasibility study of 40 patients to ensure that the protocol is feasible and to inform our sample size calculation.

Conclusions: The randomized controlled trial is designed to provide high-quality evidence on the effectiveness of the HumiGard device in potentially reducing the risk of perioperative hypothermia in patients scheduled for laparoscopic colectomy. The results will be used to improve the maintenance of adequate patient body temperature during surgery.

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KEYWORDS

insufflation; hypothermia; temperature; laparoscopy; humans; peritoneum; carbon dioxide

Introduction

Intraoperative Hypothermia

Patients undergoing colectomy or intra-abdominal surgical procedures are at risk of developing perioperative hypothermia, defined as a core temperature less than 36°C [1]. General anesthesia is one of the contributing factors to the development of hypothermia due to the disruption of normal thermoregulatory responses. Evidence exists that perioperative hypothermia is associated with an increased risk of medical complications, morbid cardiac events, surgical would infections, and extended length of stay in hospital [2].

Current Standard Practice in the United Kingdom

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends the following: (1) monitoring of patients' intraoperative temperature every 30 minutes; (2) delaying the induction of anesthesia until the patient's body temperature is greater than 36°C; (3) warming of intravenous fluids and blood products to 37°C; and (4) for procedures lasting longer than 30 mins, using a forced-air warming device lain on top of patients for warming [3].

Active warming methods do not guarantee that a patient will maintain an adequate body temperature. A recent study by Sun et al [4], which evaluated the core temperature of more than 58,000 actively warmed adults undergoing surgery longer than 60 minutes, showed that nearly half the patients developed hypothermia (body temperature <36°C) during the first hour of the procedure. Based on Lavies et al [5], the use of active warming methods reduced the perioperative incidence of hypothermia, but 53% of patients were still hypothermic in the postoperative phase.

During laparoscopic procedures, standard practice is to use dry, unwarmed CO_2 to inflate the peritoneum (insufflation). This may contribute to the risk of hypothermia and cause tissue desiccation. Insufflation with unwarmed and dry gas can result in an additional drop in temperature by 1.3°C to 1.7°C [6] and potentially contribute to the risk of perioperative hypothermia.

Intervention and Study Aims

HumiGard (Fisher & Paykel Healthcare, New Zealand) is a CE-marked medical device that humidifies and heats CO_2 for insufflation. A meta-analysis of studies that evaluated this type of insufflation demonstrated a significant difference in mean core temperature change, a small beneficial effect on immediate postoperative pain (not at day 1 or 2), with potential impact on the incidence of hypothermia. No difference was observed in patients' length of stay, analgesic consumption, and procedure duration [7,8]. In February 2017, NICE published guidance on HumiGard for preventing inadvertent perioperative hypothermia [9]. NICE found that the device showed promise, but that more research was needed before a decision could be made on routine adoption within the UK National Health Service (NHS).

This protocol is designed to address the evidence gaps identified by NICE. We aim to determine whether HumiGard used with other standard ways of warming patients results in better outcomes for patients compared with standard care alone. In addition, an economic evaluation will be carried out comparing the cost-effectiveness of HumiGard plus standard care with standard care alone.

Methods

Study Design and Population

The study is a multicenter, double-blinded (patient and assessor), sham device-controlled, parallel group randomized controlled trial (RCT). It aims to evaluate if the HumiGard insufflation device, along with standard care, can improve patient-reported quality of recovery (QoR) following laparoscopic colorectal surgery. The study will recruit patients undergoing elective laparoscopic colorectal resection for any pathology. The study is designed to be carried out in the colorectal departments of a minimum of four NHS hospitals across England and Wales.

On receiving the funding to carry out the RCT, the authors will seek a favourable opinion from Health and Care Research Wales and UK Research Ethics Committee. The trial will be registered on ClinicalTrials.gov. The protocol was prepared according to the CONSORT 2010 checklist for reporting parallel group RCTs.

Eligibility Criteria

The inclusion and exclusion criteria for patients are presented in Textbox 1.

All emergency procedures will be excluded from the study because the presence of sepsis or infection, which affects core temperature, is an additional complication during emergency procedures.

Textbox 1. Patient inclusion and exclusion criteria.

Inclusion criteria

- Adults 18 years or older
- Scheduled for elective laparoscopic, segmental, or total colectomy
- Able to give informed consent

Exclusion criteria

- Patients unable to complete study documentation
- Patients that lack the capacity to give informed consent
- Patients with a planned open laparoscopic procedure
- Laparoscopic surgery that is converted to open surgery
- All emergency procedures

Interventions

During randomization, patients will be allocated to either the treatment arm or control arm of the study at a 1:1 ratio. Patients in the treatment arm will receive humidified and heated CO_2 insufflation gas into the peritoneal cavity using the HumiGard device. These patients will also receive standard intraoperative warming methods, including warmed fluids and blood products, forced-air warming devices, and warmed blankets at the clinician's discretion.

Patients in the control arm will be treated with a sham device plus standard intraoperative warming methods, including warmed fluids and blood products, forced-air warming devices, and warmed blankets at the clinician's discretion. The sham device used in the standard care arm will be the same HumiGard device as is in the intervention arm; however, the sham device will be turned "off" so that the gas delivered to the peritoneal cavity for insufflation is not heated or humidified. The sham device will deliver CO_2 (as is the case for current standard practice in the hospital) through the HumiGard tubing. The sham device will look and sound the same as the active intervention arm.

Randomization and Blinding

A member of the research team will telephone the randomization service when a new participant has given signed informed consent to take part in the study to allow randomization to occur. This will occur on day 0 of the study (usually the morning of surgery). Randomization will happen after the patient has consented but before entry into the operating theater. This member of the research team will become unblinded to the allocation of that patient and will not be involved in data collection for that particular patient from the point of randomization onward. Randomization to one of two groups (HumiGard or sham device) will be carried out using a minimization program [10]. Minimization takes into account additional patient information, such as American Society of Anesthesiologists (ASA) grade, gender, and benign or malignant procedure type, to ensure even distribution of patients between treatment groups based on prognostic factors. The unblinded member of the research team will set up the HumiGard device or sham device ready for use according to the allocated group. Neither the patient nor the operating team will be aware of the treatment allocation.

Clinical Outcomes

The primary outcome measure is the change in patient-reported QoR-40 (quality of recovery) scores from baseline to postoperative day 1 (POD 1).

The QoR-40 is a widely used and validated questionnaire that provides a patient-reported measure of recovery following surgery and anesthesia [11]. The questionnaire includes 40 items separated across five dimensions: patient support, comfort, emotions, physical independence, and pain. The QoR-40 is a reliable and valid tool for assessment of the quality of recovery in patients. It has very high acceptability among patients and is highly sensitive to any clinical changes [12].

The secondary outcomes for this study are:

1. Change in QoR-40 scores from baseline to POD 3.
2. Change in patient-recorded pain scores from baseline to POD 1 and POD 3 using a visual analog scale (VAS). The score will range from 0 to 100.
3. The incidence of hypothermia during the surgery (body temperature drop to 36°C during the procedure as recorded in the patient's notes).
4. Duration and depth (overall minimum temperature) of hypothermia.
5. The rate of postoperative complications recorded at POD 1, POD 3, at discharge, and at POD 30. The severity will be assessed with the Clavien-Dindo scale, which is widely used for grading the severity of surgical complications in patients [13]. The Comprehensive Complication Index will be used later to create a composite score (0-100) for each patient [14].
6. The incidence of site surgical infections within the first 30 days postsurgery.
7. Length of stay in hospital from procedure to discharge (or until medically fit to discharge).
8. Resource use outcomes, including analgesia (type and dose), use of strategies to maintain perioperative normothermia (eg, warming blanket, fluid warmer), time to discharge, length of procedure, length of recovery time, and readmission to hospital.

9. Cost-effectiveness analysis of the HumiGard device compared with standard care.

Sample Size Estimation

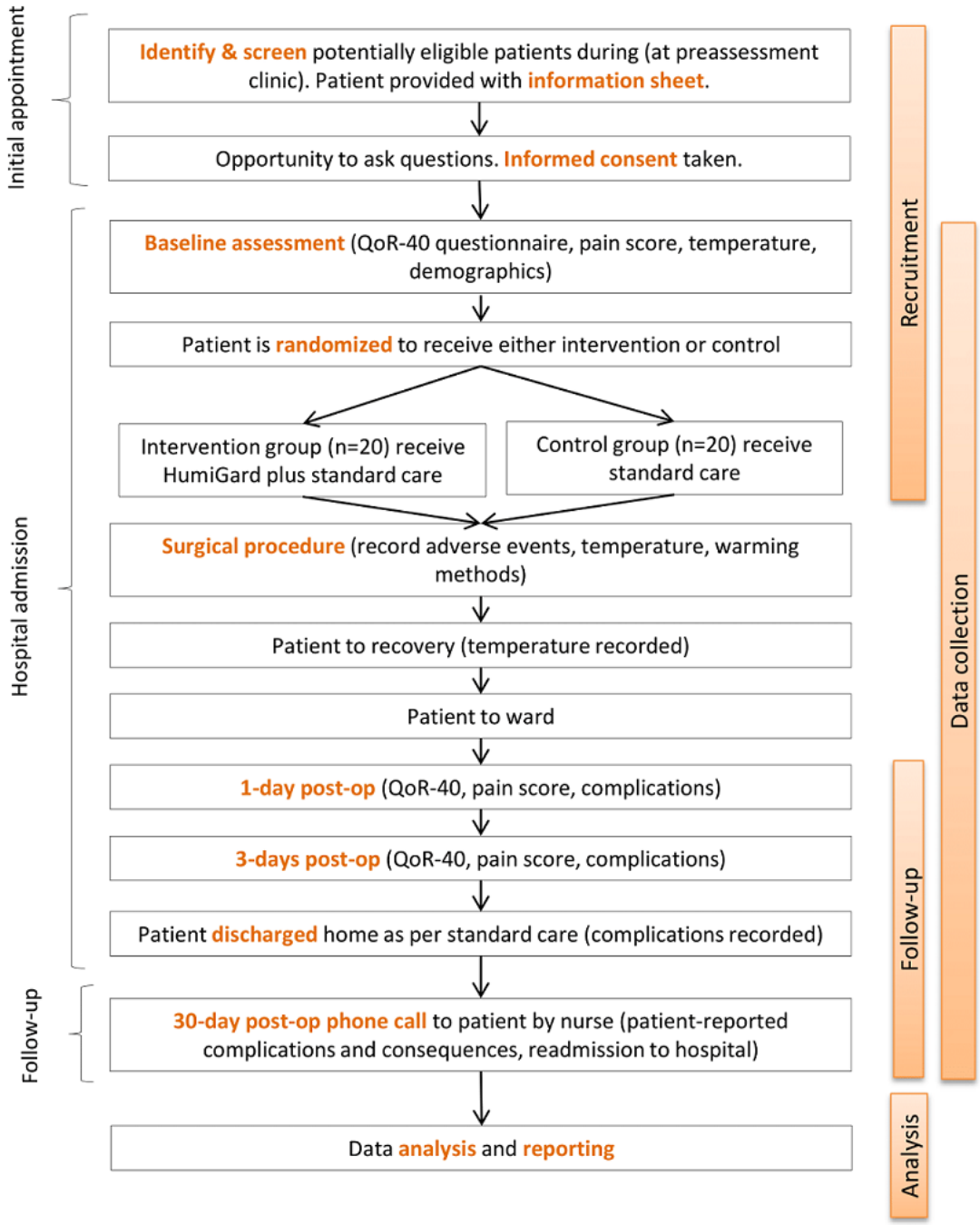
Assuming a normal distribution of the data, we calculated that 232 patients (116 in each arm) will be required for this study. This number is based on detecting the minimum clinically important difference for the QoR-40 questionnaire of 6.3 with a standard deviation of 14.0 (Myles et al [15]). The standard deviation is high compared with more recent studies, such as Moro et al [16]. The study is powered at the 90% level with a 5% significance level. We allowed for 10% of patients lost to follow-up (for QoR at 24 hours) despite the fact that questionnaires will be issued while a patient will be still in hospital. The final recruitment target of 258 will be split into two cohorts of patients (two arms) of 129 patients each.

The Study Process and Data Collection

The flowchart of the study process is presented in Figure 1.

At baseline, patient history, including age, gender, body mass index, smoking status, comorbidities, primary diagnosis, and ASA grade, will be collected. The patient questionnaires and VAS scale will be administered at baseline, POD 1, and POD 3 to patients with no knowledge of their treatment allocation. On arrival at the anesthetic room and during the procedure, the temperature will be measured using a urinary temperature probe.

Figure 1. The study process with recruitment, data collection, follow-up, and final analysis.



Patients' complications (including surgical site infections) will be reported at POD 1, POD 3, upon discharge and at POD 30. All resource use will be routinely recorded at each time point.

Data Analysis

The statistical analysis plan will be followed for all clinical and economic analyses. Intention-to-treat analysis, the primary analysis method, will take into account minimization factors and sites. Whenever possible, standard errors, confidence intervals, and *P* values will be reported for outcomes.

Assuming a normal distribution of the data, the change in QoR-40 between groups will be analyzed with ANCOVA (analysis of covariance) while controlling for the baseline. The logistic regression for incidence rates will be used to compare the incidence of hypothermia between groups. ANCOVA will be used to compare the duration and depth of hypothermia and the Comprehensive Complication Index scores between groups. The incidence of surgical site infections, length of stay and procedure, and readmission rates will be summarized with descriptive statistics.

Economic Evaluation

If the intervention is deemed clinically effective, we aim to perform a cost-consequence analysis. The analysis will consider the costs and resource consequences resulting from, or associated with, the use of the HumiGard device plus standard care compared with standard care alone. The model will be produced in MS Excel.

To fully evaluate the impact of the HumiGard device on the current health care system within the United Kingdom, we aim to design the model from an NHS perspective and have a 1-year time horizon. We aim to perform a within-trial analysis with a decision tree that incorporates the rates of complications such as surgical site infections. We will apply the standard discount rate of 3.5%, and the costs of complications and admission rates will be based on NHS reference costs. Differences in staff and bed costs, associated with factors such as length of stay will be included. The cost of analgesia and resource use needed during surgery to maintain normothermia will be incorporated into the cost model.

We will carry out a scenario analysis to validate the model, compare it with other published evidence, and test the impact of changes within the model structure on the base case results. The impact of other published and clinical data will be tested. Deterministic and probabilistic sensitivity analysis will also be performed.

Results

Service Evaluation

The preparation of the study protocol was preceded by a small-scale service evaluation carried out in the University Hospital of Wales in Cardiff, United Kingdom. The team investigated the ability and willingness of patients to complete QoR questionnaires before and after laparoscopic colorectal surgery, potential recruitment rates, and informed the design of the data capture tools and database. The study was deemed as nonresearch and approved by Cardiff & Vale University Health Board.

During one month of data collection, seven eligible patients were asked to fill in presurgery (on the day of surgery) and postsurgery (POD 1) questionnaires. The baseline characteristics, intraoperative data, and questionnaire-related completion rates are presented in Table 1. All seven patients filled in the QoR-40 questionnaires at both time points. All patients fully completed the preoperative QoR-40 questionnaire and six of seven patients fully completed all the domains from the postoperative questionnaire (one answer was missing in one of the domains). Six of seven patients completed the preoperative VAS pain question; all patients completed the postoperative VAS pain question.

Statistical analysis of the data collected was not performed due to the low number of patients.

The data obtained from the service evaluation provided "proof of principle" evidence that patients in this setting are amenable to completing the QoR-40.

Table 1. Baseline characteristics and intra- and postoperative patient information (N=7).

Characteristic	Participants
Baseline data	
Age (years), mean (range)	50 (19-70)
Sex, n (%)	
Female	5 (71)
Male	2 (29)
ASA[a] grade, n (%)	
1	1 (14)
2	4 (57)
3	2 (29)
Type of surgery, n (%)	
Laparoscopic elective colectomy	7 (100)
Open surgery	0 (0)
Intraoperative data	
Temperature at arrival to theater, n (%)	
<36°C	2 (29)
>36°C	3 (43)
Unknown	2 (29)
Temperature at the end of surgery, n (%)	
<36°C	2 (29)
>36°C	5 (71)
No change during surgery	2 (29)
Higher (range 0.3°C-1°C) than at arrival	3 (43)
Complications (during hospital stay), n	0
Surgery time (hours), mean (range)	3.33 (1.58-4.17)
Postsurgery admission	
Postanesthesia care unit, n (%)	1 (14)
Ward, n (%)	6 (86)
Hospital stay (days), mean (range)	8 (6-15)
QoR-40[b] completion rates, n (%)	
Fully completed preoperative QoR-40 questionnaires	7 (100)
Fully completed postoperative QoR-40 questionnaires	6 (86)
VAS[c] pain score completion rates	
Fully completed preoperative VAS pain score	6 (86)
Fully completed postoperative VAS pain score	7 (100)

[a]ASA: American Society of Anesthesiologists.

[b]QoR-40: quality of recovery questionnaire.

[c]VAS: visual analog scale.

Feasibility Study

Following the service evaluation and the preparation of this manuscript, the team received an unrestricted grant for a small feasibility study from Fisher & Paykel Healthcare, the manufacturer of the HumiGard device. The study will use a similar protocol to that described in this publication; however, only 40 patients will be randomized to study arms. The feasibility study will be carried out in the University Hospital of Wales in Cardiff, United Kingdom, and the results will support the funding application for the full-scale RCT described previously.

Discussion

Systematic reviews [7,8] identified significant weaknesses in the current evidence base for whether using warmed and humidified insufflation gas improves postoperative outcomes for patients. This study is designed to provide information relating to the use of the HumiGard device that is not presently available in the published literature.

Most studies identified did not have the sufficient number of patients required (>100 participants) to show any difference between the comparators. To detect a change in the primary outcome, our sample size will be appropriately powered, and the number of patients will be at least double the size of the cohorts in the published studies. Moreover, the study has a robust, multicenter design with blinding of allocation (patient and outcome assessor).

The control arm will adequately reflect current practice within the United Kingdom and is comparable to the standard practice in other countries. Patients undergoing colorectal surgery have a relatively high risk of developing hypothermia and suffering from postoperative complications due to the length and nature of the procedure as well as existing comorbidities. The inclusion of a control group will help to detect differences between the two arms of the study, if they exist.

More importantly, the study is focused on patient-reported QoR, which will provide an in-depth assessment of patients' physical recovery, level of emotional stress, and discomfort. It is likely that the QoR-40 will be more sensitive to postsurgery changes in patients' outcomes than a generic quality-of-life tool because it is focused directly on the time following surgery. Moreover, the "comfort"' section includes questions regarding shivering and "feeling too cold," which are relevant to hypothermia. Based on the short service evaluation conducted in University Hospital of Wales in Cardiff, patients are willing to fill in the QoR-40 questionnaires. Thus, QoR-40 is an appropriate tool to use during the proposed RCT.

The clinical trial will provide high-quality evidence necessary to support recommendations about whether HumiGard should be routinely adopted in the hospital setting for patients undergoing surgery. If HumiGard is shown to be effective, patients will benefit from fewer complications and quicker recovery on adoption of this technology. However, if the device is no better than standard care, the health service can avoid unnecessary investments.

One of the major limitations of this or any other medical device study is the short life span of the equipment involved. Medical devices may be expected to provide a long service life; however, it is the manufacturer's decision when a device is modified or replaced by another model. Unfortunately, the data from clinical trials and other studies are not always transferable, and new evidence must be collected to assess the clinical and cost-effectiveness of devices in which significant modifications have been made.

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Conflicts of Interest

The authors declare that during the preparation of this manuscript an unrestricted educational grant for a small feasibility study was received from the company (Fisher & Paykel Healthcare). Fisher & Paykel Healthcare had no role in the development of the protocol or the preparation of this manuscript. None of the authors have personal financial interests in the matters discussed in this manuscript.

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Abbreviations

ASA: American Society of Anesthesiologists
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
POD: postoperative day
QoR: quality of recovery
RCT: randomized controlled trial
VAS: visual analog scale

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Protocol

Effect of Cognitive Behavioral Therapy for Insomnia on Insomnia Symptoms for Individuals With Type 2 Diabetes: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Insomnia symptoms are a common form of sleep difficulty among people with type 2 diabetes (T2D) affecting sleep quality and health outcomes. Several interventional approaches have been used to improve sleep outcomes in people with T2D. Nonpharmacological approaches, such as cognitive behavioral therapy for insomnia (CBT-I), show promising results regarding safety and sustainability of improvements, although CBT-I has not been examined in people with T2D. Promoting sleep for people with insomnia and T2D could improve insomnia severity and diabetes outcomes.

Objective: The objective of this study is to establish a protocol for a pilot randomized controlled trial (RCT) to examine the effect of 6 sessions of CBT-I on insomnia severity (primary outcome), sleep variability, and other health-related outcomes in individuals with T2D and insomnia symptoms.

Methods: This RCT will use random mixed block size randomization with stratification to assign 28 participants with T2D and insomnia symptoms to either a CBT-I group or a health education group. Outcomes including insomnia severity; sleep variability; diabetes self-care behavior (DSCB); glycemic control (A_{1c}); glucose level; sleep quality; daytime sleepiness; and symptoms of depression, anxiety, and pain will be gathered before and after the 6-week intervention. Chi-square and independent *t* tests will be used to test for between-group differences at baseline. Independent *t* tests will be used to examine the effect of the CBT-I intervention on change score means for insomnia severity, sleep variability, DSCB, A_{1c}, fatigue, sleep quality, daytime sleepiness, and severity of depression, anxiety, and pain. For all analyses, alpha level will be set at .05.

Results: This study recruitment began in February 2019 and was completed in September 2019.

Conclusions: The intervention, including 6 sessions of CBT-I, will provide insight about its effect in improving insomnia symptoms, sleep variability, fatigue, and diabetes-related health outcomes in people with T2D and those with insomnia symptoms when compared with control.

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KEYWORDS

insomnia; type 2 diabetes; cognitive behavioral therapy; sleep variability; self-care; fatigue

Introduction

Background

Type 2 diabetes (T2D) is the predominant form of diabetes mellitus that results in multiple complications, including sleep difficulties [1]. It is a global health issue primarily affecting older adults [2]. It results from relative insulin deficiency and peripheral insulin resistance [3]. Consequently, T2D causes abnormal amounts of glucose in the bloodstream [4]. As a result, T2D has been linked to several complications including hyperglycemia, which may also affect multiple organs and systems [5]. As a result, hyperglycemia may lead to sleep disturbances because of associated symptoms, including headache, increased thirst, and nocturia [6].

Sleep disturbances have been shown to increase activation of the hypothalamic-pituitary-adrenal (HPA) axis [7], which may further exacerbate the management of T2D [8]. During a night of poor sleep, cortisol levels increase because of hyperactivation of the stress system *HPA*, which then leads to an increased glycation level in the blood stream [9]. As individuals with T2D are particularly susceptible to hyperglycemia, an increased glycation level may be particularly problematic [10]. To illustrate that, increasing the glucose level during a night of sleep in people with T2D may increase the bathroom visits and the number of awakenings [11]. Increasing the number of awakenings during a night of sleep is a part of poor sleep quality [12], which may further contribute in activation of the stress system [13]. This might suggest a bidirectional relationship between sleep disturbances and hyperglycemia [14]. Compounding this issue even further, previous research has shown that rates of several sleep disorders including obstructive sleep apnea, insomnia, and restless leg syndrome (RLS) are increased in people with T2D [15-17]. After controlling for age and gender, the prevalence of insomnia diagnosis is significantly higher in people with T2D, compared with those without it [15,17,18].

Insomnia is one of the most common sleep disorders in people with T2D, as more than half of their population report insomnia symptoms [17,18]. In a study of people with T2D, 8% to 17% reported difficulty falling asleep, 23% to 40% reported difficulty staying asleep, and 26% to 43% reported difficulty in both initiating and maintaining sleep [17]. In another study of 7239 individuals with T2D, 76.8% of that sample reported experiencing insomnia symptoms regularly. For those 7239 individuals, the 3 most prevalent insomnia symptoms were nocturia (43.8%), difficulty falling asleep (30.5%), and waking after sleep onset (WASO; 27.0%) [15,17].

For adults and older adults diagnosed with clinical insomnia, there are several negative effects of insomnia that are harmful to long term health, such as increases in daytime sleepiness, fall risk, fatigue, and a decline in the quality of life [19,20]. Furthermore, studies have reported that insomnia is associated with hypertension, diabetes, and cardiovascular disease [20-22]. Consequently, insomnia increases the risk of all-cause mortality 3-fold over a 15-year follow-up period [23].

Although individuals with T2D or insomnia are at increased risk of negative health outcomes, there are also unique risks to those who have both T2D and insomnia. People with T2D who experience poor sleep quality or excessive daytime sleepiness show decreased adherence to diabetes self-care behavior (DSCB) [24]. DCSB is essential in maintaining or attaining glycemic control (A_{1c}) in people with T2D [25]. Sleep quality and low sleep variability are also important for well-being and a healthy life [26,27]. Indeed, poor health and quality of life are thought to be associated with poor sleep quality in people with T2D [28-30]. In addition to deficits in sleep quality, high sleep variability is common in people with insomnia [31] and, may be, even more prominent in people with T2D [32]. Furthermore, it has been found that variability of bedtime and wake time is associated with a high level of the inflammatory biomarker called tumor necrosis factor (TNF)-alpha in people with and without insomnia [33]. TNF-alpha is associated with vascular diseases, such as atherosclerosis [34].

T2D and insomnia have a bidirectional relationship, which might be because of shared risk factors [8]. Risk factors that are commonly reported by people with both T2D and insomnia include depression, anxiety, pain, and obesity [8,19,35,36]. These health issues may exacerbate the severity of insomnia symptoms, and they may add complexity to A_{1c} [37,38]. Although several studies have examined the complex relationship between T2D and insomnia while controlling for risk factors, the underlying mechanisms of this relationship are still under investigation. Although this investigation is still in its infancy, examining the effect of treating insomnia symptoms may reveal important information for people with T2D in future studies.

Pharmacological approaches for treating insomnia have potentially serious side effects on health. Several studies have shown an association between sleeping pill prescriptions and mortality in different populations [39-44]. Different sleep medications were associated with increased risk of fall [45], motor vehicle accidents [46], and suicidality [47]. Individuals with insomnia who use benzodiazepines or nonbenzodiazepines are at high risk of developing T2D because of potential changes in insulin secretion and sensitivity [48,49]. It is a widely held view that sleep apnea is a prevalent sleep disorder in people with T2D [50]. A possible explanation of increasing the severity of sleep apnea is that hypnotics are respiratory suppressants that might contribute in vital health issues for this population [51]. The insulin sensitivity improved in people with severe sleep apnea after receiving sleep hygiene, dietary counseling, and continuous passive airway pressure (CPAP) support, which suggests that the metabolic function in people with T2D might be improved by a sleep promotion program [52]. Thus, it is important to identify safe and effective nonpharmacological treatments for people with T2D and insomnia symptoms.

The American Academy of Sleep Medicine recommends cognitive behavioral therapy for insomnia (CBT-I) as the first line of treatment for people with insomnia [53]. A meta-analysis has shown CBT-I to produce clinically meaningful improvements in sleep outcomes including sleep latency (SL), sleep efficiency (SE), number of awakenings, and total sleep time (TST) [54]. In addition, CBT-I is designed to change sleep habits as well as address misconceptions about sleep and insomnia [55]. CBT-I is superior to sleep medications in terms of cost and long-term benefits [55]. Although there is currently limited evidence about the effect of CBT-I on people with T2D, CBT-I is a potentially effective intervention given insomnia's relationship with glucose metabolism. We anticipate that CBT-I components will disrupt the associated physiological mechanisms between insomnia and T2D. Sleep restriction and stimulus control therapies are helpful in strengthening sleep homeostasis [56], which is also associated with the glucose regulation [57]. In adults with sleep restriction, increasing the TST with a simple low-cost intervention was associated with improvements in fasting insulin sensitivity [58]. Relaxation techniques are designed to minimize stress [59], which has a negative impact on the HPA axis in people with T2D [60]. These techniques are important additions in the treatment plan because of the high prevalence of psychological disorders such as depression and anxiety in people with T2D and insomnia [61]. The evidence has shown that sleep hygiene is not effective as monotherapy [62]. However, several items in the sleep hygiene could trigger DSCB, such physical activity, water consumption, and food schedule [30]. For example, avoiding excessive drinks at a night might help people with T2D minimize the bathroom visits after sleep onset [63]. The presence of nocturia is commonly reported in people with T2D, which could be one of the leading symptoms of insomnia [64]. CBT-I could compress the fragmentation of sleep, which may eventually help in reducing nocturia [64].

Objectives and Hypotheses

The primary objective of this study is to establish a protocol for a pilot study to (1) investigate the effect of 6 sessions of CBT-I on insomnia severity in people with T2D and insomnia symptoms and (2) explore the effect of 6 sessions of CBT-I on sleep variability; fatigue; A_{1c}; DSCB; sleep quality; daytime sleepiness; and the severity of depression, anxiety, and pain in people with T2D and insomnia symptoms. We hypothesized that people in the CBT-I group will have greater improvement in insomnia severity, sleep variability, fatigue, A_{1c}, DSCB, sleep quality, daytime sleepiness, and severity of depression, anxiety, and pain compared with people receiving only health education (HE). We anticipate the improvement in insomnia severity will positively impact people with T2D and health outcomes because of the relationship between insomnia symptoms and diabetes-related health outcomes.

Methods

Trial Design

The study design will be a pilot randomized controlled trial (RCT). This study will have an allocation ratio of 1:1, and this pilot RCT will be using a superiority framework to test the effectiveness of the experimental CBT-I intervention. This protocol is in accord with the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement [65], and the intervention will be described according to the Consolidated Standards of Reporting Trials 2010 guideline [66].

Participants, Interventions, and Outcomes

Study Setting

This study will be conducted at the University of Kansas Medical Center (KUMC) in the United States. The study sites are also listed on ClinicalTrials.gov [67].

Eligibility Criteria

The inclusion and exclusion criteria are shown in Textboxes 1 and 2.

Textbox 1. Inclusion criteria.

- Aged between 40 and 75 years.
- Have a type 2 diabetes diagnosis.
- Have a score of >10 on Insomnia Severity Index that indicates clinical insomnia—in addition, we will ask for reported symptoms of difficulty falling asleep, maintaining sleep, or waking up too early at least three nights/week for the past 3 months.
- Are able to understand and follow verbal commands in English—the intervention and questionnaires are available in English only; therefore, the participants must understand English language.
- Are able to travel to the University of Kansas Medical Center to attend all assessment and intervention visits at the Health Exercise and Aging Lab.

Textbox 2. Exclusion criteria.

- Self-reported neurological diseases (eg, Alzheimer disease, Parkinson disease, traumatic brain injury, stroke, and multiple sclerosis)
- A score >4 on Stop-Bang questionnaire
- Failure to pass Restless Leg Syndrome Diagnostic Index
- Brief Pain Inventory score ≥7
- Beck Depression Scale score ≥21
- Generalized Anxiety Disorder–7 score ≥15
- Pregnant women
- Self-reported the following medical issues: chronic fatigue syndrome, fibromyalgia, bipolar, seizure disorders, and rheumatic diseases
- Speech deficits or significant auditory impairment
- Current night shift work
- Heavy alcohol drinker (≥15 drinks per week for men and ≥8 for women)
- Dialysis, blindness, or transfemoral amputation

In addition, during the phone screening, we will exclude the following people: 1) Those with scores >4 on Stop Bang items including snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference, and gender. People with sleep apnea symptoms commonly report poor sleep quality and insomnia [68]. The Snoring, Tiredness, Observed apnea, Blood pressure, Body mass index, Age, Neck circumference, and Gender (STOP Bang) questionnaire will be used to screen the common symptoms related to the high risk of sleep apnea, such as the presence of snoring behavior, wake time sleepiness or fatigue, and history of obesity or hypertension [69]. Neck circumference will be measured in the active screening session. STOP Bang showed higher sensitivity and specificity (93% and 28%, respectively), compared with other screening questionnaires at polysomnography-derived apnea-hypopnea index (score of 15), which indicates severe sleep apnea [70]. In addition, a meta-analysis [71] recommended using the STOP-Bang questionnaire as a screening for sleep apnea. If interested subjects have positive scores for 5 or more categories, they are classified as being at high risk of sleep apnea [69]. Those subjects will be excluded and recommended to visit their sleep specialists. We expect some people are diagnosed with sleep apnea and they are adhered with their CPAP machine. Those people will be still included by asking them to answer the STOP Bang questionnaire with considering CPAP utilization; 2) those failing to pass the RLS Diagnostic Index [72]. The RLS Diagnostic Index is based on an algorithm to give yes or no conclusion regarding the presence of RLS. The RLS Diagnostic Index includes questions about the urge to move legs or arms to detect the risk of RLS symptoms [72]. If the RLS Diagnostic Index indicates higher RLS risk, individuals *fail* the RLS Diagnostic Index, as RLS has a negative impact on individuals' sleep, specifically, insomnia [73]; 3) those who are pregnant. As pregnancy impacts sleep, and insomnia is one of the major problems experienced in pregnancy, individuals who are pregnant will be excluded to reduce potential confounding factors [74]; 4) those who are heavy alcohol drinkers. In accordance with definitions established by the National Institute of Alcohol Abuse and Alcoholism [75], heavy drinking is typically defined as consuming 15 drinks or more per week for men and 8 drinks or more per week for women. Heavy alcohol consumption has been shown to be associated with sleep complaints among adults [76]. In addition, heavy drinking has been shown to be associated with subsequent insomnia symptoms in adults aged between 40 and 60 years [76]. Therefore, heavy alcohol drinkers will be excluded to reduce potential confounding factors; 5) those having any of the following self-reported problems: Neurological diseases—people with previous neurological disorders (eg, multiple sclerosis, Alzheimer disease, Parkinson disease, traumatic brain injury, and stroke—people with these neurological disorders usually report sleep problems [77-81]. Therefore, we want to focus on the interaction between insomnia and T2D; bipolar and seizure disorders—people with bipolar disorder and seizure disorder have complex sleep problems other than insomnia [82,83]. Furthermore, CBT-I is contraindicated for these populations [84]; chronic fatigue syndrome, fibromyalgia, and rheumatic diseases—people chronic fatigue syndrome is a medically unexplained disabling illness with nonrestorative sleep and potentially extended sleep duration [85]. Pain, fatigue, and poor sleep quality are common symptoms in people with fibromyalgia and rheumatic diseases [86-90]. Therefore, people with chronic fatigue syndrome, fibromyalgia, or rheumatic diseases will be excluded in this study; and dialysis, blindness, and transfemoral amputation—these diabetes complications may restrict people with T2D from performing components related to CBT-I; and 6) those who are shift workers. Shift workers usually report more physical and psychological distress, insomnia, and stress than non–shift workers [91]. In addition, CBT-I is contraindicated for people with shift work because CBT-I might increase sleepiness, which could put the individual at increased risk of harm.

During active screening session, the following interested participants will be excluded**:** 1) Those having scores ≥7 out of 10 on the Brief Pain Inventory (BPI) [92]. A subject with a score ≥7 out of 10 indicates severe pain symptoms. Diabetic patients with severe pain report high symptoms level of anxiety and depression and poor sleep quality [93]; 2) those having scores ≥21 on the Beck Depression Inventory (BDI). BDI

contains 21-item self-report inventory measuring the severity of depression symptoms in adolescents and adults, and participants with scores ≥21 indicate severe depression symptoms because scores above that point suggest severe symptoms level of depression [94]. Depression may lead to insomnia [95], and CBT-I may be a contraindication [96] or lead to contradictory results [97] for people with severe depression. Therefore, there is a need to exclude those people with severe symptoms level of depression from this study; 3) those having scores ≥15 on the Generalized Anxiety Disorder–7 (GAD-7) scale. Subjects who score ≥15 on GAD-7 indicate severe symptoms level of anxiety [98]. CBT-I is contraindicated for people with significant anxiety symptoms [96]; and 4) those having significant uncorrected visual, auditory impairment, and speech deficits. These health problems may affect the CBT-I delivery.

In addition, during the active screening session, we will confirm the ages between 40 and 75 years by obtaining the date of birth. People with diabetes aged between 40 and 75 years usually present with chronic insomnia [8,99]. A T2D diagnosis will be confirmed by each participant's self-report. A study previously showed that the specificity of the prevalence and incidence of self-reported T2D was 84% and 97%, respectively, and sensitivity was 55% and 80%, respectively, compared with fasting glucose, A_{1c}, and/or medication use [100]. In addition, a study suggested that self-reporting of T2D was sufficiently accurate [101]. In addition to the self-report of T2D diagnosis, we will also review the medication list to confirm the diagnosis during the screening active session.

Interventions: Experimental and Health Education

All intervention sessions will be delivered by a trained CBT-I provider. The CBT-I provider is a physical therapist who completed coursework and a Mini-Fellowship in Behavioral Sleep Medicine through the University of Pennsylvania. Ongoing mentorship will be provided by an experienced CBT-I provider. All participants will receive 6 sessions over the course of 6 weeks of either CBT-I or HE (ie, 1 session per week for 6 weeks). Sessions will last for 1 hour for both groups to mitigate the impact of social interaction. We chose HE sessions as usual care for people with T2D. Textboxes 3 and 4 describe each intervention arm with all components. The timeline of each component for the CBT-I and HE groups is provided in Figures 1 and 2.

Textbox 3. Description of cognitive behavioral therapy for insomnia components.

- Sleep restriction therapy
  - Time in bed will be limited to the total sleep time by identifying the wake time and total sleep time to increase the sleep efficiency. We will not prescribe the total time in bed to be less than 6 hours.
- Stimulus control therapy
  - This component strengthens the association between the bedtime and sleep only. We will ask participants to use the bed for only sleep and sexual activity to help train the brain. Participants will be asked to leave the bedroom if unable to fall asleep within 20 min and return when sleepy.
- Sleep hygiene
  - This component will minimize the influence of negative behaviors on sleep quality and quantity. The principles and the effects of diet, exercise, caffeine, alcohol, and environment on sleep behavior will be provided.
- Relaxation techniques
  - Diaphragmatic breathing technique promotes relaxation by using the diaphragm correctly while breathing.
  - Mindfulness reduces cognitive and somatic arousal. The principles of mindfulness (nonjudging, patience, trust, acceptance, and letting go) will be discussed.
  - Progressive muscle relaxation positively influences physiologically measured muscle tension.
  - Cognitive therapy changes detrimental beliefs and attitudes about sleep. We will work on reducing sleep effort, catastrophic predictions, worry about sleep, and fearing of insomnia relapse.
- Insomnia relapse
  - This component facilitates the understanding of the risk factors of reoccurrence. We will discuss the approaches to maintain clinical gains.

Textbox 4. Description of health education components.

- Brief sleep hygiene
  - We will discuss 8 items of sleep hygiene including exercise, comfortable bedroom, temperature of bedroom, food, liquids, caffeine, alcohol consumption, smoking, and naps. Parts of sleep hygiene, such as consistent sleep schedule and association of bed with sleep, will not be included in this brief sleep hygiene education.
- Foot care education
  - We will provide foot care education regarding the demographic and comorbidity, foot pathology and assessment, and preventive interventions. In addition, we will provide the American Diabetes Association recommendation regarding foot hygiene.
- Causes and diagnosis of diabetes
  - We will provide information about diagnosis and classification of diabetes mellitus from the American Diabetes Association. The following topics will be discussed:
    - The definition and description of Diabetes Mellitus, classification of diabetes mellitus, and other categories of glucose regulation
    - Categories of increased risk for diabetes
    - Diagnostic criteria for diabetes mellitus
      - A short animation will be provided to explain how diabetes affects the body
- Healthy diet education
  - Different dietary approaches to manage type 2 diabetes will be discussed. Articles from American Diabetes Association website will be navigated).
- Physical activity education
  - We will use a guide for adults based on the 2008 Physical Activity Guidelines for Americans. We will discuss following points: *wondering about how much activity you need each week, want to be physically active but not sure where to begin, and started a program and would like tips on how to keep it up*.

Figure 1. The timeline of the CBT-I (cognitive behavioral therapy for insomnia) intervention.

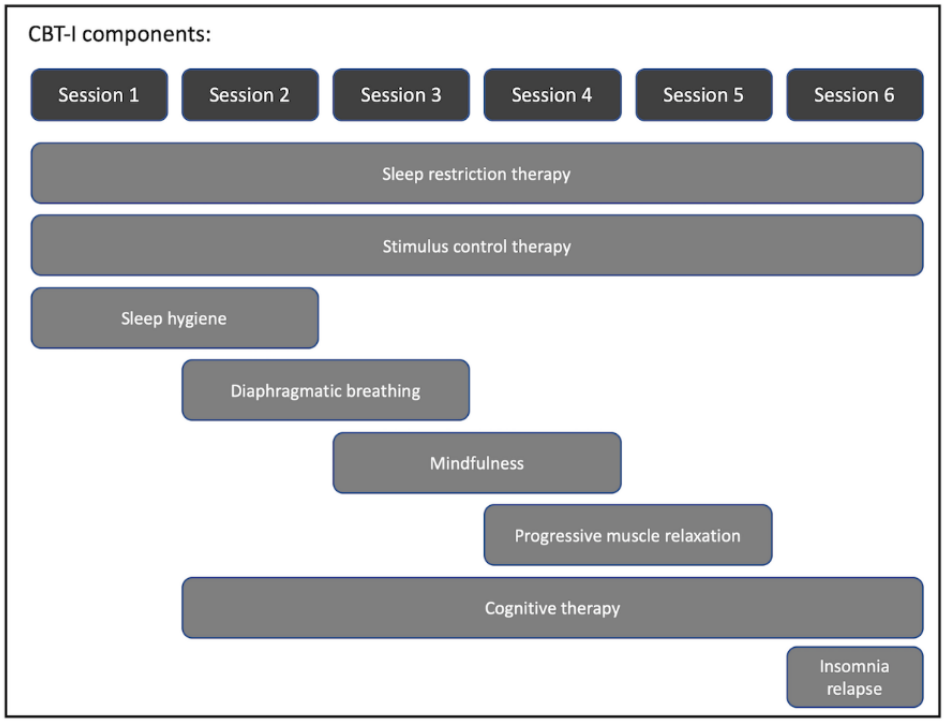
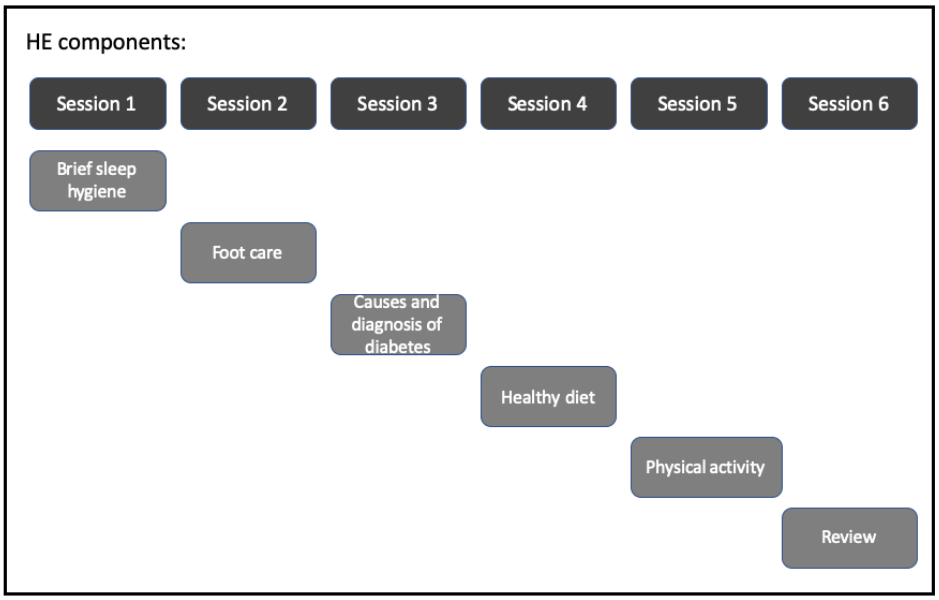


Figure 2. The timeline of Health Education.



Experimental Intervention

Participants allocated to the CBT-I group will meet with the CBT-I provider weekly for 1 hour of CBT-I sessions. CBT-I is designed to address cognitive and behavioral factors that perpetuate insomnia [102]. It includes several therapeutic components including sleep restriction therapy, stimulus control therapy, sleep hygiene, relaxation techniques, and cognitive therapy. At each session, the CBT-I provider will ask about any new difficulties, explain the outline of the session, calculate the SE of the previous 7 nights of sleep, and close the session with assessing any concerns and providing a new sleep diary. At each session, prescribed time in bed and out of bed will be determined based on calculation for SE of the weekly sleep diary. SE will be calculated as the ratio of TST and total bed time multiplied by 100. At each session, if the SE is greater than 90%, participants will be given the opportunity to go to bed 15 min earlier. If SE is between 85% and 89.9%, participants will be asked to remain on the same sleep schedule as currently prescribed. If it is less than 85%, they will be asked to move their bedtime 15 min later, although total time in bed will not be less than 6 hours.

This protocol intervention was designed based on a session-by-session guide [103].

Session 1 (60-90 Min)

Sleep restriction therapy, stimulus control therapy, and sleep hygiene will be started in this session. The sleep diary from the previous week will be reviewed to calculate the average SE from the previous 7 nights. In this session, subjects will learn the rationale and efficacy of using sleep restriction therapy and stimulus control therapy as a first line of treatment. Sleep restriction therapy is designed for individuals who are not able to initiate and/or maintain sleep [103,104]. This technique limits the time in bed to be equivalent to the TST by identifying the wake time and TST to increase the SE. Stimulus control promotes sleep drive and reinforces circadian entrainment by associating the bed to sleep only or for sex [103,104]. By applying the sleep restriction and stimulus control interventions, we will set prescribed time in bed and prescribed time out of bed by using the average of TST from previous week sleep diary and preferred time to wake up in the morning. Thus, the goal of this session is to align sleep with the opportunity to sleep, make plan in staying awake until the prescribed time in bed for sleep restriction therapy, and provide a list of activities during awake time or WASO for stimulus control therapy. In addition, sleep hygiene is implemented to minimize the influence of negative behaviors on sleep quality and quantity [103,104]. Sleep hygiene focuses on the impacts that diet, exercise, caffeine, alcohol, and environment can have on sleep [103,104].

Session 2 (30-60 Min)

Sleep titration, reviewing sleep hygiene, and introducing diaphragmatic breathing technique will be covered in this session. In this week, we will again review the sleep diary to confirm any necessary sleep titration (that is sleep restriction therapy adjustment). Sleep titration will be determined by measuring the individual's SE. An SE >90% indicates positive gain that directs upward sleep opportunity. An SE between 85% and 90% score indicates marginal gain that maintains the sleep schedule. An SE <85% score indicates negative gain that directs downward sleep opportunity. If compliance issues arise during the sleep diary review, this session will focus on reinforcing the importance of sleep restriction and stimulus control therapies. Stress and anxiety symptoms are commonly reported in people with insomnia [105]. Thus, it is also important to implement relaxation techniques at the first sessions. We will emphasis relaxation therapy for people who are not able to relax because of varied of stressors or being an anxious. One of the relaxation therapies is the diaphragmatic breathing technique that promotes muscle relaxation, breathing performance, and memory relaxation. A brief diaphragmatic breathing handout and video will be utilized during the session.

Session 3 (30-60 Min)

Similar to sessions 1 and 2, the sleep diary will be reviewed for sleep titration, and we will introduce mindfulness. Upward or downward sleep titration will be determined based on the sleep

diary. Mindfulness has shown positive effects in reducing cognitive and somatic arousal when combined with CBT-I for people with insomnia [106]. The principles of mindfulness (nonjudging, patience, trust, acceptance, and letting go) and its practice will also be introduced during this session.

Session 4 (30-60 Min)

Sleep titration and progressive muscle relaxation will be delivered in this session. Upward or downward sleep titration will be determined based on the sleep diary. Muscle relaxation therapy is a physiological intervention designed to measure and reduce muscle tension [107]. In addition, muscle relaxation therapy has been incorporated with CBT-I to improve insomnia and depression symptoms [107]. A brief progressive muscle relaxation handout and video will be utilized during the session.

Session 5 (30-60 Min)

Sleep titration and cognitive therapy will be delivered in this session. Cognitive therapy is designed to change detrimental beliefs and attitudes about sleep. The intervention content provided in sessions 1, 2, 3, or 4 may be similar to the cognitive therapy provided in session 5, although session 5 will focus on providing the cognitive therapy intervention in its entirety. During this session, we will work on reducing sleep effort, catastrophizing, anxiety about sleep, and insomnia relapse. Also, we will work on correcting negative sleep beliefs, particularly regarding insomnia. In addition, we will work on enhancing individuals' willingness to modify the sleep-related behaviors and engage in good strategies. Finally, we will continue working on sleep titration to optimize the SE.

Session 6 (30 Min)

Assessing global treatment gains and relapse prevention education will be the focus in this session. We will review the SE of each session to graphically demonstrate the participant's SE over the course of this intervention. This process will help in providing information that facilitates chronic insomnia and understands the risk factors of reoccurrence. Finally, we will discuss the approaches to maintain clinical gains and fix insomnia returns, and we will schedule participants for the reassessment session.

During each session, the CBT-I provider will use 2 documentation sheets that are nonspecific to CBT-I: a checklist and tracking sheet. These sheets will help the CBT-I provider for quality assurance and standardization of treatment sessions across participants. We do not expect these sheets to contribute to the intervention or the outcomes of this study.

The participants will be called 1 day before each session to confirm their session appointment the following day and remind them to bring their completed sleep diary. In addition, a folder will be provided at the first session to keep provided materials together for review. The CBT-I sessions will be audio recorded to assess treatment integrity if the subject agrees.

CBT-I intervention fidelity will be assessed by an independent CBT-I expert who will use a scoring sheet to assess CBT-I provider's compliance in utilizing the manual to deliver the CBT-I. The CBT-I provider will be scored on 5 scales from 0 (poor) to 6 (excellent) based on (1) how they address immediate concern, (2) how they explain the outline of the session, (3) how they discuss the sleep diary outcomes, (4) their adherence in providing the intervention, and (5) their competency in delivering each session.

Control Group

Participants allocated to the HE group will meet with the CBT-I provider weekly for 1 hour of HE sessions. The HE sessions include several components including brief sleep hygiene, foot care, diabetes classifications, healthy diet, and physical activity. During all sessions, subjects will be encouraged to engage in discussion through open questions about their experience of diabetes and lifestyle as well as their comprehension of the provided materials. Similar to the CBT-I group, session tracking sheets will be used to track new difficulties or concerns and provided education.

Outcomes

Demographic and Clinical Variables

Age, race, ethnicity, sex, marital status, education, employment, diabetes duration, medication list, and body mass index will be gathered at the first assessment session.

Sleep Outcomes

Insomnia Severity

The Insomnia Severity Index (ISI) is a self-report measure designed to evaluate the nature, severity, and impact of insomnia [108]. The ISI is a valid and reliable measure of clinical insomnia and involves 7 questions, each rated on a 0 to 4 Likert scale. Total scores range from 0 to 28, with higher scores indicating greater insomnia severity [108]. The internal consistency of ISI was excellent for community sample and clinical sample (alpha=.90 and alpha=.91, respectively). The cutoff score>10 on the ISI provided optimal sensitivity and specificity for the detection of insomnia based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, diagnostic criteria (area under the curve=0.82; 95% confidence interval 0.78-0.86) [109].

Sleep Variability

The Actigraph device is a small, noninvasive device worn on the nondominant wrist that records limb movements using electrical impulses, and it has been validated for use in people with insomnia [110]. Sleep parameters including SE, SL, TST, and WASO will be measured. In addition to the Actigraph, we will also use a sleep diary to allow for better estimation of the time in and out of bed as well as for removing invalid sleep periods that are measured by the Actigraph [111]. The sleep diary will also measure total time spent in bed, total time spent out of bed, number of awakenings, number of bathroom visits, and glucose level before and after sleep time. All sleep parameters will be presented in averages of 7 nights and the coefficient of variance (CV) will be calculated using the following equation (CV=standard deviation/mean×100) for each objective and subjective sleep parameters—SE, SL, TST, and WASO—to analyze objectively within-subject variability of nighttime sleep of 7 nights. This calculation will provide a percentage value with a higher number suggesting higher variability [112].

Daytime Sleepiness

The Epworth Sleepiness Scale (ESS) uses 8 items on a 4-point Likert scale, where the subjects rate how likely they would be to fall asleep in 8 different states of daily activities. The ESS has demonstrated satisfactory psychometric properties such as test-retest reliability (r=.82) and internal consistency (alpha=.88). The cutoff point is ≥10 to distinguish between normal from pathological sleepiness [24].

Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI) is a validated 19-item questionnaire that differentiates between poor and good sleepers. The PSQI uses 7 items on a 4-point Likert scale, and it yields a global sleep quality score that ranges from 0 to 21. Poor sleepers have scores >5, with this cutoff global PSQI score providing satisfactory sensitivity (89.6%) and specificity (86.5%). In our study, we will use a 3-factor scoring model for the PSQI (SE, perceived sleep quality, and daily disturbances), which has been tested and validated [113]. Sleep duration and SE were classified under the SE factor; subjective sleep quality, SL, and the use of sleeping medications were categorized under the perceived sleep quality factor; and the frequency of sleep disturbances and daytime dysfunction were classified under the daily disturbances factor.

Diabetes Outcomes

Diabetes Self-Care Behavior

The diabetic care profile (DCP) uses items on 5-point Likert scales to evaluate the frequency of symptoms related to diabetes. The DCP is a validated instrument that measures self-reported diabetes control and psychological and social factors associated with the management of diabetes [114,115].

Glycemic Control

A_{1c} will be determined using the hemoglobin A_{1c} test by a disposable blood finger stick test using (A1cNow+ kit; TMS Company). The A_{1c} indicates the average blood glucose level of people with diabetes over the previous 2 to 3 months and represents the current management of diabetes [116]. Every 1% drop in A_{1c} is associated with improved outcomes with no threshold effect [117].

Glucose Level

Random glucose levels will be measured using glucose meter (Contour Next EZ Blood Glucose Monitoring System, Model 7252). The results of glucose level will be presented in milligrams per deciliter to document nonfasting glucose levels [118].

Health Outcomes

Fatigue Severity

Fatigue symptoms will be measured using the Fatigue Severity Scale (FSS), which is a 9-item questionnaire that has been validated in people with diabetes [119]. The FSS measures fatigue across 5 subscales including motivation, exercise, interference with work, family, or social life. These subscales have total scores where a score <4 indicates no fatigue, scores between 4 and 4.9 indicate moderate fatigue, and a score >5 indicates severe fatigue [119].

Pain Severity Symptoms

The BPI is a valid and reliable measure to assess painful diabetic peripheral neuropathy [120]. We measured the means of the severity scale and the interference scale of the BPI.

Depression Symptoms

The BDI has high reliability and good validity [121,122]. It contains 21 self-reported items on a 3-point Likert scale, with scores ≥21 indicating severe depression symptoms [121,122].

Anxiety Symptoms

The GAD-7 uses 7 items on a 3-point Likert scale. The total score of the GAD-7 ranges from 0 to 21, with higher scores indicating severe anxiety symptoms. It has been shown to be highly sensitive and specific for the detection of anxiety symptoms, and it is correlated with other anxiety scales [123].

Participant Timeline

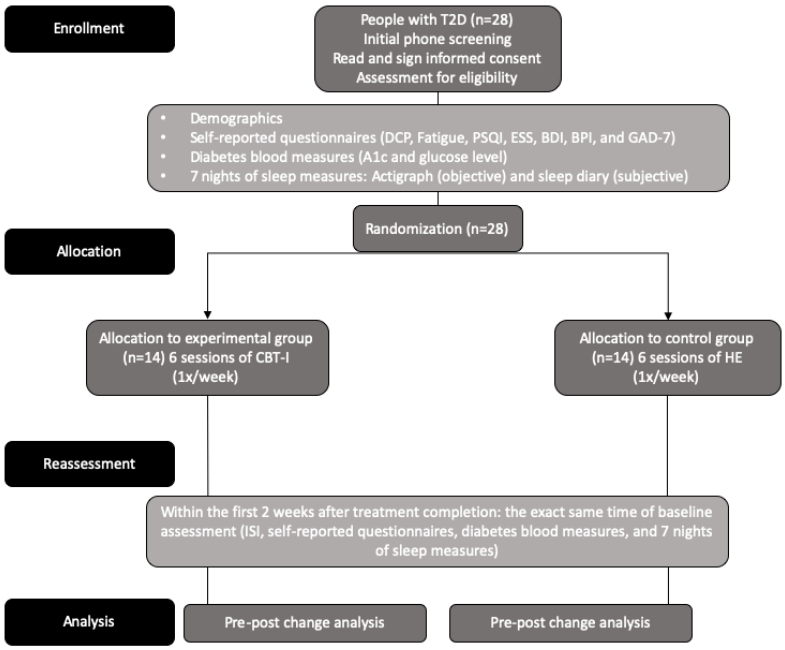
All measurements will be performed at baseline and 1 week after treatment completion (Figure 3). Participants who wish to withdraw during the intervention will be asked to complete the reassessment session.

At initial contact with a potential subject, a phone screening or diabetes clinic interview will be conducted by a member of the research team to determine whether an individual qualifies to progress to an in-person screening for the study. The phone screening interview assesses participant eligibility according to age, self-report of T2D diagnosis, insomnia severity, ability to understand English, STOP-Bang score, RLS Diagnostic Index, pregnancy status, alcohol use, night-shift work, and undiagnosed neurological disorders.

Individuals passing the phone screening will be scheduled for an in-person screening session to assess eligibility according to symptoms of pain, depression, and anxiety.

Subjects will undergo the consent process in a private room at KUMC before completing any of the in-person screening assessments. Individuals passing the in-person screening will then immediately begin baseline assessment.

Figure 3. Consort of the project. A_{1c}: glycemic control; BDI: Beck Depression Inventory; BPI: Brief Pain Inventory; CBT-I: cognitive behavioral therapy for insomnia; DCP: diabetic care profile DSCB: diabetes self-care behavior; ESS: Epworth Sleepiness Scale; GAD-7: Generalized Anxiety Disorder–7; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; and T2D: type 2 diabetes.



Sample Size

To detect the effect of CBT-I on people with T2D and symptoms of insomnia, the change in pre-post ISI was used to determine sample size. Pre-post changes using the minimal clinically meaningful difference of 8 points for the ISI in a previous study [124] were used to estimate the effect size. This calculation resulted in 10 participants per group to reject the null hypothesis of equal means when the population mean difference equals 8 with a standard deviation of 7. We accounted for an expected attrition rate of 40%, which indicated 28 subjects in both groups to detect the significant difference between groups after allowing for attrition at a .05 significant level and power of .80.

Recruitment

Subjects will be recruited from diabetes and sleep clinics at KUMC, university advertisements, community centers in Kansas City, flyers, personal referrals and newsletters, and a registry of patients from KUMC who have signed up to be contacted about potential research opportunities.

Assignment of Interventions (for Controlled Trials)

Allocation Sequence Generation

We will use random mixed block size randomization [125] to assign participants to either CBT-I (n=14) or HE (n=14) groups. Participants will be stratified by age where 62 years is the value that will stratify participants into either the older (63-75 years) or the younger (40-62 years) age group. The reason we chose age as a blocking variable is that the impact of age on sleep is more pronounced than gender [126], as older adults often have poorer [127] and lower slow wave [128] sleep, as compared with young adults.

Allocation Concealment Mechanism

Participant allocations will be placed in sealed envelopes. The envelopes are prepared by a research assistant, who withholds this information from the CBT-I provider. After finishing the baseline assessment, participants will be asked to open the sealed envelope to disclose their group allocation. Microsoft Excel will be used to create the randomization lists.

Allocation Implementation

A computer will be used to generate the random mixed block size randomization sequences. Results of the generator will be concealed from the assessor and CBT-I provider. Participants will be asked to open the sealed enveloped after informed consent and baseline assessment are completed.

Blinding

The assessor, who is blinded to group allocation, will score the Actigraph data. The assessor will have experience in scoring criteria and no involvement in providing the interventions. The CBT-I provider will not be blinded in this study.

Data Collection, Management, and Analysis

Data Collection and Methods

Insomnia severity (primary outcome); sleep variability; fatigue; DSCB; A_{1c}; daytime sleepiness; sleep quality; glucose levels; and symptoms of depression, anxiety, and pain will be measured a week before and after the intervention.

Data Management

All study-related procedure will be performed at Georgia Holland laboratory in Hemenway Life Sciences Innovation Center on the KUMC campus. All obtained participant records will be kept in locked cabinet inside the Georgia Holland

laboratory. Electronic study data will be saved in the KUMC Research Electronic Data Capture system. For voice records, all tapes will be saved on a secure university-supported network drive.

Statistical Methods

A chi-square test will be used to compare between-group differences in categorical variables. Independent 2-sample *t* tests will be used to compare differences in continuous between-group demographic characteristics and clinical variables.

For the main analysis**,** the effect of the CBT-I intervention will be investigated by calculating change scores for the insomnia severity; DSCB; A_{1c}; fatigue; sleep quality; daytime sleepiness; and symptoms of depression, anxiety, and pain. In addition, for variability of each sleep outcomes (SE, SL, TST, and WASO), CV of 7 nights before the pre- and postintervention assessments will be calculated, and change scores will be calculated. Then, independent sample *t* tests will be utilized to investigate the between-group difference in the change score means of all outcomes. A completer vs noncompleter analysis will be performed. For all analyses, alpha level will be set at .05.

Owing to the complex relationship between insomnia and T2D, some factors are needed to be controlled to fully investigate the relationship. Owing to the small sample size and possible covariates that might not be included in the power calculation, these complex relationships will be investigated using exploratory analyses. Post hoc analysis using the type and number of medications will used to address the potential confounding effects on the outcomes. Univariate linear regression will be used to control for demographic and clinical variables (covariates). The decision to perform these analyses with demographic and clinical variables will be made if there are significant between-group differences at baseline in depression symptoms, anxiety symptoms, pain symptoms, gender, diabetes duration, or body mass index. Mixed models will be used to account for the correlation between times in pre- and posttest (7 nights as random factor) sleep variability (as dependent variable) and facilitate adjustment for covariates to compare the difference in sleep variability between the CBT-I and HE groups (groups as fixed factor). Covariates will be determined if there is a difference in the baseline assessment for demographic and clinical outcomes. Those participants who are treated with CPAP will be asked to report their compliance using CPAP during baseline and postintervention assessments. Subjects who are using VPAP will be given a modified sleep diary to check off nights of CPAP compliance during the assessment sessions. An exploratory subanalysis will be utilized to investigate the difference in insomnia severity between compliance and noncompliance with CPAP. Noncompliance is defined as (1) missing more than 2 nights during the 7 nights period that the participant is wearing the Actigraph or (2) using the CPAP for <4 hours per night during this study.

Monitoring and Ethics

Data Monitoring

The primary investigator will review the dataset at least semiannually. The primary investigator's evaluation will be focused on the quality of data collection and data management. In addition, the investigators will review data in an ongoing manner for accuracy, both at a time when these data are entered into the database and during analysis.

Harms

During the pre and postassessment sessions, testing will be stopped if the subjects show signs of low blood sugar (<70 mg/dL) or if signs of dizziness or headache are noted by the assessor or reported by the participant. During assessment sessions, participants also will be instructed to stop the test at any time for a rest break, as often as needed.

There is a risk of skin redness may be associated with wearing the Actigraph for 1 week. The risks of wearing the Actigraph are nearly the same as wearing a wrist watch. If skin redness or inflammation happened, subjects may remove the Actigraph and immediately report the symptoms to research personnel. In addition, there is a risk of minor electrical shock if the Actigraph is damaged. If damage to the Actigraph occurs, subject will be asked to return it to our lab, and they will be given a replacement.

Initially, participating in a CBT-I intervention may have an increase in sleepiness, which may impact participants' fatigue, thinking ability, or functional abilities. It is anticipated that this increase in sleepiness will be temporary and should help participants sleep better in the long term.

During the in-person screening session, if suicidal intent is identified through either the BDI (question number 9, with a *2* or a *3*) or verbal statement from the participant, a suicidality protocol will be followed. The suicidality protocol is designed to provide the researcher with contact information for appropriate psychology and psychiatric professionals at KUMC.

Research Ethics Approval

The study will be performed in accordance with KUMC's Institutional Review Board and Human Subjects Committee. No individuals will be excluded based on sex, race, or ethnicity. Interested participants will be administered a structured screening interview to determine their eligibility for the study. During the consent session, all interested participant will be informed about the study's objective, risks, procedure, and potential benefits (or lack thereof).

Consent or Assent

Consent will be obtained in Georgia Holland Health Exercise and Aging Lab on the main campus of KUMC. Participants will be encouraged to ask any questions about the study as much as they need, and members of research study will answer their questions. In addition, participants will be informed if there is any change in the protocol to sign a new consent form.

Confidentiality

All data will be deidentified and stored on the KUMC research private drive, which will be secured and backed up every night. The working dataset will be stored on a password-protected computer in the primary investigator's laboratory, with access restricted to study researchers who are actively working with these data. All subject files and documents will be stored in a locked cabinet.

Results

A total of 28 participants with T2D and insomnia symptoms recruited from February 2019. This study currently completed the recruitment stage. The completion date for the study was September 2019. Our results will describe the changes in insomnia severity; sleep variability; fatigue; A_{1c}; DSCB; and severity of depression, anxiety, and pain. We will report our results in tables and figures using SPSS and GraphPad, respectively.

Discussion

Overview

Our study will be the first in conducting an RCT using CBT-I for people with T2D. If this study indicates that 6 sessions of CBT-I are effective in improving sleep and diabetes outcomes in people with T2D and insomnia symptoms when compared with HE, CBT-I could be implemented as an effective and safe treatment for this population, although more research will be needed to verify the findings of this pilot RCT.

Pharmacological interventions for sleep difficulties have shown harmful effects on people with T2D. There is a need to better understand safe intervention benefits in people with T2D. This study will contribute to the management of T2D using behavioral sleep intervention as an effective and safe treatment for people with insomnia symptoms. The results will contribute to the literature by examining the effect of CBT-I on both sleep and diabetes outcomes. This will help in understanding the effectiveness of short duration intervention designed for people with insomnia symptoms.

Strengths

The study strengths include utilizing important methods for people with T2D, such as objective measures, design, and safe intervention. Determining sleep variability using objective and subjective measures will accurately detect sleep improvement after an intervention. Using comparative groups to understand the effect of CBT-I on insomnia symptoms, sleep variability, fatigue, and diabetes-related health outcomes will add new information to the literature and improve the understanding of clinical conditions. Previous studies recommend optimizing the sleep quality and quantity for people with comorbidities. Understanding the effect of CBT-I in people with T2D will expand the generalizability of using this type of interventions.

Limitations

Some limitations in this protocol might be important to consider in future studies. First, we will not confirm the diagnosis of T2D using the current American Diabetes Association guidelines. However, a study showed that the specificity of prevalent self-reported diabetes and incident self-reported diabetes were 84% and 97% and sensitivity of 55% and 80%, respectively, compared with fasting glucose, A_{1c}, and/or medication use [100]. In addition, a study suggests that self-report of diabetes is sufficiently accurate [101]. To overcome this limitation, we will review the medication list to confirm T2D diagnosis during the in-person screening visit. Second, we might not able to distinguish the improvement in insomnia severity between controlled vs uncontrolled diabetes, which might be examined under future sleep behavioral therapy studies. Third, our study will be powered based on the ISI, and we recommend future studies to choose a diabetes outcome for conducting the power calculation. Fourth, the participants will not be blinded in the study, which may result in the control group participants looking for CBT-I providers outside of the study. We will monitor any change in pharmacological or nonpharmacological treatments during the postintervention session to help explain unexpected results. It is possible, however, that some participant may not reveal this information, which might influence the outcomes. Finally, we will not be able to monitor CPAP compliance during the intervention, but we will follow up with people in the CBT-I group to ensure no issue wearing a CPAP machine every session.

Authors' Contributions

MMA is involved in establishing the research question and protocol. AMA and SAA are involved in establishing REDcap for the data collection and data entry. JCH, JLR, CAB, JMM, PMK, and CFS are involved in establishing the protocol. MAP is involved in calculating the power. All authors approved the final version of this paper.

Conflicts of Interest

None declared.

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Abbreviations

A_{1c}: glycemic control
BDI: Beck Depression Inventory
BPI: Brief Pain Inventory
CBT-I: cognitive behavioral therapy for insomnia
HE: Health Education
CV: coefficient of variance
DCP: diabetic care profile
DSCB: diabetes self-care behavior
ESS: Epworth Sleepiness Scale
FSS: Fatigue Severity Scale
GAD-7: Generalized Anxiety Disorder–7
HPA: hypothalamic-pituitary-adrenal
ISI: Insomnia Severity Index
KUMC: University of Kansas Medical Center
CPAP: continuous passive airway pressure
PSQI: Pittsburgh Sleep Quality Index
RCT: randomized controlled trial
RLS: restless leg syndrome
SE: sleep efficiency
SL: sleep latency
STOP-Bang: snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference, and gender
T2D: type 2 diabetes
TNF: tumor necrosis factor
TST: total sleep time
WASO: waking after sleep onset

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Protocol

Cash Transfer to Adolescent Girls and Young Women to Reduce Sexual Risk Behavior (CARE): Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: The HIV epidemic in Eastern and Southern Africa is characterized by a high incidence and prevalence of HIV infection among adolescent girls and young women (AGYW) aged 15-24 years. For instance, in some countries, HIV prevalence in AGYW aged 20-24 years exceeds that in AGYW aged 15-19 years by 2:1. Sauti (meaning voices), a project supported by the United States Agency for International Development, is providing HIV combination prevention interventions to AGYW in the Shinyanga region, Tanzania.

Objective: The aim of this study is to determine the impact of cash transfer on risky sexual behavior among AGYW receiving cash transfer and HIV combination prevention interventions. This paper describes the research methods and general protocol of the study. Risky sexual behavior will be assessed by herpes simplex virus type 2 (HSV-2) incidence, compensated sex (defined as sexual encounters motivated by exchange for money, material support, or other benefits), and intergenerational sex (defined as a sexual partnership between AGYW and a man 10 or more years older). Through a qualitative study, the study seeks to understand how the intervention affects the structural and behavioral drivers of the HIV epidemic.

Methods: The trial employs audio computer-assisted self-interviewing, participatory group discussions (PGDs), and case studies to collect data. A total of 30 matched villages (15 intervention and 15 control clusters) were randomized to either receive cash transfer delivered over 18 months in addition to other HIV interventions (intervention arm) or to receive other HIV interventions without cash transfer (control arm). Study participants are interviewed at baseline and 6, 12, and 18 months to collect data on demographics, factors related to HIV vulnerabilities, family planning, sexual risk behavior, gender-based violence, and HSV-2 and HIV infections. A total of 6 PGDs (3 intervention, 3 control) were conducted at baseline to describe perceptions and preferences of different intervention packages, whereas 20 case studies are used to monitor and unearth the dynamics involved in delivery and uptake of cash transfer.

Results: The study was funded in June 2017; enrollment took place in December 2017. A total of two rounds of the follow-up survey are complete, and one round has yet to be conducted. The results are expected in December 2019 and will be disseminated through conferences and peer-reviewed publications.

Conclusions: This study will document the synergetic impact of cash transfer in the presence of HIV combination prevention interventions on risky sexual behavior among out-of-school AGYW. The results will strengthen the evidence of cash transfer in the reduction of risky sexual behavior and provide feasible HIV prevention strategies for AGYW.

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KEYWORDS

adolescent; female; HIV infections/epidemiology; HIV Infections/prevention and control; Herpesvirus 2; humans; incidence; motivation; Tanzania

Introduction

Background

The HIV epidemic in Eastern and Southern Africa is characterized by a high incidence and prevalence of HIV infection among adolescent girls and young women (AGYW) aged 15-24 years [1,2]. For instance, data from Tanzania, Lesotho, and Mozambique show a prevalence of 1%, 4%, and 7%, respectively, among girls aged 15-19 years, which increased to 3.4%, 24%, and 15%, respectively, among those aged 20-24 years [3,4]. New HIV infections among AGYW in 2015 contributed up to 25% of the new infections among the adult population (>15 years) in East and Southern Africa [5]. AGYW aged 15-24 years in this region have HIV infection rates that are two to four times higher than those of young men of the same age group [1,2,5-7].

Complex interactions between behavioral, biological, and structural factors are part of the explanation for the higher rates of HIV infection among AGYW. Behavioral factors such as intergenerational sex with older male partners who are more likely to be infected with HIV and other sexually transmitted infections (STIs) [8-11], multiple and concurrent sexual relationships [11,12], and transactional sex [11,13] have been shown to increase the risk of HIV acquisition among AGYW. Biological factors related to AGYW have also been shown to be associated with HIV acquisition among AGYW. These include immature cervix [14,15] and increased mucosal HIV exposure time [14,16], which increases the biological susceptibility of adolescent girls. Structural determinants, including poverty and gender inequality, exacerbate vulnerability to HIV infection among AGYW. These determinants affect AGYW's ability to negotiate condom use, access to STI treatment, and learn skills and access capital required to engage in income-generating activities that will enable them to avoid engaging in transactional sex to meet their daily needs [8,16,17]. Therefore, interventions aimed at addressing AGYW's HIV vulnerabilities must include a program that addresses structural factors in addition to biomedical and behavioral factors. Such programmatic strategies need to be gender responsive and evidence based to address individual, community, and structural factors contributing to the increased HIV risk in this group [18,19].

There has recently been a call to invest in interventions that help improve the income of vulnerable populations—at individual and household levels [20]. Cash transfer given with or without conditions to recipients has been used to incentivize safe sexual behavior to reduce HIV infection among economically deprived populations [21]. In the context of HIV, cash transfers are provided as a type of structural intervention for HIV prevention, which is generally combined with biomedical and behavioral prevention strategies for HIV infection—an approach commonly referred to as combination prevention [22]. Provision of cash transfer as a strategy for prevention of HIV infections has shown promising results. For example, both conditional cash transfers and unconditional cash transfers were shown to have an impact on some reproductive health outcomes among girls, including prevention of STIs and delaying marriage and childbearing [23,24]. The Zomba study in Malawi demonstrated that cash transfers provided to girls and their parents reduced HIV prevalence by 64% (95% CI 9%-86%) and herpes simplex virus type 2 (HSV-2) prevalence by 76% (95% CI 35%-91%) after 18 months of follow-up. The cash transfers achieved this impact by influencing underlying structural conditions, which, in turn, shaped sexual behavior as well as the risk of HIV infection acquisition [23]. For instance, in the Zomba study, girls in the intervention arm were 79% (95% CI 38%-93%) less likely to have sexual partners aged ≥25 years compared with girls in the control arm [23].

The Sauti (meaning *voices*) project in collaboration with the Government of United Republic of Tanzania and civil society organizations (CSOs) are providing community-based HIV combination prevention interventions among AGYW and other vulnerable populations in selected regions of Tanzania [25]. These regions include Mtwara, Kilimanjaro, Arusha, Shinyanga, Tabora, Singida, Dodoma, and Morogoro. Others are Dar-es-Salaam, Iringa, Njombe, Songwe, and Mbeya. Sauti project is described in detail elsewhere [26]. The CSOs provide reach, spread, and ability to engage the most vulnerable AGYW in the community. Sauti aims to address the biomedical, behavioral, and structural influences on AGYW's vulnerability to HIV infection by implementing community-based HIV combination prevention interventions among AGYW aged 15-24 years. Sauti's core package of interventions includes risk reduction counseling; HIV testing services; condom use skills and provision; family planning counseling and service provision; screening and treatment for STIs, gender-based violence, and tuberculosis; and alcohol and drug abuse screening and referral to services. Others are social and behavior change communication (SBCC) training sessions and economic empowerment community banking, also called the Women Organizing Resources Together Plus (WORTH+) intervention and cash transfer program (CTP). The WORTH+ intervention includes financial literacy training, which aims to build microbusiness development skills and community banking. The objectives for SBCC and WORTH+ training are detailed in Table 1.

The CTP under the Sauti project is provided to AGYW through the Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) partnership [27]. The DREAMS partnership is an ambitious endeavor aimed at reducing HIV

infections among AGYW in 10 sub-Saharan African countries through a package of health, educational, and social interventions. The partnership aims to address the structural drivers, which increase the risk of HIV infection, including sexual violence, poverty, gender inequality, and lack of education. It aims to transform AGYW in the partner countries into DREAMS women. The Sauti project is one of the primary implementing partners for community-based interventions under the DREAMS initiative in Tanzania. As part of the DREAMS partnership, Sauti is delivering cash transfer for 18 months to 12,144 AGYW who are out of school, aged 15-23 years, and who have completed 10 hours of SBCC training.

CTP villages (or neighborhoods/*mitaa* in urban settings) were identified by the Sauti project, regional and district health authorities, and other stakeholders as communities with high risk of HIV infection and economic and social vulnerability among AGYW who are out of school. The CTP is implemented in four districts of Shinyanga region (Shinyanga Municipal Council, Msalala District Council, Kahama Town Council, and Ushetu District Council) and Kyela district in Mbeya region. Each of the eligible AGYW in the five districts receive 70,000 Tanzanian Shillings (approximately US $33) delivered through mobile money quarterly.

This study describes the research methods and general protocol for a study aiming to evaluate the impact of cash transfer, delivered in the presence of other sexual and reproductive health interventions offered by Sauti project, in the reduction of risky sexual behavior among AGYW. Previous trials in sub-Saharan Africa were conducted to assess the effect of cash transfer [23,28], but none were conducted among out-of-school AGYW to ascertain the synergetic effect of cash transfer, WORTH+, and biomedical and behavioral interventions. The findings will inform scale-up of Sauti interventions among AGYW in Tanzania and potential adoption for HIV programming in sub-Saharan Africa among AGYW.

Table 1. Objectives of the social and behavior change communication and Women Organizing Resources Together Plus training sessions.

Objectives for SBCC[a]	Components of WORTH+[b] training	Objectives for WORTH+
• To identify harmful gender norms, especially norms that perpetuate gender inequality and GBV[c]. Identify and explain support systems available for GBV survivors and explain how gender and power are related.	Financial literacy	Explain basic business skills, credit management and bookkeeping, group facilitation and leadership, and conflict resolution; calculate profit, risk, product value, and identify and build a selling advantage, manage capital for growth, and monitor business health in general.
• To explain sexually transmitted infections including HIV, HIV prevention methods, and SRH[d].	SBCC	As explained under SBCC.
• To describe family planning methods and identify SRH services available. • To communicate with their partners and community to increase awareness for HIV/AIDS and participation in HIV prevention interventions. • To understand assertive communication.	Positive parenting	Identify positive parenting and children's behavior; understand factors that contribute to negative and positive behaviors, types of children's growth, how to assist groups with special needs, and how to be a role model to the child by showing positive ways of living.

[a]SBCC: social and behavior change communication.

[b]WORTH+: women organizing resources together plus.

[c]GBV: gender-based violence.

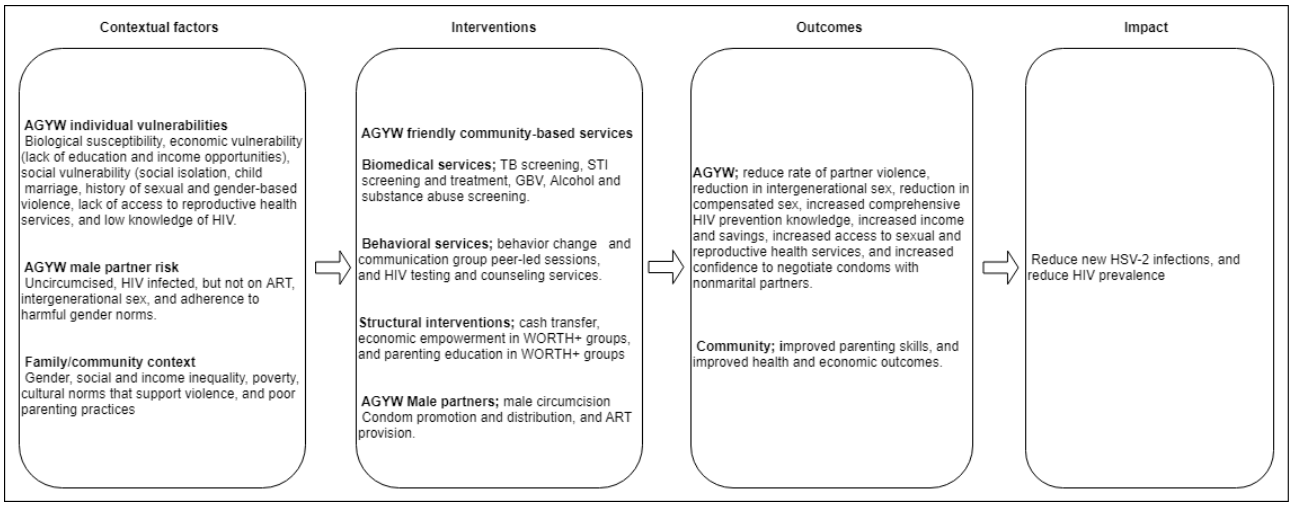
[d]SRH: sexual and reproductive health.

Aims and Objectives

The overall aim of this study is to determine the impact of cash transfer on risky sexual behavior among AGYW receiving biomedical, behavioral, and other structural interventions in Shinyanga region. The primary objective is to assess the impact of cash transfer on the incidence of HSV-2 after 18 months. Secondary objectives are to examine the impact of cash transfers on compensated sex (defined as sexual encounters motivated by exchange for money, material support, or other benefits) and intergenerational sex (defined as a sexual partnership between AGYW and a man 10 or more years older). Through a qualitative study, the study seeks to understand how the intervention impacts the structural and behavioral drivers of the HIV epidemic.

The theory of change guiding this assessment is presented in Figure 1. It presents the contextual factors contributing to the HIV vulnerability among AGYW, intervention components, outcome, and impact of the interventions. It is hypothesized that cash transfer will reduce risky sexual behavior and new HIV infections among AGYW by boosting their income and therefore increasing their consumption capacity and choices and savings and asset accumulation as well as mitigating the impact of shocks. This will, in turn, reduce risky sex including compensated and intergenerational sex, thereby contributing to a reduction in new STIs.

Figure 1. Cash transfer conceptual framework to guide the evaluation work. AGYW: adolescent girls and young women; ART: antiretroviral therapy; GBV: gender-based violence; HSV-2: herpes simplex virus type II; STI: sexually transmitted infection; TB: tuberculosis; WORTH+: women organizing resources together plus.



Methods

Study Design and Setting

This study is a two-arm cluster randomized controlled trial (RCT) implemented among AGYW with 1:1 allocation ratio, which employs mixed methods for data collection. The study is conducted in 30 clusters/communities (15 intervention and 15 control) with similar settings across three neighboring districts, namely, Kahama Town Council and Ushetu and Msalala District Councils in Shinyanga region in mainland Tanzania. A cluster or community is defined as an administrative area of the village in a rural setting or neighborhood *(mtaa)* in the urban setting. In this study, clusters rather than individuals were randomized to minimize dilution of the intervention, as the funds transferred were more likely to be shared among family members if they are allocated in different arms [29,30]. The study was retrospectively registered (trial registration: NCT03597243) on ClinicalTrials.gov, because the authors were unaware of the definition of the clinical trial per International Committee of Medical Journal Editors, as this study evaluated interventions provided by Sauti project. All future related trials will be prospectively registered.

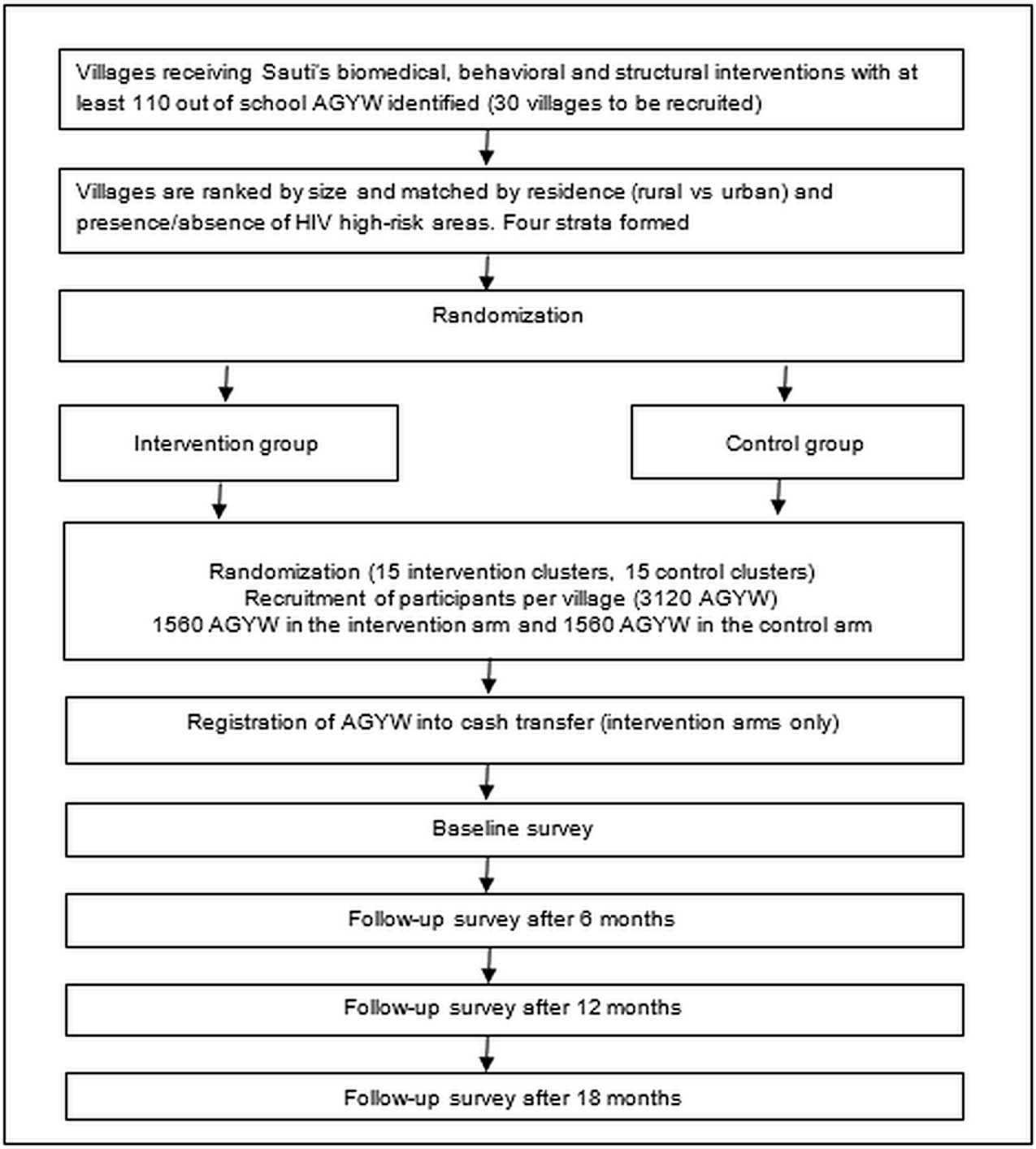
Eligibility Criteria for Clusters

Clusters in the selected councils were eligible for the trial if they were receiving Sauti interventions other than cash transfer and had at least 110 AGYW aged 15-23 years who were out of school according to the household survey conducted in all villages/*mitaa*, which were identified as potential villages to receive the CTP. Eligible clusters were randomized before implementation of the CTP.

Randomization and Blinding

All clusters that fulfilled the eligibility criteria in the three councils (Kahama town, Msalala district, and Ushetu district) were first ranked by their size and matched by residence (rural vs urban areas) and presence/absence of HIV high-risk areas (mines, plantations, and fishing areas). Therefore, four strata (rural cluster in the high-risk area, urban cluster in the high-risk area, rural cluster in the low-risk area, and urban cluster in the low-risk area) were formed. A total of 15 matched clusters with similar size were selected randomly to participate in the study across the four strata. In each matched pair, one cluster was randomly selected to receive the intervention package, and the other was automatically assigned to receive the control package. Matching was done to minimize the between-community variance in HSV-2 incidence within the matched clusters. No blinding was performed in this study, as it was not possible to blind study participants, Sauti implementers, data collectors, and data analysts because the intervention provided (cash transfer) was known to study participants, implementers, and researchers. Figure 2 presents an overview of the study design.

Figure 2. CARE study design. AGYW: adolescent girls and young women.



Participant Recruitment

In villages/*mitaa* identified as potential recipients of the cash transfer, the Sauti project conducted a household survey to identify out-of-school AGYW. Only AGYW identified through this survey constituted the population eligible for CTP and the study. This way, only AGYW who were already out of school before the initiation of the project were enrolled in the study. Following this survey, community meetings of AGYW and their caregivers were held as part of the Sauti project to introduce the study. Eligible AGYW were invited to attend SBCC training sessions. Eligible participants were as follows: AGYW aged 15-23 years, graduated from 10 hours of Sauti's SBCC sessions, and resident of the village of recruitment. Other inclusion criteria were as follows: registered into CTP (applicable to those in the CTP areas only) and currently out of school (not enrolled in primary, secondary, or tertiary education; they either have never been to school or have dropped out of school at least 1 month before study enrollment), as documented through a previous household survey of the CTP. In addition, AGYW who were willing and able to give voluntary, informed consent/assent to all study procedures, including HIV and HSV-2 testing and receiving test results, were considered eligible. Consent from parent /guardian was required for AGYW who are younger than 18 years, with the exception of emancipated minors (ie, minors who are married, have given

birth, or demonstrating full independence, eg, living alone or heading the household). AGYW found to be HIV- and HSV-2 positive at baseline or follow-up visit were not excluded from the study because excluding them is likely to disclose their HIV or HSV-2 serostatus to the community and therefore expose them to stigma and other social harms. Their data will also contribute to the analysis of the study behavioral outcomes (reporting of compensated sex and intergenerational sexual partnerships).

During SBCC sessions in the study clusters, AGYW were given information about the study. After the 10 hours of SBCC sessions, AGYW were informed about the study enrollment through information provided in their groups. This way, the potential participants were aware of dates of recruitment and location of the study site. During recruitment into the RCT, potential participants approached the registration desk for prescreening consent and eligibility screening. This process continued until the desired sample was reached.

Participatory group discussions (PGDs) and case study participants were selected purposively among the AGYW enrolled in the RCT using the baseline audio computer-assisted self-interviewing (ACASI) data. For PGD participation, participants were selected purposively to ensure maximum variability of their characteristics. Such characteristics included young versus old, never been to school versus completed primary school, heads of household versus nonheads of households, and teen pregnancy versus never been pregnant. Each PGD had 8-12 participants. For case studies, participants were selected purposively, following the experience of at least two of the following characteristics of interest: intimate partner violence, teenage pregnancy (pregnancy before 18 years of age), and living alone or as head of household.

Intervention Description

AGYW in the intervention arm received unconditional cash transfer in quarterly installments of 70,000 Tanzania Shillings (approximately US $33) through mobile money on their cellular phones plus biomedical, behavioral, and other structural interventions. The control arm did not receive cash transfer but received the other Sauti project interventions.

The first installment of cash transfer was released after registration into the CTP and completion of the baseline survey. The cash transfer was delivered for 18 months, whereas other Sauti interventions were delivered for the entire duration of the project (5 years). Table 2 presents the biomedical, behavioral, and structural interventions as defined by the Joint United Nations Programme on HIV/AIDS [31].

Table 2. Proposed components of the interventions in the control and intervention arms.

Strategy	Control arm	Intervention arm
Biomedical interventions	• Biomedical community-based health services include HTS[a], condom skills and provision, tuberculosis screening, STI[b] screening, GBV[c] screening, alcohol and substance abuse screening. • Escorted referrals are provided to GBV survivors and the GBV desk for social, legal, and medical services. Escorted referrals are also provided to HIV-positive AGYW[d] to care and treatment clinics. • Other services include FP[e] counseling and service provision and screening for nutritional assessment and counseling support.	Same as the control arm
Behavioral interventions	• SBCC[f] group peer-led sessions designed to address the significant determinants of HIV risk, gender, and reproductive health. • Community-based HIV testing and counseling services, which include risk reduction counseling provided alongside HTS. SBCC sessions include gender, gender and power issues, understanding sexuality, sexual and reproductive health systems, effective communication, STIs and HIV, risky behavior, contraception, GBV, and respectful relationships. The minimum package is 10 hours of sessions. In selected communities, AGYW receive posttest services and Alcoholics Anonymous programs.	Same as the control arm
Structural interventions	• AGYW participates in WORTH+[g] economic empowerment, health (HIV and FP) education, and parenting education groups. The WORTH+ package sessions are as follows: financial literacy sessions, dream and develop self-goals, literacy skills exercise, savings, safe money handling, loans, proper use of loans, dividends and village bank cycle, successfully selling, managing capital, and building business. Other packages in the WORTH+ package include parenting sessions, understand children, and learn parenting and being a good example to children. WORTH+ groups meet weekly and include social cohesion activities. In addition, the SASA! GBV program works with communities to address adverse gender social norms.	Same as the control arm plus cash transfer

[a]HTS: HIV testing services.

[b]STI: sexually transmitted infection.

[c]GBV: gender-based violence.

[d]AGYW: adolescent girls and young women.

[e]FP: family planning.

[f]SBSS: social and behavior change communication.

[g]WORTH+: women organizing resources together plus.

Data Collection

The study uses both quantitative and qualitative methods to evaluate the impact of the intervention on primary and secondary outcomes. The impact evaluation study collects data through the following components.

Sauti Routine Program Monitoring Data

Sauti routine program monitoring data will be used to evaluate the uptake of biomedical, behavioral, and structural interventions including the CTP. The routine program monitoring data are collected continuously throughout the program period and obtained from the program only for research participants who provided consent for their data to be used for research purposes. The data collected from the program will be used to describe the context under which cash transfer and Sauti interventions are implemented and understand the reach and coverage of interventions provided by Sauti. Specifically, the routinely collected data will be used to show fidelity (the extent to which the intervention is delivered as intended) [31] and acceptability (rate of intervention uptake, adherence to the package provided, retention, and attrition).

Cluster Randomized Trial

The baseline assessment was conducted following enrollment into the cash transfer program in a confidential environment in preidentified venues in the respective villages. Following the informed consent procedures and eligibility assessment, a structured self-administered questionnaire was administered to trial participants using ACASI. Data were collected on demographics, factors related to HIV vulnerabilities, family planning, sexual risk behavior, and GBV. All trial participants were asked to give a blood specimen for HIV and HSV-2 infection determination. Participants underwent pretest counseling, HIV test, and receive HIV test results on the same day after posttest counseling according to national HIV testing algorithms. HSV-2 infection determination was conducted at the National Institute for Medical Research (NIMR) Mwanza laboratory using the enzyme-linked immunosorbent assay technique, and the results were communicated to the participants within 2 weeks. HSV-2 test results include posttest counseling and referral for treatment of HSV-2, where needed.

Following the delivery of the intervention in the intervention clusters, the first follow-up survey (6 months after the baseline), second follow-up (12 months after the baseline), and third follow-up (18 months after the baseline) are undertaken in both clusters over 1 month. Follow-up surveys are performed in a preidentified venue used during the baseline assessment. Participants' data and blood specimen are collected at follow-up visits (6, 12, and 18 months) as well. Data and blood specimens collected are linked to the AGYW by a unique participant identification number. The interview is conducted in a private area to ensure confidentiality and anonymity of the information collected.

Qualitative Components

PGDs and case studies are used to collect qualitative data. PGDs describe perceptions and preferences of different intervention packages, whereas case studies are used to track in detail a small cohort of 20 AGYW purposely selected to monitor and unearth the dynamics involved in delivery and uptake of cash transfer. PGDs are used to collect data during the baseline survey, whereas case studies follow-ups selected participants in the intervention arm only at more regular intervals (every 6 months).

A total of 6 PGDs (3 intervention and 3 control PGDs) are conducted at baseline. Each PGD comprises 8 to 10 AGYW. Participants for the PGDs are randomly selected and approached to participate. Inclusion criteria for the PGDs include willingness to participate in a PGD; consent from the participant and parent or guardian, if applicable, as documented by written informed consent; and enrollment in the trial with complete baseline ACASI questionnaire.

Qualitative data gathering and analysis are performed as a continuous, flexible, and iterative process. Preliminary data collected through case studies are analyzed in the field (sequential analysis), after which further analysis of texts is performed to confirm or refute interim results through constant validity checks until saturation is reached.

Outcomes

End points are assessed at baseline and after every 6 months over the next 18 months. The primary outcome measure is the incident HSV-2 infection. Secondary outcome measures include HIV prevalence, reporting of intergenerational sex (sexual partnership between AGYW and a man 10 or more years older), and reporting of compensated sex (AGYW are asked to report whether they have received money or gifts in exchange for sex) in the last 6 months. Compensated sex is assessed by self-report of whether AGYW has had sex with anyone because they received money or gifts or because they expected to receive money or gifts. The primary exposure is cash transfer received. Table 3 presents the outcomes, indicators of change of outcomes, and uptake of interventions.

Table 3. Outcomes, indicators of change of outcomes, and uptake of interventions.

Factor	Variables
Primary and secondary outcomes	Herpes simplex virus type 2 incidence, HIV prevalence, reporting of intergenerational sex, Compensated sex
Indicators for change	Increased comprehensive HIV prevention knowledge, increased income and savings, increased confidence to accept an HIV test, increased confidence to negotiate condoms with nonmarital partners, and increased access to biomedical interventions (community-based HIV testing and counseling services plus, sexually transmitted infection, gender-based violence, and substance and alcohol screening and family planning)
Uptake of Sauti interventions	Individuals who received interventions or control packages; within the intervention sites, individuals who received (1) SBCC[a], cash transfer, WORTH+[b] and (2) cash transfer and combination prevention interventions; and within the control sites, individuals who received (1) SBCC and WORTH+ and (2) combination prevention interventions

[a]SBCC: social and behavior change communication.

[b]WORTH+: Women Organizing Resources Together Plus.

Data Management

The data from ACASI and qualitative interviews are collected using tablets and digital audio recorders, respectively. Data are directly transferred to the NIMR cloud storage at the end of each working day. The site supervisor synchronizes the data to the cloud. A specialized data person with permission to access data in the cloud extracts all study data and uploads them to NIMR data management system for further data cleaning and production of analytical datasets. All sound files are deidentified, transcribed, and translated before analysis.

All quantitative data are managed and cleaned in Stata (StataCorp, College Station, Texas) version 13 [32], whereas qualitative data analyses are cojointly performed by coinvestigators using NVivo software (QSR International, Melbourne, Australia) [33]. Data validation checks to identify errors and inconsistencies are programmed and run in Stata. Data queries are raised on data clarification forms and sent to the field to the appropriate member of the study team to be resolved; when a query is resolved, the database is updated accordingly. After data are clean, ACASI and laboratory data are merged using the unique study number. All electronic data are stored in password-protected database systems. There is also hardware password protection on computers, servers, and networks. All printed transcripts and paper-based forms are securely locked up in the filing cabinet with limited access.

Statistical Analysis

Sample Size

CRT is powered to detect intervention impact on the reduction of new HSV-2 infections. HSV-2 incidence was chosen as a proxy measure for HIV incidence, as the study would not be powered to detect a difference in HIV incidence in a relatively low-incidence setting such as Tanzania. A study conducted among women working in the food and recreational facilities, in a setting similar to one in this study, found an HSV-2 incidence of 35.2 per 100 person-years and 24.2 per 100 person-years among women aged 18-19 years and 20-24 years, respectively [34].

All sample size calculations were performed using methods for matched cluster randomized trials. A sample of 15 paired clusters (30 clusters) with 70 AGYW per cluster achieves >80% power to detect a difference of –0.07 between the intervention HSV-2 incidence of 13% and the control HSV-2 incidence of 20% in an 18-month period. The between-community coefficient of variation in HSV-2 incidence was assumed to be 0.25 [35], and the significance level of the test is 0.050. The sample size (70 AGYW per cluster) has been increased by 48% to 104 AGYW per cluster (1560 per arm) to account for attrition rate and background HSV-2 prevalence. It is estimated that, at baseline, HSV-2 prevalence will be 20% among AGYW aged 15-23 years [34]; the attrition rate is 10% and the nonresponse rate is 18% over 18 months.

Statistical Methods

The primary analysis will be the difference in outcome measure (proportion of HSV–2-negative AGYW who are still free of HSV-2 after 18 months of follow-up) from each matched pair of clusters across the two arms. Secondary analysis will report cumulative incidence rates using survival analysis techniques. We hypothesize that the communities receiving cash transfer will have a significantly lower cumulative incidence of HSV-2 than that of the villages not receiving the cash transfer.

HIV prevalence will be assessed by comparing the prevalence in the intervention arm against the prevalence in the control arm. The primary analysis will be the proportion of AGYW who are HIV+ at 18 months across the two arms. Secondary analysis will be performed using logistic regression analysis, adjusting for clustering and baseline HIV measurements. Cash transfer recipients are expected to have a significantly lower HIV prevalence than those in the control arm. A comparison of sexual behavior outcomes between the two arms will be made by a repeated measure logistic regression. The logistic model adjusted for clustering will be used to account for the clustering design.

Qualitative data will be analyzed following the grounded theory approach [36]. Themes will be identified through coding. Open codes will be used to capture a priori and emerging concepts. Open codes will be developed by two researchers after independently reviewing a limited number of transcripts based on emerging concepts. Following initial code development, the two researchers will compare themes and codes and develop a final coding scheme. The research team will meet to discuss emerging themes. After completing the coding for half of the transcripts, axial coding (ie, comparing code categories to the objectives of the study and findings from literature) will be applied to group open codes into abstract conceptual categories. In all, 10% of the transcripts will be double coded in NVivo to

ensure consistency between coders. The two coders will discuss and agree upon quotations from participants that best represent the themes. The coding scheme will be documented in a codebook.

Queries will be performed in NVivo to analyze themes across participants to understand (1) how the desired impact was achieved by the interventions implemented and (2) the perceptions and acceptability of the interventions.

Secondary Analysis

This study is collecting extensive data on demographics; the prevalence of HSV-2 and HIV infections; uptake of biomedical, behavioral, and structural interventions; and risk factors for HIV and HSV-2 infections among AGYW who are out of school. Secondary analysis is planned to understand how structural factors influencing vulnerability to HIV infection influence the uptake of cash transfer and other interventions and to understand how cash transfer may impact risky sexual behavior. Analysis of the longitudinal data will also be performed to explore how cash transfer impacts indicators for change and ultimately changes the outcome measure over time. The generalized estimating equations will be used for causal analysis and to verify the abovementioned theory of change.

Retention

To ensure that research participants recruited into the study are retained, the study developed strategies to optimize retention and minimize attrition rate. First, all participants in the intervention and control communities were given phones for maintaining regular contact with researchers. Second, a detailed and thorough explanation of the study visit timeline (baseline and all follow-up rounds) was given during the informed consent process. Third, during enrollment, participants were requested to provide phone numbers of their friends or relatives to facilitate tracing in the follow-up surveys. The phone numbers were updated in the follow-up rounds. Short text messages were sent before and during the time of data collection to remind and emphasize the importance of study participation in the success of the study. Fourth, the research team is working closely with CSOs, which train and support AGYW. AGYW receiving Sauti interventions in the village are trained and supported by 1-3 empowerment workers who are employees of the CSOs.

Safety Monitoring

Given that this is an impact-evaluation study conducted among participants receiving Sauti's standard biomedical, behavioral, and structural interventions, an interim analysis is not planned. For the same reason, a data and safety monitoring board is not established. This idea was approved by the institutional review boards, which granted ethics approval to the study. It is anticipated that any harm to AGYW as a result of study participation will be minimal. The study adheres to all safety guidelines established by Sauti program in defining and reporting social harm events. The social harm events resulting from study participation are closely monitored; recorded in the social harm event form; and reported to the Sauti program, CSOs, and the study principal investigator who initiates further investigations and responses, as appropriate.

Auditing

Members of the study team, representatives of the CSOs implementing the study, and the sponsor conduct regular auditing of the study activities. During auditing, a review of the informed consent forms and study-related materials and procedures is performed to ensure that informed consent forms are thoroughly and accurately filled and that all the consenting procedures are strictly adhered to. A review of study-related materials and procedures is performed to ensure that the study is conducted and reported in compliance with the protocol, good clinical practices, and ethics requirements.

Ethics

This study was approved by the Medical Research Coordinating Committee of NIMR in Tanzania (NIMR/HQ/R.8c/Vol.II/841) and institutional review board of the Johns Hopkins University (IRB00007976). Approval to conduct the study in the study communities was also provided by regional and district authorities as well as community leaders.

All AGYW graduating from SBCC sessions in the study clusters are informed about the study in group introductory session, and study information was provided in oral and written forms using Swahili language. Girls who required consent from parents/guardian were advised to bring their parents/guardians, if interested in study participation. All girls younger than 18 years of age required consent from parents/guardian and their assent to participate in the study, except for emancipated minors (ie, minors who are married, have given birth or demonstrating full independence, eg, living alone or heading the household). If a mature participant or guardian is illiterate, the consent procedure is conducted in the presence of a witness who is literate and not related to the study. AGYW willing to participate received further information on a one-to-one basis in a confidential environment guided by the participant information and informed consent form. As part of the consent process, study staff explained the study aims, procedures, any inherent risks or benefits, and their right to decline study participation or terminate participation in the study at any time, without giving reasons and affecting their health care or participation in the CT program provided by Sauti. Participants and their parents/guardians were given time to discuss participation and raise any additional questions. Consent to study participation was documented using a written consent form before any study-related data collection. Illiterate participants and parents/guardians provided a thumbprint in the presence of a witness who signed the consent.

Confidentiality

AGYW's names, their telephone numbers, and any locator information collected that identifies them are kept confidential and always under lock and key whenever not in use. Only study personnel involved in data collection have access to locator information. Locator information is only used to ensure validation of the identity of the participant in follow-up visits and for contacting the participant for participation in the follow-up rounds.

A unique study identification number and the encrypted Sauti routine identification (SRI) number (participant unique identifier

of the Sauti program) are collected using the study tools and hence captured in the database. The SRI number is encrypted before it is used for study purposes of maintaining the confidentiality of participant's information. Although the study number is used to identify the dataset for an individual participant in the study dataset, the SRI is used to link study data collected and routine data obtained from the program.

Participants and Public Involvement

This is an impact evaluation study of the interventions provided by Sauti project. AGYW were involved in the design of this study through their representative CSOs. The involvement included advising on the content of the study materials, data collection techniques such as the use of PGDs, and techniques that enhance confidentiality and anonymity (eg, ACASI). CSOs were also crucial in the recruitment of study participants and are involved in monitoring study activities and tracing of study participants. They will also be involved during the dissemination of the findings at the community and regional level.

During the development of interventions, the Sauti project involved intensive dialogues with local leaders, Ministry of Health, Community Development, Gender, Elderly and Children, Tanzania Social Action Fund, National AIDS Control Program, Tanzania Commission for HIV/AIDS, Tanzania Communications Regulatory Authority, mobile communication companies, CSOs, and AGYW representatives among other national and international stakeholders. These dialogues led to the development of the combination prevention interventions offered by the project to AGYW, including the cash transfer amount and payment modality.

Results

The study was funded in June 2017, and the enrollment took place in December 2017. The baseline study was conducted among AGYW who consented for study participation, and study participants were followed up for 18 months. Follow-up study assessments are conducted 6, 12, and 18 months postintervention initiation. A total of two rounds of the follow-up surveys postintervention are complete, and one round has not yet been performed. The results are expected in December 2019 and will be disseminated through conferences and peer-reviewed publications.

Discussion

Overview

This cluster randomized trial intends to evaluate the impact of cash transfer in the presence of combination prevention interventions in the reduction of risky sexual behavior. Previous trials in sub-Saharan Africa were conducted to assess the effect of cash transfer [23,28], but none were conducted among out-of-school girls to ascertain the synergetic impact of cash transfer, WORTH+ interventions, and biomedical and behavioral interventions.

Study Strengths and Limitations

This study has several strengths. First, the study incorporates both qualitative and quantitative data collection techniques to understand how cash transfer and other interventions synergistically mediate to reduce risky sexual behavior. Second, the study uses ACASI to collect sexual behavior and other sensitive data. Studies comparing face-to-face interviews with ACASI have reported that respondents are more likely to be open and honest when using ACASI [37,38]. Third, the study collects longitudinal data on biomedical, behavioral, and structural interventions on a large sample of AGYW (n=3120) who are out of school and therefore vulnerable to HIV infection to allow for the detection of the difference between arms. However, the study clusters are selected from Shinyanga region, which has a prevalence of HIV above the national average and may not be generalizable to other study regions with lower HIV prevalence in Tanzania.

Conclusions

This study aims to document the synergetic impact of cash transfer in the presence of other biomedical, behavioral, and structural interventions on risky sexual behavior among out-of-school AGYW. The results will strengthen the evidence of cash transfer in the reduction of risky sexual behavior and provide feasible HIV-prevention strategies for vulnerable AGYW.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Consort-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 3836 KB - resprot_v8i12e14696_app1.pdf]

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Abbreviations

ACASI: audio computer-assisted self-interviewing
AGYW: adolescent girls and young women
CSO: civil society organization
CTP: cash transfer program
DREAMS: Determined, Resilient, Empowered, AIDS-free, Mentored and Safe' women
GBV: gender-based violence
HSV-2: herpes simplex virus type 2
NIMR: National Institute for Medical Research
PGD: participatory group discussion
RCT: randomized controlled trial
SBCC: social and behavior change communication
SRI: Sauti routine identification
STI: sexually transmitted infection
WORTH+: women organizing resources together plus

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Protocol

Evaluating the Effects of a Rent Subsidy and Mentoring Intervention for Youth Transitioning Out of Homelessness: Protocol for a Mixed Methods, Community-Based Pilot Randomized Controlled Trial

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Abstract

Background: Although the risk factors associated with young people entering and becoming entrenched in street life have been thoroughly investigated, peer-reviewed evidence is scarce to nonexistent for rigorous interventions targeting social integration outcomes for young people who have experienced homelessness. From the limited research that has been done, emerging evidence signals that, although structural supports such as subsidized housing and social service providers are important, these resources alone are insufficient to help young people integrate into the mainstream society.

Objective: The overarching aim of this study is to assess whether and how rent subsidies and mentorship influence social integration outcomes for formerly homeless young people living in market rent housing in 3 Canadian cities. The primary outcome measures for this study are community integration (psychological and physical) and self-esteem at 18 months. Secondary outcomes include social connectedness, hope, and academic and vocational participation at 18 months. Exploratory outcomes include income, perceived housing quality, engulfment, psychiatric symptoms, and participant perspectives of intervention barriers and facilitators.

Methods: This is a convergent mixed methods, open-label, 2-arm parallel randomized controlled trial (RCT) with 1:1 allocation embedded within a community-based participatory action research (CBPAR) framework. The intervention will provide 24 young people (aged 16-26 years), who have transitioned out of homelessness and into market rent housing within the past year, with rent subsidies for 24 months. Half of the young people will also be randomly assigned an adult mentor who has been recruited and screened by 1 of our 3 community partners. Data collection will occur every 6 months, and participants will be followed for 30 months.

Results: Ethical approval for this study has been obtained from the Providence, St Joseph's, and St Michael's Healthcare Research Ethics Board (number 18-251). Enrollment took place from April 2019 to September 2019. Preliminary analysis of the baseline quantitative and qualitative data is underway.

Conclusions: This pilot RCT will be the first to test the impact of economic and social support on meaningful social integration for formerly homeless young people living in market rent housing. We believe that the mixed methods design will illuminate important contextual factors that must be considered if the intervention is to be scaled up and replicated elsewhere. Importantly, the CBPAR framework will incorporate the perspectives of the community, including formerly homeless young people, who are in the best position to determine what might work best in the context of their lives.

Trial Registration: Clinicaltrials.gov NCT03779204; https://clinicaltrials.gov/ct2/show/NCT03779204.

International Registered Report Identifier (IRRID): DERR1-10.2196/15557

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KEYWORDS

homeless youth; community integration; qualitative research; randomized controlled trial; housing; mentorship

Introduction

Background and Rationale

Young people comprise almost 20% of the homeless population in Canada [1]. An estimated 35,000 to 40,000 Canadian youth (aged 13-25 years) are homeless at some point during the year and at least 6000 on any given night [2,3]. Although the risk factors associated with young people entering and becoming entrenched in street life have been thoroughly investigated, peer-reviewed evidence is scarce to nonexistent for rigorous interventions targeting housing outcomes, life trajectories, quality of life, and social integration for young people who have experienced homelessness [4-7]. It must be noted that the concept of social integration is complex and often inconsistently defined and poorly measured [8]. For the purpose of this study, we drew from the literature on the social determinants of health and social exclusion and adopted a holistic definition of social integration, incorporating both the tangible (eg, access to education and a living wage) and intangible (eg, sense of connection and belonging) aspects of meaningful and equitable societal participation [4,9,10].

Intuitively, it may seem that one important way to improve the life trajectories of young people experiencing homelessness is to provide them with a home. However, from the limited research that has been done in this area, we know that formerly homeless young people continue to experience significant challenges—particularly when it comes to mainstream social integration—even after they are "successfully" housed [11,12]. Moreover, these challenges seem to persist regardless of the type of housing (eg, subsidized vs market rent) provided [13-15].

Housing and Social Integration

A longitudinal mixed methods study with 51 formerly homeless young people (aged 16-25 years) living in 2 major urban centers in Canada found that, despite living in stable or semistable accommodations (53% lived in subsidized housing), participants continued to face substantial social integration challenges such as poverty-level incomes and limited mainstream social networks [14,16,17]. Over the course of 1 year, these challenges contributed to a significant decline in hope, no gains in community integration, and a sense of being *stuck* [14,16,17]. Notably, these challenges were significantly worse for participants paying market rent [14].

A subgroup analysis of 156 young people (aged 18-24 years) with mental health challenges who participated in a 24-month randomized controlled trial (RCT) of *Housing First* (access to subsidized housing and comprehensive social service support) in 5 Canadian cities—the largest RCT of Housing First to date—indicates similar findings of social integration challenges despite the provision of a home [15]. Although the young people who received the Housing First intervention achieved significantly better housing stability compared with the treatment-as-usual group, they did not experience improvements to other outcomes such as employment, generic quality of life, and community integration relative to the treatment-as-usual group [15].

In line with the findings from both these studies, a 10-month ethnographic study conducted by the members of our team with 9 formerly homeless young people (aged 18-24 years) living in Canada's largest city highlighted that, despite the appearance of housing stability in market rent housing, the young people were experiencing significant social integration challenges [11,12]. Study participants described living a precarious existence, attributed in part to the chronic stress and exhaustion of living in poverty and to their limited knowledge about how to move forward in life [11,12]. In addition, we noted that the participants underutilized transition-related social support (eg, food banks and employment counseling) because these types of support tended to be deficit-focused (eg, focused on what youth did not have and not on what they had achieved) and located in areas (eg, homeless shelters) that reminded them of their old identities as homeless youth. Identities primarily defined, or in other words *engulfed*, by homelessness may in fact preclude young people from achieving meaningful social integration [11].

Mentorship and Social Integration

As previously mentioned, little evidence exists for effective interventions that target social integration outcomes for young people who have experienced homelessness. This includes evidence on the impact of mentorship. In fact, for formal mentorship programs in general, meta-analyses have only found small overall positive effect sizes on the psychological, emotional, behavioral, and educational functioning of participating young people [18,19]. However, there is some emerging evidence on the benefits of *natural mentors*—generally defined as an important, encouraging, nonparental adult who exists in a youth's social network—that

may be transferable to youth who have experienced homelessness.

A systematic review of natural mentoring for youth (aged 13-25 years) transitioning out of foster care showed that the young people benefited from a supportive adult not "tasked with enforcing daily rules and addressing misbehavior" and that this sort of intervention resulted in improved behavioral, psychosocial, and academic outcomes [18]. A meta-analysis of natural mentoring in youth (aged 13-24 years) discovered similar positive outcomes in the domains of social and emotional development and academic and vocational functioning [19]. Furthermore, the risk status of youth (eg, young people experiencing homelessness or living in foster care) did not moderate these positive outcomes [19]. A small (n=23) qualitative study of natural mentoring relationships among young people (aged 14-21 years) experiencing homelessness also supported these positive findings, and the authors suggested that "natural mentors could feasibly serve as a bridge in a coordinated effort to assist youth out of homelessness" [20]. Taken together, these studies show promise for mentoring interventions that incorporate the positive characteristics of natural mentors (ie, more of a friendship-like *coach* or *cheerleader* role) for young people who have experienced homelessness. Moreover, although traditional natural mentoring relationships tend to emerge organically, they can be facilitated and supported programmatically as well [15].

From the limited research that has been done with young people transitioning away from homelessness, the emerging evidence signals that, although structural supports such as subsidized housing and social service providers are important, these resources alone are insufficient to help young people integrate into the mainstream society. As it currently stands, the burden for achieving meaningful social integration is on young people, who continue to be marginalized despite achieving stable or semistable housing. Connecting formerly homeless youth with an adult who exhibits the relationship-based components of natural mentoring that young people value most (eg, genuine interest in their well-being and belief in their ability to succeed) may be key to helping young people move forward and integrate into the mainstream.

Objectives

The overarching aim of this mixed methods study is to assess whether and how rent subsidies and mentorship influence social integration outcomes for formerly homeless young people living in market rent housing in 3 urban settings.

Quantitative Objectives

The primary objective is to determine whether rent subsidies and mentorship result in better social integration outcomes than only receiving rent subsidies with regard to (1) community integration (psychological and physical) and (2) self-esteem.

The secondary objectives are to determine whether rent subsidies and mentorship result in better social integration outcomes than only receiving rent subsidies with regard to (1) social connectedness, (2) hope, and (3) sustained academic and vocational participation.

The exploratory objectives are to assess whether rent subsidies and mentorship result in better social integration outcomes than only receiving rent subsidies with regard to (1) income, (2) perceived housing quality, (3) sense of engulfment, and (4) psychiatric symptoms.

Qualitative Objectives

The qualitative objectives of the study are (1) to explore what the study participants (young people and mentors) found most beneficial about the intervention and how it could be improved and (2) to facilitate a more comprehensive and contextualized understanding of the quantitative data.

Methods

Design and Setting

This is a convergent mixed methods (ie, quantitative and qualitative data are collected concurrently and the findings, combined), open-label, 2-arm parallel RCT with 1:1 allocation embedded within a community-based participatory action research (CBPAR) framework [21,22]. We believe a mixed methods RCT is appropriate given the complex explanatory pathways (ie, social and behavioral processes that may act independently and interdependently) of this intervention [23]. The study will be conducted in 3 Canadian cities in Ontario: Toronto (population 2.8 million), Hamilton (population 552,000), and St Catharines (population 133,000).

Community-Based Participatory Action Research Methodology

With the goal of reducing health inequities through knowledge and action, CBPAR can be a powerful tool for those working with marginalized populations [24-27]. Our study team is committed to drawing on the following key principles of CBPAR from study inception to dissemination [24-27]:

- Research participants are viewed as experts in their own lives.
- Concerted effort to reduce power imbalances between the researchers and the community.
- Equal value placed on academic knowledge and experiential knowledge.
- Commitment to producing practical, actionable data to build community capacity and improve the lives of the research participants.
- Duty to remain invested with the community beyond the life of the research project.

Eligibility Criteria and Recruitment

A total of 24 young people aged between 16 and 26 years, who have experienced homelessness within the past year and are living in market rent housing, will be collaboratively recruited by our research team and our 3 community partners: Covenant House Toronto, Living Rock Ministries (Hamilton), and the Raft (St Catharines). We adopted the Canadian Observatory on Homelessness' definition of homelessness and defined homelessness to include young people who are unsheltered (eg, sleeping on the streets), emergency sheltered (eg, homeless shelter), or provisionally accommodated (eg, time-limited subsidized housing) [28].

In addition to the above age and housing inclusion criteria, study participants must be able to provide free and informed consent, fluent in English, planning on staying in or nearby the community in which they were recruited for the duration of the 24-month study, and willing to be matched with an adult mentor who has been screened and recommended by one of our 3 community partners.

Young people will be excluded from the study if they are in imminent danger of losing their housing (eg, facing jail time or impending eviction) and are enrolled in another study with enhanced financial and social support.

Potential participants will be screened for eligibility over the phone by the study coordinator. If a participant meets the eligibility criteria, the study coordinator will arrange a face-to-face meeting between the young person and a member of the research team. During this initial meeting, informed consent will be obtained and the youth will be enrolled in the study. Enrolled participants will be asked to provide baseline quantitative data before being randomized into the intervention (rent subsidies plus mentoring) or the active comparator (rent subsidies only) group.

Sample Size

This pilot study was designed with the intention of generating data and hypotheses for a full-scale study. The sample size was chosen based on the financial resources available to provide substantial rent supplements over a 2-year period, and no formal sample size calculation was performed [29].

Randomization

Participants at each of the 3 study sites (Toronto [n=12], Hamilton [n=6], and St Catharines [n=6]) will be randomized using block randomization. Randomization will be balanced by site based on random block sizes of 2 and 4. The advantage of using block randomization is to uniformly distribute participants into treatment groups within each site [30]. As small block sizes may increase the risk of guessing the allocation procedure and subsequently introducing bias into the enrollment procedure, random block sizes will be used to avoid this potential selection bias [31].

The study biostatistician will generate a unique randomization schedule for each site using SAS software (SAS Institute Inc). A research coordinator at St Michael's Hospital, who is not affiliated with the study, will be the only person with access to the randomization schedule. She will prepare sealed and sequentially numbered envelopes, separated by site (Toronto, Hamilton, and St Catharines). After each participant has been enrolled and has participated in baseline data collection, a member of the study team will select a randomization envelope from the sequentially ordered randomization envelope file to obtain the participant's group assignment. The participant's group allocation will be noted, and all opened randomization envelopes will be returned to the independent research coordinator to check for consistency in participant allocation. Typical of community-based RCTs with psychosocial interventions, blinding of research personnel, community partners, and participants to treatment allocation would not be possible owing to the nature of the intervention [32].

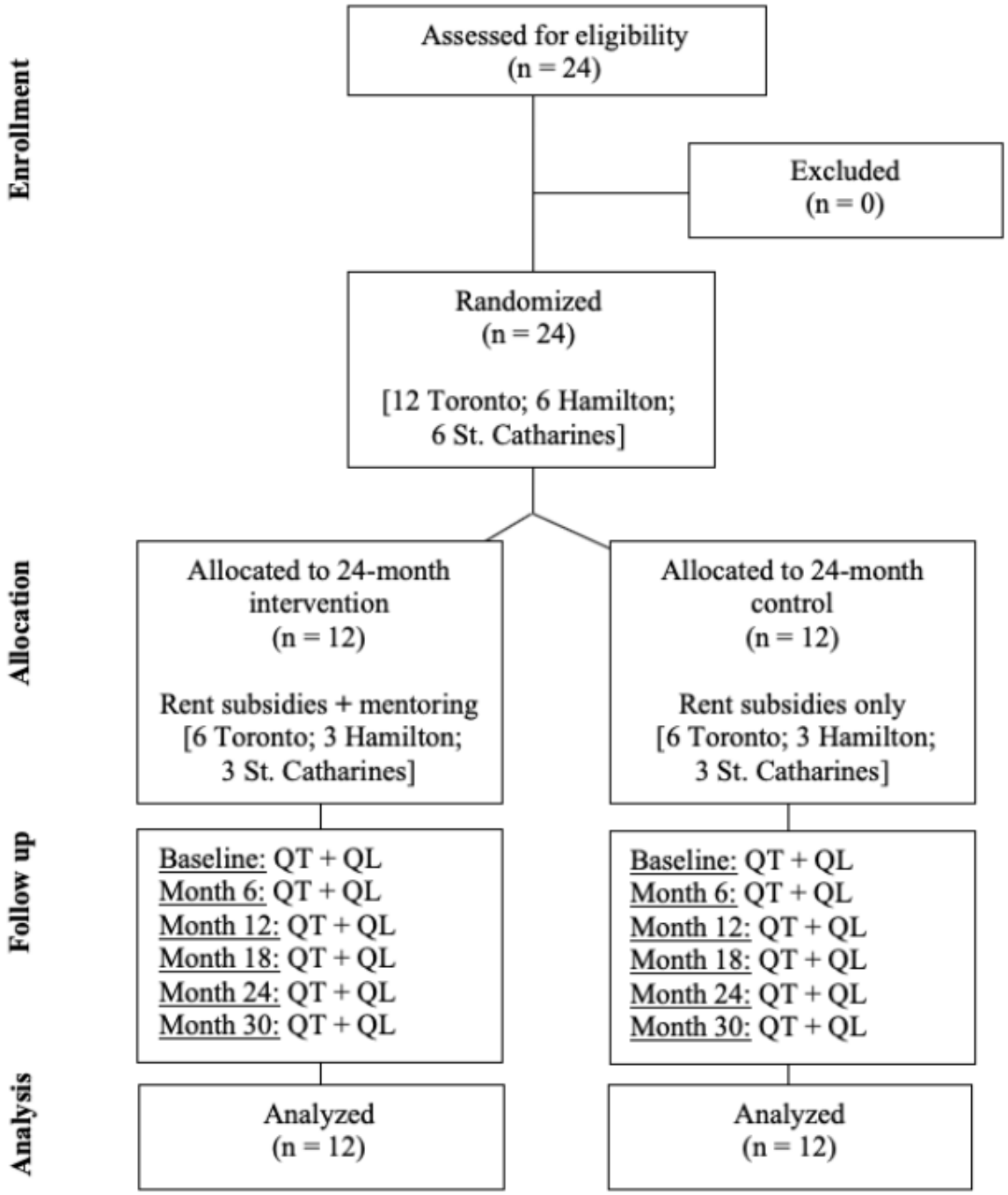
Intervention

All study participants (n=24) will receive rent subsidies for 24 months, paid directly to the landlords by our community partners. Given the higher cost of rent in Toronto, youth living in Toronto will receive Can $500/month, whereas youth living in Hamilton and St Catharines will receive Can $400/month.

Participants in the intervention group (n=12) will be matched with an adult mentor recruited and screened by one of our community partners. Covenant House Toronto has an established mentorship program and will share their comprehensive mentor screening and training resources, which will act as a guide for all sites. Working with established community resources makes practical sense; not only will this facilitate colearning and capacity building between the research team and our community partners but delivering the mentorship intervention under *real-world* conditions will also provide important insights into scalability and sustainability [33,34]. The mentors will be encouraged to incorporate the key relationship-based components of natural mentors previously described (eg, a *coach* or *cheerleader* role) to help facilitate the connection of participants to larger social networks (including education and employment). All mentors will meet monthly with their mentees for 2 years and will be expected to be in contact with their mentee via phone or text message every week. If a mentor is unable to continue their role with more than 6 months remaining in the study, the participant will be matched with a new mentor.

Our community partners will match all participants with an outreach worker (already employed by each agency and considered standard of care) who will communicate regularly with the research team, help ensure the rent subsidies are being distributed appropriately, maintain an ongoing relationship with the study participants and mentors, and monitor for red flags in participants matched in mentor-mentee relationships (eg, mentee reluctant to meet with their mentor). Figure 1 summarizes the ideal flow of participants through the study.

Figure 1. Consolidated standards of reporting trials' diagram of ideal flow of participants through the study. The quantitative measures (QT) completed with all participants will comprise 6 standardized measures to assess community integration, self-esteem, social connectedness, hope, engulfment, and psychiatric symptoms. In addition, participants will complete 2 brief questionnaires pertaining to: (1) education (includes skills training), employment, and income and (2) perceived housing quality. The qualitative measures (QL) will comprise one-on-one semistructured interviews with the same 12 participants. The interview questions will explore the participant's perspectives of the intervention and provide context to the quantitative responses.



Study Outcomes

To fully apprehend the complex explanatory pathways of the intervention, we have aligned our key outcome variables (Table 1) with the Medical Research Council guidance on evaluating complex interventions and identified more than one primary outcome measure [35,36]. The primary outcome measures for this study are community integration (psychological and physical) and self-esteem at 18 months. Secondary outcomes include social connectedness, hope, and academic and vocational participation at 18 months. Exploratory outcomes include engulfment, psychiatric symptoms, income, perceived housing quality, and participant perspectives of intervention barriers and facilitators.

Table 1. Key outcome variables.

Variables	Instruments
Primary outcomes	
Community integration (psychological and physical)	Community Integration Scale [37]
Self-esteem	Rosenberg Self-Esteem Scale [38]
Secondary outcomes	
Social connectedness	Social Connectedness Scale–Revised [39]
Hope	Beck Hopelessness Scale [40]
Enrollment in education (includes skills training)	Composite checklist
Employment	Composite checklist
Exploratory outcomes	
Income	Composite checklist
Engulfment	Modified Engulfment Scale [41]
Psychiatric symptoms	Modified Colorado Symptom Index [42]
Perceived housing quality	Perceived Housing Quality Scale [43]
Participant perspectives of barriers and facilitators	Individual semistructured interviews (youth) and focus groups (mentors) and composite checklist (mentor evaluation)

Quantitative Data Collection

Participant demographic data will be collected at baseline. Quantitative questionnaires (Table 2) will be completed at 6 points in time over the course of 30 months: baseline, month 6, month 12, month 18, month 24, and month 30. Instruments previously utilized in research with young people who have experienced homelessness [14,44] were chosen so that meaningful comparisons can be made across studies [36]. Participants will be paid an honorarium of Can $20 at each of the 6 quantitative data collection points.

Table 2. Quantitative data collection.

Instrument	Psychometric information
Beck Hopelessness Scale [40]	This 20-item scale measures motivation, expectations, and feelings about the future (internal consistency alpha=.93)
Community Integration Scale [37]	This 11-item scale measures behavioral (eg, participation in activities) and psychological (eg, sense of belonging) aspects of community integration. This scale was used extensively in the Chez Soi/At Home study [37], but psychometric properties have yet to be reported
Education, Employment, and Income Questionnaire	This 13-item questionnaire assesses education, employment, and income. We developed this questionnaire for the study
Mentor Evaluation Questionnaire	This 10-item questionnaire assesses mentor effectiveness. It will be completed at month 24 by those in the intervention group. We developed this questionnaire for the study in collaboration with our community partners
Modified Colorado Symptom Index [42]	This 14-item scale measures the presence and frequency of psychiatric symptoms experienced in the past month (internal consistency alpha=.90 to .92)
Modified Engulfment Scale [41]	This 30-item scale measures the degree to which an individual's self-concept is defined by their experience of homelessness (internal consistency alpha=.91). We have adapted the scale for this study, substituting *experience of homelessness* for *illness*
Perceived Housing Quality [43]	This 7-item scale measures participants' perception of housing choice and quality. This scale was used extensively in the At Home/Chez Soi study [37], but psychometric properties have yet to be reported. We have shortened it from 10 items (At Home/Chez Soi) to 7 relevant items
Rosenberg Self-Esteem Scale [38]	This 10-item scale measures global self-worth (internal consistency alpha=.77 to .88)
Social Connectedness Scale–Revised [39]	This 20-item scale measures belongingness—the degree to which an individual feels connected to others (internal consistency alpha=.92)

Qualitative Data Generation

Qualitative measures are an important feature of this study and will comprise semistructured individual interviews with study participants and focus groups with mentors. A total of 12 participants (6 from Toronto, 3 from Hamilton, and 3 from St Catharines) will be purposively chosen to participate in 6 semistructured individual interviews, which will take place at baseline, month 6, month 12, month 18, month 24, and month 30. We will select 6 participants from the intervention group (rent subsidies plus mentorship) and 6 from the control group (rent subsidies only) for qualitative interviews. All mentors (n=12) will be invited to participate in 2 focus groups, which will take place at month 12 and month 24. The questions posed during the semistructured interviews and focus groups will be conversational and exploratory in nature with particular attention to understanding how mentoring and/or rent subsidies influence social integration outcomes for formerly homeless young people living in market rent housing. To get a better sense of each young person's living situation and to minimize researcher-participant power imbalance [33], the individual interviews will take place in or nearby the young people's homes. The individual interviews and focus groups will be audio recorded and transcribed verbatim. Given the emergent nature of qualitative inquiry, we expect the interview and focus group questions to evolve over time as key preliminary themes begin to surface [45,46]. Young people participating in semistructured interviews will be paid an honorarium of Can $30 at each interview.

Data Analysis

One major critique of mixed methods RCTs is that, typically, there is no true integration (ie, *mixing*) of quantitative and qualitative findings at the level of analysis or interpretation [23]. Moreover, it is often unclear whether or how the quantitative and qualitative researchers have worked together to maximize the potential synergies between these different approaches [23]. With this in mind, our study team, comprising researchers with quantitative and qualitative expertise, worked together to develop this study protocol and anticipate meeting quarterly to discuss the emerging analysis and to explore (and follow up on) similarities or discrepancies between the quantitative and qualitative data to determine how the subjective experiences and statistical analysis compare.

Quantitative Analysis

All analyses will be performed using the intention-to-treat principle. Baseline characteristics of the intervention and control groups will be summarized using mean, standard deviation, median, and interquartile range for continuous variables and frequencies and proportions for categorical variables. Differences in group trajectories from baseline to 30 months follow-up will be explored using scatterplots and box plots. Group mean differences with 95% confidence intervals in continuous outcomes at 18 months (psychological community integration, self-esteem, social connectedness, hope, perceived housing quality, sense of engulfment, and psychiatric symptoms) will be estimated using analysis of covariance, including an indicator of intervention group and the baseline value of the outcome. We will perform regression diagnostics and will repeat analyses using the nonparametric Wilcoxon rank sum test if there are extreme outliers or influential observations. For the count outcome of physical community integration, groups will be compared at 18 months using graphical tools and the nonparametric Wilcoxon rank sum test. For binary outcomes at 18 months, such as sustained academic and vocational participation, and income above low income cut-off, differences in proportions with 95% confidence intervals will be estimated and tested using the chi-square or Fisher exact test. If there are high rates of attrition or missing interviews, we will consider performing multiple imputation.

Qualitative Analysis

In keeping with the emergent, iterative nature of research using a qualitative design [45,46], data analysis and interpretation will begin immediately after the first qualitative data generation session at baseline. To conduct a more nuanced analysis of the data, the transcriptionist will be instructed to note short responses, uncooperative tones, and literal silence [46,47]. Before each subsequent qualitative data generation session, members of the research team will conduct a preliminary data analysis, reading the interview transcripts multiple times, separating the data into coded segments, making analytic memos beside sections of the transcripts, identifying emerging themes, and comparing and contrasting these among respondents, and compiling new questions [21,45]. Those participating in the individual interviews and the focus groups will be asked for their perspectives on the emerging interpretations at each visit and these perspectives will play a key role in helping shape the data analysis and help ensure the trustworthiness of the data [21,48]. The Web-based application Dedoose will be utilized to assist with sorting and coding the qualitative data.

Public Involvement

We worked closely with our community partners to design this study and amended the design based on their feedback. For example, we initially proposed a study design where only half the young people would receive rent subsidies with the other half receiving *treatment as usual*; however, we abandoned this idea after our community partners challenged the ethics of not providing rent subsidies to young people living a precarious existence and desperate for immediate, tangible support to help them remain in market rent housing. In addition, we have formed a community advisory board and are meeting on a semiannual basis. We are also in the process of developing a newsletter to disseminate emerging findings to our community partners.

Ethics and Dissemination

All data collected will be kept in strict confidence. Although the participants' names will appear on the consent forms, pseudonyms (created by the participants) will be used in place of their real names on all documents related to data generation, including the audio recordings and interview transcripts. All electronic data will be stored on a secure server at the MAP Centre for Urban Health Solutions at St Michael's Hospital and will be accessible only to select members of the research team. The audio recordings from the individual interviews and focus groups will be deleted once the transcripts have been stored on the secure server and entered into the Dedoose application.

Paper copies of the data (eg, consent forms and standardized quantitative measures) will be stored in a locked filing cabinet at the MAP Centre for Urban Health Solutions—an area accessible only to those with electronic key access. All paper and electronic files will be retained for a period of up to 5 years from study closure.

In keeping with our CBPAR methodology, we are committed to disseminating evidence *with* our community partners to build community capacity and improve the lives of the young people participating in this study [24,27]. With an emphasis on *actionable* data [24], we anticipate disseminating our findings broadly to both academic and community-based audiences in a variety of formats ranging from scientific journal papers to oral presentations. Deidentified participant data will be available from the lead author upon request once the study is completed.

Results

Ethical approval for this study (protocol version January 13, 2019) was obtained in November 2018 from the Providence, St Joseph's, and St Michael's Research Ethics Board (REB; number 18-251). Any amendments to the study protocol will be reviewed by our community partners and approved by the Providence St Joseph's and St Michael's Healthcare REB before implementation. Enrollment took place from April 2019 to September 2019. We have enrolled 24 young people in the study. Preliminary analysis of the baseline quantitative and qualitative data is underway.

Discussion

This pilot RCT will be the first to test the impact of economic and social support on meaningful social integration for formerly homeless young people living in market rent housing. We believe the mixed methods design will illuminate important contextual factors that must be considered if the intervention is to be scaled up and replicated elsewhere. Importantly, the CBPAR framework will incorporate the perspectives of the community, including formerly homeless young people, who are in the best position to determine what might work best in the context of their lives.

Young people recruited for this pilot study will be a small sample of youth connected to urban-based social service providers in the province of Ontario, Canada. Thus, the findings may not be generalizable to formerly homeless young people living in other contexts and/or not connected to social service agencies.

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Authors' Contributions

NT conceived the study. RN provided statistical expertise. All authors contributed substantially to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CBPAR: community-based participatory action research
REB: Research Ethics Board
RCT: randomized controlled trial

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Protocol

An Electronic Health Intervention for Latina Women Undergoing Breast Cancer Treatment (My Guide for Breast Cancer Treatment): Protocol for a Randomized Controlled Trial

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Abstract

Background: Among Latinas and Hispanics (henceforth referred to as Latinas), breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths. However, few interventions have been developed to meet the needs of Latina women undergoing active treatment for breast cancer.

Objective: This paper aims to describe the procedures and methods of *My Guide for Breast Cancer Treatment* and the plans for conducting a multisite randomized controlled trial to investigate the feasibility and preliminary efficacy of this smartphone-based app for Latina women in active treatment for breast cancer.

Methods: Study participants will be randomized to the *My Guide for Breast Cancer Treatment* intervention or the enhanced usual care control condition for 12 weeks. Participants will have access to innovative features such as gamification via virtual awards to reinforce usage and an adaptive section that presents targeted material based on their self-reported concerns and needs. Using a stepped-care approach, intervention participants will also receive telecoaching to enhance their adherence to the app. Study outcomes and intervention targets will be measured at study enrollment (before randomization), 6 and 12 weeks after initial app use. General and disease-specific health-related quality of life (HRQoL) and symptom burden are the study's primary outcomes, whereas anxiety, depression, fear of cancer recurrence, physical activity, and dietary intake are secondary outcomes.

Results: Recruitment began in August 2019 and is expected to be completed by August 2020. We expect to submit study results for publication by fall 2020.

Conclusions: *My Guide for Breast Cancer Treatment* has the potential to improve HRQoL and reduce symptom burden, and increase access to supportive care resources among Latina breast cancer patients.

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KEYWORDS

breast cancer; Latina; health-related quality of life; eHealth; randomized controlled trial

Introduction

Background

Among Latinas/Hispanics (henceforth referred to as Latinas), breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths [1]. Compared with non-Latina breast cancer survivors (BCSs), Latina BCSs report multiple disparities including poorer health-related quality of life (HRQoL), greater symptom burden, greater cancer-related psychosocial needs [2-4], less breast cancer knowledge, and more dissatisfaction with information related to breast cancer care [5]. Prior studies show that poorer HRQoL is related to lower levels of adherence to disease surveillance and adjuvant treatment [6,7], and interventions designed to improve HRQoL specifically for Latina BCSs can improve adherence to posttreatment care and health outcomes [2,8,9]. However, given the documented disparities beyond HRQoL, interventions targeting Latina BCSs must also provide education about cancer-related symptoms and evidence-based tools to manage symptoms and associated distress.

Objectives

To address poor HRQoL among Latina BCSs, our team previously developed and pilot tested *My Guide*, a smartphone-based app designed specifically for Latina BCSs to improve HRQoL and reduce symptom burden after completing primary breast cancer treatment [10]. The initial *My Guide* app is available in both English and Spanish, expanding its reach to underserved Latina BCSs. Preliminary findings show that *My Guide* is feasible for Latina BCSs to use (eg, acceptable app usage and high user satisfaction) [11]. However, many of our participants noted that they wished that they had access to the app content *during* treatment.

To date, few interventions have been developed to meet the needs of Latina women undergoing active treatment for breast cancer [12]. There is a critical need for culturally informed interventions designed to address the supportive care needs of Latina women in active treatment, particularly for primarily Spanish-speaking women [3]. Given the high rates of internet and smartphone use documented among US Latinos [13], electronic health–based interventions may capitalize on opportunities to provide scalable resources to Latinas undergoing active treatment while limiting participant burden [14-17].

In light of the limited technology-assisted interventions specifically designed for Latina women undergoing active treatment for breast cancer, more studies are needed to establish the feasibility of smartphone-based interventions for Latinas during active cancer treatment [12]. In response to the feedback from our participants enrolled in the *My Guide* pilot study and the dearth of literature regarding interventions for Latina breast cancer patients actively undergoing treatment, we have developed *My Guide for Breast Cancer Treatment*. The purpose of this paper is to describe the procedures and methods of this follow-up intervention. Guided by Bowen et al's conceptual model of feasibility studies [18], we describe the plans for conducting a multisite, randomized controlled trial (RCT) to establish the feasibility of *My Guide for Breast Cancer Treatment* for Latina women undergoing breast cancer treatment.

Methods

Hypotheses

We hypothesize that Latina women will find *My Guide for Breast Cancer Treatment* feasible for accessing information related to breast cancer and its treatment and for learning strategies to improve symptom management, self-efficacy, communication, and stress. We also hypothesize that women randomized to the *My Guide for Breast Cancer Treatment* app will have better primary outcomes (ie, HRQoL) and secondary outcomes (ie, symptom burden, anxiety, depressive symptoms, and distress) than women randomized to an enhanced usual care control condition.

Study Design

This RCT is designed to assess the preliminary feasibility and efficacy of the *My Guide for Breast Cancer Treatment* smartphone app for improving HRQoL and symptom burden in Latina women receiving treatment for primary breast cancer. After providing informed consent, participants will be randomized to the *My Guide for Breast Cancer Treatment* intervention condition or to the enhanced usual care control condition. Randomization will be stratified by recruitment site and language (ie, English and Spanish). Participants randomized to the *My Guide for Breast Cancer Treatment* intervention condition will have access to the smartphone app for 12 weeks and will be encouraged to use the app for 1.5 hours each week. The *My Guide for Breast Cancer Treatment* app is accessible on all smartphones (eg, Apple and Samsung) as well as tablets and computer websites. It is available in both English and Spanish, and participants will be provided the app in their preferred language. Participants randomized to the *My Guide for Breast Cancer Treatment* intervention condition will be oriented to the app and instructed to use it for 1.5 hours each week for a duration of 12 weeks. A 12-week intervention timeframe was selected based on previous studies indicating benefits in HRQoL and symptom burden outcomes after 10 weeks of behavioral interventions and the expected length of adjuvant treatments [19-21]. Thus, we believe that 12 weeks will allow sufficient time for participants to access and benefit from the *My Guide for Breast Cancer Treatment* app content. Intervention participants will also be assigned a bilingual telecoach for the duration of the study. Using a stepped-care approach [22], intervention participants will receive weekly telecoaching calls based on their level of adherence to the recommended app usage.

Study outcomes and intervention targets will be measured at study enrollment and before randomization (T1), 6 weeks postbaseline (T2), and 12 weeks postbaseline (T3). All assessment time points will consist of measures assessing our primary outcomes, intervention targets, and secondary outcomes. In addition, all participants will complete a sociodemographic questionnaire at T1, and participants randomized to the intervention condition will be asked to complete an exit survey at T3. Assessments are estimated to take approximately 35 min to complete. Participants randomized to the intervention condition will also be asked to complete brief, 3-min, weekly questionnaires throughout the course of the 12-week

intervention. See section *Data Collection and Outcomes* for greater detail. Participants will be compensated US $100 for their participation in the study and receive partial reimbursement for telephone data usage plans. Participants without an internet-enabled device will be provided one for the duration of the study. All study procedures and assessments have been approved by the institutional review board (IRB) of record for this multisite study (Northwestern IRB).

Participants

Participants will be 60 Latina women who have been diagnosed with stage I-IIIA breast cancer, have completed surgery (eg, mastectomy and lumpectomy), and are actively receiving adjuvant treatment for breast cancer (eg, chemotherapy, radiation, and biologic therapy). We will enroll participants from the Robert H. Lurie Comprehensive Cancer Center at Northwestern Memorial Hospital, the University of Illinois Health System, and various community-based support groups sponsored by ALAS-WINGS, a Chicago-based nonprofit organization for Latina breast cancer patients.

Eligibility

We will identify participants through screening of the electronic medical record (EMR), and final determinations for study eligibility will be made based on a self-report questionnaire via telephone interview. To be included in the study, participants must (1) be female, because male breast cancer patients represent less than 1% of the breast cancer cases; (2) have a diagnosis of stage I-IIIA breast cancer; (3) have completed surgery for breast cancer; (4) be within any timepoint of the adjuvant treatment trajectory for breast cancer (eg, chemotherapy, radiation, surgery, and biologic therapy); (5) be at least 18 years of age; (6) be able to speak and read English or Spanish; (7) be able to provide informed consent; and (8) self-identify as Hispanic/Latina ethnicity. Participants will be excluded from the study if they (1) have a hearing, motor, visual, or voice impairment that would preclude completion of study procedures; (2) have been diagnosed with a psychotic disorder, bipolar disorder, dissociative disorder, or any other diagnosis for which study participation would be inappropriate or dangerous; (3) endorse suicidal ideation, plan, or intent; (4) endorse illicit substance or alcohol dependence; or (5) have been diagnosed with dementia. Patients with metastatic disease will not be included in this study, as they have more extensive treatment regimens and substantially different needs relative to patients with earlier stages of breast cancer.

Randomization

Eligible participants who provide informed consent will be individually randomized using a 1:1 ratio to either the intervention condition (*My Guide for Breast Cancer Treatment*) or the control condition (enhanced usual care) for a total of 3 months.

Study Conditions and Delivery

My Guide for Breast Cancer Treatment Development and Content

My Guide was initially designed to improve HRQoL and reduce symptom burden among Latina BCSs (ie, BCSs who have completed active treatment) [10]. *My Guide for Breast Cancer Treatment* has been adapted from *My Guide* to expand its reach to Latina women in active treatment for breast cancer. The *My Guide* app incorporates elements in the published literature on symptom management in breast cancer literature and investigators with ample clinical expertise and experience conducting behavioral and symptom management research with Hispanic BCSs. The content for both iterations of the intervention were informed by models of stress and coping, cognitive behavioral stress management [23-25], the extant literature related to psychosocial adaptation to breast cancer [26-28], and studies evaluating these models and skills among Latina BCSs [8,9,26,27,29-31]. *My Guide* and *My Guide for Breast Cancer Treatment* are culturally informed by Latina values and beliefs including familism, fatalism, external locus of control, and culturally shaped gender roles (ie, Machismo and Marianismo) [30,32,33]. In addition, they both address challenges that may disproportionally affect Latina women, such as language barriers and concerns related to citizenship. In addition, to address low literacy concerns, all the intervention content is accessible through an audio format that is embedded within each app.

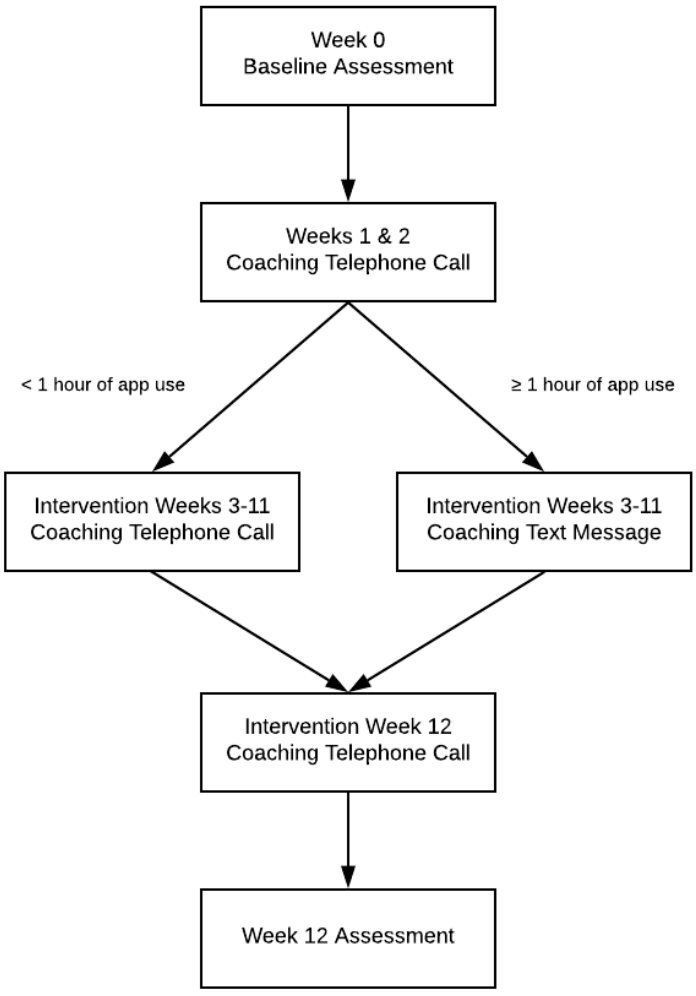
My Guide for Breast Cancer Treatment expands the scope and focus of the intervention by including additional content specifically for women in active treatment. In addition, *My Guide for Breast Cancer Treatment* includes content related to diet, physical activity, and general health information for breast cancer patients. The *My Guide for Breast Cancer Treatment* intervention content is organized into 6 modules as described in Table 1, which include content related to breast cancer education (eg, disease-related information and common breast cancer treatments); common physical, psychological, and emotional symptoms women may experience during and after breast cancer treatment; changes to daily life (eg, responsibilities at work and home and relationships with close family and friends); and local community resources for Latinas with breast cancer. In addition, for easy reference, videos and audio recordings from all the sections are listed and organized by topic in the last module (*Listen and Learn*).

All intervention participants will be assigned a trained, bilingual telecoach who will provide telecoaching using a stepped-care approach (Figure 1) to enhance adherence to the recommended *My Guide for Breast Cancer Treatment* app usage. In a given week, participants who use the app for less than 1 hour will be considered nonadherent to the recommended app usage and will receive a telecoaching call. Participants who use the app for 1 hour or more will be considered adherent to the recommended usage and will not receive a telecoaching call. Rather, adherent participants will receive a reinforcing SMS text message. The 1-hour cut-off was based on data from the previous *My Guide* trial for cancer survivors in which participants' average use of the study app exceeded 1 hour per week [10].

Table 1. *My Guide for Breast Cancer Treatment* main content modules.

Module	Description of information provided	Examples
Managing My Symptoms	Common physical and psychological symptoms patients experience during and after cancer treatment	Nausea and vomiting, fatigue, lymphedema, sadness, worry
Managing My Emotions	Emotions commonly experienced during and after cancer treatment	Anger, anxiety, sadness/depression; improving thoughts and feelings; expressing your feelings
Understanding Your Breast Cancer	Breast cancer, adjuvant cancer treatments and related side effects	Breast cancer and treatments overview; following doctor recommendations
Living Well After Treatment	Maintaining a healthy lifestyle during treatment	Diet and physical activity content specific for patients with cancer
Friends and Family	Changes in roles and responsibilities at home and work, relationships with family and friends, and daily activities during and after cancer treatment	Changes to relationships, sexual/intimacy, and at work; advice for singles; talking to your doctor
Community and Everyday Support	Local community organizations and resources for Latinas in the Chicagoland area for additional support	Spanish support groups, transportation assistance, financial assistance

Figure 1. Telecoaching stepped-care protocol.



The telecoaching calls will be brief (15 min) and focus on encouraging adherence to *My Guide for Breast Cancer Treatment* using the principles of motivational interviewing [34]. During the first call, participants will complete a decisional balance exercise with their telecoach to identify and address potential ambivalence about using the app for the recommended time. Guided by the telecoach, participants will set weekly goals regarding their app usage for the upcoming week, which will be reviewed in subsequent telecoaching calls. A central topic of the telecoaching calls will be barriers and facilitators to app usage, allowing telecoaches to problem solve with participants and set future app usage goals. Importantly, the goal of telecoaching calls is not to deliver intervention content but rather to facilitate adherence to the *My Guide for Breast Cancer Treatment* app.

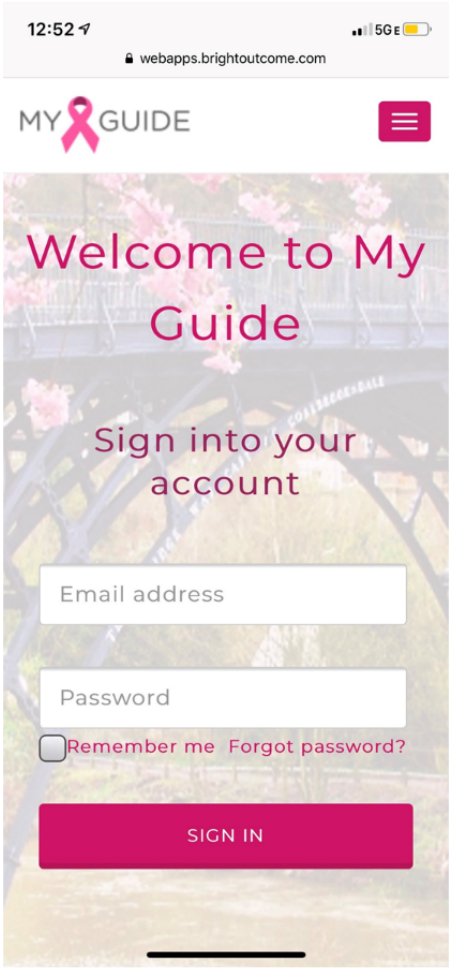
All telecoaches will receive training in motivational interviewing and goal setting with a particular focus on sensitivity to issues relevant for Latina women (eg, cultural beliefs that may influence coping and health behaviors). Telecoaches will have access to participants' app usage through a study administrative site. All telecoaching calls will be audio-recorded, and approximately 20% of the telecoaching calls will be reviewed weekly in supervision with a licensed clinical psychologist to monitor intervention fidelity.

One of the most significant additions to the intervention app is that *My Guide for Breast Cancer Treatment* will be individually tailored to each participant's self-reported primary concerns/symptoms. Upon randomization, participants in the intervention condition will complete a questionnaire based on the MD Anderson Symptom Inventory [35] to assess for common breast cancer and breast cancer treatment–related concerns, complaints, and symptoms. *My Guide for Breast Cancer Treatment* will then organize the app presentation such that content related to each participant's 3 to 5 top-rated concerns/symptoms are most easily accessible in a separate tab titled "Just for Me." Participants will complete this questionnaire every 2 weeks, with subsequent content-related changes made to their "Just for Me" tab. As tailored information is added to this tab, the most recent additions will appear at the top of this tab, and older content will move to the bottom. Notably, participants will still have access to all of the intervention content. However, this adaptive feature will help participants focus on and prioritize their primary concerns and needs.

Each week participants will be incrementally rewarded/reinforced for the time spent using the *My Guide for Breast Cancer Treatment* app. Gamification is use of game-design elements to engage and motivate individuals to achieve a goal [18]. Although the gamification features are becoming increasingly popular in behavioral and medical interventions, only a few studies have demonstrated their potential effectiveness [36-38]. *My Guide for Breast Cancer Treatment* contains 3 levels of virtual reinforcement in a given week. Participants may receive a virtual ribbon after completing 30 min of app use, a virtual medal after completing 45 min of app use, and a virtual trophy after completing 60 min of app use. Therefore, participants who use the app for a full hour each week for the length of the study can receive a total of 12 ribbons, 12 medals, and 12 trophies [39].

The smartphone app for the *My Guide for Breast Cancer Treatment* intervention condition is currently in development with Bright Outcomes Company (see Figure 2).

Figure 2. Screenshot of the *My Guide* smartphone app.



Participants will be able to securely log in to the app, and participant usage and engagement with video/audio features will be captured and sent to a secure and Health Insurance Portability and Accountability Act–compliant medical school server housed at Bright Outcomes. Security measures to protect privacy threats associated with users' computers and devices include the following measures: users are automatically logged out of intervention and assessment tools after 20 min of inactivity; any data stored locally are automatically encrypted based on the user authentication information and cannot be accessed without this information; all information collected by the app will be immediately transmitted to the secure server; and no app data will be saved to the phone's memory.

Participants randomized to the enhanced usual care control condition will receive care as usual and printed educational materials from the National Cancer Institute related to breast cancer and survivorship [40], patient education in either English or Spanish, as well as a list of Chicago-based supportive care resources and organizations. They will not receive a smartphone app or telecoaching during the study. Participants randomized to the control condition will be given access to the *My Guide for Breast Cancer Treatment* app after completing the T3 assessment, a period of 3 months.

Data Collection and Outcomes

Consistent with past research, the feasibility of *My Guide for Breast Cancer Treatment* intervention will be evaluated by assessing the acceptability and demand of the app [18]. Acceptability of the app will be assessed at T3 using a previously tested app satisfaction questionnaire [20] that measures the usefulness, satisfaction, learnability, and usability of *My Guide for Breast Cancer Treatment*. Above average scores will be considered acceptable. Demand will be measured with study recruitment, retention, and participant use of *My Guide for Breast Cancer Treatment* (eg, frequency of log-ins, time spent using the app, and content accessed). Recruitment and retention rates of 70% or more will be considered acceptable based on our prior work and published studies [20,41,42].

All measures will be administered in each participant's preferred language. For assessments completed in Spanish, we will use measures that have either been previously translated to Spanish and validated or measures that were translated to Spanish for this study by IRB-approved translators.

Participants will complete a self-report sociodemographic questionnaire at T1 including questions related to age, racial background, Latina ancestry, income, employment, relationship status, educational attainment, years living in the United States, and subjective social status using the MacArthur scale [43]. Participants will self-report clinical information including time since breast cancer diagnosis and surgery, stage of diagnosis, type of surgery, current treatment regimen (eg, chemotherapy and radiation), additional medications, medical comorbidities (assessed using the Charlson Comorbidity Index [44]), and past or current psychiatric diagnoses. Financial toxicity will be measured using Comprehensive Score for financial Toxicity-Functional Assessment of Chronic Illness Therapy [45]. All self-reported medical- and disease-related information will be verified via medical chart review.

Health-Related Quality of Life

At T1 to T3, participants will complete the Functional Assessment of Cancer Therapy-Breast (FACT-B). The FACT-B has been extensively used among breast cancer patients [46,47] and measures physical, emotional, social, and functional well-being, as well as breast cancer–related concerns over the past 7 days using a 5-point response scale [46]. Participants randomized to the *My Guide for Breast Cancer Treatment* intervention condition will also complete the rapid version of the Functional Assessment of Cancer Therapy-General (FACT-G7) on their smartphones every week throughout the 12-week intervention. The FACT-G7 assesses the most prominent HRQoL concerns among cancer patients and is both valid and reliable [48]. The FACT-G7 takes approximately 5 min to complete and is therefore an ideal brief measure of HRQoL to include in a smartphone-delivered intervention.

Symptom Burden

At T1 to T3, participants will complete the Breast Cancer Prevention Trial (BCPT) symptom questionnaire. The BCPT is a 25-item questionnaire that asks participants to use a 5-point response scale to rate their level of discomfort with common breast cancer–related symptoms during the past 4 weeks [49].

Anxiety and Depression

Anxiety and depressive symptoms will be measured at T1 to T3 using the Patient-Reported Outcomes Measurement Information System (PROMIS) [50,51] via brief computer adaptive tests (CATs). With CATs, participants' responses guide the system's choice of subsequent items from a bank of 29 items for anxiety and 28 items for depression.

Fear of Cancer Recurrence

At T1 to T3, participants will complete the Concerns About Recurrence Scale to assess fears about breast cancer recurrence [52]. Items address numerous life domains that could be impacted by a breast cancer recurrence, such as physical health and relationships. Participants are asked to use a 5-point response scale to indicate the extent to which they felt threatened by a recurrence in each domain.

Physical Activity

Physical activity will be measured at T1 to T3 using the International Physical Activity Questionnaire (IPAQ)-short form [53,54]. This measure consists of 7 items that assess physical activity over the past 7 days, and participants record the number of days per week or minutes per day spent doing specific activities. Previous reviews have demonstrated that the IPAQ-short form has high reliability [55,56], and the test-retest reliability of the questionnaire was at an acceptable level [55].

Dietary Intake

Dietary intake will be measured at T1 to T3 using the Brief Dietary Assessment Tool for Latinas [57]. This screening tool assesses fruit, vegetable, and fat intake over the past month.

Self-Efficacy

A total of 3 self-report questionnaires will be used to measure cancer-relevant self-efficacy at T1 to T3. First, the Communication and Attitudinal Self-Efficacy scale for cancer

(CASE-cancer) is a psychometrically valid 12-item measure. A total of 2 CASE-cancer subscales will be used to assess a person with cancer's self-efficacy in communication and information seeking [58]. Participants rate their level of confidence related to 12 skills using a 4-point response scale. This measure has been previously used with Latina BCSs [58,59]. Second, the PROMIS Self-Efficacy for Managing Emotions CAT will be administered, which assesses a person's level of confidence to (1) manage symptoms of anger, anxiety, depression, disappointment, discouragement, frustration, and helplessness and (2) prevent symptoms from interfering with daily activities [60]. This measure has an item bank of 25 items. Finally, the 3-item "Assertiveness" scale from the Measure of Current Status will be used to assess a participant's degree of confidence about asking and expressing their needs [61].

Breast Cancer Treatment Knowledge

The Knowledge about Breast Cancer questionnaire will be used to assess knowledge related to treatment at T1 to T3. This scale consists of 16 true or false statements regarding general breast cancer knowledge. The average number of correct responses will be calculated. This questionnaire was previously tested with a large sample of Spanish-speaking Latina BCSs [62] and used in the initial *My Guide* pilot study [10].

Cancer-Specific Distress

The Impact of Events Scale will be used to assess cancer-specific distress at T1 to T3. This measure comprises 2 subscales assessing the frequency of intrusive thoughts and avoidance following a stressful event [63,64].

Analytic Plan

Descriptive statistics will be used to characterize the overall sample, each condition, and study acceptability and demand. To examine preliminary differences in feasibility between study conditions, we will use the chi-square test, Fisher exact test, and nonparametric Mann-Whitney *U* test for non-normal data, as appropriate. With 30 participants per study condition, there will be 80% power to detect approximately one-half SDs, assuming a 2-tailed test and a type I error rate of 5%. All power calculations were run using PROC POWER in SAS version 9.4.

For each study outcome, average changes from pre intervention to post intervention will be calculated via means (SD) and 95% CIs, and the mean changes within study condition will be converted to effect sizes. An analysis of covariance approach will be used to examine differences between the intervention and control conditions in follow-up scores, after adjusting for baseline score. Established cut-offs will also be referenced for clinically meaningful differences for the FACT-B and FACT-B subscales to identify ranges and patterns of changes in scores across conditions from baseline to follow-up.

Data Management

All study data will be managed and stored in Research Electronic Data Capture (REDCap), a secure Web-based research data management system hosted at Northwestern University. All IRB-approved research team members will have access to REDCap. REDCap will be used to organize EMR data and to administer all study questionnaires. The *My Guide for Breast Cancer Treatment* administrative interface will capture participants' app usage and weekly questionnaire data, which will be uploaded to REDCap to centralize all research information. Once all data are collected, the data will be imported into SPSS for data cleaning and analysis.

Results

Recruitment began in July 2019 and is expected to be completed by August 2020. We expect to submit study results for publication by fall 2020.

Discussion

Overview

The aim of the *My Guide for Breast Cancer Treatment* study is to improve HRQoL and reduce symptom burden among Latina women undergoing active treatment for breast cancer. To the best of our knowledge, this is the first bilingual, smartphone-based supportive care app for Latinas women with breast cancer in active treatment. Providing a supportive and behavioral intervention that focuses on cancer treatment education and self-management during active treatment has the potential to improve patient-reported outcomes and clinical outcomes during active treatment and into survivorship.

Compared with the first version of the *My Guide* smartphone app, our team implemented substantial changes in this version of the *My Guide for Breast Cancer Treatment* app. Adding an adaptive functionality offers *My Guide for Breast Cancer Treatment* users a more personalized approach to delivering the intervention content, and the addition of a gamification via virtual ribbons, medals, and trophies provides users with encouragement to sustain use of the app across the length of the study. Unlike our first *My Guide* study [10] that included a 2-month longitudinal trial, we have extended the time frame of this study to 3 months to accommodate the expected time frame during which our study participants will be receiving adjuvant treatment. These strategic changes make this version of the *My Guide for Breast Cancer Treatment* app and this study design better suited for women in active treatment.

Limitations

A few limitations of the study protocol warrant discussion. First, because the focus of this study is on breast cancer patients who are in active treatment, long-term cancer survivors will not be enrolled in this study, which limits study generalizability. In addition, women who are preparing for surgery will not be included in this study. However, *My Guide for Breast Cancer Treatment* does include a focus on the postsurgical recovery phase such as information related to postsurgical symptoms (eg, pain and lymphedema) and information related to reconstructive surgery.

Future Directions

There are several areas for future directions. If found feasible, future studies should establish the efficacy of *My Guide for Breast Cancer Treatment* across a nation-wide, heterogeneous sample of Latina women diagnosed with breast cancer. Currently, the *My Guide for Breast Cancer Treatment* app does

not include any social media aspects; the potential benefit of adding a social media component to *My Guide for Breast Cancer Treatment* may be another important direction for future iterations of the app. In addition, given the multiple components of this feasibility trial (ie, app, telecoaching, and SMS text messaging), another important future direction will be to disentangle the effects of each component of the intervention on study outcomes.

Findings from this second study of the *My Guide for Breast Cancer Treatment* app are expected to contribute to the literature by establishing the efficacy of a smartphone-delivered intervention to enhance self-management during breast cancer treatment for improving HRQoL and symptom burden among Latina patients. Given the technology-based delivery of this app, the *My Guide for Breast Cancer Treatment* app has the potential for nation-wide scalability and therefore can increase access to supportive care resources among Latina breast cancer patients.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the Chicago Cancer Health Equity Collaborative.
[PDF File (Adobe PDF File), 608 KB - resprot_v8i12e14339_app1.pdf]

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Abbreviations

BCS: breast cancer survivor
BCPT: Breast Cancer Prevention Trial
CASE-cancer: Communication and Attitudinal Self-Efficacy scale for cancer
CAT: computer adaptive test
EMR: electronic medical record
FACT-B: Functional Assessment of Cancer Therapy-Breast
FACT-G7: Functional Assessment of Cancer Therapy-General
HRQoL: health-related quality of life
IRB: institutional review board
IPAQ: International Physical Activity Questionnaire
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Improving Oral Health in Older Adults and People With Disabilities: Protocol for a Community-Based Clinical Trial (Good Oral Health)

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Abstract

Background: Low-income older adults experience disparities in oral health problems, including caries and periodontal disease, that can exacerbate already high levels of chronic and acute health problems. Behavioral interventions have been shown to improve oral health status but are typically administered in institutional rather than community settings. Furthermore, multiple simultaneous interventions at different levels in the locations where people live and work are likely to have more impact and sustainability than single interventions in clinical settings.

Objective: This paper outlines a protocol for conducting a bilingual 5-year community-based trial of a bilevel intervention that addresses community norms, beliefs, intentions, and practices to improve oral health hygiene of vulnerable older adults living in publicly subsidized housing. The intervention utilizes (1) a face-to-face counseling approach (adapted motivational interviewing [AMI]) and (2) resident-run oral health campaigns in study buildings.

Methods: The study's modified fractional factorial crossover design randomizes 6 matched buildings into 2 conditions: AMI followed by campaign (AB) and campaign followed by AMI (BA). The total intervention cycle is approximately 18 months in duration. The design compares the 2 interventions alone (T0-T1), and in different sequences (T1-T2), using a self-reported survey and clinical assessment to measure Plaque Score (PS) and Gingival Index (GI) as outcomes. A final timepoint (T3), 6 months post T2, assesses sustainability of each sequence. The intervention is based on the Fishbein integrated model that includes both individual and contextual modifiers, norms and social influence, beliefs, attitudes, efficacy, and intention as predictors of improvements in PS, GI, and oral health quality of life. The cognitive and behavioral domains in the intervention constitute the mechanisms through which the intervention should have a positive effect. They are tailored through the AMI and targeted to building populations through the peer-facilitated oral health campaigns. The sample size is 360, 180 in each condition, with an attrition rate of 25%. The study is funded by National Institute of Dental and Craniofacial Research (NIDCR) and has been reviewed by University of Connecticut and NIDCR institutional review boards and NIDCR's clinical trials review procedures.

Results: When compared against each other, the face-to-face intervention is expected to have greater positive effects on clinical outcomes and oral health quality of life through the mediators. When sequences are compared, the results may be similar but affected by different mediators. The arm consisting of the BA is expected to have better sustainability. The protocol's unique features include the comparative effectiveness crossover design; the introduction of new emotion-based mediators; the balancing of fidelity, tailoring, and targeting; and resident engagement in the intervention.

Conclusions: If successful, the evaluated interventions can be scaled up for implementation in other low-income congregate living and recreational settings with older adult collectives.

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KEYWORDS

oral health; elderly; oral hygiene; prevention; clinical trial; crossover design

Introduction

Older adults [1-7] and adults with disabilities [1] experience a high prevalence of tooth decay, periodontal disease, edentulism, unmet oral health treatment needs, and impaired oral health quality of life. Oral health is associated with systemic health problems [8] and chronic diseases of older adulthood. For example, declining cognitive function [9], dementia associated with serum *Porphyromonas gingivalis* (a causal pathogen for periodontitis), high immunoglobulin G [10], and xerostomia resulting from multiple medication use, cancer treatments, and diabetes are associated with poor oral hygiene, high levels of decay, tooth loss, and edentulism [11-13]. Periodontal disease is associated with heart attack and stroke [14-16], and periodontal treatment can improve control of diabetes mellitus [13]. In addition, poor oral health affects oral health quality of life [8].

There continue to be significant ethnic and racial, class, and medical disparities with respect to oral disease, oral health care, and oral health–related quality of life [7,17-19]. Oral health problems have a greater impact upon quality of life among older African Americans as compared with whites on every dimension and especially in psychological discomfort, pain, and functional limitations [7,20,21]. US and international bodies recognize the importance of addressing oral health through hygiene improvement [4,22] and Good Oral Health behavioral management [23-25]. There is general agreement that sustainable promotion of public health interventions requires a multilevel approach [26-29] and that multilevel approaches that include cognitive, social, behavioral, and norms change components are needed to reduce disparities in oral health and other systemic health conditions.

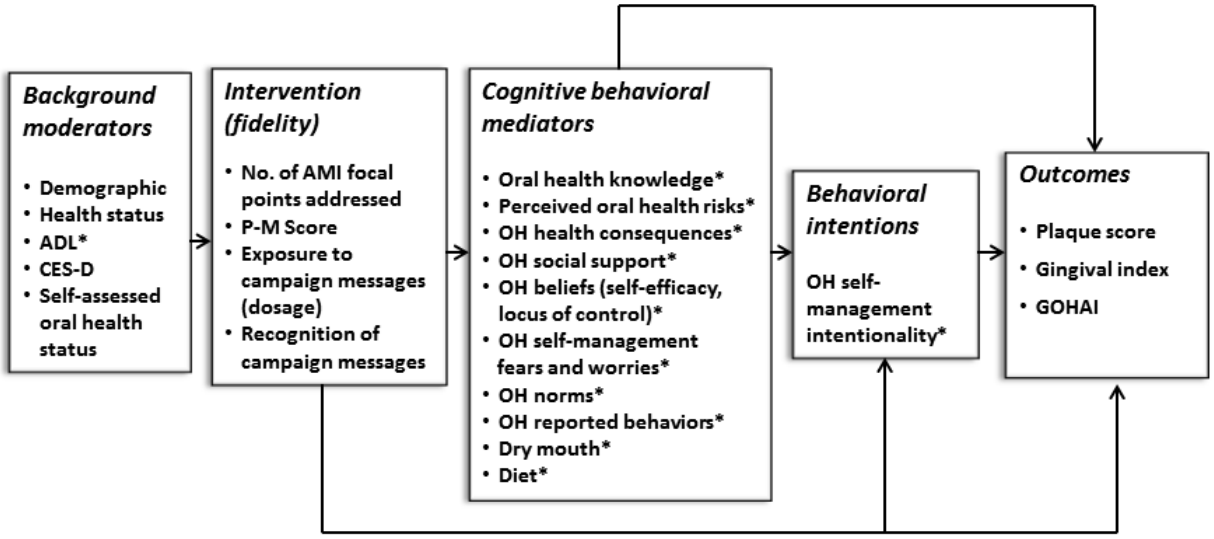
Improving oral health of older adults, especially low-income and racial and ethnic minority adults who also suffer from disproportionate rates of chronic diseases such as cardiovascular disease and diabetes, is a primary national and international priority [30]. The development of low-cost preventive interventions conducted in locations where older adults live can lead to potentially sustainable normative support for oral hygiene, locally tailored and targeted approaches, and ongoing positive changes in specific oral health practices (brushing, flossing, cleaning mouth and tongue, and cleaning dentures.). Such interventions can reduce short- and longer-term psychosocial and economic costs associated with debilitating oral health problems and may help to prevent exacerbation of chronic illness and disability.

The approach described in this protocol offers important innovations with respect to public health dentistry and preventive oral health interventions for older adults. Public health dentistry typically does not tackle multilevel approaches to community-based prevention, especially with older adults. The study protocol describes a bilevel approach in line with the recognition that multilevel interventions in public health have greater impact and sustainability than single interventions. Furthermore, it is based on a theoretical framework, the Fishbein integrated model (IM) supplemented by Bandura's notions of self-efficacy and practice to mastery [31-33]. This approach includes constructs or mechanisms of change that are operationalized at both the individual and the group levels to improve knowledge, build pro oral health norms, reinforce self-efficacy and intentionality to engage in oral health self-management, and increase behavioral skills.

The study uses adapted motivational interviewing (AMI), a more structured approach to motivational interviewing (MI) with individuals. MI has been found useful in individual level oral health and hygiene interventions with adults [34,35]. AMI offers a more appropriate approach to public health interventions with older adults and adults with disabilities because it is partially scripted in advance, thus standardizing the operationalization of IM's theoretical domains. The AMI intervention developed for this study tailors the intervention to individual needs [36].

This paper describes the study protocol for the community-based clinical trial entitled: Good Oral Health—*A Bilevel Intervention to Improve Oral Adult Oral Health.* The Good Oral Health study is a theoretically driven bilevel intervention to address oral hygiene self-management among older adults with limited resources, experiencing multiple health disparities (National Institute of Dental and Craniofacial Research [NIDCR] grant number DE24168). The study utilizes a crossover design to test a face-to-face counseling intervention against an interactive approach to change oral health norms and behaviors delivered through oral health fairs or campaigns. Both approaches target the same cognitive and behavioral domains as specified in the study's theoretical model (see Figure 1) [37]. Other unique features of the study design are its attention to fidelity of implementation plus tailoring and targeting to individuals and groups and the engagement of peer educators as partners in the intervention. The primary outcomes are clinical assessment of Plaque Score (PS) and Gingival Index (GI), both standard measures for evaluating oral health interventions [38,39]. A secondary outcome is perceived oral health quality of life [8,40]. There is evidence that cognitive behavioral interventions can improve GI and PS in low-income populations [41-43]. This study is expected to show the positive effects of such an intervention with an understudied low-income population of vulnerable older adults including those with disabilities who are residents of subsidized senior housing and experience significant oral health disparities. Multimedia Appendix 1 provides a summary of the study protocol.

Figure 1. Good Oral Health study theoretical framework. ADL: Activity of Daily Living; AMI: adapted motivational interviewing; CES-D: Center for Epidemiologic Studies Depression; GOHAI: General Oral Health Assessment Index. OH: oral health. * indicates AMI focal points and campaign messaging.



Methods

Study Design

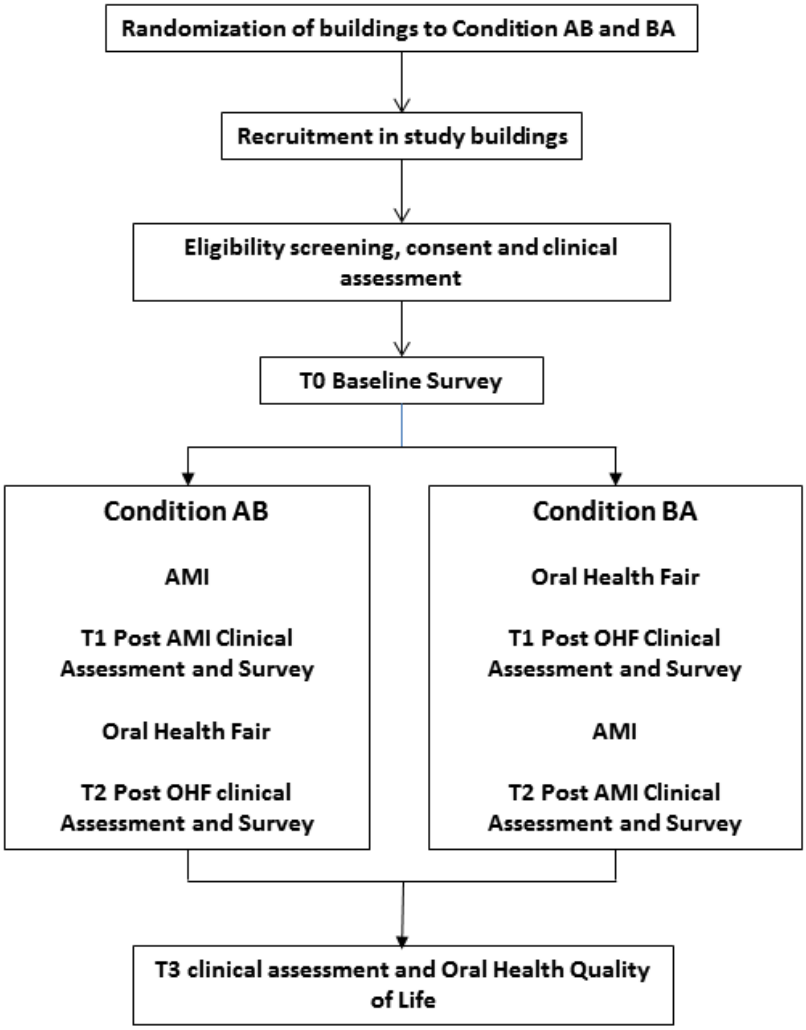
The study is based on a pilot intervention that evaluated the results of an individualized face-to-face AMI intervention combined with a resident-managed oral health campaign in one rent-subsided older adult building in central Connecticut [44]. The intervention was successful in improving gingival health and reducing plaque, but the relative impact of each of the intervention components could not be evaluated because they were held simultaneously. The clinical trial protocol is designed to disaggregate and compare the individual and combined effects of the face-to-face intervention and the oral health campaign using a modified fractional factorial crossover design [45]. The design allows for disaggregating a pilot study that combined 2 interventions (AMI and oral health campaign) with positive results to enable an evaluation of which of the 2 components would have the best effect. Sequencing (systematic recombining), an element of the modified fractional factorial design (MFFD) is an efficient way of determining whether one combination or another has a better immediate and long-term effect. The MFFD design avoids the cost of multiple sites and control groups. The intervention activities are linked to the conceptual domains in the adapted Fishbein model (see Figure 1).

The primary study aims are to evaluate the 2 main components of the intervention, the AMI and the oral health campaign, against each other and in different sequences and to assess the mechanisms (norms, beliefs, attitudes, intentions, and practice) through which the intervention operates at each time point.

The study hypotheses include the following: (1) the face-to-face intervention component of the overall intervention (AMI) will produce better short-term clinical outcomes and changes in mediators than the oral health campaign component; (2) the oral health campaign component followed by the individual component will produce better midterm and long-term clinical outcomes than the individual component followed by the oral health campaign; (3) the 2 sequences will result in differences in changes in the mediating cognitive domains at midterm; (4) within the face-to-face component, exposure to more mediating domains will result in better clinical outcomes; and (5) both conditions will have an equivalent effect on the secondary outcome—oral health quality of life at end point.

The study is a group randomized controlled trial (GRCT) in which 6 study buildings of between 125 and 375 apartment buildings housing independently living adults aged 62 years and older and people with disabilities are matched by size and randomized to one of 2 conditions (AMI followed by campaign [AB] and campaign followed by AMI [BA]), 3 buildings in each condition. In condition AB, the face-to-face intervention (A) precedes the oral health campaign (B) and in condition BA, the sequence is reversed. Buildings are selected based on size and geographic distance from one another; paired based on population age, ethnicity, and gender characteristics; and randomized by the study's biostatistician. The procedure is described in the study protocol, which can be found on the study website [46]. Prior network studies in similar buildings [47,48] indicate that there is little or no communication among residents across buildings, and residents do not move from building to another. Thus, the risk of contamination is low. However, those who do move from one study building or condition to another will be eliminated from the study. The intervention is administered in 3 cycles of 18 months each, 2 buildings per cycle, 1 from each condition. Measures are taken at baseline (T0), after the first intervention (T1), after the second intervention (T2), and 6 months post T2 (T3); T0-T1 measures assess the impact of one intervention against the other, T1-T2 measures assess the impact of both interventions in different sequence, and T2-T3 evaluates outcome sustainability (see Figure 2).

Figure 2. Good Oral Health study design. AB: adapted motivational interviewing followed by campaign; AMI: adapted motivational interviewing; BA: campaign followed by adapted motivational interviewing. OHF: oral health fair.



Study Site

The 6 study buildings are located in low-income areas of 3 Connecticut towns. The ethnic and racial composition of the population in these buildings consists of approximately 40% African American/Caribbean; 45% Latinos (mainly Puerto Ricans); and 10% to 15% other residents, mainly of European American or South/South East Asian origin. The rate of people with disabilities ranges from 15% to over 40%. To participate, buildings must have a common space and private locations for surveys and clinical assessments. Memoranda of agreements are signed with the managements of all buildings to guarantee participation and exempt building management from responsibility for any adverse intervention consequences. The study population speaks English, Spanish, or both. All materials used for recruiting, consenting, survey administration, and implementation of both intervention approaches are translated from English to Spanish and back translated to ensure that meaning in the 2 languages is preserved. Recruitment and all interventions are conducted in both languages or either language based on the participant's choice.

Study Participants and Sample Size

The study population includes 360 residents, approximately 60 from each building, totaling 180 in each condition. The expected attrition rate over 4 time points is 25%. The inclusion criteria include (1) being aged 18 years and older, (2) having permanent residence (6 months or more) in study buildings, (3) living without conservator, (4) judged competent to give informed consent by responding correctly to 5 simple questions about the study during the consent process, and (5) 2 or more natural teeth. The exclusion criteria include (1) being temporary or short-term building resident; (2) being under conservatorship, (3) cognitively unable to give informed consent or respond to 3 to 5 questions about the study, (4) being edentulous; (5) having a history of infective endocarditis, prosthetic cardiac valve replacement in past 6 months, or insertion of an arterial stent or myocardial infarction in past 6 weeks or being on dialysis. The study is approved annually by the University of Connecticut Health institutional review board (IRB) and by NIDCR and Rho consultants.

Study Recruitment

Recruitment takes place during the first 5 to 6 months of each 18-month intervention period in each cycle. Recruiters are bilingual and of diverse ethnic and racial backgrounds, matching the backgrounds and languages of most participants. Steps in recruitment include initial discussions with building management, tenant associations, or other internal administrative bodies; 2 formal presentations to building residents, followed by presence on site several times a week; and informal engagement with residents and hosting of informal events, gatherings, and refreshments in community rooms and on building floors throughout the recruitment period. Public events sponsored by the study are conducted in communal spaces that can accommodate individuals with disabilities or in wheelchairs.

Participants found to be eligible are contacted within 2 to 3 days for an appointment to obtain informed consent and to conduct the clinical assessment. At the appointment, they are rescreened, informed about the study, and written consent is obtained. Consent forms are read to participants in English or Spanish, regardless of reading ability. Participants who are unable to read give verbal consent, which is recorded by the consenter and witnessed by a second member of the study staff. The signatures of both are recorded on the form with the participant's name. Ineligible participants are invited to join an *oral health campaign* committee in their building.

Once consented, participants in the study are clinically assessed after which they are scheduled for a survey within the next 2 weeks. Retention is encouraged through continuous staff presence in the intervention buildings, phone calls and face-to-face reminders, home visits, casual encounters, flyers, face-to-face communication, and study-hosted social events such as bingo and ice cream socials throughout the study. These methods have been found to be useful for retention in prior studies on other health topics with similar populations in subsidized senior housing [29,44,49]. After completion of these steps, participants are engaged in scheduled one-on-one sessions (AMI) or for participation in oral health fairs, depending on the building. One month after having completed each of these interventions, participants complete a survey and clinical assessment (T1) and enter into the second phase of intervention. This is followed by a third survey and clinical assessment (T2) 1 month after completion of the second intervention. Furthermore, 5 to 6 months after the third evaluation point, participants receive a final clinical assessment and repeat the oral quality of life scale (T3).

Interventions

The 2 interventions are conducted orally and through demonstrations to accommodate those with limited literacy. Participation does not require the ability to read.

Condition 1 (Adapted Motivational Interviewing Followed by Campaign): Adapted Motivational Interviewing With Individual Participants

The individual-level intervention (AMI) is based on a successfully piloted 45-min adapted motivational interview protocol [44] administered in English or Spanish by trained African American and Latino interventionists. It takes place within 2 to 4 weeks after completing the most recent survey (baseline or T1 depending on the condition). AMI intervention tailoring is based on 5 key elements: (1) an initial focused conversation with the participant about issues of concern, (2) responses that are below the cutoff point on the 12 mediator domains in the study model (see Table 1), (3) a review of the plaque scoring sheet that illustrates each person's deposition of plaque to help target brushing, (4) a brushing flossing skills assessment using a typodont and videos on brushing and flossing, and (5) a written and signed plan of action. A formula determines whether a participant falls above or below a designated cutoff point for each domain. Any participant who falls below the cutoff point on any domain receives an intervention for that domain. The domain cutoffs for each participant are calculated based on the most current survey: in condition AB, they are calculated on the study baseline survey, and in condition BA, they are calculated on the T1 survey.

Cutoffs were developed during the pilot study by deciding whether domain mean scale scores or individual scale or index items were the best indicators of intervention need. These decisions are summarized in Table 1. A software formula calculates individual cutoffs and transfers the results to an Access data form that documents the AMI intervention. Facilitators use this form to prepare their intervention material by first identifying domains below the cutoff that require intervention followed by checking the survey results for those domains to identify specific items with incorrect responses. Domains and items that need attention are recorded on a *focal point checklist* for use in the intervention.

Table 1. Domain scales and cutoff scoring.

Domain	Scale description	Cutoff points
1. Activity of daily living	8 items with response categories 0 (no help needed); 1 and 2 help needed.	Need help on any of these
2. Oral health knowledge	7 items, true/false (Items in both scales are 4-point Likert scales from 1=strongly disagree to 4=strongly degree)	<5 correct
3b. Oral health self-efficacy	5 items	>Mean of items <3 (disagree and strongly disagree)
4b. Locus of control	7 items (only 1 considered for cutoff)	If response to single item was agree or strongly agree
3. Oral health norms: beliefs about importance of oral hygiene	9 items, Likert scale with 4=very important and 1=not at all important.	1 or 2 on any item (not at all important, not very important)
4. Oral health social support	4 options (Likert scale with 0=no and 1=yes)	If all sources are *0* (none)
5. Oral hygiene behaviors	6 options (Likert scale with 1=never and 6=more than twice a day)	Brushing: <2 times per day; flossing: <1 time per day
6. Perceived oral health risks	5 questions, 4-point Likert scale	Mean <3 (4=very unlikely, 3=unlikely, 2=likely, 1=very likely)
7. Self-management worries	23 questions, 4-point scale, 1=very and 4=to not at all	Mean <3 for scale (4=not at all, 3=not much)
8. Self-management fears	5 questions, 4-point Likert scale, 1=very to 4=not at all	Mean <3 (4=not at all, 3=not much)
9. Oral health self-management intentionality	10 items, 3-point Likert scale (0=no, 1=some, 2=good possibility)	Mean <1 (0=no possibility, 1=slight possibility)
10. Dry mouth	8 yes/no questions	Yes to at least one question
11. Diet	5 items, 5-point Likert scale from never to >5 times daily.	>2-3 times a day on any item
12. Plaque Score/Gingival Index	Range from 0 to maximum of approximately 192 for each.	Mandatory for All participants regardless of score.

To prepare for each AMI administration, the intervention facilitators create a file in advance, consisting of the completed intervention focal point check list, duplicates of a plan of action form, and the most recent clinical assessment showing the distribution of plaque.

The AMI is conducted in a private location in each building. Interventionists are required to address brushing and flossing and a minimum of 2 to 3 other cognitive or behavioral mediators. They record elements of the patient narrative in the Access data form and discuss each focal point with the participant using an interactive dialogue approach and referring to a standard script to correct misunderstandings, expand knowledge, and explore barriers to intention (knowledge, beliefs, and attitudes). To target brushing and flossing, interventionists show participants the results of their most recent plaque assessment and brief videos demonstrating techniques for brushing and flossing teeth. Participants then practice on a typodont and are scored for brushing, flossing, and denture cleaning techniques using a standardized skills assessment checklist, and scores are calculated from 1 to 4 for each (1=lowest, and 4=highest). The scoring is repeated until the participant achieves maximum improvement (practice to mastery), and the final score is recorded as a process evaluation data point. In the final step, interventionists review the discussion with the participant and help the participant to build a plan for addressing the main cognitive domains that impede their own oral health self-management and improving oral health hygiene behavior. Participants receive a copy of their plan, and a duplicate is kept in the file along with the focal point checklist, the Access focal points and PS data sheets and the skills assessment scored sheet. AMI administrations are audio recorded as a quality check with consent. Tailoring is accomplished through directing interventionist comments to the concerns raised in the participant's opening narrative and the specific domains that require attention because of their low scores.

Fidelity to the AMI protocol is achieved through annual trainings, observation, and feedback on AMI delivery in each cycle. All AMI sessions are audio recorded with permission of the participant, and 10% of the recorded sessions are reviewed in every cycle in English and Spanish. Research charts are reviewed before filing to ensure case documentation such as recording cutoff domains, referral to a general study-approved script to address the domains, maintaining a hard copy and digital records of participant responses to domain-related discussions, participant concerns, and the participant plan. Furthermore, 10% of the research charts are reviewed every 6 months to ensure that intervention forms are complete.

Condition 2: Resident-Assisted Oral Health Campaign

The oral health campaign consists of 3 oral health fairs co-organized by a trained volunteer team of building residents (the campaign committee) that collaborates with bilingual study interventionists. The campaign protocol is based on the IM cognitive behavioral theory that guides the study, and processes derived from communications theory [50,51]. It is modeled

after other tailored/targeted theoretically based large-scale communication interventions, scaled to fit the constraints of public housing settings. The local campaign model utilizes a group norms approach that relies on the social influence of a collective of motivators (in this case, residents and members of the intervention staff) [40] rather than a peer led diffusion-of-information model [52]. With this approach, recruits may be, but do not have to be identified as peer or opinion leaders to be included. Each committee consists of approximately 6 to 8 members, all screened ineligible for the study.

Efforts are made to attract both men and women representing the general pattern of diversity in each building for the campaign committee. As contributing participants in the study, they are asked to sign the IRB-approved consent forms agreeing to their participation as committee members. A small gift certificate and certificate of accomplishment are given to each committee member at the end of the campaign sequence in a public setting.

Committee members undergo a 12-session training program (see Table 2) of approximately 1.5 hours each, and makeups are possible for members who have missed a session. The curriculum is available on the study website [46]. The study staff provides refreshments at each session. Subsequently, staff and campaign committee members work together to organize and staff tables at each campaign event, representing each of the 12 domain messages.

Table 2. Oral health campaign curriculum.

Sessions	Description
Session 1	Orientation and group identity
Sessions 2-3	Introduction to Good Oral Health campaign; protecting and respecting other residents
Sessions 4-5	Learning about oral health and hygiene self-management; creating a campaign event schedule
Sessions 6-7	Creating an oral health campaign plan
Sessions 8-9	Developing theoretically based materials and messages
Session 10	Preparing and practicing for campaign event
Session 11	Finalizing campaign posters
Session 12	Finalizing and practicing campaign roles and activities (including scripts for facilitating discussion at session tables, welcome station, passport administration, and signup sheets

All residents in each building are invited to each of the campaigns, and they sign in at the door. Each attendee receives a passport that includes a space to check their presence at each message table. The passport records their name and exposure to and evaluation of each table visited. These data are entered into a computer database and provide (1) overall attendance of enrolled participants at each of 3 sessions, (2) unenrolled participants who attend each session (reach), (3) dosage (number of tables each participant visits at each campaign), and (4) whether they liked or did not like their experience at the table (acceptability). Passports of participants are placed in their research charts.

All oral health fairs are required to include the following:

1. Bilingual message tables, 1 per theoretical domain, with messages, games, activities, and/or handouts staffed with bilingual study staff and at least one campaign member.
2. A 15- to 30-min bilingual presentation by the dental hygienists on general issues of importance in oral health and hygiene maintenance.
3. A question-and-answer period in which members of the audience can raise questions with the speakers on any topic related to oral health in the language of their choice.

Resident members of the Campaign Committee and research staff are stationed at each domain table designed to foster discussions with each participant based on their questions, issues, and concerns related to the domain assigned to the table (eg, diet, worries about self-management, perceived risks associated with poor oral health, brushing, and flossing). These activities are followed by snacks, music, and prizes.

Sample Size and Power

Sample size calculations were based on the primary outcomes of continuous measures of GI and PS using estimates of effect and variation from a pilot grant. The MFFD design has 2 sequences (AB and BA) and 2 periods (1 and 2). Power was based on the first period, which conceptually can be considered a 2-arm parallel design with cluster randomization at the building level. Assuming a typical intraclass correlation in the range of 0.01 or 0.02, a design with 6 clusters of n of 56 for each condition would have effective sample sizes of approximately 160 to 220, respectively [53]. With n of 153 per group, our study has more than 95% power to detect a priori identified clinically meaningful mean differences.

Measures

The study evaluation design includes intervention moderators, mediators, process variables, and outcome measures. All alpha coefficients are from the study's baseline data.

Primary Outcomes (Clinical Assessments)

The primary outcomes are obtained through clinical assessments of oral hygiene status. The PS is a plaque scoring scheme developed by O'Leary et al [38] consisting of dichotomous presence or absence scores for bacterial plaque on each of 6 tooth surfaces using erythrosine disclosing solution. The nontoxic vegetable-based solution is applied to the teeth by the examining hygienist. The number of surfaces stained red is

calculated over the total number of surfaces, and PS is expressed as a percentage of surfaces with plaque or a ratio. The GI [39] assesses the gingival status related to 6 surfaces of each tooth. Each surface is scored for gingival inflammation: 0=no visual signs of inflammation, 1=slight change in color and texture of the gingiva but no bleeding, 2=visual sign of inflammation and bleeding upon swiping, and 3=overt inflammation and spontaneous bleeding. The index is calculated by summing each surface GI and dividing by the total number of surfaces (mean value). Individual scores are summed to obtain a mean.

Secondary Outcome Measure

The *General Oral Health Assessment Index* (GOHAI) measures oral health quality of life. A commonly used 12-item measure, it was initially developed for older adults and has been used with low-income populations [54]. Responses for each statement are Likert scales ranging from 0 (always) to 4 (never); 3 items are reversed coded. Response codes are summed across the 12 statements to give a 0 to 48 overall score (Cronbach alpha coefficient=.801).

Intervention Mediators

Oral Health Knowledge

Oral health knowledge is a 7-item true/false test based on a previously developed knowledge test used with low-income older African Americans [55] (Cronbach alpha coefficient=.66).

Perceived Oral Health Risks

Perceived oral health risks consists of 5 questions asking about the chances of getting cavities, cancer, toothache, gum problems, and hospitalization because of an oral health problem, on a 4-point scale from very unlikely (4) to very likely (1; Cronbach alpha coefficient=.761).

Oral Health Social Support

Oral health social support is assessed with 2 questions developed in the pilot study [44]:

1. Who do you go to for health information in this building (check all that apply)? The responses are no one, other residents, building management, and people who come to provide services in the building. The scores range from 0 to 4.
2. How many residents do you talk to if you need information about health problems and how to handle them, not counting the building managers or others who work there? The responses are no one, 1 to 2, 3 to 4, and 5 or more. The scores range from 0 to 3.

Oral Health Beliefs

Oral health beliefs include 2 subscales of the Dental Coping Beliefs Scale [56-58]; *Self-efficacy* and *Locus of Control*. The *Self-efficacy* scale consists of 5 items, and *Locus of Control* is measured with 7 items Responses to items for both subscales are 4-point Likder scales ranging from strongly agree (4) to strongly disagree (1) adapted from the study by Sherer et al [59]. Self-efficacy scores range from 5 to 20, with higher scores indicating higher self-efficacy (Cronbach alpha coefficient=.603). Locus of control scores range from 7 to 28, with higher scores indicating lower external locus of control (Cronbach alpha coefficient=.72).

Oral Health Self-Management Fears and Worries

These are 2 new scales that include items identified by residents in focus groups, related to the topic. Both scales were piloted with good results during the pilot study phase (Oral Health Self-Management worries: Cronbach alpha coefficient=.90; Oral Health Self-Management fears: Cronbach alpha coefficient=.75). The *Oral Health Self-Management Worries Scale* consists of 23 items focused on worry or embarrassment related to taking care of teeth, mouth, and dentures. Approximately one-third of the study population overall has dentures. Responses are on a 4-point scale ranging from (1) very worried to (4) not at all worried. Scores range from 23 to 92, with higher scores indicating less concern (Cronbach alpha coefficient=.91). The *Oral Health Self-Management Fears scale* consists of 4 items about fears of the health consequences of not caring for teeth and gums. Items are assessed on a 4-point scale from (1) very to (4) not at all. Scores range from 4 to 16, with higher scores indicating less fear (Cronbach alpha coefficient=.82).

Oral Health Norms

Oral health norms (perceived importance of actions) is measured with a 9-item scale that assesses the perceived importance of oral hygiene behavior from (very important 4) to not important at all (1; Cronbach alpha coefficient=.688).

Oral Health-Reported Behaviors

Questions on frequency of brushing teeth, flossing teeth, and cleaning dentures. Responses to each are never (0), once a week (1), a few times a week (2), once a day (3), twice a day (4), and more than twice a day (5).

Oral Health Self-Management Intentionality

It uses the protocol described by Ajzen and Fishbein [60] and Tedesco et al [61,62], adapted for the clinical trial based on pilot data. Participants rate the possibility (likelihood) of performing 10 oral health behaviors on a 3-point Likert scale (0=no possibility to 2=good possibility).

Dry Mouth

It is an index consisting of 8 questions with yes/no responses related to indicators of dry mouth adapted from a study by Gerdin et al [63]. Responses are yes (1) and no (0).

Sugar Intake

It is an index that consists of 5 questions related to the consumption of sweet or starchy foods with responses including never (0), once in a day (1), 2 to 3 times a day (2), 4 to 5 times a day (3), and more than 5 times a day (4; Cronbach's alpha coefficient=.619).

Intervention Process Variables

Intervention process variables include the number of focal points addressed in the intervention based on the total number of scores below the cutoff points for main cognitive and behavioral domains measured and addressed in the intervention; exposure to norms-based campaign measured with dosage (record of presence at event); and survey questions that record post

exposure recognition of campaign messages including recalled participation in fairs, recognition of logos and messages, and perceived impact of fairs on self-management.

Additional Measures

Demographic Background Information

Items include age, gender, building, length of time in building, length of time in United States, marital status, race and ethnicity, current living arrangement, times moved in the past year, work status, religious engagement, income and income satisfaction, language use, telephone, transportation availability, home care, and health/dental health insurance.

Activity of Daily Living

Activities of daily living (ADLs) is a widely used measure of the physical functioning status of an individual. It consists of 8 behaviors that indicate ability to take care of personal basic needs [64,65]. The responses are 0 (no help), 1 (need some help), and 2 (unable to do activity even with help).

Center for Epidemiologic Studies Depression Scale Short-Form

Center for Epidemiologic Studies Depression (CES-D) Scale Short-Form is a 10-item short version of the CES-D screening instrument that measures depressive symptoms in community populations. The Spanish version of the 10-item CES-D has been validated for use with Puerto Rican older adults and used in several studies of older adults, including senior residents of public housing in the study area [66-68]. Responses are no=0, yes=1 and scores range from 0 to 10, with a higher score indicating more symptoms of depression (Cronbach alpha coefficient=.631).

Health Status

It consists of two indices: (1) an index assessing current health status based [66] on self-reported diagnosis of 13 physical health problems common in older adults and (2) an index of physical health distress based on whether each physical problem is perceived as preventing normal participation in daily activities. Responses are yes/no to each item. Responses are summed for each variable.

Self-Assessed Oral Health Status

It is a single 4-point Likert scale of subjective oral health status [40], ranging from poor (1) to excellent (4).

Data Management and Quality Checks

All survey data are collected using the Questionnaire Development System (QDS) [69] software and face-to-face administration. Once the interviewer or other field team member realizes a potential data entry error, immediately after the interview, he or she will notify the data manager to double check the entered responses and will correct any error in QDS Data Warehouse. The data manager may also identify key variable entry errors during the data management process. All changes are automatically documented and tracked for quality control. The data are uploaded into QDS Warehouse in batches and cleaned and amalgamated into a data analysis database for each cycle. In addition, 3 separate databases collect all participant tracking and intervention and clinical assessment data. These data are converted to a spreadsheet and merged into the master data analysis survey database by cycle. Data files for the 4 time points are integrated first for T0-T1, then for T0-T1-T2, and finally for T0-T3 to allow for longitudinal short, intermediate, and long-term analyses. AMI intervention data quality is checked by reviewing the first 5 files and an additional 5 files chosen randomly per cycle in hard copy and audio files in English and Spanish. Survey quality checks are conducted every 6 months to review missing data or errors in entry. Records are kept of any changes in data analysis files related to routine cleaning, and additional records are kept for variable recodes, new variable construction, and outliers during the analysis of the baseline data and subsequent time points.

Data Analysis

A comprehensive statistical plan addresses the modified fractional factorial crossover design. The usual inspection for outliers and influential data points is conducted along with summary statistics and evaluations of distributions of the data. In the case of nonnormal data, we use standard transformations (eg, log transformations) or explore alternatives (eg, nonparametric approaches or other distributions such as Poisson) or create categorical or nominal variables.

For period 1, the parallel-arm phase, standard approaches for a parallel 2-arm randomized study are conducted for the first period of the sequence, across all buildings. This analysis allows direct comparison of the AMI versus the campaign approach for clinical outcomes (study hypothesis 1). For periods 1 and 2, assessing sequence of interventions, study hypothesis 2, which sequence gives better clinical outcomes, are addressed using repeated-measures models. Depending on whether the outcome is continuous or dichotomous, we will use general linear mixed models or general estimating equations to fit a model with intervention and period effects using the MIXED procedure in SAS. Each set of measures from the same person (eg, gingival outcomes) is treated as a correlated cluster of data. An auto-correlation structure of 1 is likely to be appropriate. Customized contrasts can be constructed to make comparisons between time points. Time-varying covariates can be used in these models, and some missing data (under missing at random or missing completely at random assumptions where applicable) are allowable.

For baseline and health status variables, as this study randomizes at the level of site and individuals are not randomized, we will stratify some results (or adjust in models) for demographics such as age, gender, and marital status and individual characteristics such as health status, ADLs, depressive symptoms (CES-D), and oral health status (self-assessment). Any variable that shows potential for confounding or effect modification will be accounted for appropriately in all stages of the analysis.

For intervention variables, as all subjects are exposed to the same interventions, we will unpack the intervention into (1) dosage (percentage of talking points covered for all focal points —domains—addressed in the intervention and (2) exposure to focal point messages during campaigns. Study hypothesis 5 regarding dosage of interventions will be assessed by creating an ordinal scale that measures an individual's exposure to talking points through participation in the AMI and exposure to

messages via campaigns, thus creating a measure of dosage. We will then assess if dosage predicts better outcomes. This can be done directly (eg, compare mean gingival scores across dosage levels with analysis of variance) or dosage can be used as a predictor variable in the statistical models and causal pathway analyses. Practice to mastery (a 4-point Likert scale) and focal points (count variable) can be analyzed using similar techniques and approaches.

To address the secondary outcome of GOHAI, we will conduct a set of secondary analyses with GOHAI as a continuous outcome. It will also be incorporated into our statistical/mediator models as a predictor to see if it acts as an effect modifier.

To address cognitive mediators, the following variables will be incorporated into the causal pathway analysis to address example hypotheses 3 and 4: knowledge, oral health beliefs/norms, social support, oral hygiene behaviors, fears/worries, practice to mastery, and behavioral intentions. We will use longitudinal mediation to compare the two conditions (AMI followed by oral health campaign against oral health BA) in terms of whether they differ significantly in the amount of change that they engender in the GI and PS, indirectly through the mediators measured in our model.

We are interested in examining whether there is a change in our mediators over time, and if so, whether this change significantly leads to a change in behaviors, as assessed by the GI and PS. Recent methodological studies actually show that the analysis of change is more appropriately captured by specifying change (differences) in self-efficacy and our other mediators and behavioral outcomes between adjacent time points (ie, T2-T1 and T3-T2) as latent difference scores [70-73], and explicitly modeling these change scores to represent dynamic change, that is, the impact of change in the mediators on change in the behavioral outcomes.

Hypothesis #3 will be tested using latent change score analysis specifying AMI and campaign as predictors of change in behavioral beliefs (ΔBB), OH social support (ΔSS), locus of control beliefs (ΔCB), self-efficacy (ΔSE), fears/worries (ΔF/W), social norms (ΔSN),practice to mastery (ΔP2M), and behavioral intentions (ΔBI) from baseline to first and second follow-up.

To test hypothesis 4, we will conduct dynamic mediation using latent change (difference) score mediation analysis. The analyses will be conducted in Mplus 7, where change (difference) scores representing differences in each mediator and outcome variable from baseline to final follow-up that is, T2-T1 (ΔT_{21}) and T3-T2 (ΔT_{32}) will be generated. It is the difference scores of the mediators and outcome variables that are modeled. Generally speaking, causal paths specifying latent (true) change, represented by change in knowledge, oral health beliefs/norms, oral health social support, oral hygiene behaviors, fears/worries, practice to mastery skills, and behavioral intentions in going from T1 to T2 and T2 to T3 will be specified, to predict change in GI and PS at T3 (ie, ΔGingival $index_{32}$, ΔPlaque $score_{32}$). To assess the impact of the change in self-efficacy (ΔSE), on changes in GI scores (ΔGingival index), direct and indirect paths from change in self-efficacy from baseline to first follow-up (ΔSE_{21}) that predict the change in GI at the final follow-up (ΔGingival $index_{32}$) will be specified and tested. Select direct and indirect paths from change scores of the other mediator variables to change scores of behavioral outcomes will also be specified in a similar fashion, and all these relationships will be tested simultaneously [74].

Results

This study was funded in 2014, recruitment was initiated in mid 2015, after extensive reviews of the study, protocol and human subjects materials, as well as a full NIDCR 2 day site visit, as is normal for a U grant or cooperative agreement. All data collection was completed in July 2019, and analysis of the baseline data began in April 2019. Since the study is a clinical trial, the funders did not approve consideration of study data till all intervention data were collected by January 2019, to avoid any potential biasing of results. One paper summarizing the baseline association of moderators with study outcomes is in press, and another under review. Other papers are in process on the association of mediators with outcomes at baseline, changes from baseline to the first post assessment, evaluating one intervention approach against the other and diffusion effects of the oral health campaign to nonattenders.

Discussion

Approximately 330,000 seniors or 16% of all public housing residents in the United States live in subsidized public housing and another 500,000 live in subsidized Section 8 housing [75]. As a place-based intervention, the study offers a model that could conceivably reach over 20% of all low-income older adults in the United States in some form of publicly supported congregate housing. Adults with disabilities in publicly subsidized senior housing constitute an additional reachable population. Thus, the proposed intervention has the potential to improve oral health and hygiene in a population of older adults and adults with disabilities who have limited access to dental care and who are often left out of public health and prevention programs.

The study's modified fractional factorial approach disaggregates 2 components of a successful pilot intervention without the added expense of a control. Its comparative-effectiveness, crossover design allows for a comparison of the 2 primary components separately and together in different sequences. Finally, unlike many interventions, it adds a long-term sustainability component to evaluate which sequence has better sustaining power with respect to clinical and secondary outcomes. The GRCT design is implemented under maximally controlled conditions in a community setting, making it a model for community-based clinical trials.

Residents of low-income senior housing across the nation are very diverse. This protocol offers a bilingual approach that is culturally and individually tailored. All materials and research tools are developed, translated, and back translated for use in both English and Spanish, consistent with recommendations in the National Institutes of Health 2009 conference on interventions to improve oral health [76], and the interventions are tailored or targeted. The individual intervention is tailored

to the social, clinical, and psychological needs of the individual based on scores on scales measuring mediating mechanisms. Targeting in the oral health campaign component is made possible through peer involvement in designing theoretically driven oral health messages and participants' engagement with staff intervention experts and peer educators around mediators and oral hygiene skills. The theoretical model also encourages intervention fidelity by tailoring campaign information to each of the theoretical mediators. The engagement of building resident volunteer peers in development and implementation of the oral health campaign introduces practices known to be effective in communications interventions. These include delivery of messages through respected peer educators as well as expert role models, the active engagement of participants in games and other interactive learning experiences to enhance adult learning, the development and delivery of theoretically driven messages based on peer educator understanding of the language and concerns of their peers and other residents, and the development of resident capability to dispense information and instructions on appropriate oral health self-management.

The study is also unique in its use of clinical assessments and biomarkers in a community residential setting. These assessments are cost-effective and have implications for clinical and research programs in other community settings. Finally, emotions are now understood to play a role in prevention and treatment adherence [77]. Pilot work demonstrated the centrality of worries in oral health and hygiene self-care; however, there is no measure of oral health self-management worries. Pilot study data were used to create a new measure of oral health and worries that has promise as a predictor in that study and will be further tested in this clinical trial as a potentially valuable emotions-based predictor of poor oral health hygiene.

The intervention protocol should show potential for making much needed significant improvements in oral health behaviors of older adults (aged 62 years and older) and younger adults with disabilities (primarily aged 50-62 years) in publicly supported senior residences, especially as these rent-supported buildings now include up to 40% people with disabilities, an often unreached low-income population. Both interventions also can be implemented in senior centers or other places where older adults and people with disabilities gather, such as federally or state-funded lunch programs, and the AMI can be implemented easily and inexpensively at home as well. All of these opportunities can help to reduce the long-term need for acute dental care and treatment and can positively impact on diabetes and cardiovascular disease, which are problems associated with poor oral health in both of these vulnerable low-income populations.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Slide presentation detailing protocol components.
[PDF File (Adobe PDF File), 1693 KB - resprot_v8i12e14555_app1.pdf]

Multimedia Appendix 2
Peer-reviewer report from the National Institute of Dental and Craniofacial Research.
[PDF File (Adobe PDF File), 188 KB - resprot_v8i12e14555_app2.pdf]

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Abbreviations

AB: adapted motivational interviewing followed by campaign
ADL: activity of daily living
AMI: adapted motivational interviewing
BA: campaign followed by adapted motivational interviewing
CES-D: Center for Epidemiologic Studies Depression
GI: Gingival Index
GOHAI: General Oral Health Assessment Index
GRCT: group randomized controlled trial
IM: integrated model

IRB: institutional review board
MFFD: modified fractional factorial design
NIDCR: National Institute of Dental and Craniofacial Research
PS: Plaque Score
QDS: Questionnaire Development System

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Protocol

Implementing Digital Storytelling for Health-Related Outcomes in Older Adults: Protocol for a Systematic Review

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Abstract

Background: The number of older adults is increasing rapidly worldwide. Older adults face a unique set of challenges and may experience a range of psychological comorbidities. Advances in multimedia technology have allowed for digital storytelling to be utilized as an intervention for health-related outcomes.

Objective: The primary aim of the proposed systematic review is to examine the reported health-related outcomes for older adults engaged in digital storytelling. The review also aims to examine the methods associated with digital storytelling, characteristics of digital story products, and implementational considerations.

Methods: This protocol adheres to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols. We will systematically search selected electronic databases to identify studies that meet our eligibility criteria. From the included studies, data will be extracted and synthesized using a narrative approach and summarized in tables. The methodological quality of the included studies will be assessed using the Mixed Methods Appraisal Tool.

Results: Systematic searches, data extraction and analysis, and writing of the systematic review are expected to be completed by the end of 2019.

Conclusions: The proposed systematic review will summarize the existing studies using digital storytelling to improve health-related outcomes for older adults. Results from this review will provide an evidence base for the development of digital storytelling interventions that are effective and implementable with older adults.

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KEYWORDS

aging; health; psychology; mental health; memory

Introduction

Background

By the year 2050, it is anticipated that the number of people worldwide aged 60 years and older will double to 2.1 billion, and the number of people aged 80 years and older is expected to triple [1]. Although the majority of older adults enjoy health and happiness in their later years, a unique set of challenges are faced by this section of the community—for example, many will experience the loss of family and friends, a decline in physical and cognitive ability, and an increased dependency on others and many will undergo uncertainty as they anticipate impending death. As a result, many older adults experience poor mental health and live with several psychological comorbidities including depression and anxiety [2], social isolation, and loneliness [3,4]. Those with depression and anxiety report poorer quality of life than those with just comorbid physical conditions [5], and the presence of poor physical health, along with psychological conditions, stressful life events, and a lack of social connectedness, has been linked to suicide in late life [6]. These compounding difficulties highlight the importance of developing innovative interventions for improving and maintaining psychological health in later life.

Storytelling in later life through reminiscence has been recognized as an activity to support well-being in later life [7]. Recalling past events, in reminiscence, life review and other approaches may improve psychological well-being through several mechanisms. Such mechanisms may include encouraging a positive sense of self, eliciting pleasant memories to reduce negative mood states, promoting beliefs of self-mastery and ability to problem solve, and supporting ego integrity—the ability to accept one's highs and lows and to integrate past experiences and find a meaning or greater purpose in the events of one's life [8]. In telling their story, older adults may benefit from the opportunity for emotional expression, the ability to express their identity, and the experience of being listened to [9]. Reminiscence and life story work with older adults has often produced tangible artifacts such as storybooks, collages, and memory boxes [10], so that stories can be recorded, kept, and shared with others.

Owing to the advances in the capability and accessibility of multimedia technologies, it is now possible to produce digital life story artifacts with relative ease. Digital storytelling is a process that involves using multimedia technology to combine images, sounds, and narration into a film that documents one's lived experiences [11]. It has been used across disciplines in a variety of ways, largely utilized in educational settings [12,13], participatory research [14,15], and community engagement [16]. It can be facilitated with groups or with individuals, with a view to engaging participants in recording and sharing their lived experiences to educate others [17], to preserve stories and strengthen community bonds [18], and to assist participants in deepening their understanding of their lives and circumstances [19].

The use of digital storytelling to improve the health of older adults is an emerging area of research, with studies employing significantly varied methods published across a range of disciplines. Such studies suggest that digital storytelling may be used with older adults as a tool to improve mood [20,21], enhance memory [21], increase social connectedness [20,22,23], encourage personalized care practices among those who require it [23], and promote intergenerational learning [24,25].

To date, no published systematic review has evaluated the methods for and health-related outcomes of digital storytelling for older adults. This protocol proposes a review that aims to systematically examine the current state of digital storytelling with older adults, concerning outcomes of digital storytelling, methods for digital storytelling, and characteristics and content of the resulting digital story products. It also aims to examine factors related to the implementation of digital storytelling—this may include outcomes such as acceptability, feasibility, adoption, and adherence [26]. It aims to do so to provide a model for future digital storytelling interventions that promise to be effective and implementable for their intended purpose.

Objectives

This systematic review aims to answer the following questions:

1. What are the health-related outcomes of digital storytelling with older adults?
2. How does the process of, and the products created by, digital storytelling vary?
3. What are the implementational considerations in digital storytelling with older adults?

Methods

Protocol and Registration

This protocol was developed in adherence with the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines [27]. The systematic review will also adhere to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28]. This protocol is under review for registration with the International Prospective Register of Systematic Reviews.

Eligibility Criteria

Study Designs

Given that digital storytelling remains a relatively new area of research across various health care disciplines, it is anticipated that there is considerable heterogeneity in study designs. Relevant research has taken the form of quantitative, qualitative, and mixed methods studies. We will be inclusive in our eligibility criteria: we will review a range of study designs, including quantitative (eg, randomized, nonrandomized, quasi-randomized, and cluster randomized controlled trials; pilot trials; open trials; case studies; cross-section studies; cohort studies; and case-control studies), qualitative, and mixed methods studies, provided that at least one health-related outcome is reported in relation to digital storytelling participation (see the Outcomes section below).

Participants

We will include studies in which participants are older adults, defined for the purpose of this review according to the United Nations classification as those aged 60 years or above [1]. We will exclude studies if the age range for the sample begins under 60 years, even if the mean age is above 60 years; studies will only be included if all participants are identified as being aged above 60 years. Participants will not be excluded on the basis of their health—samples of participants may include those with dementia or mild cognitive impairment and other age-related illnesses. Participants may reside in the community or institutional settings, such as long-term care facilities, retirement communities, hospices, palliative care, and hospitals.

Intervention

Interventions of interest will be those that engage participants in digital storytelling. We will define a digital story as a short (eg, 3-5 min) multimedia clip (eg, images, videos, narration, and music) that is centered on the lived experience of older adult participants. There may be varying levels of participant involvement in technical production; for example, digital stories may be produced entirely by participants or produced on their behalf partly or wholly by others such as researchers, carers, or volunteers.

Studies will be included if their primary aim was to assess digital storytelling outcomes for participants other than older adults (eg, participants engaged in creating digital stories with older adults to assist with their understanding of the challenges of old age) and if health-related outcomes for older adults are reported as additional outcomes. Studies will be excluded if digital storytelling was used in conjunction with another intervention where the effects of digital storytelling alone are not reported or cannot be ascertained.

Comparator Groups

Any type of control group may be present in studies included for review.

Outcomes

This systematic review is primarily interested in the health-related outcomes for older adults who participate in digital storytelling. Such health-related outcomes may include mood, memory, quality of life, and social engagement. These outcomes may be measured and reported quantitatively (eg, using validated psychometric assessment tools) or qualitatively (eg, as a result of participant interviews that were transcribed and analyzed thematically). In addition, secondary outcomes include (1) process characteristics (ie, information related to the process of digital storytelling, eg, length of participation and level of involvement in technical production), (2) product characteristics (ie, variation in digital stories produced as a result of a digital story process, eg, length of story and presence of audio-visual components such as still photographs, videos, music, and narration), and (3) factors related to the implementation of digital storytelling with older adults—this may include acceptability, adoption, appropriateness, feasibility, fidelity, cost, coverage, and sustainability outcomes [26].

Report Characteristics

We will include studies for which we can access the full-text reports, which were published in scholarly journals or unpublished in the case of dissertations and theses and were written in English with no restrictions on the country of origin or the year of publication.

Search Methods for Identification of Eligible Studies

We will conduct a search of the following databases using a planned search strategy to identify published studies: MEDLINE (Scopus), Embase (Scopus), PubMed, PsycINFO, Web of Science, Cumulative Index of Nursing and Allied Health Literature (EBSCO), Academic Search Complete (EBSCO), Abstracts in Social Gerontology (EBSCO), Psychology and Behavioral Sciences Collection (EBSCO), Health Source: Nursing/Academic Edition (EBSCO), and SocINDEX (EBSCO). Unpublished studies will be identified by searching ProQuest Dissertations and Theses and Open Access Theses and Dissertations.

Selected search terms were chosen to describe the population and characteristics of the intervention necessary for inclusion in the review. An example strategy for database searching is as follows:

1. (“older adult*” OR “elder*” OR “older person*” OR “older people*” OR “dementia”) AND
2. (“story” OR “stories” OR “storytelling” OR “biographi*” OR “biography*”) AND
3. (“digital” OR “multimedia” OR “virtual”)

A preliminary search of the databases mentioned above has been conducted to ensure that the search strategy is viable and the scope of the search is feasible. An example preliminary search of MEDLINE and EMBASE via Scopus produced 170 records based on the following query string:

(TITLE-ABS-KEY (“older adult*” OR “elder*” OR “older person*” OR “older people*” OR “dementia”) AND TITLE-ABS-KEY (“story” OR “stories” OR “storytelling” OR “biographi*” OR “biography*”) AND TITLE-ABS-KEY (“digital” OR “multimedia” OR “virtual”))

Finally, we will examine the reference lists of all included studies to identify any relevant studies that may have been missed from the original search.

Data Collection and Analysis

Selection of Studies

The titles and abstracts of studies produced by the combined database search will be collated using reference management software, and duplicates will be removed. The first author will screen the titles and abstracts to remove reports that are irrelevant, before retrieving full-text reports of the remaining entries. A coauthor acting as the second reviewer will independently screen at least 25% of the titles and abstracts, and disagreements will be resolved through discussion, consulting a third reviewer to reach consensus where needed. The first author will then screen the full-text reports against the eligibility criteria for inclusion in the review, noting reasons for study exclusion. Again, a coauthor acting as the second reviewer will independently screen at least 25% of the full-text reports against the eligibility criteria, and disagreements will be resolved through discussion, consulting a third reviewer to reach consensus where needed. If more information is required, we will contact study authors where possible. The study selection process will be documented using the PRISMA flow chart, reporting the number of studies resulting from each stage of selection and the reasons for study exclusion [28].

Data Extraction and Management

We will use a pilot-tested standardized data collection form to extract and manage data from the included studies. Extracted data will include publication information (eg, name of authors, title, and country of origin), study design (eg, quantitative such as randomized and nonrandomized trials, pilot trials, open trials, and case studies; qualitative; and mixed methods), participant information (eg, sample size, age, gender, health conditions, and source of participants such as community or care settings), health-related outcomes for quantitative studies (eg, reported descriptive statistics and significance levels), health-related outcomes for qualitative studies (eg, reported theme-level findings), process (eg, length of participation and level of involvement in production) and product (eg, length of story and content of story) characteristics, and reported implementational challenges to digital storytelling. If there are multiple reports of a single study, such reports will be identified and the extracted

data will be collated and presented as findings from a single study.

One reviewer will independently extract study data from all included studies. A second reviewer will independently extract data from at least 25% of the included studies. If there are discrepancies, these will be resolved by discussion, and a third reviewer will be consulted to reach consensus where necessary. Where possible, we will contact the study authors if more information is needed.

Data Synthesis

Given the anticipated heterogeneity in study designs, populations, and outcomes, a meta-analysis will not be feasible. As such, a narrative synthesis approach of the aggregate data will be used [29]. We will use tables to summarize and present participant demographics, health-related outcomes, and process and product characteristics.

Furthermore, we will describe the participant information, process characteristics, product characteristics, and factors related to the implementation that are shared among studies and are unique to individual studies or specific health-related outcomes.

Assessment of the Methodological Quality and Risk of Bias of the Included Studies

To assess the methodological quality of the included studies, the Mixed Methods Appraisal Tool (MMAT) will be used [30]. The MMAT is designed to concurrently assess the quality of studies with different methods, including qualitative, quantitative, and mixed methods studies. A detailed presentation of the ratings on each criterion, rather than presenting overall numerical scores, will be carried out to provide a more sensitive evaluation of the methodological quality. To increase validity, a coauthor acting as the second reviewer will assess the quality of at least 25% of the included studies. Disagreements will be resolved through discussion and consensus, consulting a third reviewer where necessary.

Results

Systematic searches, data extraction and analysis, and writing of the systematic review are expected to be completed by the end of 2019.

Discussion

Globally, the number of older adults is rapidly rising [1]. Challenges faced by the aging population today contribute to their poor psychological well-being, and many older adults live with several psychological comorbidities [2-4]. Innovative interventions such as digital storytelling are increasingly being utilized, and there is a need to evaluate the evidence base for such interventions.

Applying the methods outlined in this protocol, the aim of the proposed systematic review is to examine the use of digital storytelling with older adults. Primarily, the study aims to examine documented health-related outcomes for older adults. It also aims to present a summary of the various methods for digital storytelling and digital story products that emerge from the interventions. The systematic review will also assess the methodological quality of the evidence presented and will provide a discussion of the limitations of the review. Importantly, the findings from this review aim to assist in developing a model for digital storytelling interventions that is tailorable to older adults for specific health-related outcomes and has the capacity to be effective and implementable. The findings of this study will be published in a peer-reviewed journal and potentially presented at academic conferences.

Authors' Contributions

JS and SB devised the protocol. JS wrote the manuscript with inputs from other authors. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

MMAT: Mixed Methods Appraisal Tool
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Leveraging Smart Health Technology to Empower Patients and Family Caregivers in Managing Cancer Pain: Protocol for a Feasibility Study

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Abstract

Background: An estimated 60%-90% of patients with cancer experience moderate to severe pain. Poorly managed cancer pain negatively affects the quality of life for both patients and their family caregivers and can be a particularly challenging symptom to manage at home. Mobile and wireless technology (“Smart Health”) has significant potential to support patients with cancer and their family caregivers and empower them to safely and effectively manage cancer pain.

Objective: This study will deploy a package of sensing technologies, known as Behavioral and Environmental Sensing and Intervention for Cancer (BESI-C), and evaluate its feasibility and acceptability among patients with cancer-family caregiver dyads. Our primary aims are to explore the ability of BESI-C to reliably measure and describe variables relevant to cancer pain in the home setting and to better understand the dyadic effect of pain between patients and family caregivers. A secondary objective is to explore how to best share collected data among key stakeholders (patients, caregivers, and health care providers).

Methods: This descriptive two-year pilot study will include dyads of patients with advanced cancer and their primary family caregivers recruited from an academic medical center outpatient palliative care clinic. Physiological (eg, heart rate, activity) and room-level environmental variables (ambient temperature, humidity, barometric pressure, light, and noise) will be continuously monitored and collected. Behavioral and experiential variables will be actively collected when the caregiver or patient interacts with the custom BESI-C app on their respective smart watch to mark and describe pain events and answer brief, daily ecological momentary assessment surveys. Preliminary analysis will explore the ability of the sensing modalities to infer and detect pain events. Feasibility will be assessed by logistic barriers related to in-home deployment, technical failures related to data capture and fidelity, smart watch wearability issues, and patient recruitment and attrition rates. Acceptability will be measured by dyad perceptions and receptivity to BESI-C through a brief, structured interview and surveys conducted at deployment completion. We will also review summaries of dyad data with participants and health care providers to seek their input regarding data display and content.

Results: Recruitment began in July 2019 and is in progress. We anticipate the preliminary results to be available by summer 2021.

Conclusions: BESI-C has significant potential to monitor and predict pain while concurrently enhancing communication, self-efficacy, safety, and quality of life for patients and family caregivers coping with serious illness such as cancer. This exploratory

research offers a novel approach to deliver personalized symptom management strategies, improve patient and caregiver outcomes, and reduce disparities in access to pain management and palliative care services.

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KEYWORDS

cancer; pain; sensors; caregivers; smart health; opioids; palliative care

Introduction

Background and Significance

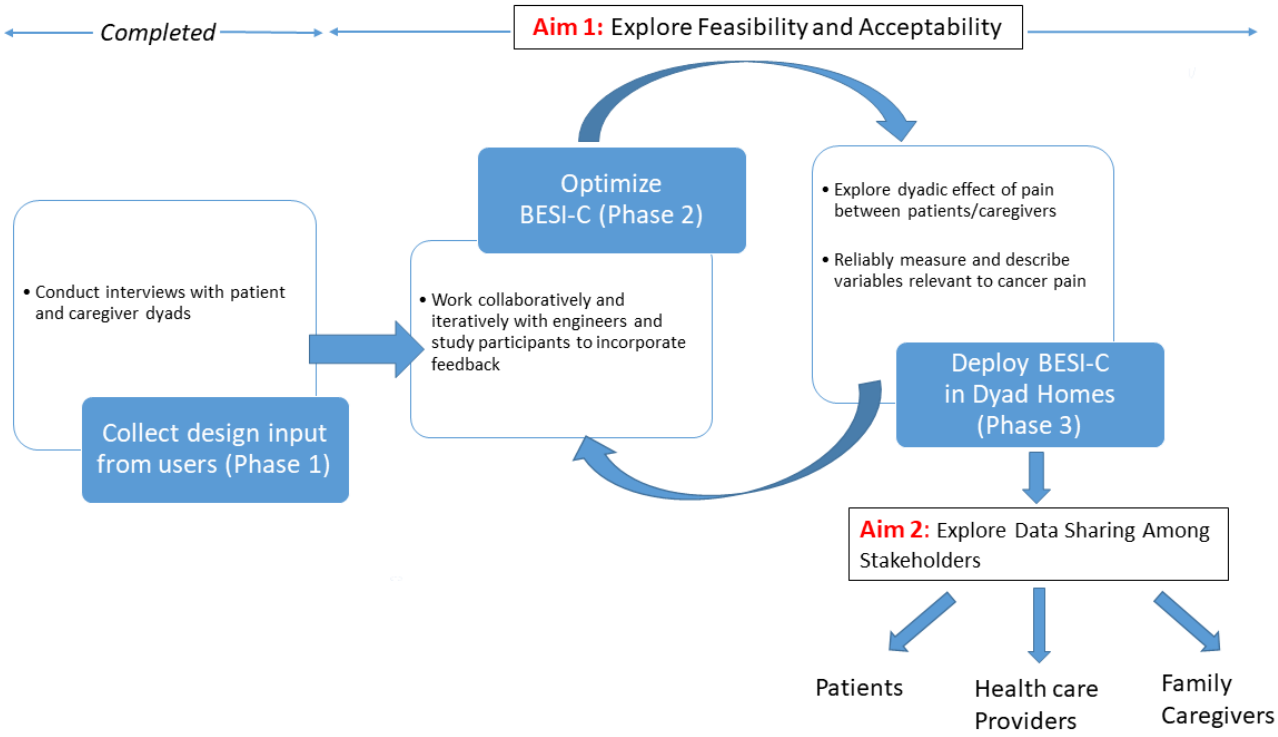
Pain remains a significant problem in cancer care. The biggest fear of patients diagnosed with advanced cancer is not always dying—it is dying in pain [1]. Likewise, family caregivers do not necessarily fear a loved one dying—they fear watching them suffer [2,3]. Unfortunately, for over 15 million Americans coping with cancer [4], these fears are justified. Despite 30 years of effort and imperatives issued by leading health organizations (including landmark reports from the World Health Organization [5], the National Academies of Medicine [6,7], the American Society of Clinical Oncology [8,9], and The National Institutes of Health [10]) to improve pain management, an estimated 60%-90% of patients with cancer still experience moderate to severe pain [11,12]. Poorly managed cancer pain has serious ramifications, negatively affecting sleep, adherence to treatment, mood, and overall quality of life—for *both* patients and their family caregivers [2,11,13,14]. Difficult pain that is not addressed effectively and promptly can escalate, increasing distress and suffering for both patients and caregivers. Witnessing untreated pain is also a significant stressor for family caregivers and can have a lasting, damaging psychological impact [2,15,16]. An especially difficult type of cancer pain to manage is “breakthrough” pain—sudden, often unpredictable, increases in pain [17].

Managing pain in the home context can be extremely challenging. Most cancer symptom management occurs in the ambulatory (outpatient and home) setting, and when patients with cancer are weakened by the effects of treatment or progression of disease, family caregivers commonly assume primary responsibility for managing complex symptoms [3,13,18,19]. For example, family caregivers must be able to detect and interpret physiological, social, and emotional cues to help determine the degree of pain the patient is experiencing, make independent decisions about when and how to intervene, and accurately evaluate and relay to health care providers how well the intervention worked [15]. Complicating cancer pain management is the reality that opioids, a key class of medications used to control serious cancer pain, are potentially drugs of misuse [20]. Given concerns regarding the national “opioid epidemic” [21], it is imperative that patients with cancer and their family caregivers have the support and tools to safely assess and manage pain [22]. We also know that there is a reciprocal dimension to patient and caregiver distress [23-25], but a better understanding of these dyadic and contextual factors are needed to inform effective interventions [2]. Mobile and wireless technology (“Smart Health”) can improve health outcomes for patients with a myriad of health conditions, including cancer [26,27]. A key benefit of leveraging Smart Health technology is the ability to collect a wide range of relevant data passively, minimizing invasiveness and burden—an important consideration for people coping with the stressors of advanced illness. Harnessing Smart Health technology is a critical next step in future research to optimally and comprehensively support patients and family caregivers [28] and has significant potential to help those coping with advanced disease, such as patients receiving palliative care or hospice services [29-31]. To date, technology-based interventions for patients with cancer have largely focused on recording and tracking self-reported symptom data and communicating the results to health care providers [27,32-34]. Research gaps and opportunities include leveraging technology to support family caregivers in managing distressing symptoms, especially pain [35], in the home environment [27,32,36]; identifying patient and caregiver needs in real time [37]; and using theory to inform interventions [28].

Preliminary Work

This research builds upon pioneering in-home sensing technology originally developed by members of our team to support the care of patients with dementia, known as BESI (Behavioral and Environmental Sensing and Intervention) [38-40]. Simply stated, BESI is a package of sensing technologies set up in a patient’s home, designed to unobtrusively and reliably collect behavioral, physiological, and environmental data. All the data collected by BESI are centrally integrated to paint an in-depth picture about the health and behavior status of individuals and dyads. BESI-C (BESI-Cancer) specifically focuses on factors that may influence cancer pain. Importantly, the design of BESI-C has been informed by end-user feedback gathered during qualitative interviews with cancer patient-family caregiver dyads (Phase 1, Figure 1) recruited from The University of Virginia Palliative Care Clinic. These interviews confirmed that dyads are open to novel technology to help manage cancer pain at home (consistent with prior research [31]), are receptive to pilot testing BESI-C, confirmed our proposed variables to measure with BESI-C, and did not identify additional variables to measure. This preliminary dyad input assisted in the iterative design of BESI-C, particularly related to the smart watch app.

Figure 1. Overview of BESI-C study design. BESI-C: Behavioral and Environmental Sensing and Intervention for Cancer.



Theoretical Frameworks

This research is grounded in two interrelated conceptual models: the Social-Ecological Model (SEM) and the Dyadic Stress Model. The SEM [41] supports a primary goal of this research, which is to better understand the complex interplay of patient, patient-caregiver dyad, and home environment characteristics that influence the experience of cancer pain. For example, understanding a patient's individual activity and pain levels (intrapersonal level) will involve consideration of dyadic dynamics that exist between the patient and the family caregiver (interpersonal level) that are, in turn, nested within the broader context of the home setting (environmental levels). Levels of the SEM and how they map to relevant variables measured by BESI-C are summarized in Figure 2. The Dyadic Stress Model posits that life stressors, such as cancer, have a reciprocal impact on patients and their caregivers [42]. For example, understanding how patients' pain may affect caregiver sleep, and vice versa, is a key aspect of this research.

Figure 2. Health variables measured by Behavioral and Environmental Sensing and Intervention for Cancer and related sensing modalities.

Health Variable	Participation	Users	Sensing modality	Acquired information and time of assessment
Social Ecological Model level: Individual (patient and/or caregiver)				
Movement	Passive	Patient, caregiver	Wearable	Step count, accelerometer; *Continuous*
Sleep/Rest	Passive	Patient, caregiver	Wearable	Extrapolated from movement and heart rate data; *Continuous*
Heart Rate	Passive	Patient, caregiver	Wearable	Biological marker of pain/stress; *Continuous*
Location	Passive	Patient, caregiver	Wearable and in-situ sensors	Room level localization; patient–caregiver proximity; *Continuous*
Social Ecological Model level: Interpersonal (dyad: patient ⟺ caregiver)				
Patient Ecological Momentary Assessment	Active	Patient	Wearable	Medication use, pain levels, distress levels; mood, sleep quality, social interaction; *When pain event marked by patient and daily survey*
Caregiver Ecological Momentary Assessment	Active	Caregiver	Wearable	Medication use, pain levels, distress levels, mood, sleep quality, social interaction; *When pain event marked by caregiver and daily survey*
Social Ecological Model level: Environment (home)				
Home Context	Passive	Not applicable	In-situ sensors	Ambient context (light, noise, temperature, barometric pressure, humidity); *Continuous*

Purpose

The overall purpose of this research is to deploy BESI-C and evaluate its feasibility and acceptability among patients with cancer-family caregiver dyads. Our primary aims are to explore the ability of BESI-C to reliably measure and describe variables relevant to cancer pain in the home setting and to better understand the dyadic effect of pain between patients and family caregivers. The secondary aim is to explore how to best share collected data among key stakeholders (patients, caregivers, and health care providers). We hypothesize that patient-caregiver dyads will accept BESI-C in their homes and that BESI-C can reliably capture relevant variables related to cancer-related pain. We are particularly interested in assessing the ability of BESI-C to capture and identify precursors to breakthrough cancer pain, which is notoriously difficult to predict and manage [17]. The ultimate, long-range goal is that data collected from BESI-C can inform and train personalized models that find correlations between environmental contexts and behavioral events, identify precursor patterns related to cancer pain, and provide real-time notifications for early intervention. Early, real-time notifications are important to prevent escalation of pain and distress levels. Currently, the BESI-C system is being utilized in the research domain only, as we must first validate accurate predictive models for breakthrough cancer pain. Once these models have been validated, which will require further work with a larger sample, we hope that BESI-C will be integrated into routine outpatient oncology/palliative care. In this context, BESI-C could deliver real-time personalized interventions to patients and caregivers and share data in real time with patients, caregivers, and health care providers to help direct care management and improve patient and caregiver outcomes.

Methods

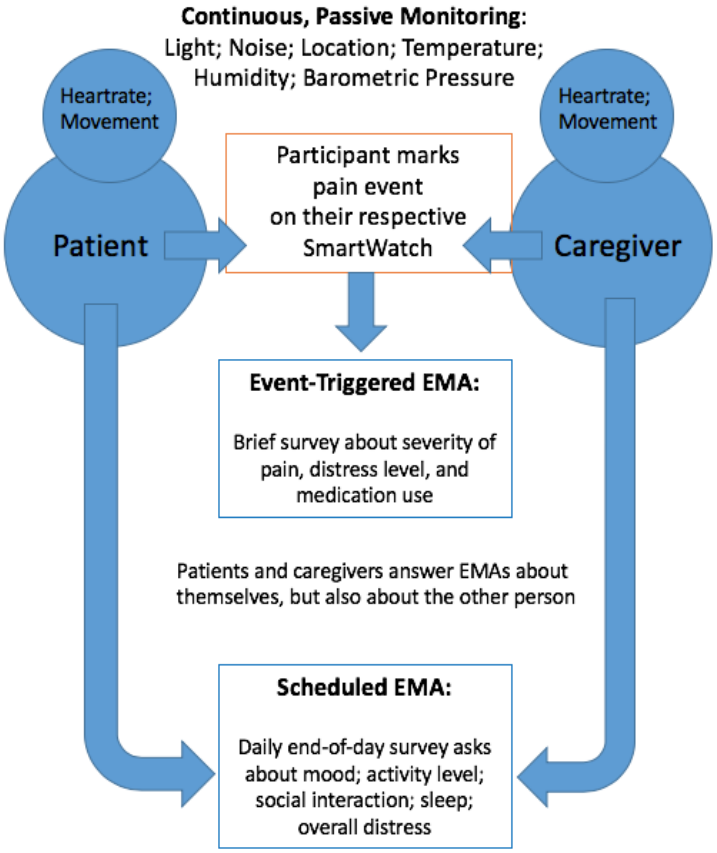
Recruitment

The study sample is designed to best capture patients and family caregivers coping with difficult cancer pain in the home context. We aim to recruit 20 dyads (patients with cancer and their primary family [informal, unpaid] caregiver) from an academic medical center outpatient palliative care clinic. The number of dyads reflects the scope of this pilot and the primary goal of evaluating feasibility and acceptability. Key patient inclusion criteria include (1) diagnosis of locally advanced or metastatic malignancy, (2) currently taking prescribed opioids for cancer-related pain, (3) ability to understand English and interact with the smart watch, and (4) scores of ≥6 on the NIH PROMIS Cancer Pain Interference scale measures [43]. Key caregiver inclusion criteria include living with the patient full time, identifying as the primary family home caregiver, and the ability to understand English and interact with the smart watch.

Study Design

This is a multiphase, descriptive pilot study (Figures 2 and 3). The study was approved by the University of Virginia Institutional Review Board.

Figure 3. The Behavioral and Environmental Sensing and Intervention for Cancer assessment model. EMA: ecological momentary assessment.



Rationale for Selection of Variables

Variables for data collection via BESI-C (Figure 2) have been selected based on (1) their relevance to pain as identified in the extant literature (eg, fatigue/sleep) [44-46]; (2) technology capabilities of the BESI system [40]; (3) literature documenting the impact of ambient factors such as light, noise, and temperature on the quality of life for patients with advanced illness [47]; (4) attention to reducing study burden in an already stressed and extremely ill patient population [48]; and (5) validation through previously conducted dyad interviews by our research team. Our goal is to collect a range of data variables, grounded in empirical science, while balancing dyad burden, to thoroughly understand contextual and environmental factors that influence pain in this vulnerable group and ultimately develop accurate predictive models, which is a key clinical and scientific gap.

Architecture of the Behavioral and Environmental Sensing and Intervention for Cancer System

The in-home BESI-C system includes four primary components (Figures 4 and 5):

Figure 4. The Behavioral and Environmental Sensing and Intervention for Cancer system architecture for passive data collection: (left to right) Bluetooth Estimote beacons, patient and caregiver smart watches, base station, and sensor relay stations. EMA: ecological momentary assessment.

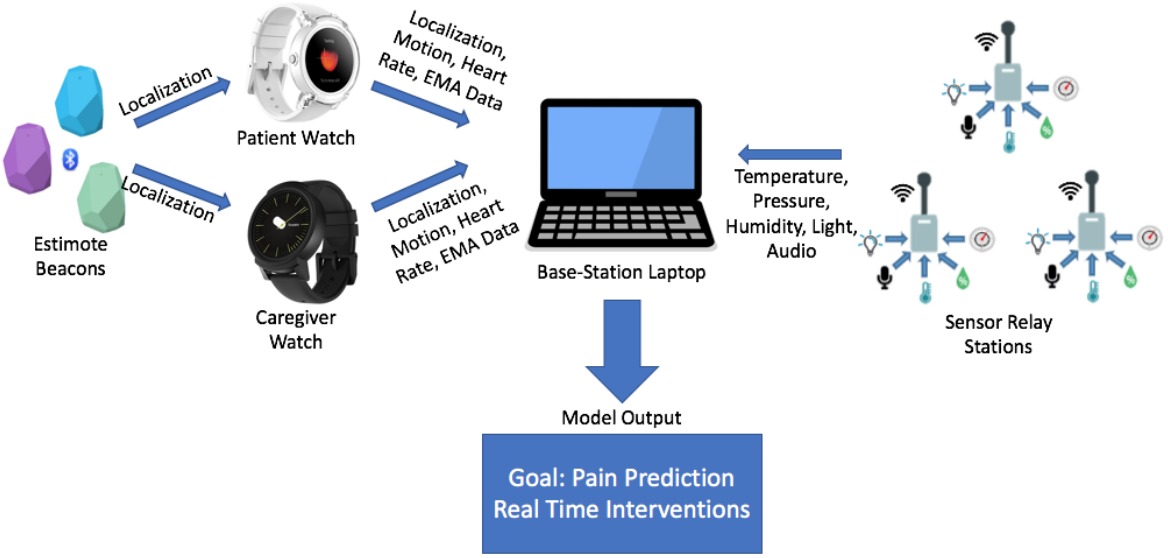


Figure 5. The Behavioral and Environmental Sensing and Intervention for Cancer system architecture for active data collection, examples of smart watch ecological momentary assessments for patient pain events (top), and caregiver pain events (bottom). See Multimedia Appendix 1 for more details.

Smart Watches

Smart watches (Wear OS Fossil Sport Watch, Fossil, Richardson, Texas) will be worn by both the patient and the family caregiver to passively collect photoplethysmogram heart rate and motion data (via accelerometer and step count) and actively collect ecological momentary assessment (EMA) data. Consistent with the scope and aims of this pilot study, we elected to use a well-known commercial off-the-shelf wearable. Although this device does not have 510k clearance, we prioritized wearability of the smart watch with the

acknowledgement we are *not* using collected data to direct or alter clinical care [49].

EMAs are brief, contextual assessments commonly used in mobile health to measure symptoms in real-time and send reminders or targeted messages to participants [50]. Each smart watch is programmed with a custom BESI-C app designed for either the caregiver or patient. The BESI-C custom smart watch app includes a platform for patients and caregivers to independently mark and evaluate experienced/perceived pain events, record opioid medication use, and complete a daily EMA survey that asks a series of brief "1-click" questions to evaluate factors such as mood, sleep quality, activity level, and amount of social interaction. Iterative design of the BESI-C custom app has prioritized ease of user interface, speed and simplicity in completion of EMAs, battery life optimization, and low burden and interference with activities such as sleep. EMA survey question format and sequence were developed in consultation with the home institution's Center for Survey Research. Dyads are asked to wear the watches as much as possible during the deployment and are provided with two watches to swap out when battery life decreases.

Sensor Relay Stations

Custom-built environmental sensor stations are strategically deployed in each primary room of the dyad home to passively and continuously collect data on room-level temperature, light, humidity, barometric pressure, and ambient noise. "Primary" rooms include those where participants tend to spend the most time and generally are the living room, bedrooms, and kitchen. We place sensors in consultation with dyads and only with their permission. Environmental data streams are integrated and transmitted to the base station.

Bluetooth Beacons

Commercially available Bluetooth Low Energy Estimote Beacons (Estimote Inc, New York) that continuously broadcast device identification information are deployed strategically in the dyad's home, and their broadcast signals are received by the smart watches. Using the smart watches' received signal strength indicator, the BESI-C app is able to determine the wearer's approximate distance from each beacon, thereby enabling room-level localization of the wearer and an estimation of patient-caregiver proximity.

Base Station

A BESI-C configured laptop is placed in an unobtrusive location within the dyad's home to provide a cyber-physical platform for data offloading and remote system monitoring. Of note, internet access allows remote system monitoring, but is not required for actual data collection. If patients or caregivers are outside of their home, they can still enter data on the smart watch, which are stored locally on the watch until the participant returns home and is reconnected to the BESI-C network. If a dyad does not have reliable internet access in the home, a mobile hotspot is set up to allow remote system monitoring.

Data Collection

BESI-C is currently being deployed within the homes of patient-caregiver dyads for approximately 10-14 days, consistent with a pilot study and to minimize dyad burden. Investigators remotely monitor BESI-C system fidelity, and deidentified data streams are uploaded to an approved secure cloud server. The environmental sensors and localization beacons are installed in the patient's home and are not relocated (for example, if the patient is admitted to the hospital), as we are interested in capturing the home context and how that may influence pain. However, the wearable sensor (smart watch) will continue to collect data regardless of the participant location. We are able to discern when dyads are at home by looking at the localization data and reviewing a ground truth daily log that we ask participants to keep during deployment. Passively collected physiological and environmental variables (eg, heart rate, ambient noise) are continuously collected without any interaction needed by the patient or caregiver. Actively collected behavioral and experiential data involve the caregiver or patient interacting with their smart watch to mark the time of a pain episode and describe the event (Multimedia Appendix 1). For example, patients or caregivers are asked to push a button or tap the screen on the smart watch when the patient is experiencing an episode of cancer pain, as perceived by the respective participant. If a pain event is marked, this will generate a brief EMA, which will ask the participant to rate the severity of pain on a simple 0 (no pain) to 10 (worst pain imaginable) scale, their distress level, their perceived partner's distress level, and if any opioid pain medications or other pain-reducing measures (eg, position change, hot/cold pack) were taken. If an opioid medication or other pain-reducing measure is taken, a repeat EMA is automatically deployed to the participant's smart watch approximately 30 minutes later to see if pain has decreased. If a participant indicates an opioid was *not* taken for a pain event, we ask them to tell us why (eg, not time yet, concerned taking too much medication, side effects, pain not bad enough, out of pills, some other reason). Additionally, a brief end-of-day EMA survey (approximately 10 questions) asks participants to rate their activity, mood, sleep, social interactions, and overall distress levels over the past day and is used to corroborate passively collected data streams. For example, if a patient reports being "very active" in their daily EMA survey, we can corroborate this with passively collected accelerometer, localization, and step count data. Dyads are also asked to keep a simple, ground-truth, daily paper-based log to record any unusual activity or significant events that occur during the deployment.

We have established *a priori* feasibility and acceptability endpoints for BESI-C data collection, both qualitative and quantitative. *Feasibility* measures are operationalized as (1) logistic barriers related to in-home deployment (eg, physical constraints within the dyad home related to placing environmental sensors); (2) technical failures related to data capture and fidelity (eg, environmental sensors disengaging from the BESI-C network or heart rate data not correlating with accelerometer data); (3) smart watch wearability metrics (Textbox 1); and (4) patient recruitment and attrition rates. *Acceptability* is operationalized as dyad perceptions and receptivity to BESI-C. This endpoint is assessed at the time of removal of BESI-C from a dyad's home by (1) a brief, structured interview asking about their general experiences with the system and (2) completion of a brief Likert-style survey, which asks

participants to agree or disagree with statements such as, "I found the BESI-C system bothersome" or "I would be willing to have BESI-C in my home for a longer period of time." At deployment completion, we also verify with the dyad any notable clinical or contextual events that may have occurred during the deployment and affected collected data, such as unanticipated visits to the emergency department or prolonged power outages.

Sharing data among key stakeholders is a critical element of understanding how to best support patients and caregivers in managing cancer pain in the home setting. This objective is grounded in principles of learning health systems, which have been advocated by the National Academies and the American Society of Clinical Oncology as an effective strategy to achieve timely, cost-effective, sustainable, targeted, and scalable improvement in health care delivery [51-53]. At the time of removal of BESI-C from a dyad home, we share with patients and caregivers a brief, graphical summary of their deployment data. In sharing these results, we record dyad opinions and feedback regarding the summary sheets in an informal talk-aloud conversation (Textbox 2). We also share these summaries with health care provider clinical collaborators to gather their feedback and opinions about their preferred content of data and how they would like the data displayed/presented.

Textbox 1. Smart watch wearability metrics.

- Proportion of complete versus incomplete ecological momentary assessments
- Percentage of time smart watch is worn
- Average length of time to complete ecological momentary assessments
- Number of interrupted/"snoozed" ecological momentary assessments
- Number of "dismissed" ecological momentary assessments
- Frequency and duration of times watch put in "do not disturb" mode
- Number of "low battery" notifications

Textbox 2. Example questions asked of dyads to assess data summaries.

- Does this summary capture the information you are most interested in?
- What information do you find most helpful? Least helpful?
- Is there information you would like to see that is not included in this summary?
- Do you think you need to see different information than your partner? If so, can you provide some examples?
- What information, if any, would you like shared with your health care provider?
- Who else would you like to see this information and why?
- Does this summary seem to accurately represent your experience?
- How would you like this information to be shared with you? (eg, paper print out, website, mobile app)

Privacy and security have been carefully considered for this pilot and are addressed in the following ways: (1) the BESI-C system does not record raw audio data, only preprocessed features related to ambient noise characteristics that do not enable reconstruction of conversation content; (2) the system contains no cameras; (3) sensors are only deployed in rooms approved by the participants and never in highly personal areas such as bathrooms; (4) participants can turn off sensors at any time, simply stop wearing the smart watch, or put the smart watch in to a temporary "do not disturb" mode; (5) all data streams are deidentified, contain no patient identifiers, and are labelled only with a study identification number; and (6) all data collection and streaming are performed within the confines of a local, offline Wi-Fi network via a dedicated router and base station laptop, where the laptop is the sole online device and is equipped with multiple stages of security authorization both locally and remotely.

Data Analysis

Data Collected by the Behavioral and Environmental Sensing and Intervention for Cancer System

Exploring initial data validity is an essential aspect of this exploratory research, as we aim to establish which variables are most important to measure and how we can best capture and analyze these data. Full-scale, real-time data analysis is beyond the scope of this pilot. For these important reasons, BESI-C does not currently alter or direct patient care or medication use in any way; participants are carefully counseled to follow standard procedures for notifying their care team if they experience concerns or changes with their health status. However, using principles of signal processing and machine learning [54,55], we will conduct preliminary analysis to explore the ability of the sensing modalities to infer and detect behavioral events and environmental contexts and to examine patterns, relationships, and concordance between actively and passively collected data. For example, to better understand the dyadic effect of pain, we can mine the data to explore if pain

events are equally marked by caregivers and patients; how they are respectively characterized in terms of severity and perceived burden; and how this corresponds with medication use, mobility, sleep, heart rate, and home/room environmental data (eg, temperature, light, noise). We anticipate focusing analysis on *severity* of pain events (those marked as ≥5 and with corresponding moderate/high levels of distress) and *frequency* of pain events (increased number of marked pain events in a specified time period, regardless of severity or distress level). Multimedia Appendix 2 lists example analysis questions and hypotheses. Initial exploratory predictive modeling analysis will identify outcome variables for future research.

Feasibility and Acceptability Measures

Feasibility measures will be recorded through a structured research audit log, and descriptive statistics will be used to summarize key metrics such as the number of completed daily EMA surveys and results from Likert surveys. Qualitative data from structured interviews with dyads will be recorded and coded using traditional content analysis to assess patterns and themes [56].

Results

The two-year grant funding has begun, and Institutional Review Board approval was granted in July 2019. Data collection is currently in progress. As of October 2019, four dyads have been enrolled and completed deployments. We expect the results to be published in summer 2021.

Discussion

Overview

This pilot study explores an innovative solution to the challenge of managing cancer pain at home by using a low-burden Smart Health system—BESI-C—to support patients with cancer and their family caregivers. If successful, this model will represent a paradigm shift in how we manage symptoms at home, by being able to monitor, predict, and anticipate distressing symptoms, so we can intervene earlier and more effectively with targeted, personalized approaches. This initial research focuses on breakthrough cancer pain, as it has been shown to be a particularly difficult symptom management issue and because managing pain is a foundational goal of palliative care, a specialty that focuses on optimizing the quality of life for patients and caregivers [57]. However, the long-term vision is that the BESI-C system could be customized to monitor and support a variety of in-home pain scenarios, such as patients enrolled in home hospice programs or patients and caregivers managing chronic, nonmalignant, or postoperative pain.

Our interdisciplinary research makes valuable short-term and long-term contributions in both the clinical and scientific arenas. Specifically, (1) palliative care research is challenging, as the symptom burden is high and interventions must be carefully designed. Smart Health technologies such as BESI-C can collect a wide range of relevant data passively, minimizing invasiveness and burden, which is a critical consideration for this population [48]. (2) Most Smart Health interventions rely on apps that live on people's smartphones [58-60]. BESI-C is unique in that it is a packaged sensing system that lives in people's homes through embedded sensors and can collect rich, in-depth data that facilitate personalized system learning, predictive models, and effective targeted interventions [38-40]. (3) How interactions between patients and family caregivers impact symptoms is understudied [28,36], and our research will integrate passively (eg, heart rate) and actively (eg, self-reported pain levels) collected data from *both* the patient and caregiver to better understand how pain may impact the dyadic relationship and vice versa. (4) We know little about specific patient-caregiver behavioral and contextual variables that influence pain and how best to monitor them [61]; as such, BESI-C offers an innovative approach to identify the variables required to develop and deliver timely, tailored, personalized interventions. (5) Managing patient symptoms remotely can be challenging; BESI-C can support patients by providing health care providers with data to inform care management decisions. (6) Pharmacological management of serious cancer pain hinges primarily on opioid therapy, which can be highly effective, but also problematic; our research offers a strategy for safer monitoring and use of opioids in the home setting, which is a particularly critical public health issue [20].

We see tremendous opportunities to advance the work of BESI-C beyond this initial pilot research. Future planned work with BESI-C includes deploying BESI-C with a larger sample of diverse high-risk, high-need populations (eg, dyads living in rural areas); conducting full-scale, real-time, retrospective data analysis to develop predictive models related to symptom manifestation and develop and deploy tailored interventions; continuing to refine and iterate BESI-C's sensing and data capture capabilities, such as with voice-activated technology; linking BESI-C to electronic medical health records and using principles of Learning Health Systems [51-53] to share data among relevant stakeholders (patients, family caregivers, and health care providers) to inform care management decisions in real-time; testing the ability of BESI-C to impact clinically relevant system-level variables, such as hospital admissions for pain or unplanned discharges from home hospice due to uncontrolled symptoms; addressing scalability, specifically regarding streamlining of deployment procedures and automating remote monitoring and data analysis (eg, in the future, we envision a simplified BESI-C system that could be installed by patients/caregivers themselves); and considering the use of BESI-C with other pain populations, such as patients coping with postoperative pain, neurological disorders, or chronic nonmalignant pain.

Limitations

A primary limitation of this research (but consistent with the scope and intent of a pilot study) is that we cannot provide clinical interventions or notifications, as we must first confirm data fidelity and develop algorithms for real-time data analysis. Thus, our work at this time is descriptive, and patients and caregivers are given standard of care instructions regarding whom to contact and when, for clinically related questions or emergencies.

Conclusions

Managing difficult pain at home is stressful for patients with cancer and their family caregivers. Leveraging Smart Health technology such as with BESI-C has significant potential to monitor, predict, and anticipate challenging symptoms and enhance communication, self-efficacy, safety, and overall quality of life for patients and family caregivers coping with serious illness. This exploratory research offers a novel approach to deliver personalized symptom management strategies to improve patient and caregiver outcomes and reduce disparities in pain management.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed functional specifications of Behavioral and Environmental Sensing and Intervention for Cancer smart watch app for patients and caregivers.
[PDF File (Adobe PDF File), 1845 KB - resprot_v8i12e16178_app1.pdf]

Multimedia Appendix 2
Examples of correlations to explore with preliminary data analysis of Behavioral and Environmental Sensing and Intervention for Cancer.
[DOCX File, 14 KB - resprot_v8i12e16178_app2.docx]

Multimedia Appendix 3
Peer-review report from the American Cancer Society.
[PDF File (Adobe PDF File), 189 KB - resprot_v8i12e16178_app3.PDF]

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Abbreviations

BESI: Behavioral and Environmental Sensing and Intervention
BESI-C: Behavioral and Environmental Sensing and Intervention for Cancer
SEM: Social-Ecological Model
EMA: ecological momentary assessment

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Protocol

Defining the Supportive Care Needs and Psychological Morbidity of Patients With Functioning Versus Nonfunctioning Neuroendocrine Tumors: Protocol for a Phase 1 Trial of a Nurse-Led Online and Phone-Based Intervention

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Abstract

Background: Online information resources and support have been demonstrated to positively influence the well-being of people diagnosed with cancer. This has been explored in past literature for more common cancers; however, for rare cancers, such as neuroendocrine tumors (NETs), there are little to no support or resources available. Despite relatively good prognoses, the quality of life (QoL) of patients with NETs is significantly lower compared with samples of mixed cancer patients and the general population. Patients with NETs also typically report unclear and difficult pathways of disease management and treatment, given the heterogeneity of the diagnosis. There is a vital need to improve the availability of disease-specific information for this patient group and provide supportive care that is tailored to the unique needs of the NET patient population.

Objective: This study described the protocol of a study aimed to better understand the outcomes and experiences of patients diagnosed with NETs and to develop and pilot test a nurse-led online and phone-based intervention that will provide tailored supportive care targeted to NET subgroups (functioning vs nonfunctioning).

Methods: This is a multisite cohort with 3 phases, incorporating both quantitative and qualitative data collection. Phase 1 is a mixed methods prospective cohort study of NET patients identifying differences in patient experiences and priority of needs between NET subgroups. Phase 2 utilizes results from phase 1 to develop an online and nurse-led phone-based intervention. Phase 3 is to pilot test and evaluate the intervention's acceptability, appropriateness, and feasibility.

Results: Currently, the project is progressing through phase 1 and has completed recruitment. A total of 138 participants have been recruited to the study. To date, patient-reported outcome data from 123 participants at baseline and 87 participants at 6-month follow-up have been collected. Of these, qualitative data from semistructured interviews from 35 participants have also been obtained. Phase 2 and phase 3 of the project are yet to be completed.

Conclusions: Limited research for patients with NETs suggests that QoL and patient experiences are significantly impaired compared with the general population. Furthermore, past research has failed to delineate how the clinical variability between those with functioning and nonfunctioning NETs impacts patient supportive care needs. This study will improve on the availability of disease-specific information as well as informing the design of a nurse-led online and phone-based supportive care intervention tailored for the unique needs of the NET patient population.

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KEYWORDS

cancer; neuroendocrine tumors; NETs; supportive care interventions; telehealth; eHealth

Introduction

Background

It is well established that online information resources and support have a significant impact on the well-being of people diagnosed with cancer [1-3]. To date, there are several tools available for more common cancers, such as breast and prostate cancer, which have a significant impact on the patient experiences of those users [4]. Some of these tools include Internet Cancer Support Groups [5], Comprehensive Health Enhancement Support Systems [6], and bulletin boards [1,7]. More specifically, online information resources and supports were shown to increase hope, universality [1], positive emotions [7], and psychological well-being [5]. However, for those diagnosed with a rare cancer, such as neuroendocrine tumors (NETs), where patients commonly report poorer quality of life (QoL), there are little to no support or resources available [8]. This is even further complicated given that NETs can appear almost anywhere in the body [9]. In addition, NETs can range from being hormone expressive (functioning) and highly symptomatic to nonexpressive (nonfunctioning) and potentially having no symptoms at all [10]. There is an urgent need to better understand the differences in the patient experiences and information and supportive care needs of each NET subgroup (functioning vs nonfunctioning) [8]. These findings can be used to develop online information resources, tools, and support that is tailored to the 2 subtypes of NETs.

NETs are a heterogeneous group of rare cancers that derive from the neuroendocrine cell system [11]. Within Western populations, the incidence of NETs in 2012 was 14.02 per 100,000 according to the Surveillance, Epidemiology, and End Results Program [12]. Although still considered rare, the increasing prevalence of NETs is a worldwide phenomenon [12,13], possibly owing to the detection of early-stage disease and stage migration [14]. With NETs arising across the neuroendocrine system, these malignancies can affect almost any organ; however, they are most commonly found in gastrointestinal sites, typically that of the small intestine, appendix, pancreas, stomach, colon, rectum, and bronchopulmonary sites [15-18].

The clinical presentation and symptom severity of these tumors can vary greatly from patient to patient and, more broadly, between functioning and nonfunctioning NETs. NETs are classified by their secretory potential as functioning or nonfunctioning, depending on their ability to produce peptides that cause distinctive hormonal syndromes such as carcinoid syndrome [9,19,20]. Symptoms associated with functioning NETs are generally those that are caused by the secretion of hormones and those that consequently result in carcinoid syndrome or other secretory syndromes (eg, due to hypersecretion of insulin, gastrin, and glucagon). In the case of carcinoid syndrome, these symptoms largely include flushing of the skin and secretory diarrhea and are highly distressing to patients and have a significant impact on their physical and social functioning [11,21]. In addition, carcinoid syndrome can also result in clinical symptoms such as hypotension or hypertension, bronchoconstriction, and carcinoid heart disease [22]. Compared with patients with a functioning NET, patients with nonfunctioning NETs are often left managing the uncertainty of an asymptomatic cancer [23].

The 5-year survival rates for both functioning and nonfunctioning NETs are estimated at 68% [24], with treatment options varying from surgery, cytotoxic chemotherapy, somatostatin analogs, and targeted biological agents, depending on tumor location and disease stage and grade [25-29]. Despite relatively good prognoses, the QoL of patients with NETs is significantly lower compared with samples of mixed cancer patients and the general population [30-32].

Health-Related Quality of Life and Patient Experiences

Research on the patient experience and overall QoL of those diagnosed with NETs is limited in comparison with more common types of cancer such as breast [33], lung [34], and prostate cancer [35,36]. There is, however, evidence to suggest that QoL is significantly impaired in people with NETs when

compared with the general population, as assessed by the Euopean Organization for Research and Treatment core, Quality of Life Questionnaire (EORTC QLQ-C30; Role functioning, large-sized difference, 32 points; Social functioning, medium-sized difference, 14 points; and Global QoL, large-sized difference, 18 points) [31,37]. Patients with NETs also score worse on QoL subscales compared with a mixed sample of cancer patients and survivors [30]. The severity and burden of NET-specific symptoms, for example, the frequency of bowel movements and the presence of skin flushing, have been found to correlate with a decrease in overall QoL [38]. Likewise, patients with NETs who are also experiencing symptoms associated with carcinoid syndrome report poorer QoL than patients with NETs who do not have carcinoid syndrome [30]. QoL can also be impacted by the complications of treatment of the disease itself, for example, surgery, somatostatin analogs, chemotherapy, and radiotherapy.

In addition to poorer QoL, a recent qualitative study found that patients with NETs report from their perspective that disease management and treatment pathways are unclear and difficult to navigate. It also highlighted that there is a need for support that is responsive to the specific needs of this group [8]. Indeed, patients with NETs reported low levels of satisfaction with the organization of care, and lower levels of satisfaction were associated with higher levels of anxiety and impaired psychosocial function [39]. Taken collectively, these results indicate the little to no information and support tailored to the unique needs of the NET population.

Principles Underpinning the Design of a Patient-Centered Intervention

To address potential differences in unmet needs between NET subgroups, the Schofield and Chambers framework will be used to develop a tailored intervention. This intervention will provide targeted supportive care for patients with NETs according to the clinical characteristics and psychosocial profile of patients with functioning and nonfunctioning NETs.

The Schofield and Chambers framework emphasizes 7 key requisite components to be considered to design and develop an intervention that will be effective, clinically feasible, and sustainable [40]. The framework builds on the Medical Research Council framework for complex interventions, which provides a guideline that can be used to assist with the development and evaluation of health interventions such as targeted supportive care and health information [41]. According to Schofield and Chambers, there are 7 key features required in the development of an intervention to achieve effective and easy translation into usual care: (1) targeting a cancer type and stage, (2) tailoring to individuals' unique needs, (3) promoting self-management, (4) efficient intervention delivery, (5) ensuring evidence-based and theoretical grounding, (6) specifying protocol training and adherence, and (7) confirming stakeholder acceptability [40].

Aims and Objectives

The aim of this study is to describe the protocol of the Defining NETs study. The overarching aims of this study are to better understand the outcomes and experiences of patients diagnosed with NETs and to develop and pilot test a nurse-led online and phone-based intervention that provides tailored supportive care targeted to NET subgroups.

More specifically, the objectives of this study are as follows:

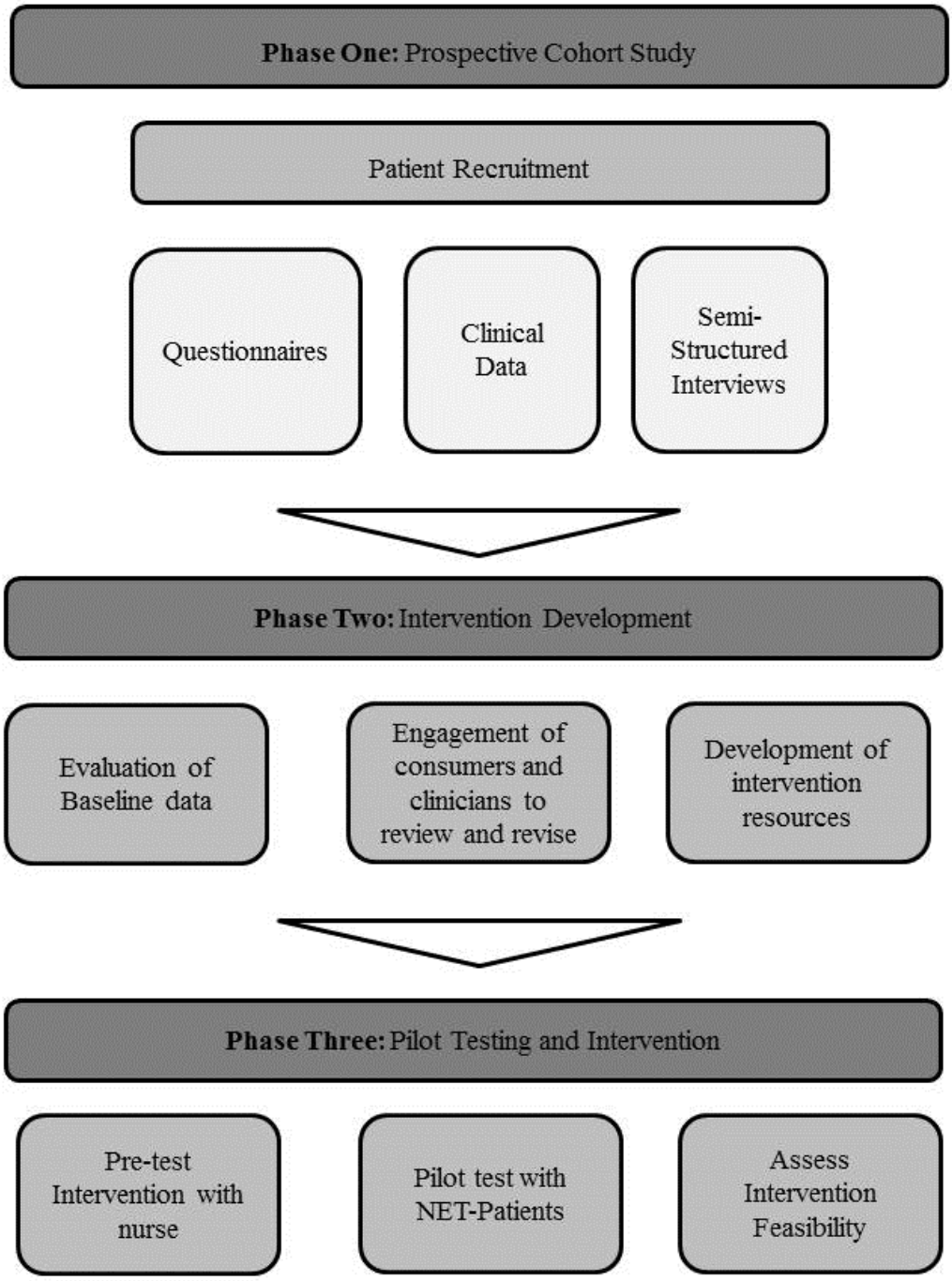
1. To describe and compare the psychosocial (Patient-Reported Outcomes Measurement Information System [PROMIS] short forms assessing anxiety, depression, fatigue, pain interference, pain intensity, sleep disturbance, physical function, satisfaction with social roles and activities, supportive care needs, and experiences of the health care system), QoL (EORTC QLQ-C30 and Gastrointestinal Neuroendocrine QoL Module [GINET21]), and clinical characteristics of patients with functioning and nonfunctioning NETs within 6 months of diagnosis and then again 6 months later;
2. To conduct qualitative interviews to gain a better understanding of the experiences, care preferences, and information needs of patients with NETs;
3. To design and develop an intervention involving online triaging and the delivery of informational resources using multimedia, diagrams, and text, with phone-based nurse follow-up targeted to NET subgroups, as appropriate, and tailored to the individual's psychosocial and clinical profile;
4. To pilot test the intervention and assess the acceptability and clinical utility of the intervention through a service that is accessible to patients nationwide from both metropolitan and rural areas.

Methods

Study Design

A concurrent mixed methods triangulation design will be conducted with 3 phases incorporating both quantitative and qualitative data collection. Both data forms will be used to identify differences in patient experiences and priority of needs between the NET subgroups. Phases are displayed in Figure 1.

Figure 1. Flow chart of study phases. NET: neuroendocrine tumor.



Phase 1: Prospective Cohort Study

Study Setting

The study will be conducted at 6 sites across Australia. Participatory sites are the Peter MacCallum Cancer Centre in Melbourne, Victoria, with additional recruitment sites at the Royal North Shore Hospital and Northern Cancer Institute (New South Wales), the Lyell McEwin Hospital (South Australia), Royal Brisbane Hospital (Queensland), and the Fiona Stanley Hospital (Western Australia).

Eligibility Criteria

Eligibility to this study requires a patient to (1) have a histologically confirmed diagnosis of a NET within the past 6 months, (2) be aged 18 years or older, (3) be able to understand English, (4) have their NET classified as either functioning or nonfunctioning by their treating oncologist, (5) be well enough

to participate in the study as determined by the patients' treatment team, and (6) not demonstrate psychological or cognitive difficulties that would preclude study participation as defined by the treatment team's cognitive or psychiatric assessment or patient's disclosed medical history.

A participant will be withdrawn if they (1) become cancer free or (2) withdraw consent. Discontinuation due to adverse events could be either at the request of the participant or the discretion of the investigator(s).

Outcomes and Measures

Potentially eligible patients will be identified by their treating clinician and classified as either functioning or nonfunctioning based on their clinical diagnosis. At the time of consent, patients will complete a baseline questionnaire, and thereafter a 6-month follow-up questionnaire. Profiles of the psychosocial, QoL, and clinical characteristics of patients with functioning and nonfunctioning NETs will be developed based on patient-reported outcome data and clinical data extracted from medical records at baseline and 6-month follow-up. Those participants who consent to the opt-in interview will be contacted by the study team to complete a semistructured interview.

The following measures form part of the patient questionnaires:

Psychological morbidity, symptoms, and functioning

- Emotional Distress Anxiety-Short Form 7a and Emotional Distress Depression-Short Form 8b
- Fatigue-Short Form 7a
- Pain Interference-Short Form 6b and Pain intensity-Short Form 3a
- Sleep Disturbance-Short Form 8b
- Physical Function-Short Form 10a
- Satisfaction with Social Roles and Activities-Short Form 6a

Emotional distress, fatigue, pain, sleep disturbance, physical functioning, and satisfaction with social functioning will be assessed using the PROMIS short forms listed above. Items comprising each short form were first evaluated using classical test theory indices. Unidimensionality was confirmed via confirmatory factor analytic techniques [42], and then, item response theory modeling and expert review were used to identify items measuring the entire spectrum of the construct targeted by each scale. All relevant short forms are standardized, accurate, and efficient self-report measures, and all these short forms were specifically developed for use in clinical oncology research [43].

Supportive Care Needs Survey

The Supportive Care Needs Survey (SCNS) is a 34-item questionnaire incorporating 5 scales [44]. These scales assess physical and daily living needs, psychological needs, sexuality needs, patient care and support needs, and health system and information needs. The SCNS demonstrates acceptable reliability and validity [44].

Cancer-Specific Health-Related Quality of Life and Gastrointestinal Neuroendocrine Module

The EORTC QLQ-C30 is a 30-item questionnaire incorporating 5 functional scales (physical, role, cognitive, emotional, and social functioning); 3 symptom scales (fatigue, pain, and nausea/vomiting), a global health status scale; and 6 single items assessing dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact [45]. Its reliability and concurrent and criterion validity have been demonstrated in numerous studies [45-47].

The QLQ-GINET21 module is a 21-item questionnaire consisting of 5 scales (endocrine, GI treatment, social function, and disease-related worries scale) and 4 single items (muscle/bone pain symptom, sexual function, information/communication function, and body image). The QLQ-GINET21 is a valid tool for assessing QoL in patients with NETs [48].

National Health Survey—Cancer Patient Experiences Survey

A total of 21 items have been extracted from the National Cancer Experience Survey used to assess patients' understanding of their diagnosis and treatment, adequacy of communication, and experiences with hospital staff. These 21 items were adapted for collecting information from patients with functioning or nonfunctioning NETs about their experiences of the health care system following their diagnosis, and this survey was demonstrated to have good content validity [49].

Demographics and Clinical Variables

A range of demographic and clinical information will be collected pertaining to the individual's characteristics (eg, age, gender, language, living arrangements, postcode, occupation, work status, and level of income).

Clinical data collection will occur at baseline and 6 months post baseline and will include a medical record audit to identify clinical information such as date of diagnosis, presence or absence of functional syndrome, primary site, grade, list of and frequency of diagnostic imaging, primary treatment details, length and number of hospital stays, involvement with hospital services, or referrals at the time of recruitment. At follow-up, information pertaining to the participants' status—alive and disease free, alive with disease, lost to follow-up, or deceased (including date and cause of death and autopsy [if performed])—disease progression/recurrence (including date of detection) and progression-free survival; as well as any additional diagnostic imaging and additional treatments details will be collected.

To further investigate the supportive care needs of patients diagnosed with functioning and nonfunctioning NETs, patients will be asked to participate in an optional semistructured phone interview. Semistructured open-ended questions have been developed to allow participants to share their experiences and preferences.

Recruitment

Recruitment will take place from outpatient clinics and chemotherapy day units at participating sites. For each site, a research team will screen and identify new and newly diagnosed

patients attending clinics that are potentially eligible. Eligibility will be confirmed with the treating clinician before any approach to clarify details from the medical records. The study will be described, and patients will be provided with a copy of the Participant Information and Consent Form (PICF), a baseline questionnaire, and a reply-paid envelope. Any questions the patient may have will be answered, and the patient will be informed that their involvement in the study is completely voluntary. If the patient wishes to participate, they will be asked to sign the PICF and complete the baseline questionnaire. Similarly, 6-month follow-up questionnaires will be posted out to participants with a reply-paid envelope for participants to return the completed questionnaires in. The study coordinator will call the patient to follow-up the return of these forms if they have not been received after a period of 1 week. Patients who decline to participate will be asked for verbal consent to collect basic demographic and clinical information from their records to examine potential recruitment bias. Reasons for refusal will be recorded.

Data Collection Methods

Patient Experience Questionnaire

All patient-reported outcome questionnaires will be collected from participants at baseline and again at 6-month follow-up in reidentifiable format and reviewed for completeness of data. Any missing data will be followed up with the participants. The reason for any remaining missing data will be noted on an electronic tracking database.

Medical Records Audit

All clinical data to be collected will be written into a paper-based Case Record Form, which will then be entered into an electronic database. Baseline and follow-up clinical data will be collected from the medical records of participating sites.

Qualitative Semistructured Interview

Patients will be asked to participate in an optional semistructured phone interview to discuss their experiences, care preferences, and information needs as a person with a NET. This interview will be conducted over the phone by a trained interviewer. On the basis of the aims, semistructured open-ended questions have been developed to allow participants to share their experiences and preferences. Given the semistructured format, additional questions and prompts will be used as necessary, as it is anticipated that themes/issues will be identified during the interview. This will allow the participant to share their individual experiences. It is anticipated that approximately 20 participant interviews will be completed for each NET group, however, to ensure that no more than a feasible amount of patients are recruited to the semistructured interview, the opt-in check box will be removed once enough participants have been recruited to achieve saturation of qualitative data themes.

The duration of the interview will be between 30 and 45 min. The interview will be recorded using a Dictaphone and transcribed verbatim for analysis.

Statistical Considerations

Sample Size

It is estimated that approximately 170 eligible cases will be seen across all sites over a 17-month recruitment period, with an approximate split of 50% functioning and nonfunctioning NET patients. With 80% consent rate and 10% attrition, this will provide a sample of 136 at baseline and 122 at 6-month follow-up. The expected sample will provide 80% power to detect medium-sized differences between groups on continuous outcomes (0.48 SD at baseline and 0.51 SD at follow-up), assuming a 2-sided, alpha=.05 independent samples *t* test.

Quantitative Analysis of Patient-Reported Outcome Measures, Demographics, and Clinical Data

Descriptive statistics will be used to summarize demographic and clinical characteristics and patient-reported outcomes by group at baseline and follow-up. Statistics will include counts and percentages for nominal valued variables and means and standard deviations or medians and interquartile ranges, as appropriate, for continuous valued variables.

Dichotomous valued variables will be compared between groups using Fisher exact test. Nominal valued variables will be compared between groups using Pearson chi-squared test of independence. Responses to patient-reported outcome measures at baseline and follow-up will be compared between groups using independent samples *t* tests; between-groups differences on EORTC QLQ-C30 scales and items will be interpreted using evidence-based guidelines [50]. In the absence of evidence-based guidelines for the SCNS and PROMIS measures, the Cohen d effect size will be calculated and interpreted using existing conventions [51]. If a nonparametric method is required, differences in medians will be examined using the bootstrap percentile method [52]. The number of bootstrap replications will be set at 10,000.

All data will be entered in SPSS version 23 or higher (Chicago, IL), and SPSS will be used for scoring, descriptive analysis, and parametric tests. If a nonparametric method is required, data will be imported into R version 3.3.3 (or higher), and the R package *pairwise CI* will be used for this purpose [53]. Alpha will be set at .05 for all analyses, and all tests will be 2-tailed.

Qualitative Analysis of Semistructured Interviews

Patient interviews will be transcribed and analyzed using qualitative content analysis. Specifically, interviews will be coded and categorized into 2 groups representing functioning and nonfunctioning NETs patient responses. Similar codes across the 2 categories for functioning and nonfunctioning NETs patients will then be explored as global themes informed by ground theory [54,55]. Coding labels will be created by 2 independent experienced qualitative researchers, who will examine and discuss each other's coding and thematic analysis to promote rigor and interrater reliability [56].

Phase 2: Development of the Nurse-Led Phone-Based Intervention

In collaboration with the Unicorn Foundation, this study will develop and pilot test an intervention to augment this service.

Unicorn Foundation

The Unicorn Foundation is an Australian not-for-profit medical foundation that aims to educate and support people who have a NET, as well as their families, by promoting better awareness and knowledge of the disease. The Unicorn Foundation advocates research in the area and has worked with clinical researchers to raise money and fund pilot testing of NET clinical trials. In addition, the foundation independently funds the employment of a registered nurse, offering the support of a NET Nurse hotline.

Current utilization of the NET Nurse hotline has been estimated by the Unicorn Foundations data monitoring at approximately 350 incoming calls over a 6-month period, with callers originating across all Australian states and territories. In addition, the location of callers is estimated at 59% from metropolitan areas and 41% of callers from rural areas, where access to NET-specialized physicians is likely to be limited. In addition, the Unicorn Foundation website offers a range of online resources such as updates on current NET research, access to support groups, and information on NETs.

The accessibility to this service nationally makes it an optimal avenue for disseminating and implementing evidenced-based approaches to provide better quality of care for those accessing information. This study will expand upon this service and provide a more structured response for patients with information that is tailored to meet the needs of NET patients based on their clinical characteristics and from information that has been derived from both clinical and patient-reported outcome data collection.

Development Framework

In line with the Schofield and Chambers framework, the design and development of the intervention will be guided by the 7 key features required to achieve effective translation into usual care and practice [40]:

1. Targeting cancer type and stage: To gain an understanding of the problem, patients recruited to the study are classified as either functioning or nonfunctioning by their treating oncologist based on their clinical presentation of distinctive hormonal syndromes and symptoms associated with functioning NETs [9,11,19-21] versus the asymptomatic profile of nonfunctioning NETs [23]. Intervention content will be developed based on quantitative and qualitative data on patient experiences and care preferences. The intervention will target the 2 subgroups and provide tailored supportive care around aspects of information on their disease, symptom burden, and self-care management.
2. Tailoring to individual's unique needs: The delivery of the intervention will be tailored to suit individual needs. NET patients utilizing the Unicorn Foundation website will have access to online information and tools to access support. Users will be triaged online via the website based on symptom severity and distress. Relevant information will be delivered online as part of the intervention content will be tailored in depth based on the first phase of triaging. If the patients' needs or concerns are not resolved, the intervention approach will be progressively stepped up to the top tier, which will be a phone-based nurse follow-up. In adopting this approach, the nurse will be able to prioritize the most vulnerable patients, increasing efficacy of the service and making patient encounters more meaningful and useful.
3. Promoting self-management: Promoting self-management of disease by providing patients with the resources and skills to address issues around symptom assessment, problem solving, and goal setting may reduce distress and ultimately health care use by enhancing the uptake of health behaviors [50,51]. The intervention will provide users with online information and resources to help facilitate self-assessment and symptom management. Nurse-led phone-based follow-up will also use motivational interviewing techniques to enhance self-management behavior change by adopting a client-centered method thought to encourage self-motivation [52].
4. Efficient intervention delivery: The delivery method of this intervention utilizes existing resources and infrastructure via the Unicorn Foundations website and Nurse Hotline service. Using this method of delivery adopts a low-intensity approach, improving efficiency by being a tool that can be easily integrated as an ongoing clinical service.
5. Ensuring evidence-based and theoretical grounding: The content of the intervention will be based on theory and available evidence. Content development will be based on analysis of both quantitative and qualitative data collected in the prospective cohort study that will describe the psychosocial, QoL, and clinical characteristics of patients with functioning and nonfunctioning NETs. Patient experiences and care preferences reported during semistructured interviews will also form part of the deliverable content of the intervention. The delivery mode is likely to incorporate media visual, textual, and diagrammatic resources and one-to-one telephone support. For example, the intervention may include patient experience videos, flowchart diagrams of treatment pathways, and fact sheets.
6. Specifying protocol training and adherence: A standardized manual for the one-to-one nurse-led telephone consultations will be developed, specifying the (1) content of the intervention consisting of, but not limited to, a description of NETs and their subgroups, method of triaging patients, symptom burden, patient care preferences, assessment of needs, and coaching in relevant self-care strategies and (2) training and supervision procedures. The development of a protocol of standardized content and training will ensure a comprehensive knowledge base and consistent reproducible delivery of the intervention content.
7. Confirming stakeholder acceptability: Stakeholder acceptability will be optimized throughout the design process by involving consumers, consumer advocacy group, allied health professionals, medical oncologists, and clinical NET nurses in the development of the phone-based nurse-led intervention [53,57]. All members of the stakeholder committee will also review iterative revisions of the intervention and resource manuals.

Phase 3: Pilot/Feasibility Study

Study Setting

The study will be conducted via the Unicorn Foundation website.

Pilot Testing of Intervention

Pretesting the Intervention

Online triaging will be tested by the research team to ensure functionality. A nurse with experience managing NET patients will be trained in intervention delivery, including confirming eligibility of callers, assessing the online triage, and delivery of intervention material. The nurse will also be trained on eliciting and responding to emotional and informational cues, goal setting, and motivational interviewing and will receive feedback on practice sessions. All intervention content will be recorded for quality assurance.

Over a 12-week period, 20 callers will be recruited via the Unicorn Foundation Nurse Hotline and invited to participate in a small-scale pilot study. Callers will be screened to determine their eligibility to participate. Eligibility criteria will be the same as used in phase 1, with the addition of the participant being able to speak as well as understand English to ensure comprehension and effective communication via the Nurse Hotline. Once eligibility is confirmed, callers will be given access to the online triage tool, which will determine the intervention content that will be delivered. Participants will also have the option to receive a nurse-led phone-based follow-up to address any ongoing concerns.

Assessment of Successful Implementation

The success of the implementation of the intervention will be assessed based on the taxonomy of 8 conceptually distinct implementation outcomes. These consist of, acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability [58,59]. Of these outcomes, 3 will be assessed to determine the successful implementation of the intervention. These consist of (1) acceptability and satisfaction with various aspects of the intervention; (2) appropriateness, relevance, and suitability of the intervention; and (3) feasibility, practicability, and suitability for everyday use of the intervention [58,59].

Measurement of the acceptability appropriateness and feasibility domains will consist of a semistructured interview. Both the participants and the provider will be questioned on their level of satisfaction with the content and its delivery as well as the usefulness and practicability of the material. The number of people invited to participate in the pilot study and the percentage who consent to participate will be recorded as a measure of feasibility and indication for suitability of everyday use.

Interviews will be transcribed, coded, and categorized into 2 groups representing functioning and nonfunctioning NETs patient categories. Similar codes across the 2 categories for functioning and nonfunctioning NETs patients will then be explored as global themes informed by ground theory [54,55]. Coding labels will be created by 2 independent experienced qualitative researchers, who will examine and discuss each other's coding and thematic analysis to promote rigor and interrater reliability [56]. These analyses will be used to iteratively refine the intervention.

Data Management

Data Monitoring

The study has received ethics approval from the Human Research Ethics Committee of Peter MacCallum Cancer Centre. No significant risks to participants are anticipated. Questionnaire responses will be scored within 3 working days of being received, so as to ensure that any high distress scores reported in questionnaires will be reported to the treating clinician and/or nurse coordinator in a timely manner. Participants may then be referred to receive treatment from a qualified psychologist; however, this procedure will be determined by, and is dependent upon, each site's standard of care with respect to referral procedures.

Safety

Any adverse or unexpected outcomes that occur as a result of the study will be documented, and copies will be provided to site investigators and the principal investigator within 24 hours. The principal investigator will proceed to report any such adverse event to the Human Research Ethics Committee.

Ethics and Dissemination

Ethics approval was obtained from the Human Research Ethics Committee of Peter MacCallum Cancer Centre (project number 16/08L), Human Research Ethics Committee of the Northern Sydney Local Health District in New South Wales (project number RESP/16/73), Human Research Ethics Committee of the Central Adelaide Local Health Network in South Australia (project number Q20160901), Human Research Ethics Committee of Royal Perth Hospital (project number RGS0000000632), and Human Research Ethics Committee of the Royal Brisbane and Women's Hospital (project number 17/QRBW/400). Results will be widely disseminated to the funding body and oncology conferences and meetings and through peer-reviewed publications.

Results

Currently, the project is progressing through phase 1 and has completed recruitment. A total of 138 participants have been recruited to the study. To date, we have patient-reported outcome data from 122 participants at baseline and 87 participants at 6-month follow-up. Of these, qualitative data have been collected from 35 participants who consented to a semistructured interview. Phase 2 and phase 3 of the project are yet to be completed.

Discussion

Limited research suggests that patients with NETs have significantly impaired QoL compared with the general population [30,60]. However, given the heterogeneity of this diagnosis and the broad spectrum of symptom severity patients may experience [11,21], current research also fails to delineate how this clinical variability impacts patient supportive care needs. This study will address and improve on the availability

of disease-specific information as well as informing the design of supportive care tailored for the unique needs of the NET patient population. Using the Schofield and Chambers framework [40], a tailored intervention will be developed that will provide targeted supportive care for patients with NETs according to the clinical characteristics and psychosocial profile of patients with functioning and nonfunctioning NETs.

This research initiative will be the first concerted effort to differentiate the priorities and needs of patients with functioning and nonfunctioning NETs comparing the QoL, psychological morbidity, health care system experiences, and clinical profile of these 2 distinct NET patient subgroups. This project is innovative, and to our knowledge, this study is a world-first initiative that will collaborate with the NET national advocacy group, consumers, behavioral scientists, medical oncologists, and specialist NET nurses to iteratively design and pilot test a phone-based nurse-led intervention. The expected benefits of this study are that in combining the expertise across disciplines to form collaboration between medical oncologists, professional nurses, behavioral scientists, consumers, and consumer advocacy groups, this initiative capitalizes on multidisciplinary perspectives to develop a model that will improve the supportive care of patients with NETs.

To date, no research has delineated the differences between patients with functioning and nonfunctioning NETs in terms of their experiences, QoL, psychosocial, and daily functioning needs. Therefore, the development of an intervention that targets these differences and can provide tailored supportive care that is accessible to all patients across metropolitan and rural areas has the propensity to optimize current care.

The intervention will build on the existing Unicorn Foundation online platform and phone counseling to improve the current care of patients with NETs by providing targeted tailored support via the Unicorn Foundation website and nurse-led phone-based support hotline. This intervention also has the potential to be accessible to all patients irrespective of their demographical location. This initiative offers a novel, patient-centered approach to the supportive care of patients diagnosed with NETs that will lead the way nationally and internationally. This work will lead to a large-scale randomized controlled trial to evaluate the impact of this novel intervention on patient health outcomes.

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Authors' Contributions

LG, MM, KG, and PS conceived of, designed, and acquired funding for the study. LG developed the study protocol and procedures and obtained ethics approval. LG, KG, AD, MR, TP, NP, MK, DW, DR, GK, SL, JL, AM, MM, MG, and PS are responsible for acquisition of data. LG, KG, and PS are responsible for the analysis and interpretation of data. LG drafted the manuscript. All authors were involved in revising the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EORTC QLQ-C30: Euopean Organization for Research and Treatment core, Quality of Life Questionnaire
GINET21: Gastrointestinal Neuroendocrine QoL Module
NETs: neuroendocrine tumors
PICF: Participant Information and Consent Form
PROMIS: Patient-Reported Outcomes Measurement Information System
QoL: quality of life
SCNS: Supportive Care Needs Survey

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Protocol

Understanding Implementation of a Digital Self-Monitoring Intervention for Relapse Prevention in Psychosis: Protocol for a Mixed Method Process Evaluation

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Abstract

Background: Relapse is common in people who experience psychosis and is associated with many negative consequences, both societal and personal. People who relapse often exhibit changes (early warning signs [EWS]) in the period before relapse. Successful identification of EWS offers an opportunity for relapse prevention. However, several known barriers impede the use of EWS monitoring approaches. Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement, and Recovery (EMPOWER) is a complex digital intervention that uses a mobile app to enhance the detection and management of self-reported changes in well-being. This is currently being tested in a pilot cluster randomized controlled trial. As digital interventions have not been widely used in relapse prevention, little is known about their implementation. Process evaluation studies run in parallel to clinical trials can provide valuable data on intervention feasibility.

Objective: This study aims to transparently describe the protocol for the process evaluation element of the EMPOWER trial. We will focus on the development of a process evaluation framework sensitive to the worldview of service users, mental health staff, and carers; the aims of the process evaluation itself; the proposed studies to address these aims; and a plan for integration of results from separate process evaluation studies into one overall report.

Methods: The overall process evaluation will utilize mixed methods across 6 substudies. Among them, 4 will use qualitative methodologies, 1 will use a mixed methods approach, and 1 will use quantitative methodologies.

Results: The results of all studies will be triangulated into an overall analysis and interpretation of key implementation lessons. EMPOWER was funded in 2016, recruitment finished in January 2018. Data analysis is currently under way and the first results are expected to be submitted for publication in December 2019.

Conclusions: The findings from this study will help identify implementation facilitators and barriers to EMPOWER. These insights will inform both upscaling decisions and optimization of a definitive trial.

Trial Registration: ISRCTN Registry ISRCTN99559262; http://www.isrctn.com/ISRCTN99559262

International Registered Report Identifier (IRRID): DERR1-10.2196/15634

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KEYWORDS

telemedicine; schizophrenia; implementation science

Introduction

Background

Psychotic disorders are common [1], and schizophrenia is one of the top 15 leading causes of disability worldwide [2]. Relapse is common in schizophrenia, with up to 80% of people experiencing one 5 years after onset [3]. Relapse is associated with increased costs to mental health services, with 70% of the UK mental health care costs being for unplanned inpatient hospital care for relapses [4,5] and a similar picture reported in Australia [6]. Relapse is associated with unwanted outcomes such as reduced social functioning [7]. Relapse also reduces the quality of life of both people with psychosis and their carers [8]. More frequent hospitalizations because of relapse are associated with reductions in relationship quality between service users and staff [9]. Staff wanting to intervene during early relapse report that they often struggle to engage with service users who have become mistrustful of their services [10]. In summary, relapses are associated with high financial and human costs, so detecting and intervening promptly to prevent the negative consequences of relapse is a crucial goal for schizophrenia care [11].

Relapse is the culmination of a process of changes that commence days and sometimes weeks before psychosis symptoms reemerge or are exacerbated [12,13]. These early warning signs (EWS) include affective changes and incipient psychosis. Although a Cochrane review of interventions targeting recognition and management of EWS of relapse in schizophrenia found significant effects for reduced relapse and rehospitalization rates [14], trial quality was poor regarding randomization, concealment, and blinding. Therefore, these interventions need to be more rigorously evaluated using high-quality randomized controlled trial (RCT) methodologies. Until this happens, relapse prevention interventions based on EWS cannot be recommended for routine implementation within health services [14].

Further barriers to implementation of approaches focused on EWS include their uncertain diagnostic utility [13], which may result in unnecessary intervention from mental health staff (false positives). Furthermore, in mental health services, the delivery of treatment through scheduled and routine appointments can result in EWS being missed because these experiences may not coincide with scheduled visits, thus reducing the opportunity for detection during times of actual need [15]. Finally, service users can be apprehensive about telling staff how they feel because this could trigger unwanted interventions such as hospitalization [16], which may act as a barrier to help seeking. Fear of relapse is linked to service users having more traumatic experiences of psychosis and hospital admission and greater fear of symptoms such as voices and paranoia [17] and experiencing fear of relapse appears to be linked to actual relapse events [18].

Digital interventions may enhance relapse prevention through the prompt identification and communication of EWS of relapse. The use of and enthusiasm for digital interventions for psychosis is reasonably high in service users [19-21], and current evidence of digital interventions' acceptability and adherence rates suggests that these approaches are feasible [22]. Therefore, multiple strands of evidence suggest that it is time to develop a digital intervention to enhance relapse prevention and to test using RCT methodology. Implementation research explores the transfer of interventions from clinical trials into general usage [23]. Although RCTs are considered to be the most rigorous way of evaluating effectiveness in the medical context by providing substantial rigor and strong internal validity; in contrast, external validity (ie, implementation outcomes such as whether the intervention will be utilized within routine clinical practice) is often compromised [24]. Therefore, RCT methodologies alone may not answer research questions about implementation.

Early Signs Monitoring to Prevent Relapse in Psychosis and Promote Well-Being, Engagement, and Recovery Study

Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement, and Recovery (EMPOWER; ISRCTN: 99559262) is a proof-of-concept, cluster randomized controlled trial (c-RCT) to establish the feasibility of conducting a definitive RCT comparing EMPOWER against treatment as usual. This aim will be addressed by establishing the parameters of the feasibility, acceptability, usability, safety, and outcome signals of an intervention as an adjunct to usual care that is deliverable in the UK and Australian community mental health service settings. The EMPOWER study has approvals from the West of Scotland Research Ethics Service (GN16MH271 Reference 16/WS/0225) and Melbourne Health Human Research Ethics Committee (HREC/15/MH/344). The specific aims of EMPOWER are as follows:

1. to enhance the recognition of EWS by service users and their carers,
2. to provide a stepped care pathway, that is either self-activated or in liaison with a community health care professional (and a carer if a person has one), and
3. to then trigger a relapse prevention strategy that can be stepped up to a whole team response to reduce the likelihood of psychotic relapse.

EMPOWER is a just-in-time adaptive intervention (JITAI) [25]. JITAI is a term used to describe an intervention design that aims to address the dynamically changing needs of individuals via the provision of the type or amount of support needed at the right time and only when needed [26]. The EMPOWER app is a key part component of the EMPOWER intervention; the app prompts people with psychosis to input data once a day (through pseudorandom mobile phone invitations) via a repeated sampling method known as ecological momentary assessment (EMA) [27]. There are 22 questions that correspond to 13 different domains (activity, anxiety, coping, delusions, fear of recurrence, feeling threatened, hope, mood, other people, precipitants—such as sleep, seeing things, self, and voices—with an optional additional personal item) described further in the main trial protocol.

During the first 4 weeks of app usage, a baseline is established, which enables the EMPOWER algorithm to calculate the magnitude of future changes to support decision making.

Following the baseline period, EMPOWER has the potential to trigger a response (decision point, in JITAI taxonomy) every time a participant responds to an EMA prompt (or fails to respond to a prompt for several days). Data entered by the participant responding to an EMA prompt were analyzed by the algorithm, resulting in one of the following responses: (1) if the algorithm detected no overall change in well-being, a generic message is randomly generated; (2) if the algorithm detected a small change (defined as an increase of over 1 SD from baseline) when a message tailored to the specific domain breach was generated. For example, if 1 SD change in sleep was detected, then the message featured sleep content; and (3) if the algorithm detected a higher change (defined as a change of over 2 SD away from baseline over 3 days), then this results in a check-in prompt (which is described further in the main trial protocol).

The EMPOWER system also allowed participants to use the app to view periodic graphs of their reported data (raw EMA data) and keep a diary of how they are feeling and why (stored locally only). Peer support workers helped set up and individualize the app for users and facilitated information exchange through their own lived experience of mental health problems to augment the individualized self-management aspect of support available via the app. Service users could review their app data with peer support workers as a means of promoting curiosity and reflection on the patterns of well-being over time. Regular telephone contact from peer support workers for the duration of the study aimed to maintain participant motivation for continued engagement with the app. Peer support worker calls also provided an opportunity for routine troubleshooting of any technical issues that arose with the app and for the identification of any adverse effects from the intervention.

The EMPOWER study aimed to recruit up to 86 service users between participating community mental health services in Glasgow (the United Kingdom) and Melbourne (Australia) along with staff members and relatives or carers (if the participant wishes this) who support a service user. EMPOWER meets the definition of a complex intervention by the Medical Research Council (MRC) [28]: it has various components, is being tested across 2 international sites, and includes mental health staff and carers as participants in addition to service users.

Mental health service users' perspectives about interventions are rated low in the evidence hierarchy, with RCT evidence (especially in systematic reviews) coming out on top [29]. However, even with strong RCT evidence, no relapse prediction system for schizophrenia will be useful if it is not able to be integrated into clinical care and used by clinicians and patients [30]. Furthermore, a recent proof-of-concept trial for a digital intervention in psychosis concluded that more research was needed to understand service users' and other stakeholders' perspectives on digital health systems to maximize implementation [15]. The design of digital interventions for mental health problems such as psychosis could be optimized if interventions are both valued by staff and patients and, therefore, compatible for long-term use and meeting clinical and scientific standards [31]. Use of current RCT methodologies in understanding complex interventions falls short of comprehensively explaining interventions [32]—with qualitative research being recommended [33] to enhance understanding. The benefit of qualitative implementation research exploring user experiences is illustrated by another study that identified barriers and facilitators to implementation for a digital intervention for bipolar disorder [34], which would have been missed if the focus was only on predefined outcome measures using a standard RCT approach. Service users reported that they felt motivated to use the intervention because of their positive relationships with the research team delivering the intervention.

Process evaluations are studies that run alongside a clinical trial, earning them the nickname of *trial siblings* [35]. Process evaluations look into the different components of a complex intervention, how it is delivered, and what happens when people interact with an intervention [36]. Process evaluations can improve the validity and interpretation of outcomes, help refine the intervention, and provide necessary information to help inform upscaling decisions for digital interventions. Therefore, a process evaluation will help answer questions about implementation that the EMPOWER c-RCT alone cannot [24]. In a pilot study such as EMPOWER, process evaluators are usually interested in facilitators and barriers to implementation so that strategies to ensure quality implementation can be put in place in time for a definitive evaluation [37]. A process evaluation can also support the development of implementation theories [37] that provide conceptual tools for researchers to understand, describe, and explain key aspects of dynamic and emergent implementation processes observed during trials for mental health interventions [38-40], including digital interventions for schizophrenia [41].

A process evaluation with a key focus on the usage of qualitative methods can enhance the understanding of the implementation process during the EMPOWER trial and illuminate user perspectives on key implementation issues such as acceptability, feasibility, and deliverability. As highlighted within their literature review of process evaluation frameworks, Marr et al [36] express concern that there is a common assumption within process evaluation frameworks that the interaction with an intervention is experienced in much the same way by different stakeholders and across different settings. We argue that given the complex and multicomponent nature of the EMPOWER intervention, the targeting of service users, carers, and mental health staff within the intervention program theory, and the intervention being tested across 2 international sites, it is doubtful that a process evaluator could identify key evaluation domains utilizing a predefined framework. Therefore, it was considered necessary to develop a process evaluation framework suited to the needs of trialists who wish to make decisions about potential upscaling and to ensure better that the needs of service users, carers, and mental health staff are addressed.

Early Signs Monitoring to Prevent Relapse in Psychosis and Promote Well-Being, Engagement, and Recovery Process Evaluation Aims

In no particular order of importance, we aim to use the process evaluation for the following:

1. To understand the feasibility process of recruitment into the EMPOWER c-RCT by mapping out barriers and facilitators, which may be useful learning for a future full-scale trial.
2. To use the data collected after the recruitment is completed to develop a deep understanding of the experiences of the diverse group of stakeholders involved in the EMPOWER c-RCT, including members of the research team. A particular focus will be on identifying barriers and facilitators for implementation, acceptability, and feasibility.
3. To develop an implementation theory to understand and explain important aspects of the implementation process during the trial, including the impact of context (including psychological changes) on observed implementation outcomes.

We will now describe how the process evaluation aimed to address these through the development of a process evaluation framework and several key studies.

Methods

Process Evaluation Paradigm and Design

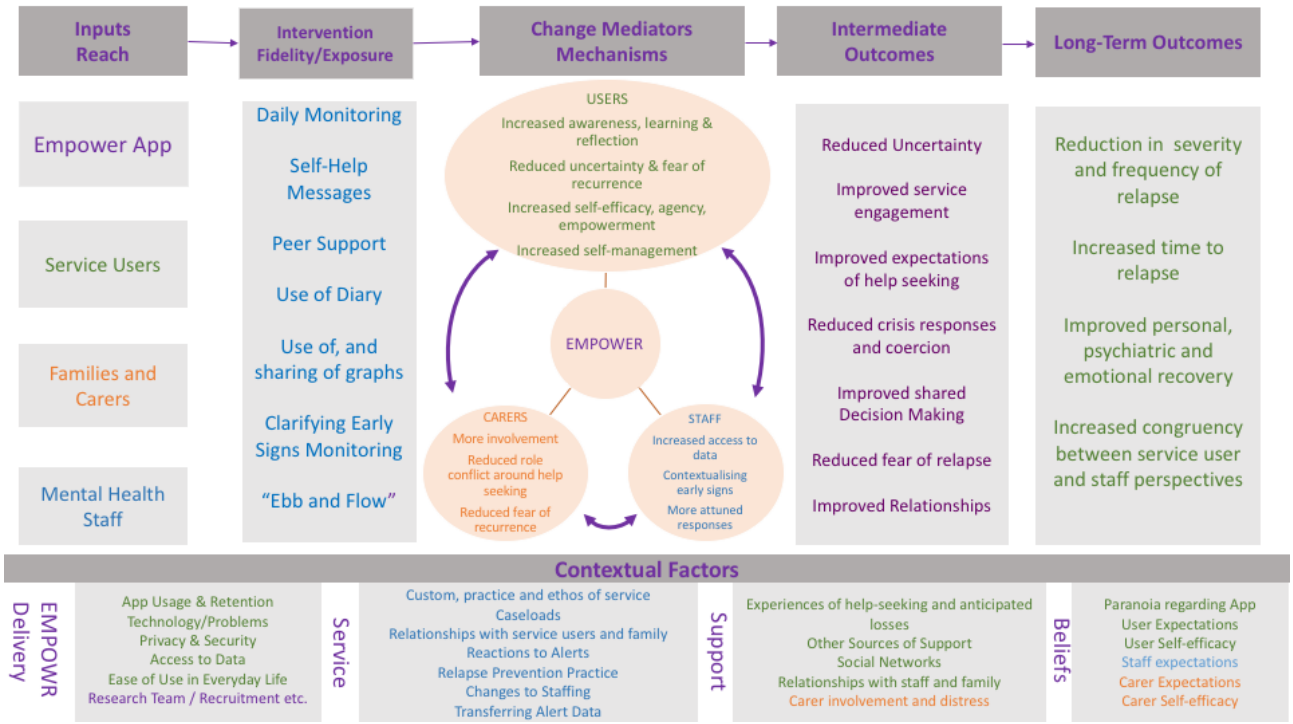
The MRC framework for process evaluations [37] highlights the importance of integrating mixed methods results from process evaluations to better understand what is observed within clinical trials. An explicit epistemological stance is also recommended as a way of reconciling the paradigms of quantitative and qualitative approaches within a single process evaluation [42]. However, our literature review suggests that epistemological positions invoked within process evaluations are not always reported within published protocols. We present a brief description of how we arrived at our epistemological stance, and how this shaped methodological choices.

Conjunctive theorizing (aiming to create appropriately complex rather than simplified abstractions of organizational phenomena) [43] is a recommended approach within implementation research [44] because such an approach situates implementation as subject to multiple interacting influences. With this in mind, it was decided to approach our process evaluation by choosing a research paradigm that focuses on understanding implementation from multiple stakeholder viewpoints. Constructivism presents such a paradigm [45]. Constructivism, although commonly assumed to be associated with qualitative enquiry, is not necessarily aligned with any particular methodological stance [46], and therefore, it provided no prescriptive guidance for methods chosen within our process evaluation. However, adopting a constructivist paradigm was critical in thinking about how to best develop research questions and choose methods that would maximize the understanding of participant experiences and develop a theory for interpreting these. This approach has been successfully used by Maar et al [36]. They reported that their approach resulted in process evaluation data that were relevant to their stakeholders and allowed for emergent understandings of implementation throughout the trial.

Designing the Early Signs Monitoring to Prevent Relapse in Psychosis and Promote Well-Being, Engagement, and Recovery Constructivist Approach to Process Evaluation

Following the selection of an epistemological paradigm, the development of our process evaluation framework (Figure 1 was achieved through the following steps:

Figure 1. The logic model-based process evaluation framework for the Early Signs Monitoring to Prevent Relapse in Psychosis and Promote Well-Being, Engagement, and Recovery (EMPOWER) study.



1. A process of mapping out the key EMPOWER components as listed in the trial protocol.
2. Analysis of key implementation themes constructed from formative qualitative work conducted before the trial involving 25 focus groups held with mental health staff, carers, and service users across international sites in both the United Kingdom and Australia [47].
3. A literature review of digital health evaluation issues, particularly those relevant to psychosis.
4. Choice and application of a process evaluation framework.
5. A final process of validity checking, where the proposed process evaluation framework developed from steps 1 to 3 was presented to researchers who had developed EMPOWER.

Formative Qualitative Work

Following mapping out key EMPOWER components as described in the protocol (step 1), our formative qualitative work conducted in advance of the trial [47] was key to developing the process evaluation framework (step 2 of our process) and will be described briefly. The person-based approach to intervention evaluation [48] provided a useful guide for structuring the qualitative data as the process evaluation team developed the framework. Qualitative research is valued within the person-based approach because it allows exploration of participants' understandings of factors or processes involved in intervention implementation. The formative qualitative work guided the process evaluators to develop process evaluation domains (based upon expected implementation facilitators and barriers) relevant to mental health staff, service users, and carers. For example, service user participants predicted that app user experience would be a key implementation factor, and therefore, the qualitative interview schedule (see Study 2A) had questions to explore this.

Brief Literature Review of Psychosis-Specific Evaluation Issues

Our formative qualitative work also suggested both carers and service users (but especially service users) feel that they are in a disempowered position compared with staff within the current relapse management. Our literature review (step 4) identified that structural symbolic interactionism (a social theory) [49] had been used as a theoretical framework to understand power differences in interactions between mental health staff and service users in psychosis research within a constructivist paradigm [50]. When mental health staff believe someone diagnosed with a psychotic disorder is experiencing relapse, they prioritize their *risk management* role that has more positional power than role enactments focused on service user experiences [50]. In other words, service users reported feeling unable to influence decisions made by staff about treatment during this time and reported that their views of the situation were not valued.

Structural symbolic interactionism posits that individuals adopt positions that are recognized social categories (eg, being a carer). According to structural symbolic interactionism, a role is a set of expectations associated with a position, such as service user expecting a mental health professional to have a specific set of skills to manage relapse in psychosis [50]. At its heart, structural symbolic interactionism posits that people in their roles have agency when they interact both with each other and with interventions, but social structure always constrains interactions. For example, service user interactions are constrained by being in a relatively disempowered social role compared with the staff. Overall, although constructivism invites researchers to consider that all experiences are constructed, it falls short at explicitly considering how different people in their roles interact together and how existing power differentials might shape these interactions. Therefore, we used structural symbolic interactionism to enable us to think critically about power and ensuring the subjective views, and implementation experiences of relatively disempowered groups such as service users are valued in this process evaluation.

Choice and Application of a Process Evaluation Framework

Our brief literature review also revealed a tension in process evaluation research, where research could be focused on implementation outcomes valued by mental health staff, service users, and carers [36] or be focused on addressing implementation outcomes valued by clinical researchers [37]. This was an important consideration because the overall aim of our process evaluation is to make an evidence-based comment on the acceptability, feasibility, and deliverability of the EMPOWER intervention. Although stakeholder implementation outcomes are important, they are not the whole story, and data also need to be suitable for researchers who work in clinical trials. Our attempt to address this tension within our constructivist paradigm is discussed next.

A logic model is a diagrammatic representation of an intervention, describing anticipated delivery mechanisms (eg, how resources will be applied to ensure implementation), intervention components (what is to be implemented), hypothesized mechanisms of impact (the mechanisms through which an intervention will work), and intended outcomes [51]. Logic models are recommended as a way of documenting the core functions of a process evaluation and providing a way to structure process evaluation findings. The logic model presented here (Figure 1) represents a process evaluation framework developed to be sensitive to the unique worldview of staff, service users, and carers. Choosing to incorporate the MRC process evaluation framework ensures that data generated during our process evaluation are valid for making accurate decisions about intervention implementation and improvement and also in contributing to the implementation research field more generally. In line with our constructivist paradigm, this pragmatic step reflected our view that trial researchers and staff are an active part of the enquiry and that process evaluation outcomes are not objective data but are shaped by researcher choices.

A lack of shared terminology within process evaluations can produce challenges when comparing process data from similar interventions across different trials [52,53]. This reduces the opportunity for inclusion of process data within systematic reviews. Utilizing the MRC process evaluation framework (enhanced by including the construct of *exposure* from the study by Matthews et al [54] to foreground the views of end users

explicitly) provided the following taxonomy of key process evaluation terminology:

1. Reach: The extent to which the intervention reaches the target audience.
2. Fidelity: The extent to which the EMPOWER intervention is delivered as intended.
3. Exposure: The extent to which participants received and understood the different elements of the intervention.
4. Mechanisms of impact: The intermediate mechanisms through which an intervention creates an impact. This information is used to develop theories to understand why interventions reach implementation outcomes observed in trials.
5. Context: Factors external to the intervention that may influence its implementation or whether its mechanisms of impact act as intended.

Overall, our process evaluation framework builds upon the definition of context utilized within the MRC framework by considering what aspects of context are important for mental health staff, carers, service users, and researchers within the EMPOWER study and for valuing each group. Therefore, we hope that our process data will be specific enough to be relevant to the unique perspectives of our diverse stakeholders but general enough to allow for the inclusion of process characteristics within implementation evidence synthesis [55].

Finalization of Process Evaluation Framework and Validity Checking

The validity of relationships posed within a logic model is reported to be strengthened through triangulation [56]. Therefore, the finalization of process evaluation (step 5) domains and the construction of the logic model (Figure 1) was facilitated through a discussion between the process evaluators and the research team. The final step was an iterative process involving critical feedback from members of the EMPOWER research team (including investigators and trial managers) working in both the United Kingdom and Australia. Ultimately, this step served as a final validity check to ensure that the proposed framework also made sense to the research team who had designed the intervention.

Planned Process Evaluation Studies

The next subsection describes the planned process evaluation studies and their intended integration. As per MRC process evaluation guidance [37], all studies are based upon key areas of interest within our process evaluation framework (Figure 1), which is briefly described for each study in turn. The process evaluation studies were or will be carried out by a Doctor of Philosophy student (SA), a clinical psychology trainee (SBe), and a Master's student (BM) who are semi-independent from the research team. SA and SBe are supervised by the chief investigator of the EMPOWER trial (AG). BM is supervised by SB and SA. For all studies, the process evaluators will be blind to any c-RCT outcome until it is published. Overall, all 6 studies inform each other by exploring implementation from the viewpoints of trial staff, mental health staff, service users, and carers.

Study 1A: In-Depth Ethnographic Exploration of Recruitment

Background

Developing an understanding of the context of the recruitment process is important in understanding implementation feasibility [57]. Ethnography is recommended within process evaluation of complex interventions because this method enables process evaluators to understand process data within its social context and can produce internally valid data that can enhance the development of implementation theories [58]. Beyond standard ethnographic observations of how the researcher team carries out implementation processes, trial documents such as protocols and minutes of meetings are recommended as an essential source of ethnographic enquiry to understanding implementation more thoroughly [59].

Aim

The study aims to provide an account of the context in which recruitment to the trial occurred (Process Evaluation Aim 1).

Process Evaluation Framework

The process evaluation framework includes contextual factors.

Status

Data collection is complete, and analysis is ongoing.

Ethnography

A detailed analysis of minutes from meetings held in both the United Kingdom and Australia to provide a detailed account of recruitment concerning implementation feasibility and lessons for potential upscaling.

Study 1B: Focus Group of Researcher Recruitment Experiences

Aim

The study aims to create an in-depth understanding of researcher insights about the recruitment process beyond what can be observed in ethnography (Process Evaluation Aim 1).

Process Evaluation Framework

The process evaluation framework includes contextual factors or EMPOWER delivery.

Focus Groups

After initial recruitment, the UK and Australian focus groups were run with the research assistants, trial manager, and chief investigator to enquire about their experiences of the recruitment process. A focus group schedule can be seen in Multimedia Appendix 1.

Status

Data collection is complete, and analysis is ongoing.

Analysis

Focus groups will be transcribed verbatim. Posttranscription, the focus group data will be analyzed inductively utilizing a thematic analysis approach [60]. All qualitative data will be stored in the latest version of NVivo, providing a transparent audit trail.

Study 2A: Qualitative Interviews With Service Users, Carers, and Staff

Aim

The study aims to explore participants' experiences of implementing and trialing the EMPOWER intervention, including their perceptions of any barriers and facilitators (Process Evaluation aim 2). Qualitative process data were collected through individually based in-depth interviews.

Process Evaluation Framework

The process evaluation framework includes all the factors.

Interviews

An interview guide was developed for each stakeholder group: mental health staff, carers, and service users. The service user interview schedule was developed to explore service user experiences of key components of the EMPOWER intervention (including *nondigital* areas such as interacting with peer support workers) as listed in the process evaluation framework. Mental health staff's and carer's interview schedules were developed to explore how these groups interacted with the intervention both directly and indirectly through interactions with a service user enrolled in the study. Furthermore, all interview schedules were designed to explore further anticipated mechanisms of change developed from formative qualitative work [47]—all schedules can be seen in Multimedia Appendices 2-4.

Participants

The participants include staff, service users, and carers in the United Kingdom and Australia.

Recruitment and Procedure

Within the United Kingdom, we purposively recruited a subsample of service users who provided their informed consent to participate in the EMPOWER study and who were randomized to the EMPOWER intervention arm. The purposive sampling strategy for approaching service user participants was developed from early-stage observations of the recruitment process. These early observations suggested that the following features might be relevant implementation factors: service user gender, service users inputting the same score every day (which would impact on the ability of the intervention to detect change), frequency of engagement with peer support workers, and whether a participant had experienced a relapse and an adverse event during intervention usage [61]. Therefore, we aimed to speak to participants who demonstrated a variety of the aforementioned characteristics to understand their experiences. We aimed to approach participants for interviews throughout the trial (following completion of baseline and during the 12-month follow-up period). The decision to collect qualitative interview data throughout the duration of the trial was to try and naturalistically capture the varied and evolving experiences of different participants over time.

Ethical approval for qualitative interview work with mental health staff, carers, and service users was received as part of an ethics amendment from West of Scotland Research Ethics Service (GN16MH271 Ref: 16/WS/0225) and Melbourne Health (HREC/17/MH/97 Ref: 2017.010). During the amendment application, it was decided by the ethics service that, because interviews with mental health staff and carers linked to a service user would involve them reflecting upon the service user's experiences, mental health staff and carers will only be invited to participate in qualitative interviews if a service user provided their informed consent for this.

If a participating service user gave consent to the interview staff, we approached the mental health staff who had been involved in responding to ChIPs associated with changes in EWS or relapse episodes (as defined by the program theory) during their involvement in the study. If the service user provided consent to interview a carer, their carer was invited to participate soon after the service user was interviewed.

Status

Data collection has finished, and analysis not yet complete.

Analysis

Interviews will be transcribed verbatim. Posttranscription, the interview data will be analyzed inductively utilizing a thematic analysis approach [60].

Study 2B: Qualitative Interviews with Early Signs Monitoring to Prevent Relapse in Psychosis and Promote Well-being, Engagement, and Recovery Trial Staff

Aim

The study aims to explore trial staff experiences of implementing key EMPOWER intervention components (peer support work and ChIPs), including their perceptions of any barriers and facilitators (Process Evaluation Aim 2). Qualitative process data were collected through individually based in-depth interviews.

Process Evaluation Framework

The process evaluation framework includes contextual factors or EMPOWER delivery.

Participants

The participants include peer support workers, trial staff involved in developing the peer support role within EMPOWER, and trial staff responsible for ChIPs.

Interviews

Interview schedules were developed for peer support workers and staff who are responsible for ChIPs. The interview schedule for peer support workers explores the delivery of peer support from the perspective of peer support workers by exploring their interactions with service users, which can include discussing EMPOWER app data. The interview schedule for trial staff involved in developing the peer support worker role explores their perceptions of how the peer support worker role has emerged from conception to delivery within the trial. Finally, the interview schedule for staff responsible for ChIPs explored the delivery of this intervention component from the perspective of the trial staff involved. All interview schedules are available in Multimedia Appendices 5-7

Recruitment and Procedure

All relevant trial staff members in both the United Kingdom and Australia were invited to take part in one-to-one interviews.

Status

Data collection has finished, and analysis is not yet complete.

Analysis

Interviews will be transcribed verbatim. Posttranscription, the interview data will be analyzed inductively utilizing a thematic analysis approach [60].

Study 3: Development of Network Models

Background

The EMA data (daily ratings on a 1-7 Likert scale) generated through intervention usage was available to service users in its raw form via the graph function; service users could view their data and opt to share their data with others. However, the same data may reveal relationships between the well-being domains, which EMPOWER assesses. In network models, mental disorders such as schizophrenia are not conceptualized as common causes of symptoms but as conditions that arise from the interaction between symptoms [62]. A potential avenue of network research is the prediction of the course of mental distress from network characteristics of individuals. Network structure may demonstrate early warning signals, a term (distinct from EWS) describing temporal patterns of connectivity, which may indicate the upcoming onset of relapse for a specific individual [63]. Therefore, network models may present a useful means to quantify and understand the context of service user well-being during intervention usage and the relative influence of the 13 different well-being domains. In line with the EMPOWER program theory as defined in the protocol that will be published elsewhere, we are particularly interested in the fear of recurrence [18]. Little is known about such early warning signals in a relapse in psychosis, and it is hoped that exploring routine EMA data collected during the trial may provide an insight into the general phenomenology of well-being over time.

Aim

The study aims to better understand the context of service user well-being during intervention usage by building network models of psychosis during the stable, EWS, and clinical relapse phases—with the 3 states defined as per EMPOWER program theory (Process Evaluation Aims 2 and 3).

Process Evaluation Framework

The process evaluation framework includes change mechanisms or contextual factors.

Network Analysis

Exploratory network analysis will be performed using relevant packages on the most recent version of R.

Status

At the time of writing this paper, the data have not yet been analyzed in any form.

Study 4: Exploratory Analysis of User Engagement

Background

Previous digital schizophrenia research studies use an EMA response rate of 33% for data to be considered reliable [64,65]. Although acknowledging that the criteria for determining EMA response feasibility varies in the literature [66], it is vital to determine what factors are associated with opportunities to maximize engagement. To the best of our knowledge, there are no guidelines for defining a required level of engagement with peer support. For example, a participant meeting a peer support worker 3 times was considered to be sufficient [67] but was not based on firm guidance. Therefore, there is a need to develop summary statistics about the levels of peer worker engagement.

Aim

The study aims to summarize and describe engagement with key components of the EMPOWER intervention and place these within a meaningful context (Process Evaluation Aim 2 and 3). Response to daily EMA prompts will be taken as a proxy for app usage. In addition, engagement with peer support will be defined from the number of actual peer support contacts compared with potential peer support worker contacts. Data will be analyzed retrospectively following completion of the trial.

Process Evaluation Framework

The process evaluation framework includes fidelity or change mechanisms.

Analysis

The analysis will include descriptive statistics of engagement levels (with both app and peer support) that will be triangulated with contact notes and qualitative process evaluation interviews.

Status

Usage data have been analyzed descriptively, but further analysis is not yet complete.

Results

Overview

At the time of writing this paper, no analysis is complete for any study. EMPOWER was funded in 2016, recruitment finished in January 2018. Data analysis is currently under way and the first results are expected to be submitted for publication in December 2019.

Integration of Results

There is currently no consensus on what information is best for making decisions on whether an intervention is feasible for upscaling into a definitive trial [68]. Therefore, we recognized that data from the EMPOWER process evaluation could address a fundamental research question posed by Matthews et al: *Are identified barriers and challenges to implementation of the intervention planned for and surmountable?* [54]. In line with Matthews et al's recommendations, the triangulated overall interpretation resulting from these studies will be presented as a strengths, weaknesses, opportunities, and threats (SWOT) analysis [69] that will list identified implementation barriers

and challenges encountered during the EMPOWER intervention c-RCT, whether these were expected or unexpected, and if the process evaluation data suggest these are surmountable within an upscaled definitive clinical trial. This final result will be presented as an independent report to the relevant decision-making parties with recommendations (if relevant) for adaptations to the intervention.

Discussion

Principal Findings

This protocol describes 6 studies that utilize mixed methods to generate process evaluation data for the EMPOWER trial. These studies inform each other. The process evaluation data will be utilized to develop a SWOT analysis to more fully understand implementation within the EMPOWER pilot c-RCT through implementation outcomes constructed as being meaningful for mental health staff, carers, and service users. Ultimately, the findings from this process evaluation will provide evidence not available from other sources of evaluation within the trial to help inform upscaling decisions. Furthermore, the pilot c-RCT will allow the process evaluators to test the validity of the process evaluation framework by allowing for the emergence of unexpected outcomes within the implementation process. Any such implementation outcomes that deviate from the proposed framework will be used to restructure and refine the logic model to build a process evaluation framework that is more valid for understanding the actual implementation process.

Although the process evaluation framework was developed to be highly relevant to the process evaluation requirements for the EMPOWER study, this process evaluation may nonetheless provide data that are useful to other researchers. Theoretical understandings of how digital interventions create change are in their infancy; therefore, it is recommended that researchers prioritize qualitative methods [70] that foreground the discovery of how participants (in their own words) utilize interventions. Any potential benefit of digital interventions depends on users engaging with an intervention [71]. Engagement with digital interventions consists of 2 definitions: first, the extent to which an intervention is actually used (indicated by nonsubjective quantitative measures such as passively recording frequency of intervention usage), and second, as a subjective experience characterized by attention, interest, and affect (usually indicated through subjective measures such as questionnaires or interviews) [72]—concerningly, substantial heterogeneity in the use of measures has been noted [73]. Little is currently known about what aspects of a digital intervention are relevant for user engagement for a digital intervention for psychosis. This process evaluation will integrate nonsubjective measures (usage statistics) with subjective measures of engagement (through qualitative interviews) to develop a theory for understanding behavioral mechanisms underpinning engagement (or nonengagement) in people with psychosis.

To be suitable for fully informing behavioral change, theories need to capture individual differences and changes over time [74]. Most existing behavioral change theories lack utility for JITAIs because their static nature fails to capture the temporal dynamics of intervention usage over time [25]. Little is known about the subjective user experience of using JITAIs for psychosis. Therefore, the EMPOWER process evaluation provides an opportunity to develop an internally valid theory to better understand relationships between observable and objective measures of intervention usage with the subjective experiences of self-monitoring in people with psychosis. Such an understanding has broader implications for the management of psychosis and can inform the development of digital interventions for people with similar mental health problems, building on learning from previous qualitative work [75-80].

Limitations

This research should be considered within its limitations. The formative qualitative work used to develop our framework included a large sample size for qualitative research. However, it is still not possible to make any claims about generalizability, and because this formative research was based on consultation and was not user led [81,82], its relevance to end users may be limited. Furthermore, there is a risk that important implementation outcomes were not uncovered through our prior qualitative work because of issues such as participants not feeling comfortable speaking within a focus group environment. Therefore, although the process evaluation framework appeared relevant to stakeholder needs constructed from focus group data, this is likely not a complete picture of actual stakeholder needs.

Participation within qualitative process evaluation interviews has been suggested [83] to represent a highly motivated group of service user participants who are not necessarily representative of the target population as a whole. Therefore, although discovering user insights in their own words is a key aspect of our constructive process evaluation approach, we may miss valuable user insight from this methodological choice. Furthermore, trial staff (who are members of the EMPOWER research team) may feel uncomfortable speaking freely within interviews because of the limited pool of participants, meaning that it may be possible to identify participants from quotes within qualitative data. A further significant limitation is that data collection ended for several studies before this protocol could be submitted for publication. However, formal data analysis was not initiated until the finalization of the protocol for publication.

Conclusions

There are strengths to this study. By transparently stating our process evaluation development, aims, and proposed studies, we hope to contribute to good practice within this field [84] and share our learning. Publication of the protocol does not prohibit further process evaluation studies but ensures clarity that any such further study will be to explore unexpected consequences that were not anticipated within our predefined process evaluation framework. In line with recent recommendations to improve implementation research [53], the development of our constructivist process evaluation framework explicitly aimed to explore understandings between stakeholders and implementation science researchers.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group schedule for Study 1A.
[DOCX File , 14 KB - resprot_v8i12e15634_app1.docx]

Multimedia Appendix 2
Interview schedule for study 2A.
[DOCX File , 18 KB - resprot_v8i12e15634_app2.docx]

Multimedia Appendix 3
Interview Schedule for Process Evaluation work done on Study 2A.
[DOCX File , 22 KB - resprot_v8i12e15634_app3.docx]

Multimedia Appendix 4
Process evaluation interview schedule for service users.
[DOCX File , 22 KB - resprot_v8i12e15634_app4.docx]

Multimedia Appendix 5
Interview schedule for study 2B.
[DOCX File , 27 KB - resprot_v8i12e15634_app5.docx]

Multimedia Appendix 6
Interview schedule for Study 2B.
[DOCX File , 25 KB - resprot_v8i12e15634_app6.docx]

Multimedia Appendix 7
Interview Schedule for Study 2B.
[DOCX File , 18 KB - resprot_v8i12e15634_app7.docx]

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Abbreviations

c-RCT: cluster randomized controlled trial
EMA: ecological momentary assessment
EMPOWER: Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement, and Recovery

EWS: early warning signs
JITAI: just-in-time adaptive intervention
MRC: Medical Research Council
RCT: randomized controlled trial
SWOT: strengths, weaknesses, opportunities, and threats

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Protocol

Quantification of Airborne Resistant Organisms With Temporal and Spatial Diversity in Bangladesh: Protocol for a Cross-Sectional Study

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Abstract

Background: Antimicrobial resistance is a widespread, alarming issue in global health and a significant contributor to human death and illness, especially in low and middle-income countries like Bangladesh. Despite extensive work conducted in environmental settings, there is a scarcity of knowledge about the presence of resistant organisms in the air.

Objective: The objective of this protocol is to quantify and characterize the airborne resistomes in Bangladesh, which will be a guide to identify high-risk environments for multidrug-resistant pathogens with their spatiotemporal diversity.

Methods: This is a cross-sectional study with an environmental, systematic, and grid sampling strategy focused on collecting air samples from different outdoor environments during the dry and wet seasons. The four environmental compartments are the frequent human exposure sites in both urban and rural settings: urban residential areas (n=20), live bird markets (n=20), rural households (n=20), and poultry farms (n=20). We obtained air samples from 80 locations in two seasons by using an active microbial air sampler. From each location, five air samples were collected in different media to yield the total bacterial count of 3rd generation cephalosporin (3GC) resistant *Enterobacteriaceae*, carbapenem-resistant *Enterobacteriaceae*, vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus*.

Results: The study started in January 2018, and the collection of air samples was completed in November 2018. We have received 800 air samples from 80 study locations in both dry and wet seasons. Currently, the laboratory analysis is ongoing, and we expect to receive the preliminary results by October 2019. We will publish the complete result as soon as we clean and analyze the data and draft the manuscript.

Conclusions: The existence of resistant bacteria in the air like those producing extended-spectrum beta-lactamases, carbapenem-resistant *Enterobacteriaceae*, vancomycin-resistant *Enterococci*, and methicillin-resistant *Staphylococcus aureus* will justify our hypothesis that the outdoor environment (air) in Bangladesh acts as a reservoir for bacteria that carry genes conferring resistance to antibiotics. To our knowledge, this is the first study to explore the presence of superbugs in the air in commonly exposed areas in Bangladesh.

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KEYWORDS

antimicrobial resistance; airborne resistomes; air quality; global health; planetary health; environmental risk assessment

Introduction

Antimicrobial resistance is considered a rapidly progressive global public health issue with the potential of environmental transmission to a larger extent. However, very little information is available on the transmission of antimicrobial resistance through the air. Additionally, the capacity to carry and propagate resistance of these resistomes is poorly studied worldwide. There is a recognized need to examine the existence of such bacteria that have the ability to confer resistance through atmospheric air. Bangladesh is an important location to study this pathway. This study can provide critical insight into antimicrobial resistance transmission and help determine where efforts could be implemented to reduce environmental transmission.

Antimicrobial resistance is a widespread and alarming issue in global health, causing more than 700,000 deaths every year [1]. In Bangladesh, the insufficient and poor guidelines for the disposal of antibiotic residues into the environment from pharmaceuticals or clinical settings and the high population density have made its environment favorable for the wide dissemination of antimicrobial resistance. In addition to use in human therapy, antibiotics are used extensively in animal farming and eventually, a large amount of antibiotics and their residues are disseminated into the environment through both air and water [2]. Again, environmental contamination with human and animal-originated bacteria contributes significantly to the mechanism of development of extensive antimicrobial resistance [3]. This occurs when the unlimited genes contained in the bacteria circulating in air invade other pathogenic bacteria through mobile genetic elements and may be transformed to antibiotic resistance genes like integrons, transposons, and plasmids [4,5].

Based on few studies conducted on the presence of antimicrobial resistance in the environment, the spatial and seasonal diversity of antibiotic resistant bacteria are well established [6-11], but the diversity in air is not well studied. In case of detection of airborne resistomes, most of the studies have been conducted in clinical settings, pharmaceutical industries, animal farms, laboratory settings, or highly polluted sites [12-27]. However, there is a gap in the quantification of airborne resistomes in both high-risk and low-risk areas like urban versus rural areas and poultry/industry versus nonpoultry/residential areas in the same study area as well as their transmission dynamics with seasonal differences.

Additionally, several anthropogenic events also enhance the ability of antibiotic resistance genes to be transferred horizontally and pose a further risk for the environment to act as a reservoir for resistant bacteria [28,29]. Unfortunately, we are not quite aware of the presence of resistant genes in the air or their capability of transmission to humans. This needs to be explored, especially the transmission potential of pathogenic resistant bacteria [30]. Another less-exposed area of research is the climatic and seasonal variability (eg, humidity, rainfall, temperature) in the environmental transmission of antimicrobial resistance. Therefore, the quantity of organisms and diversity of antibiotic resistance genes will vary depending on the air in different environments and seasons. The alarming situation is the presence of the same genes in clinically ill patients, which is supported by different studies [31-33]. A study [34] conducted on the hospital air environment yielded 25% multidrug-resistant organisms. This study will address not only the presence of resistant organisms in the air, but also the clonal distribution of those organisms based on seasonal variation. Therefore, we will be able to identify the risky environments effectively.

The main study objective is to detect the existence of resistomes in the air samples from outdoor environments of Bangladesh, which carry genes that confer resistance to antibiotics with temporal and spatial diversity. We hypothesize that the outdoor environment (air) in Bangladesh acts as a reservoir for bacteria carrying genes that confer resistance to antibiotics with temporal and spatial diversity. The specific objectives of the study are as follows:

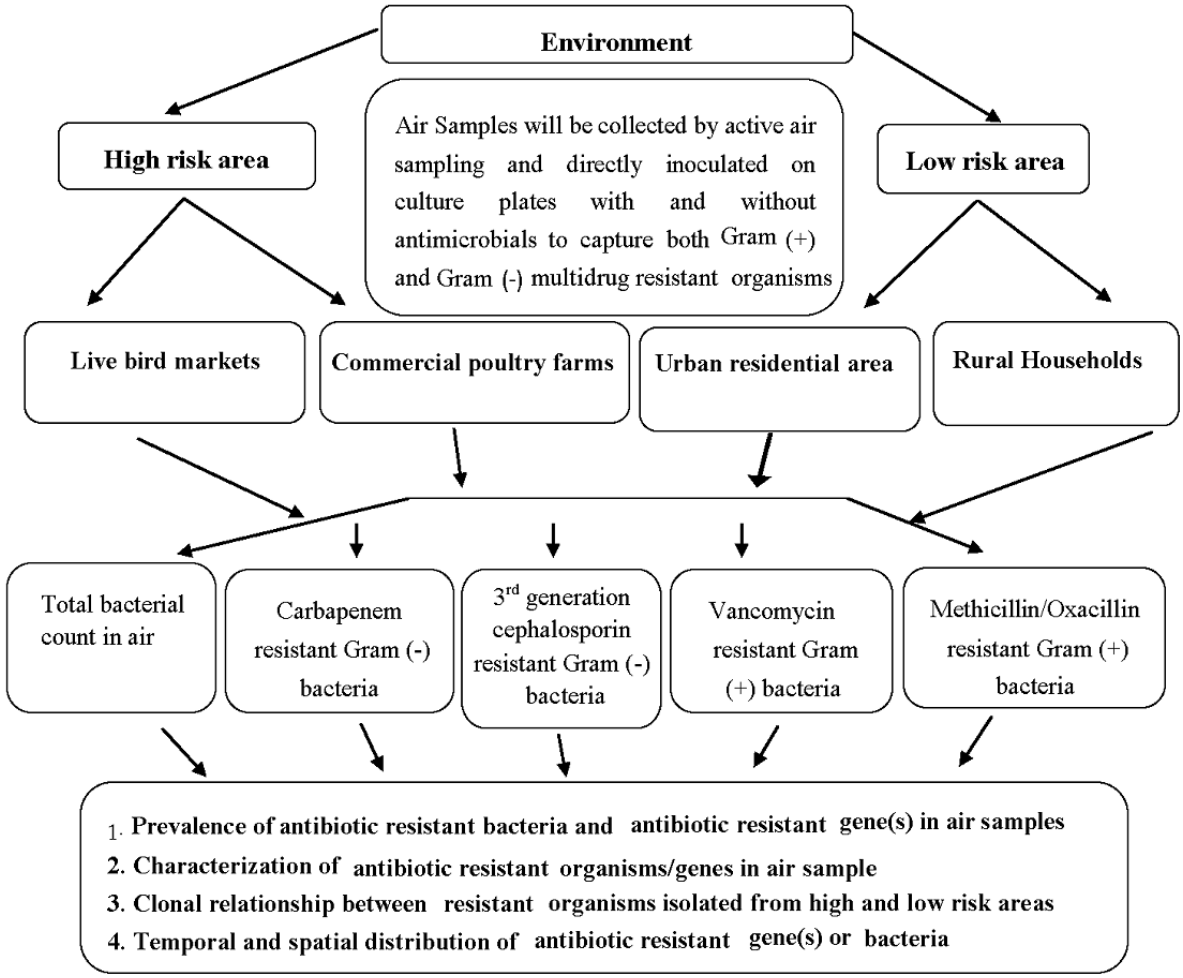
1. To determine the prevalence of antibiotic-resistant bacteria in the air samples of outdoor environments (both poultry and residential) in Bangladesh that carry genes conferring resistance to antibiotics.
2. To characterize antibiotic-resistant organisms using different phenotypic and genotypic methods.
3. To explore the clonal relationship between antimicrobial resistant organisms isolated from high- and low-risk areas.
4. To identify the temporal and spatial distribution of resistant bacteria in outdoor environments of Bangladesh.

Methods

Overview

This is a cross-sectional pilot study designed to collect air samples from high-risk and low-risk environments in urban and periurban settings of Bangladesh, mainly the Dhaka metropolitan area and Mirzapur Upazilla (subdistrict) of Tangail District. Environmental systematic and grid sampling will be followed according to approaches described by Keith [35]. This is suitable for finding hotspots for target organisms/genes over a specific period of time, as samples are taken at regularly spaced intervals. Data collection started in January 2018, and the laboratory analysis is currently ongoing. The live bird markets and commercial poultry farms are considered to be high-risk areas, while the urban residential areas and the periurban households are low-risk areas (Figure 1).

Figure 1. Sampling strategy and framework.



Geospatial Mapping

Mapping with GIS software (ArcGIS, Esri, Redlands, California) will plot concentrations of resistant genes and antimicrobial-resistant bacteria in environmental compartments (high- and low-risk areas) in each location using GPS coordinates. Temporal variation will be observed by comparing the magnitude of resistant bacteria and genes in the dry season with those in the wet season.

Collection of Air Samples From Study Sites

Air samples from commercial poultry farms, live bird markets, rural households, and urban residential areas will be collected. All active sampling will be performed using the same Surface Air System Sampler (SAS Super 180 Microbial Air Sampler, Bioscience International, Rockville; Figure 2), with a flow rate of 180 L/min. The following media will be used for collection of samples: standard plate count (SPC) agar (Oxoid, Hampshire, United Kingdom) for aerobic plate count, MacConkey agar (BD Difco, Becton Dickinson, New Jersey) supplemented with cefotaxime (1 mg/L) and MacConkey agar supplemented with meropenem (0.5 mg/L) to obtain gram-negative resistant organisms, Mannitol Salt agar (MSA) (Oxoid) supplemented with oxacillin (8 mg/L), and Slanetz and Bartley (SB) agar (Oxoid) medium supplemented with vancomycin (6 mg/L) to obtain gram-positive resistant organisms. During sampling, the aspirating head will be removed from the air sampler. An identified, closed, and prepared plate will be inserted, and the plate lid will be removed. The aspirating head will be replaced again to cover the plate. The required volume and air flow rate will be adjusted, and the air sampler will be started. Subsequently, the airflow will be directed into the agar surface of the plate and at the end of a cycle, the aspirating head will be removed. The plate will be closed with the lid and removed from the air sampler. An identical method will be followed for different types of agar plates in each location, although the air volume will be different (ie, 1000 L for MacConkey, MSA, and SB agar and 100 L for SPC agar). After sampling, the plates will be carried in a carrying case and transported to the laboratory.

Figure 2. Active microbial air sampler.

Processing and Laboratory Analysis of Air Samples

Analysis of Antibiotic Resistance Genes in the Air Metagenome

According to the manufacturers' instruction and using QIAamp DNA Mini Kit (QIAGEN, Germany), total DNA from the culture sweeps will be extracted after counting colonies on SPC agar plates. The colonies will then be incubated for 44 hours at 37°C. High-throughput sequencing will be performed using an Illumina MiSeq sequencing system (Illumina, San Diego, CA). The downstream analysis quality will be ensured by removing raw reads, with an average quality score below 20 or with length less than 100 bp (101 bp in length) or having three or more ambiguous nucleotides. The high-throughput sequencing will be carried out by the "Index 101 PE" (paired-end sequencing; 101-bp reads and 8-bp index sequence) sequencing strategy. There will be almost the same quantity of clean reads in this manner for each sample. The processing of the call sequences as well as raw fluorescent images will be carried out through a base-calling pipeline (Sequencing Control Software, Illumina). Metagenomic analyses will be carried out with the filtered clean reads (almost 1.6 GB per sample) after removal of the raw reads contaminated by an adapter (>15 bp overlap) or having three or more "N" [36,37]. The antibiotic resistance genes in the samples will be identified through alignment of the Illumina sequencing reads via offline BLAST (Basic Local Alignment Search Tool) against a self-established database. Similarity above 90% and alignments ≥25 amino acids are the identification criteria of a read to be confirmed as an antimicrobial resistance gene based on its best BLAST hit (blastx) [36].

Culture of Samples to Identify Antibiotic-Resistant Gram-Positive and Gram-Negative Organisms

All the culture plates (except SPC) exposed to air during air sampling will be incubated at 37°C, with 44 hours for SB agar and 18-24 hours for MacConkey agar and MSA. After incubation, each plate will be counted for both types of colonies (typical and atypical). To achieve clean/pure cultures, 3-4 phenotypically different isolated colonies will be subcultured from each plate on corresponding antibiotic-supplemented agar media. Following incubation (mentioned earlier), culture sweeps from each plate will be dissolved in tryptic soy broth cryovials containing 30% glycerol. These will be preserved at –80°C for future usage.

Antimicrobial Susceptibility Testing

By using different antibiotic discs, the agar diffusion test will determine the antimicrobial susceptibility as per the Clinical and Laboratory Standards Institute (CLSI 2016) guidelines [38]. Third-generation cephalosporin-resistant isolates will be tested for extended spectrum beta-lactamase (ESBL) production by performing combination disc tests. Vancomycin-resistant *Enterococci* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), and methicillin-resistant *Staphylococcus aureus* (MRSA) will be confirmed by reviewing the susceptibility test results.

Detection of Antibiotic Resistance Genes

Polymerase chain reaction for genes specific for each of the resistance phenotypes (for ESBL: CTX-M, TEM, SHV; for carbapenem: NDM; for VRE: vanA; for MRSA: mecA) will be carried out according to the procedures described previously [39-42].

Genetic Fingerprinting of Isolates

Phenotypically same isolates (with or without similar resistance pattern) obtained from different locations or time periods will be further tested by pulsed-filed gel electrophoresis to determine their clonal diversity and dispersion.

Test for Antibiotic Resistance Plasmid

Plasmid DNA extraction and analysis from resistant isolates will be executed through the rapid alkaline lysis method and horizontal gel electrophoresis in 0.8% agarose gels, respectively [43]. The unknown plasmid size will be assumed by using known standard plasmid marker following gel electrophoresis

for which the plasmids *Escherichia coli* V517 (1.4, 1.8, 2.0, 2.6, 3.4, 3.7, 4.8 and 35.8 MDa), pDK9 (140 MDa), R1 (62 MDa), RP4 (36 MDa), and Sa (23 MDa) will be considered as standards. Both filter mating and broth mating assays will be performed for conjugation at 30°C for 18 hours. The donor will be the resistant bacterial isolates when *E. coli* J53 (AziR, F−) and *E. coli* MC1061 (SmR, F−, nonlactose fermenting) will be recipients. MacConkey agar will be used for the selection of both *E. coli* J53 and *E. coli* MC1061 transconjugants. However, MacConkey agar will contain sodium azide (100 mg/L) and cefotaxime (20 mg/L)/cefoxitin (16 mg/L) for *E. coli* J53 and ampicillin (50 mg/L) for *E. coli* MC1061 transconjugants. The antibiotic susceptibility test will be performed to confirm transconjugant colonies. Using the alkaline lysis method described above, plasmid DNA will be extracted from transconjugants [43].

Estimation of Sample Size

The primary objective of this study is to determine the prevalence of antibiotic resistant organisms with resistance gene characterization in air samples from different locations and during different seasons. However, there are no baseline data available about measuring antimicrobial resistance in air samples. No prior assumptions were possible to show the anticipated variation in different exposures or seasonal contexts, although some prior knowledge has been utilized [29]. In this exploratory study, we have estimated 5% probability and 95% confidence, which requires a sample size of 59, as per the formula for sample size calculation of pilot studies published by Rik Crutzen et al [44]. Owing to the large number of study settings, we have included 80 sampling units for each season, which includes 20 live bird markets, 20 rural poultry farms, 20 periurban households, and 20 urban residential areas. The sampling bias is expected to be reduced through this strategy and will provide robust findings based on repeating the sampling in wet and dry season conditions.

Outcome Variables

The outcome variables that will be assessed are as follows:

1. The prevalence of antibiotic-resistant organisms and resistance genes (positive occurrence of resistant bacteria/genes as a proportion of the number of samples) from each environmental location
2. The geospatial distribution of antibiotic resistant organisms and antibiotic resistance genes in study areas
3. The temporal prevalence of resistant bacteria and concentration of resistant genes in dry and wet season to assess seasonal variation in antimicrobial resistance
4. The identification of high-risk environments for air borne pollution with antimicrobial resistance

Data Analysis Plan

In this study, we will determine the presence of resistant organisms in air samples by total counting (colony-forming units per liter) at different study sites in Bangladesh. Significant differences in carriage rates of antibiotic-resistant organisms (and concentrations of resistant genes) in high- and low-risk environments will be determined by Chi-square and independent *t* tests. Hence, significant predictors will be identified. For identification of significant risk factors, logistic regression analysis will be used. Repeated measures analyses will be applied to examine whether there is significant seasonal variation in the prevalence of antimicrobial resistant bacteria and concentrations of antimicrobial resistance genes (paired *t* test or repeated measures analysis of variance). Count regression models like Poisson, negative binomial, and zero inflated count will be used, where appropriate, for antibiotic resistance count data.

Results

The Research Review Committee and Ethical Review Committee of International Centre for Diarrhoeal Disease Research, Bangladesh, have approved this research protocol (protocol number: PR-17048). A unique study identification number was assigned to all air samples to ensure anonymity of the study sites. The study started in January 2018, and the collection of air samples was completed in November 2018. We have received 800 air samples from 80 study locations in both dry and wet seasons. Currently, the laboratory analysis is ongoing, and we expect to receive the microbiological results by October 2019. After completion of data cleaning and analysis, the manuscript submission is anticipated to be submitted before fall 2020. In addition to publication in a high-impact, peer-reviewed journal and as per the dissemination plan, the study results will be shared with the study participants, with scientific communities, with relevant government authorities, and in related conferences or workshops.

Discussion

Overview

The rise and spread of superbugs have become a key public health and planetary health concern worldwide. Infections caused by multidrug-resistant bacteria are linked to greater mortality rates than antimicrobial-susceptible bacteria [45]. For therapeutic purposes, medically important antimicrobials are used extensively in agricultural and farming industries for disease prevention (eg, prophylaxis and metaphylaxis), treatments, and growth promotions. More than two-thirds of antimicrobials are consumed in the livestock sector each year. It is projected that by 2030, there may be a massive increase (up to 67%) in global antimicrobial use in food-producing animals, especially in Brazil, Russia, India, China, and South Africa (BRICS) [46]. The antimicrobial resistance problem is severe, not only in developed countries but also in nonindustrialized countries. Scarcity of antimicrobial usage policies and substandard hygiene situations are the precipitating factors that drive antimicrobial resistance issue to be more challenging [47].

The burden of the antimicrobial resistance rate depends on the population of a country and its environment. Bangladesh is a highly populated country; therefore, the rate of antimicrobial resistance is extensive due to rapid spread of antimicrobial-resistant organisms. Antimicrobial resistance genes are conferring their resistance value to a wider community including both animals and humans, through close interactions with the environment and the wastes that are disposed in the

environment, directly affecting the food chain [48]. Due to the extensive use of antibiotics as therapeutic and prophylactic in farming, bacterial resistance may be developed by either chromosomal gene mutation or gene acquisition through different mechanisms like transformation, transduction, or conjugation [49]. Continuous accumulation of multiple mutations have caused the genome to become resistant to antibiotics. To screen the antimicrobial resistance genes, whole genome sequencing is an important tool for understanding the antimicrobial resistance mechanisms. Whole genome sequencing helps evaluate the number of mutations and particular mechanisms of the mutated gene that drive antimicrobial resistance to develop new drugs (antibiotic) and diagnose the disease state and treatment process [47]. Primary biological aerosol particles such as bacteria, viruses, pollens, and mold spores are important components of airborne particulate matter (PM), and abundant pathogenic bacteria have been identified from PM2.5 and PM10 samples [50]. However, these compounds from pollution and other sources are not prioritized during analysis. Our study will also focus on the resistant bacteria as an integral part of air pollution.

Intrinsic genetic determinants of resistance factors are harbored by bacteria with macromolecules in the environment. Robust evidence suggests that such macromolecules developing "environmental resistomes" are a source from which clinically relevant bacteria acquire antibiotic resistance genes [51]. Poultry, the most common rural domestic species, is considered a major driver for selection of antimicrobial resistance from the environment to human/animal due to fecal shedding of resistant bacteria. As poultry feces are used as fertilizers and household members share sleeping spaces with poultry animals, antibiotic use in poultry in the last 6 months has been reported by more than 50% poultry owners [37]. Commercial poultry farm areas harbor the antimicrobial-resistant isolates in the air, and humans are easily exposed to these antimicrobial-resistant isolates during inhalation of dust and particles. Consequently, antimicrobial-resistant organisms can build up a strong biofilm in the intestinal tract of humans. Through excretion of stool and other body fluids, these can be spread in the environment. Urban live bird markets are the largest site of bird slaughtering, with no proper waste management setting, and the huge amounts of wastes are directly passed into environment through dust and direct wash out [14].

The importance of environmental compartments as the transmission hub of antimicrobial resistance is well established. However, airborne resistomes and their transmission pathway are poorly studied. Without containment of environmental reservoirs, antimicrobial resistance prevention policy will fail [52]. The occurrence of pathogenic resistant organisms and resistance genes in atmospheric air of different locations will guide researchers and policy makers to adopt new strategies for the containment of this alarming issue. However, further large-scale studies need to be carried out to link the clinically important organisms and airborne resistomes. To achieve this, One Health surveillance needs to be carried out in humans (both healthy and clinical patients), animals, and environments at the national level.

Strengths and Limitations

Regarding the strengths, our study will focus on the air resistomes, which is a less explored environmental dimension of antimicrobial resistance transmission dynamics. To our knowledge, this is the first study to explore the presence of superbugs in the air in commonly exposed areas in Bangladesh. The limitation exists in the small sample size and lack of baseline data from the atmospheric environment of Bangladesh. Therefore, the findings may not be generalizable for all areas in the country.

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Authors' Contributions

MA and MAI conceptualized the idea and developed the study protocol and field methods with study supervision; MA, MAI, MIH, SRS, and NA formulated the laboratory protocols; MA, MAI, and MRI worked on the sample size estimation and analysis plan; MIH and SRS are responsible for the sample processing and laboratory experiments; MA wrote the original draft; and all authors reviewed, edited, and contributed substantially to writing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the International Centre for Diarrhoeal Disease Research, Bangladesh.
[PDF File (Adobe PDF File), 501 KB - resprot_v8i12e14574_app1.pdf]

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Abbreviations

BLAST: Basic Local Alignment Search Tool
CRE: Carbapenem-resistant *Enterobacteriaceae*
CLSI: Clinical and Laboratory Standards Institute
ESBL: Extended-Spectrum Beta-Lactamase
MRSA: Methicillin-resistant *Staphylococcus aureus*
VRE: Vancomycin-resistant *Enterococci*

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Protocol

Photodynamic Therapy Using a New Painless Light-Emitting Fabrics Device in the Treatment of Extramammary Paget Disease of the Vulva (the PAGETEX Study): Protocol for an Interventional Efficacy and Safety Trial

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Abstract

Background: Extramammary Paget disease of the vulva (EMPV) is a rare skin disorder commonly seen in postmenopausal Caucasian females that appears clinically as red, eczematous, pruriginous, and sometimes painful lesions. Although most cases are noninvasive, EMPV may be associated with an underlying or distant adenocarcinoma. EMPV has a chronic and relapsing course. The reference treatment is based on local surgical excision with negative margins. However, disease frequently extends far from the visible lesion, and surgical margins are frequently positive. Topical photodynamic therapy (PDT) is an established treatment modality for various dermatooncologic conditions. For example, red light irradiation with the Aktilite CL 128 and Metvixia (Galderma SA) as a photosensitizing molecule is a conventional protocol approved and widely used in Europe for PDT treatment of actinic keratosis, but this treatment is not yet widely used for EMPV because it has never clearly been demonstrated and is very painful.

Objective: The aim of the study is to investigate the efficacy and safety relating to the medical device PAGETEX as a new painless PDT device using Metvixia in the treatment of vulvar Paget disease. The primary end point is the disease control rate at 3 months in 30% of the patients included, defined as stability, partial response, or total response, considering the extent of the lesion. Secondary end points are the disease control rate at 6 months, patient quality of life, level of pain experienced by the patient at each PDT session, severity of erythema, presence of protoporphyrin IX in Paget cells after each PDT session, and overall satisfaction level of the patient.

Methods: The trial is an interventional, exploratory, simple group, nonrandomized, and single center (Lille University Hospital) study. Twenty-four patients will be included according to Simon's optimal plan. Therapeutic procedure is based on a cycle of two PDT sessions with the PAGETEX medical device at 15-day intervals (Metvixia incubation during 30 minutes and 635 nm red light illumination with a low irradiance for 2 hours and 30 minutes for a total fluence of 12 J/cm²). At the assessment session, 3 months after inclusion, if the control of the disease is partial or null, the patient will complete another cycle of two PDT sessions. A final evaluation will be performed in all patients at 6 months. Analyses will be performed using SAS version 9.4 software (SAS Institute Inc). The characteristics of the patients at baseline will be described; qualitative variables will be described by numbers and percentages, and quantitative variables will be described either by the mean and standard deviation for Gaussian distribution

or by the median and interquartile range (ie, 25th and 75th percentiles). The normality of the distributions will be tested by a Shapiro-Wilk test and checked graphically by histograms.

Results: First patient was included in September 2019 and clinical investigations are planned until August 2022. The final results of this study are expected to be available in January 2023.

Conclusions: This clinical trial aims to evaluate the efficacy and safety of a new PDT protocol for the treatment of EMPV. The PAGETEX device could become the treatment of choice if it is effective, painless, and easy to implement and use in hospitals.

Trial Registration: ClinicalTrials.gov NCT03713203; https://clinicaltrials.gov/ct2/show/NCT03713203

International Registered Report Identifier (IRRID): PRR1-10.2196/15026

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KEYWORDS

photodynamic therapy; extramammary Paget disease of the vulva; light emitting fabrics; methyl aminolevulinate

Introduction

Extramammary Paget disease of the vulva (EMPV) is invasive in 20% of cases. If the invasion is less than 1 mm, the evolution is the same as that of noninvasive lesions. Beyond 1 mm, or when there is an underlying carcinoma, the prognosis is worse with a risk of remote lymph node metastases [1].

The disease is usually observed in Caucasian women over age 70 years and is revealed by pruritus. The lesion is red and ulcerated with an irregular surface and is often mistaken for an eczematized inflammatory lesion. The disease sits on the lips and sometimes bilaterally extends to the perianal region. The actual extension may be more important than the clinical lesions, and multiple biopsies can be used to evaluate the extent of the lesions to guide the surgical procedure.

Histologically, the disease is characterized by intraepidermal proliferation of large epithelioid cells with abundant and clear granular or vacuolized cytoplasm. The reference treatment is based on surgical excision. This surgical treatment is facilitated by new techniques in plastic surgery and anesthesia that will limit postoperative sequelae. Unfortunately, besides the fact that the surgery is sometimes mutilating, local recurrences are also very frequent (up to 45% of the cases) even if the margins of excision are healthy [2]. Since the prognosis of EMPV is good in the absence of invasive zone or underlying adenocarcinoma, the treatment of choice is surgical removal of the plaque with margins of 1 cm. Alternative conservative treatments such as laser therapy, radiotherapy, chemotherapy, and the application of topical treatments (imiquimod, corticosteroids) or topical photodynamic therapy (PDT) offer an interesting alternative, but they are mostly invasive and painful [3].

It is therefore essential to have a painless therapeutic alternative allowing a complete remission rate without functional or aesthetic sequelae. PDT is a technique based on the combination of photosensitizing molecules (PS) capable of focusing in tumor cells and a focused light of an appropriate wavelength (PS dependent). The combination of these two factors specifically targets the injured tissues and destroys them. PS is administered topically and is more or less selectively concentrated in the damaged tissue by irradiation that is used at a wavelength appropriate to the photosensitizer and which leads to necrosis or apoptosis of the cells. The photosensitizer used most often is a precursor of porphyrin, 5-aminolevulinic acid (5-ALA), and recently its methylated form, methyl aminolevulinate (MAL), was authorized in France under the name Metvixia. Conventional PDT usually includes incubation of 5-ALA or MAL for several hours. Applied to the skin, these prodrugs are converted endogenously by the biosynthetic pathway of heme in protoporphyrin IX (PpIX) and other intermediate photosensitive porphyrins, leading to a high and selective accumulation of PplX in the target lesion. Production of PpIX is visible by fluorescence when lesions are illuminated with a blue light. Abnormal cells accumulate more photosensitizer than normal cells. Illumination of these cells, using an appropriate light source, leads to apoptosis and selective necrosis of tumor cells, while sparing healthy adjacent tissues [4,5].

According to the product characteristics summary, Metvixia has been approved for use in combination with red light, so MAL-PDT has recently been introduced in clinical trials as a therapeutic option in EMPV [6-9]. The mode of delivery of light is one of the major concerns in PDT. Light sources marketed and used for the photodynamic treatment of skin lesions are generally flat, while the surfaces to be treated are mainly curvy. Thus, Moseley [10] showed that two commercialized LED devices did not provide a homogeneous light, and he demonstrated that the fluence rate could be 30% lower at a distance of only 2 cm than that delivered in the central zone. To overcome this disadvantage, the development of a flexible light source appears to be an interesting solution. The development of such technology, incorporating optical fibers into a flexible structure that emits fractional light, appears to provide a therapeutic solution for nonplanar anatomical surfaces such as curved surfaces and body extremities. A PDT device incorporating light-emitting fabrics (LEFs) is in use in several clinical studies [11-13] run by the Lille University Hospital for the treatment of actinic keratoses, and the first results seem to be promising, particularly with regard to the pain felt by patients.

The medical device PAGETEX consists of a textile diffuser support incorporating LEFs to diffuse light from a laser source. The complete device constitutes a source of nonlaser optical radiation and makes it possible to deliver a diffused and homogeneous illumination on vulvar lesions of the EMPV with an objective to perform an effective and painless PDT treatment on the affected region. This clinical protocol aims to evaluate

the efficacy and safety of a new PDT protocol for the treatment of the EMPV.

Methods

Trial Design

The study is interventional, exploratory, simple group, nonrandomized, and single-center. A total of 24 patients will be included according to Simon's optimal plan: 8 patients will be included in a first step and 16 other patients in a second step if and only if the test is not stopped in step 1.

Setting

The study will be conducted at the Lille University Hospital, Lille, France, in the department of dermatology over a period of 30 months until the end of August 2022. Twenty-four patients will be recruited within 24 months and followed for 6 months.

Device

PAGETEX is a new illumination device consisting of a light diffuser support (Figure 1) incorporating three LEFs (Figure 2) to diffuse a red light from a medical laser source. Each LEF is connected to a 635 nm laser source (ML7710-630-EID707788 medical laser system, Modulight Inc), which is set to deliver a light dose of up to 12 J/cm². This light dose is controlled by an Ophir PD300 photodiode sensor connected to an Ophir Laser Star Bright power meter (Ophir Optronics Solutions Ltd). The light diffuser support is positioned on the vulva area and held with a medical panty (Figure 3).

Figure 1. PAGETEX light diffuser support.

Figure 2. PAGETEX light emitting fabrics.

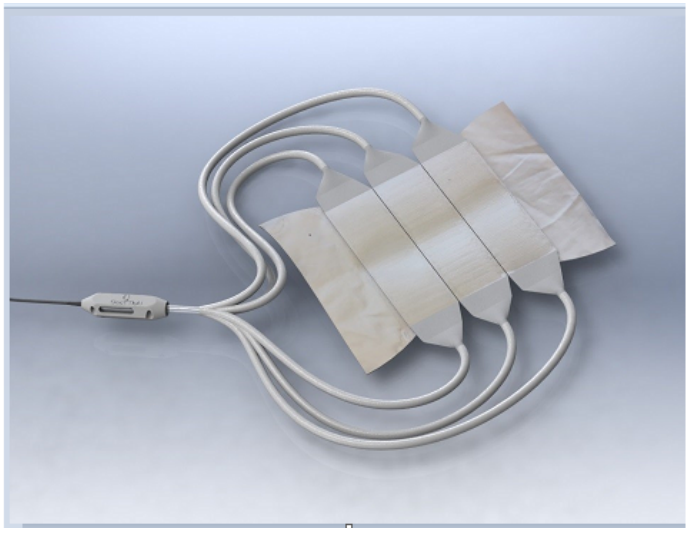
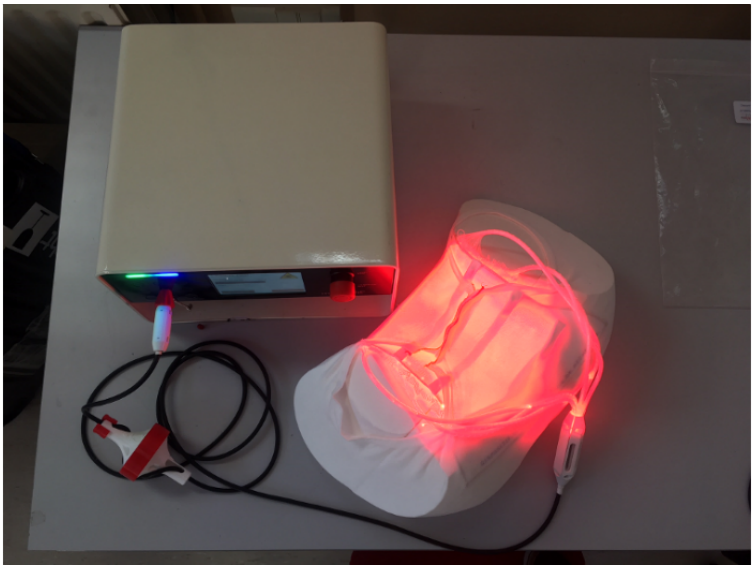


Figure 3. Complete device with medical panty, light diffuser support and laser source.



Participants

To be eligible for the study, patients must meet all of the inclusion criteria described in Textbox 1. Patients cannot have any of the exclusion criteria.

Study Objectives and Outcomes

The main aims of the study are the efficacy of the device based on the disease control rate (stable, partial, or complete) considering the extent of the lesion at 3 months in 30% of the patients included and safety of the device based on the evaluation of adverse and serious adverse events.

Key secondary objectives are the disease control rate at 6 months, evolution of the quality of life, level of pain during PDT session, presence of Paget cells after staining of biopsies, presence of fluorescence in selected lesion after each PDT session, and evaluation of the tolerability and overall satisfaction level of the patient. Table 1 below details study objectives and outcomes.

Textbox 1. Selection criteria.

Inclusion criteria:

- Women over age 18 years
- Diagnosis of noninvasive primary or recurrent after surgical resection Paget disease of the vulva
- Extramammary Paget disease of the vulva confirmed by biopsy within 1 year

Exclusion criteria:

- Invasive Paget disease
- Underlying adenocarcinoma
- Treatment with imiquimod 5% cream in the last 3 months
- Photodynamic therapy used to treat extramammary Paget disease of the vulva lesions in the last 3 months
- Use of photosensitive agents in the last 3 months
- Allergic or hypersensitivity to methyl aminolevulinate or any of the other ingredients in this medication (propyl p-hydroxybenzoate, cetostearyl alcohol, methyl p-hydroxybenzoate)
- Allergic or hypersensitivity to peanut or soya due to the presence of peanut oil in Metvixia
- Diagnosis of porphyria or immunity disorders (HIV, transplantation)
- Treatment with topical corticosteroids on the affected area in the last 3 months

Table 1. Outcomes and descriptions.

Outcomes	Inclusion[a]	PDT 1[b]	PDT 2[c]	Evaluation M3[d]	PDT 3[e]	PDT 4[f]	Evaluation M6[g]
Primary outcomes							
Evaluation of lesion area and aspect by investigator and a blinded independent committee of physicians from standardized photographs taken during inclusion	x			x			x
Disease control rate (stable, partial, complete response)				x			x
Local tolerance (adverse event, serious adverse event, concomitant treatments)		x	x	x	x	x	x
Secondary outcomes							
Evaluation of pain: visual analog scale graduated from 0 (no pain) to 10 (unbearable pain)		x	x		x	x	
Severity of erythema (chromametry)	x			x			x
Quality of life and satisfaction (DLQI[h], FSFI[i], SF-36[j], and HADS[k])	x			x			x
Satisfaction questionnaire							x
Presence of Paget cells: Positive/negative biopsy	x			x			x
Presence of protoporphyrin IX in selected lesion (fluorescence detection)		x	x		x	x	

[a]Inclusion: D0.

[b]PDT 1: photodynamic therapy within 30 days or at D0.

[c]PDT 2: photodynamic therapy 15 days after PDT 1 (±2 days).

[d]Evaluation M3: D0 + 3 months (± 7 days).

[e]PDT 3 (optional): photodynamic therapy within 30 days after M3.

[f]PDT 4 (optional): photodynamic therapy 15 days after PDT 3 (±2 days).

[g]Evaluation M6: D0 + 6 months (±7 days).

[h]DLQI: Dermatology Life Quality Index.

[i]FSFI: Female Sexual Functioning Index.

[j]SF-36: 36-item Short Form Health Survey.

[k]HADS: Hospital Anxiety and Depression Scale.

Sample Size

A minimum efficacy of 30% was set, and efficacy of 60% is expected to be achieved [14]. The hypotheses tested are P≤0.30 (H0) and P≥0.60 (H1), where P corresponds to the rate of patients with disease control at 3 months. Based on an optimal 2-step Simon plan (5% unilateral test), a total of 24 patients is required to test these hypotheses with a power of 80%: 8 patients are included in a first step, and the trial is stopped if the number of patients with a disease control at 3 months is less than or equal to 3; the PAGETEX device is considered not sufficiently effective. Otherwise, 16 additional patients are included in a second step. The PAGETEX device is not considered sufficiently effective if, on the 24 patients included (step 1 + step 2), the number of patients with a disease control at 3 months is less than or equal to 10.

Allocation and Randomization

There is no randomization; all patients receive PDT treatment with the PAGETEX device.

Implementation and Blinding

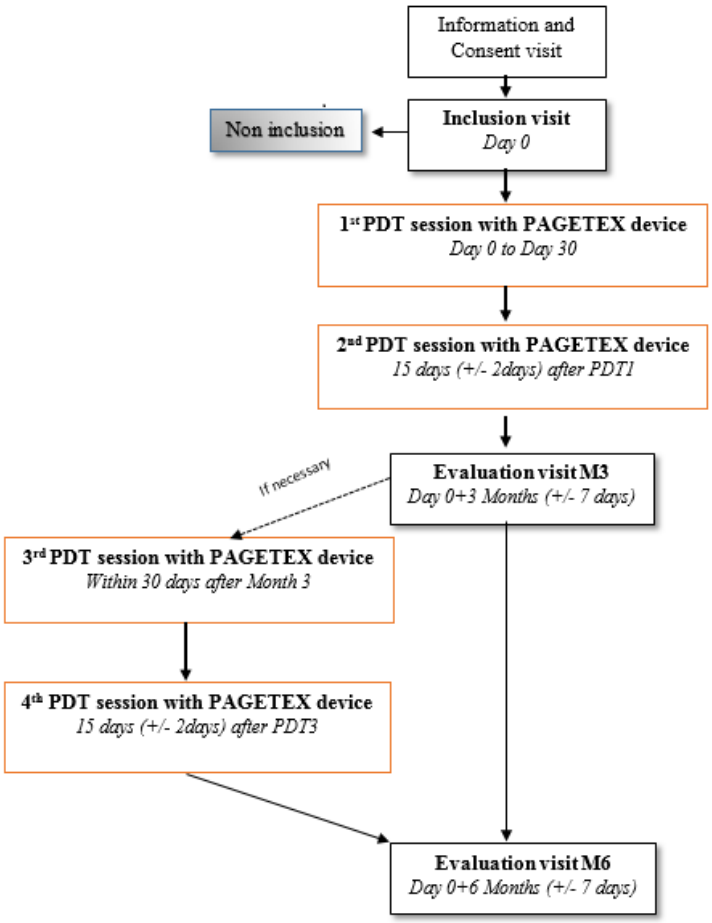
The study is not concerned with blinding as it is an uncontrolled clinical trial on a single group of patients receiving the same PDT treatment. However, to minimize the bias of investigator evaluation, an independent medical committee will evaluate the type of clinical response (stable, partial, complete, or no response) obtained at 3 and 6 months from standardized lesion photographs. Data will also be analyzed without blinding.

Intervention

The course of the study is based on the protocol of PDT treatment with the Aktilite CL 128 (Galderma SA) applied in the dermatology department, to which have been added the investigation procedures specific to our research.

As shown in the flowchart (Figure 4), after inclusion visit, patients who meet all the criteria for inclusion and none of exclusion criteria are invited to come to the investigation site for 2 sessions of PDT and one evaluation visit at month 3. If necessary and if the disease control rate is not sufficient, patients are retreated with two sessions of PDT. A final visit at 6 months is made for all subjects in order to define the disease control rate.

Figure 4. Progress of study visits. M: month; PDT: photodynamic therapy.



Preparation and Treatment of Lesions

At the inclusion visit, the investigator evaluates the appearance of the patient's skin and the extent of the lesion. The largest vulvar lesion is selected, photographed, and measured with the Fotofinder dermoscope (Fotofinder Systems Inc) in natural light to define the basic extension of the disease before treatment. To confirm the presence of Paget cells and noninvasive EMPVA, a biopsy (3 mm in diameter and 2 to 3 mm deep) of the selected area is performed or results are obtained if the patient has had a biopsy within 1 year. The investigator grades the erythema, and pigmentation of the lesion is measured with the CR-400 Chroma Meter (Konica Minolta Sensing Europe BV). Colorimetric data and photograph of the lesion will be used as a basis for evaluation of disease control rate.

During PDT sessions, Metvixia is applied with a spatula on the selected vulvar lesion (approximately 1 mm thick and over an area of 5 to 10 mm of normal skin surrounding the lesion). The treated area is covered with a transparent occlusive dressing for 30 minutes. Then the light diffuser support is installed and retained by a medical textile panty. Illumination with 635 nm red light (12 J/cm^2) is applied for 2 hours and 30 minutes. Pain is measured with a visual analog scale, and adverse events are collected.

At the evaluation visits, 3 and 6 months after initial treatment, the investigator and a blinded medical committee evaluate the disease control rate (stability, partial, or total response) by comparing the evolution of the selected lesion in terms of color and measures between the current visit and the first one. Table 2 shows all study procedures (exams and acts) performed during the trial.

Table 2. Study procedures and measures.

Action	Inclusion[a]	PDT 1[b]	PDT 2[c]	Evaluation M3[d]	PDT 3[e]	PDT 4[f]	Evaluation M6[g]
Informed consent	x						
Medical examination	x	x	x	x	x	x	x
Selection criteria	x						
Photographs of lesions under natural light	x	x	x	x	x	x	x
Biopsy	x			x			x
HCG[h] pregnancy test		x	x		x	x	
Erythema gradation	x			x			x
Erythema measurement with CR-400 Chroma Meter	x			x			x
DLQI[i], FSFI[j], SF-36[k], and HADS[l] questionnaires	x			x			x
Application and incubation of Metvixia		x	x		x	x	
Illumination process		x	x		x	x	
Photographs of lesions under fluorescent light		x	x		x	x	
VAS[m] measurement of pain		x	x		x	x	
Evaluation of tolerance/AE[n]/SAE[o]		x	x	x	x	x	x
Patient satisfaction							x

[a]Inclusion: D0.

[b]PDT 1: photodynamic therapy within 30 days or at D0.

[c]PDT 2: photodynamic therapy 15 days after PDT 1 (±2 days).

[d]Evaluation M3: D0 + 3 months (± 7 days).

[e]PDT 3 (optional): photodynamic therapy within 30 days after M3.

[f]PDT 4 (optional): photodynamic therapy 15 days after PDT 3 (±2 days).

[g]Evaluation M6: D0 + 6 months (±7 days).

[h]HCG: human chorionic gonadotropin test.

[i]DLQI: Dermatology Life Quality Index.

[j]FSFI: Female Sexual Functioning Index.

[k]SF-36: 36-item Short Form Health Survey.

[l]HADS: Hospital Anxiety and Depression Scale.

[m]VAS: visual analog scale.

[n]AE: adverse events.

[o]SAE: serious adverse events.

Variables and Data Collection

Collected data consisted of demographic data, medical history reviews, previous medical and surgery treatments, and assessments of the subjects' skin erythema. For female subjects of childbearing age, a urine pregnancy test is performed at screening and before each PDT treatment. Visual analog scale of pain and questionnaires (Dermatology Life Quality Index [DLQI], Female Sexual Functioning Index [FSFI], 36-item Short Form Health Survey [SF-36], Hospital Anxiety and Depression Scale [HADS] and satisfaction) are used.

Data Management

The data are collected through a case report form and saved in an electronic file (database). All participants receive a trial identifier, and only the investigator knows the personal details. The sponsor's monitor plans several monitoring visits, after the first inclusion in the study site location and periodically to assess data quality and study integrity. The sponsor's monitor reviews study records and directly compares them with source documents, discusses the conduct of the study with the investigator, and verifies that the facilities remain acceptable. The monitoring of the trial is carried out according to the monitoring plan. A planning meeting with the principal investigator is held before the start of the trial. During the trial, several checkpoints are defined, including the presence of signed informed consent forms obtained by the investigator, respect of the inclusion and exclusion criteria, reporting of any adverse events, and the monitoring of all steps of patient follow-up. At the end of the trial and once the final analysis is completed and validated, all the files are sealed and archived according to

specific procedures in a secure location in the sponsor clinical research department.

The trial support unit coordinates data management. The database is stored and secured on the network of Lille University Hospital. Before the closeout of the database, data monitoring is performed using SAS software (SAS Institute Inc) based on consistency rules set with the project manager (eg, missing data, outliers, and inconsistency between several variables). The data are analyzed in the Unit of Methodology, Biostatistics and Data Management of Lille University Hospital (UMBD). Only the investigator participating in the study or a collaborator designated by the physician and participating in the study may modify the data. The data concerning this study are archived for a minimum period of 15 years from the end of the research or its early termination without prejudice to the laws and regulations in force.

Statistical Methods

All statistical analyses will be performed independently within the UMBD under the responsibility of Professor A Duhamel. Analyses will be performed using the SAS 9.4 or higher software (SAS Institute Inc). Characteristics of the patients at baseline will be described; qualitative variables will be described by numbers and percentages, and quantitative variables will be described either by the mean and standard deviation for Gaussian distribution or by the median and interquartile range (ie, 25th and 75th percentiles). The normality of the distributions will be tested by a Shapiro-Wilk test and checked graphically using histograms.

To answer to the main objective, the rejection rules of Simon's optimal plan will be used. According to Simon's optimal plan, after including 8 patients in a first step, the experimental treatment (PDT treatment with the PAGETEX device) will be rejected if the number of patients with disease control at 3 months (assessed by the investigator) is less than or equal to 3. If the trial continues in the second stage, the experimental treatment will be rejected if, out of the 24 patients, the number of patients with disease control at 3 months is less than or equal to 10. The 95% bilateral confidence interval of the 3-month disease control rate will be calculated. The control rates of the disease and its 95% confidence interval, as assessed by the investigating physician and the independent committee, will be calculated. Changes in the quality of life, sexual quality of life, anxiety, and depression measured by the DLQI, HADS, FSFI, and SF-36 questionnaires will be estimated using a mixed linear model (covariance pattern) including time (inclusion visit, visit at 3 months, visit at 6 months) as the fixed effect. The pain experienced measured by the visual analog scale will be described as a continuous variable and as a qualitative variable to 4 classes. Severity of the erythema assessed by a 4-point ordinal scale will be described at each time (inclusion, 3 months, and 6 months). Severity of the erythema evaluated at follow-up visits will be compared to severity of the erythema evaluated at the inclusion visit using the Wilcoxon signed-rank test. Percentages of patients with a decrease in severity grade at 3 months and 6 months compared with baseline will be described. Evolution of the severity of the erythema quantified by a colorimetry will be evaluated by the same method. The presence of fluorescence in Paget cells after each PDT session will be described to prove the production of PpIX. The link between the presence of fluorescence after each PDT session and the disease control rates at 3 months and 6 months will be studied using a Fisher exact test. Finally, rates of patients with at least one Paget cell in the thickness of the epidermis biopsies, patient satisfaction questionnaires scores, and frequencies of adverse events will be described.

Ethical Considerations

The trial is conducted in accordance with principles enunciated in the Declaration of Helsinki, as well as International Council for Harmonisation guidelines and article L1121-4 of the French Health Code. The study protocol has been submitted for review and approval by the French Ethics Committee (2018-68) and the French National Agency for the Safety of Medicines and Health Products (2018-A01873-52 and 2018-002604-13). The trial was registered at ClinicalTrials.gov [NCT03713203]. The investigator must ensure that subjects are informed clearly and fully about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from each subject prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study. The rights, safety, and well-being of the subjects are the most important considerations and should prevail over interests of science and society.

Patient Confidentiality and Involvement

Patients or the public were not involved in the conceptualization or carrying out of this research. Concerning treatment of personal data, this study is in compliance with the French methodology of reference (MR0001), which is a simplified declaration of data from medical research to the French National Data Protection Authority. The only persons authorized to access data and modify files generated by the study will be persons directly involved in the study. The participants will have access to the data and be able to modify them at any moment through one of the referring investigators of the study. The sponsor affirms the patient's right to protection against invasion of privacy.

Results

The first patient was included in September 2019. Evaluation of disease control in the first 8 patients will determine the study's continuation (early 2020). The final visit of the last patient is expected to August 2022. Analysis of the results is scheduled for the end of 2022, and results are expected to be published at the beginning of 2023.

Discussion

PDT using 5-aminolevulinic acid has been employed sporadically to treat EMPV even if it is not the common treatment of this pathology [15,16]. MAL-PDT is a relatively simple procedure to treat large and multiple lesions and can be repeated without functional or cosmetics effects. This clinical trial is the only trial registered on ClinicalTrials.gov that investigates the efficacy and safety of PDT in EMPV. But its

boundaries are that disease evolution is difficult to evaluate because symptom improvement is based on a medical opinion by comparison of photographs and the limitation of the penetration of MAL at a depth of around 2 to 3 mm for a wavelength of 630 nm according to the thickness of the lesions. In case of positive results, a randomized trial comparing PDT with imiquimod will be performed.

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Authors' Contributions

FL was responsible for drafting manuscript and writing the study protocol. CM, LM, DS, and SM were responsible for the collection of scientific background, conception of the methodology, and design of the study protocol. PD, ET, LZ, and SM were responsible for the design, conception, and validation of the device. All authors have read and approved the manuscript. AD is responsible for the statistical plan.

Conflicts of Interest

None declared.

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Abbreviations

5-ALA: 5-aminolevulinic acid
DLQI: Dermatology Life Quality Index
EMPV: extramammary Paget disease of the vulva
FSFI: Female Sexual Functioning Index
HADS: Hospital Anxiety and Depression Scale
LEF: light-emitting fabric
MAL: methyl aminolevulinate
PDT: photodynamic therapy
PpIX: protoporphyrin IX
PS: photosensitizing molecule
SF-36: 36-item Short Form Health Survey
UMBD: Unit of Methodology, Biostatistics and Data Management

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Protocol

Development and Implementation of a Nurse-Led Model of Care Coordination to Provide Health-Sector Continuity of Care for People With Multimorbidity: Protocol for a Mixed Methods Study

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Abstract

Background: Innovative strategies are required to reduce care fragmentation for people with multimorbidity. Coordinated models of health care delivery need to be adopted to deliver consumer-centered continuity of care. Nurse-led services have emerged over the past 20 years as evidence-based structured models of care delivery, providing a range of positive and coordinated health care outcomes. Although nurse-led services are effective in a range of clinical settings, strategies to improve continuity of care across the secondary and primary health care sectors for people with multimorbidity have not been examined.

Objective: To implement a nurse-led model of care coordination from a multidisciplinary outpatient setting and provide continuity of care between the secondary and primary health care sectors for people with multimorbidity.

Methods: This action research mixed methods study will have two phases. Phase 1 includes a systematic review, stakeholder forums, and validation workshop to collaboratively develop a model of care for a nurse-led care coordination service. Phase 2, through a series of iterative action research cycles, will implement a nurse-led model of care coordination in a multidisciplinary outpatient setting. Three to five iterative action research cycles will allow the model to be refined and further developed with multiple data collection points throughout.

Results: Pilot implementation of the model of care coordination commenced in October 2018. Formal study recruitment commenced in May 2019 and the intervention and follow-up phases are ongoing. The results of the data analysis are expected to be available by March 2020.

Conclusions: Nursing, clinician, and patient outcomes and experiences with the nurse-led model of care coordination will provide a template to improve continuity of care between the secondary and primary health care systems. The model template may provide a future pathway for implementation of nurse-led services both nationally and internationally.

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KEYWORDS

continuity of patient care; multimorbidity; nurse led; integrated health; transitional; chronic disease

Introduction

Background

Increasing prevalence and complexity of multimorbidity across populations is a global phenomenon [1-3]. This constitutes one of the most significant challenges for health care in the 21st century [4]. In general, care for patients with multimorbidity is fragmented and not coordinated, especially between health care settings, such as primary and secondary care [5,6]. Current models of care delivery focus on single-disease-specific management, resulting in attendance at multiple specialist medical clinics, and do not support continuity of care, placing a significant burden on both patients and hospitals [3,7].

In an attempt to improve efficiencies within health care, nurse-led clinics and services have emerged over the past two decades [8,9]. Their effectiveness has been demonstrated on a number of levels, responding to the complexity of care coordination required by patients [10,11]. This includes the use of a person-centered approach [9], positive patient experience and satisfaction [9,12], and counseling and interventions to support chronic medication adherence [8,13].

In Australia, providing continuity in health care for people with chronic and complex disease is problematic, partly due to differences between federal and state government policies as well as structures and funding systems for the primary and secondary health care sectors [14]. This issue poses a challenge for nurse-led services to provide integrated models of care and lead continuity of care strategies between the health sectors at local service levels. Nurse-led models of care can provide a solution, in part, to the barriers associated with developing nonfragmented care in order to provide effective management for people with multimorbidity. It is, therefore, timely that a model of care trialing cross-sector collaboration is implemented. In Australia, the primary and secondary health care sectors will have congruent access to patients' health care information through national strategies, such as My Health Record [15] and Health Care Homes [16]. These strategies, although in their infancy, if supported at local service and health network levels, can be used to leverage communication and collaboration by nurses to improve continuity of care. However, there remain few studies examining nurse-led models of care to improve continuity of care [17,18]. Despite the success of nurse-led services in a range of other contexts, their effectiveness in supporting continuity of care between the secondary and primary health sectors for people living with multimorbidity is yet to be determined.

Multimorbidity and Nurse-Led Models of Care

Chronic diseases, including cardiovascular disease, diabetes, chronic lung disease, and cancer, are collectively responsible for almost 70% of all deaths worldwide. In the United Kingdom, the United States, and Australia, between 22% and 25% of the population live with multimorbidity, defined as having two or more chronic conditions concurrently; the prevalence of multimorbidity is even higher in the older population [2].

Multimorbidity is associated with poorer health outcomes, increased care fragmentation [1,19], higher health service utilization, and higher health care costs [20,21]. Existing models of care are based on a medical model of health service delivery and are designed to manage a single disease; therefore, they are not suitable for the complexity of health care associated with the presence of multiple chronic conditions [3,22,23]. Additionally, clinical guidelines predominantly focus on a single disease, potentially contributing to conflicting medication and care management for people with multimorbidity [24]. The traditional single-disease focus of current health care models and practices is also unsuitable for people with multimorbidity due to a lack of holistic care management and coordination [3,22,23].

Continuity of care is acknowledged as an essential component of high-quality care [25]. However, it is evident that chronic and complex health care management poses a challenge for health care systems to provide and promote continuity of care for people with multimorbidity [1]. A person-centered approach rather than a single-disease management program will provide more effective, high-quality care [4]. A coordinated comprehensive patient-centered model that focuses on continuity of care across the health system is especially needed for people with multimorbidity [6,26,27].

The relationship between aspects of continuity of care and patient satisfaction, improved health outcomes, a reduction in hospital admissions, and a reduction in health care utilization has been established [17,25,28,29]. In a recent scoping study [6] it was identified that in relation to multimorbidity management, models and elements of care were focused on general integrated care, as previously applied to single-disease management; therefore, they were unsuitable to the specific care required for the complexity associated with multimorbidity. The details of models of care require further study, specifically the role of nursing and nurse-led services to improve continuity of care and care coordination for people with multimorbidity.

Methods

Ethics and Registration

Ethical approval was obtained by the Human Research Ethics Committee (HREC) (reference number: HREC/17/RAH/552) at the University of South Australia (application ID: 200958) and the Central Adelaide Local Health Network (CALHN) (reference number: R20171204).

Aims

The overall aim of this study is to determine the feasibility of implementing a nurse-led care coordination service from the outpatient setting to provide continuity of care across the secondary and primary health care settings for people with multimorbidity. The specific aims are as follows:

1. Develop and implement a model of care for a nurse-led service to provide continuity of health care for people with multimorbidity.
2. Identify nursing interventions associated with implementation of a nurse-led service model of care.
3. Identify barriers and enablers to implementing a nurse-led service.
4. Identify structures, processes, and outcomes required to implement a nurse-led service and achieve continuity of care.

Design

Overview

The study design comprises action research with the application of the research spiral: "plan, act, observe, reflect, and re-plan" [30]. A Donabedian model [31] of evaluating structure, process, and outcome in health care will guide data collection during the action research cycles. There is precedence in the application of this model, not only in health care evaluation [32] but also in defining and evaluating nurse-led services [10,33]. The categories of structure, process, and outcome will include the measurement of stakeholder views and clinical staff and patient experience related to continuity of care across secondary and primary health care settings over time. The research will be conducted in two phases.

Phase 1: Initial Action Research Cycle

The goals of Phase 1 are as follows:

1. Consult with the Multidisciplinary Ambulatory Consulting Service (MACS) staff and associated stakeholders regarding the components and development of a nurse-led service model of care; for specific stakeholders, see Participants section and Table 1 below.
2. Review evidence in relation to nurse-led services, nursing interventions, and associations with continuity of care for people with chronic disease.
3. Review evidence in relation to best practice management of people with multimorbidity.
4. Collaboratively develop a nurse-led service model of care.
5. Develop operational roles, guidelines, and protocols to implement the nurse-led service model of care.

Phase 1, the initial action research cycle, will focus on two interventions. First, we will complete a systematic review to identify the effectiveness of nurse-led services to improve continuity of care for people with chronic disease (international prospective register of systematic reviews [PROSPERO] registration number: CRD42018095780). The second focus will be on stakeholder engagement; a series of forums, workshops, and meetings will engage stakeholders and collaboratively develop a model of nurse-led care coordination.

This action research cycle will inform the development of an evidence-based model of care for a nurse-led service and prepare the clinical team for nurse-led service implementation. Figure 1 depicts the Multimorbidity Nursing Model of Care action research study design; included is the systematic review and stakeholder forum informing development and planning of the nurse-led care coordination service and subsequent iterative implementation of the nurse-led service.

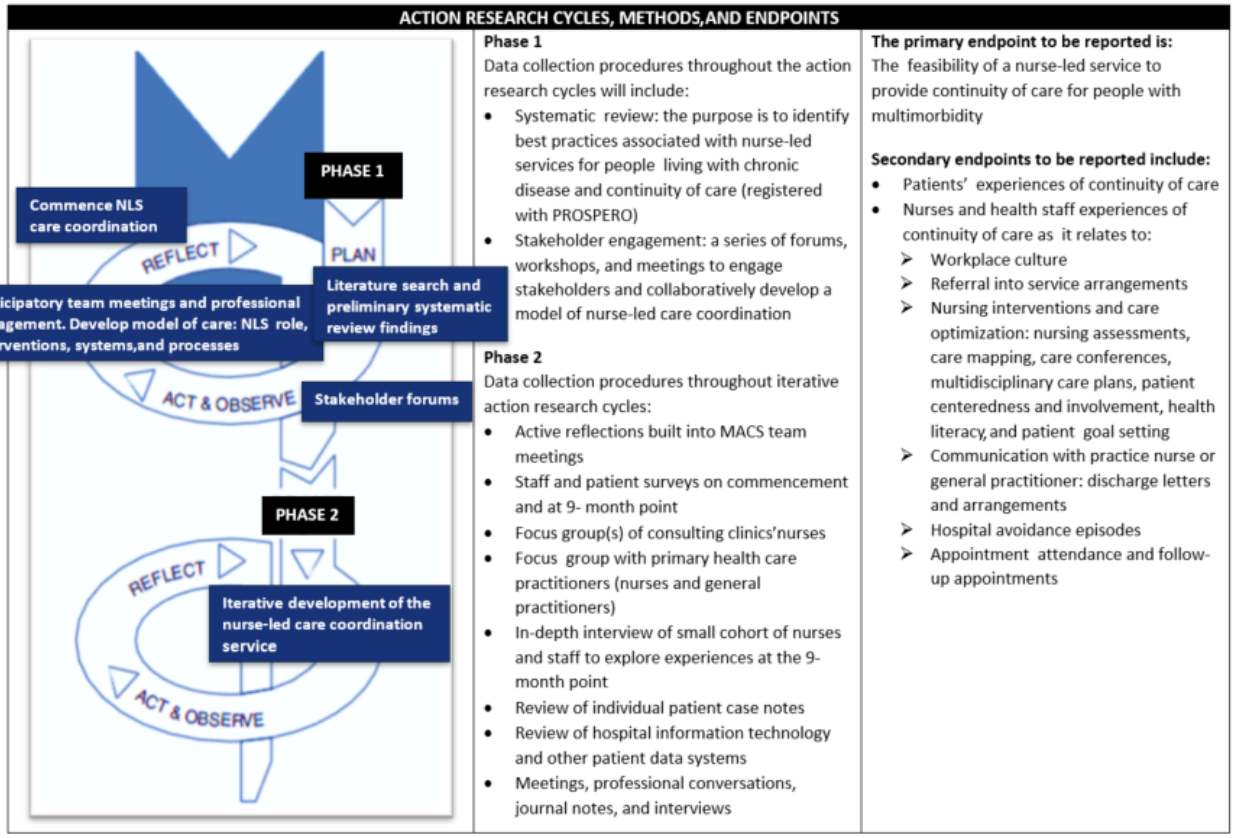
Table 1. Study participants and eligibility criteria.

Eligibility criteria	Stakeholders	Health care staff	Patients
Inclusion criteria	Attendees at the stakeholder forums and workshop; stakeholders include health care professionals, primary and secondary health care executives, relevant academic and clinical participants, and consumer representatives (n=40)	Health care staff from the tertiary referral center and outpatient service associated with implementing and/or working in, or in collaboration with, the nurse-led care coordination service or outpatient services (n=30) Health care staff associated with implementing and/or working in collaboration with the nurse-led care coordination service: from the primary health care sector (n=10)	All patients receiving care from registered nurses within the MACS[a], the nurse-led care coordination service, attending a general practitioner service or the PHC[b] sector associated with the MACS (n=30 in clinic) Patients who have previously attended multiple medical outpatient clinic appointments (n=100 postal surveys)
Exclusion criteria	Nil	Nil	Patients with cognitive impairment

[a]MACS: Multidisciplinary Ambulatory Consulting Service.

[b]PHC: primary health care.

Figure 1. Design of the Multimorbidity Nursing Model of Care study. MACS: Multidisciplinary Ambulatory Consulting Service; NLS: nurse-led services; PROSEPERO: international prospective register of systematic reviews.



Phase 2: Subsequent Action Research Cycles

The goals of Phase 2 are as follows:

1. Trial implementation of the nurse-led service model of care over a series of iterative action research cycles.
2. Implement nurse-led service care coordinator role.
3. Implement associated protocols and guidelines to operationalize the nurse-led service model of care.
4. Evaluate action research cycles in terms of changes to nursing interventions, service structures, processes, and outcomes.

Phase 2, the subsequent action research cycles, will employ a mixed-methods approach with multiple data collection points. During implementation of the nurse-led model of care coordination, nursing roles and interventions, service structures, processes, and outcomes will be observed, refined, and reimplemented. Patient, nurse, and health care staff experience as well as organizational culture impacts will be measured. The structures and processes within the nurse-led service will be evaluated by recognized data collection instruments that examine patient and health care staff experiences of continuity of care, patient-related quality of life, and staff experience of organizational culture (see Table 2 for data collection instruments and characteristics). Nursing roles, tasks, skills, and knowledge will also be evaluated (see Table 2).

Table 2. Data collection instruments and characteristics.

Author (publication year); instrument	Instrument primary purpose and adaptation; Continuity of care domain	Validation, reliability, and context for use	Number of items; Response options
Glasgow et al, (2005) [34]; Patient Assessment of Chronic Illness Care (PACIC) survey	A validated patient self-report instrument to assess the extent to which patients with chronic illness receive care that aligns with the Chronic Care Model. Measures care that is patient-centered, proactive, and planned and includes collaborative goal setting; Problem-solving and follow-up support	A practical instrument that is reliable and has face, construct, and concurrent validity	The PACIC consists of five scales and an overall summary score
MacColl Center for Health Care Innovation (2000) [35]; Assessment of Chronic Illness Care (ACIC V3.5) survey	The ACIC addresses the basic elements for improving chronic illness care at the community, organization, practice, and patient level—a*dapted for use in the MACS*[a]*setting*; Relational, management, and informational continuity	Preliminary data indicate that the ACIC is responsive to changes that teams make in their systems and correlates well with other measures of productivity and system change	Seven dimensions—each dimension includes a number of items; Point value is attributed to a choice of four levels across each item
The EuroQol[b] Group (1990) [36] and Herdman et al (2011) [37]; Patient EQ-5D[c]	The EQ-5D is a standardized measure of health status, applicable to a wide range of health conditions and treatments. Developed by the EuroQol Group, it provides a simple, generic measure of health for clinical and economic appraisal.	Widely validated and contextualized; translated into over 170 language versions	Five dimensions (each with three or five levels), 15 items, and cross-walk value sets available to convert three-item survey to meaningful value equivalent to five-item survey; Tick box and visual analog
Berglund CB et al (2015) [38]; Patient satisfaction and continuity of care	The survey was originally developed for the patient-physician outpatient encounter [39]. It proved to capture changes in patient satisfaction over time. It has since been adapted to capture the patient-nurse outpatient encounter; Relational, management, and informational continuity	No formal validity and reliability testing, however, item generation including the testing procedure provides sufficient content validity	12 multiple-choice items, including items concerning waiting time, continuity of care, length of visit, information, interpersonal manner, and fulfilment of expectations; 4-point scale from 1 (Not at all) to 4 (Very much)
Uijen AA et al (2011 [40] and 2012 [41]); Nijmegen Continuity Questionnaire (NCQ)	To measure continuity of care from the patients' perspectives across primary and secondary care settings; Personal continuity, team continuity, and cross-boundary continuity	Internal consistency, content validity, structural validity, and construct validity	28 items in three subdomains; 5-point scale from 1 to 5
Stokes T et al (2005) [42]; General Practitioners' Views on Continuity of Care survey	Measures the perceived importance of the types of continuity of care and doctor or practice characteristics that may influence attitudes toward personal continuity of care—*adapted for nurse-patient context*; Relational, management, and informational continuity	Good internal consistency (alpha=.78). The scale score correlated highly with the overall rating of the importance of personal continuity (P<.001)	25 items over four domains; 5-point scale from 1 to 5
Cameron KS et al (2011) [43]; Organizational Culture Assessment Instrument	Assesses six key dimensions of organizational culture: dominant characteristics of an organization, organizational leadership, management of employees, organizational glue, strategic emphasis, and criteria of success	Widely tested	Six dimensions with four alternatives (24 items); 4-point scale from A to D
Gardner G et al (2017) [44]; The Advanced Practice Nursing Role Delineation Questionnaire (APRD)	A self-assessment tool that provides a standardized understanding of advanced practice. It is designed to support health service planning, cross-discipline team development, and demonstration of achievement of practice at this level.	Evidence based	Five items: clinical care, optimizing health systems, education, research, and leadership; 5-point scale from 0 to 4

[a]MACS: Multidisciplinary Ambulatory Consulting Service.

[b]EuroQol: European Quality-of-Life Scale.

[c]EQ-5D: European Quality-of-Life Five-Dimension Scale.

Setting

The setting for this study is an outpatient MACS at a large secondary, tertiary referral, hospital.

Participants

1. Stakeholders. These will consist of attendees at the forums and workshop:

a. Representative health professionals from the MACS clinic.
b. Consumer representatives and advocates.
c. Representative leadership associated with the MACS clinic (ie, nursing and medical).
d. Representatives from the primary health network and private sectors (n=40).

2. Health care staff. There will be two health care staff groups:
   a. Health care staff within the MACS or from the outpatient service (n=130).
   b. Health care staff from the primary health network or the private sector. For example, clinical staff working in general or community settings (ie, primary health care sector) and have patients who attend or could attend the MACS clinic (n=10).

3. Patients. There will be two patient groups:
   a. Patients who have previously attended the MACS clinic prior to implementation of the nurse-led care coordination service (n=100).
   b. Patients who would usually attend the MACS clinic following implementation of the nurse-led care coordination service (n=30).

Data Collection and Analysis

This action research study is largely qualitative but includes a quantitative descriptive element. There will be an initial stakeholder forum to develop the domains for a model of nurse-led care coordination. When the model is developed, it will be validated through current literature and a follow-up-focused workshop of stakeholders (see Table 3). Stakeholders at the forum and workshop will include health care staff and executives from both the primary and secondary heath care sectors, as well as other relevant academic and clinical participants (see Table 1). The nurse-led model for care coordination will then be implemented and refined through a series of iterative action research cycles. Data will be collected throughout the action research cycles (see Table 3).

Table 3. Data collection and analysis: survey and interview schedule.

Event and survey tool	Data collection point	Participants	Analysis
Stakeholder forums and validation workshop: activities guided by the Australian Primary Health Care Nurses Association, Building Blocks [45], and Donabedian's categories of structure, process, and outcome [31]	At stakeholder forums and validation workshop events	Key stakeholders: registered nurses (level one), nursing middle management, general practitioners, pharmacists, allied health, and executives across both primary and secondary heath care sectors, along with consumer, academic, and professional association representation (n=60)	Thematic analysis
Patient Assessment of Chronic Illness Care (PACIC) survey [34]	Prior to nurse-led service implementation, January-April 2019	MACS[a] outpatients who attended clinic prior to model of nurse-led care coordination implementation (n=100)	Descriptive statistics and thematic analysis
Assessment of Chronic Illness Care (ACIC V3.5) survey [35]	Prior to nurse-led service implementation, January-April 2019	MACS outpatients who attended clinic prior to model of nurse-led care coordination implementation (n=100)	Descriptive statistics and thematic analysis
Patient experience and continuity of care in clinics survey [38]	First appointment	MACS outpatients who attended clinic after model of nurse-led care coordination implementation (n=30-40)	Descriptive statistics and thematic analysis
Patient EQ-5D-3L[b] health questionnaire [36,37]	At first and second appointments	MACS outpatients who attended clinic after model of nurse-led care coordination implementation (n=30-40)	Descriptive statistics
Patient experience and continuity of care in clinics, Nijmegen Continuity Questionnaire (NCQ) [40,41]	At second appointment or at 3-6 months	MACS outpatients who attended clinic after model of nurse-led care coordination implementation (n=30-40)	Descriptive statistics and thematic analysis
General Practitioners' Views on Continuity of Care survey [42,46]	At commencement, then at 3-6 months	Nurses working in the MACS outpatient clinic (n=2)	Descriptive statistics and thematic analysis
Doctor and allied health staff experience and continuity of care survey [42,46]	At commencement, then at 3-6 months	Doctors and allied health staff working in the MACS outpatient clinic (n=3-10)	Descriptive statistics and thematic analysis
Primary health care staff experience and continuity of care survey [42,46]	At commencement, then at 3-6 months	Health care staff managing MACS patients in the primary health care sector; general practitioner rooms or community services (n=10)	Descriptive statistics and thematic analysis
Nurse experience and continuity of care survey, other than MACS [42,46]	At commencement	Nurses, other than the MACS nurses, working in outpatient clinics (n=80)	Descriptive statistics and thematic analysis
The Advanced Practice Nursing Role Delineation Questionnaire (APRD) [44]	At commencement and at 6 months	Nurses working in the MACS clinic and outpatient clinic nurses (n=2)	Descriptive statistics and thematic analysis
Staff workplace culture survey [43]	Commencement and at 6 months	All health care staff working in the MACS outpatient clinic (n=5-10)	Descriptive statistics and thematic analysis
Survey: question bank	At 6 months via email	Director of nursing and nursing director (n=2)	Thematic analysis
Interview, with questions from bank, and ongoing reflective meetings	At 6 months and ongoing	Head of unit (n=1)	Thematic analysis
Interview and ongoing reflective meetings	At 6 months and ongoing	MACS nurses (n=2)	Thematic analysis
Interview and ongoing reflective meetings	At 6 months and ongoing	MACS team (n=5-10)	Thematic analysis
Focus group questions from bank	At 6 months	Consulting clinics nurses (n=10-20)	Thematic analysis
Patient medical record	Following patient recruitment	MACS outpatients who attended clinic after model of nurse-led care coordination implementation (n=30-40)	Descriptive statistics

[a]MACS: Multidisciplinary Ambulatory Consulting Service.

[b]EQ-5D-3L: European Quality-of-Life Five-Dimension Three-Level Scale.

Qualitative Data

Thematic analysis based on the phases of Braun and Clarke [47] will be used as outlined in Table 4. The process of thematic analysis will identify categories of information and develop model domains for developing a model of nurse-led care coordination. It is anticipated that the model will be pragmatic and consider specific continuity of care strategies to be implemented as part of the nurse-led care coordination service. Thematic analysis will also be used to analyze survey and interview data to reveal patients', nurses', and health care staff's experiences of continuity of care, before and after implementation of the nurse-led model of care coordination. Through the process of thematic analysis, an account of what is happening in the situation (ie, nurse-led service within the multidisciplinary MACS clinic) and how it is happening will be identified [47]. Braun and Clarke's practical approach is useful for comparing multiple data sources (ie, from patients, nurses, and health care staff) [47,48].

Table 4. Process of thematic analysis, adapted from Braun and Clarke [47].

Phase	Activity
Analysis	
Familiarization with data	Transcribe data and formulate ideas; analysis starts here and continues throughout the process
Generation of initial codes	Systematically code and collate entire dataset
Search for themes	Sort different codes into possible *candidate* themes
Review of themes	Refine and finalize candidate themes
Naming and defining of themes	Develop thematic map of data, further refine themes, and perform final analysis
Production of the report	Perform inductive thematic analysis, which will emphasize understanding the patients' and nurses' experience of the nurse-led service

Quantitative Data

Quantitative data from questionnaires and/or medical records related to patients', nurses', and health care staff's experiences of continuity of care and the nurse-led model of care coordination and demographic data, as well as data relating to the nurse-led model of care coordination, continuity of care, and patient progress or outcomes will be analyzed (see Table 3). Analysis will use descriptive statistical methods including means, medians, and interquartile ranges where appropriate. Differences between variables will be analyzed using either two-tailed *t* tests or the Wilcoxon ranked-sum test where appropriate. A *P* value of less than .05 will be considered statistically significant. All statistical analyses will be conducted using NVivo 10 (QSR International) and SPSS, version 25 (IBM Corp).

Validity and Reliability

The nurse-led model will be collaboratively developed at a series of stakeholder—secondary and primary health sectors—forums. The forums will also be developed with reference to the Australian Primary Health Care Nurses Association Building Blocks for nurse-led clinics [45]. A follow-up validation workshop and literature search will further refine the model. Implementation of the model through iterative research cycles will continue the validation process as elements change in response to user experiences. Interventions aligned with the model will be based on real-world experience in the nurse-led service, a consensus approach, and systematic findings from the literature.

Recognized and validated instruments will be used to collect data in relation to continuity of care, patient centeredness, workplace culture, and the practice role and level of the nurses (see Table 2). A concurrent approach to data collection and analysis will allow the separate use of quantitative and qualitative methods within a single cycle of data collection and analysis. This will allow both sets of data to be interpreted together, providing a richer and more comprehensive response to research questions [49].

Results

Pilot implementation of the model of care coordination commenced in October 2018. Formal study recruitment commenced in May 2019 and the intervention and follow-up phases are ongoing. The results of the data analysis are expected to be available by March 2020.

Discussion

Expected Results

Nurse-led services and clinics have been widely implemented in primary health care settings and, increasingly, in outpatient departments but not with the purpose of improving continuity of care between the two sectors. The evidence for nurse-led services to improve continuity of care for people living with multiple chronic diseases and complex care needs has not been established. This proposed study is significant because it aims to develop a model of care for nurse-led services, based on both research and stakeholder experience. This model, focusing on patient-centered care and the nursing role to coordinate care to achieve continuity across the health care sector, has not been previously trialed for people with multimorbidity.

It is anticipated that the model of care for a nurse-led care coordination service will support the implementation of continuity of care strategies. These strategies may include assessment of risk of hospital readmission; patient readiness for change; well-coordinated, individualized, multidisciplinary health care plans; patient self-management strategies; and coordinated communication between the secondary and primary

health care sectors. Ideally, these will result in improved patient and staff experiences and health outcomes. Development of the model followed by a series of action research cycles of testing and refining the model will ensure that the research incorporates both theory and practical experience related to continuity of care across the health sector. This action research approach will, therefore, focus on what works within a *real-world* clinical setting. It will produce a patient-centered model of care for nurse-led services that provides a template for continuity of care, articulating the nursing role and service for adaptation throughout diverse health care systems within Australia and potentially worldwide.

Limitations

As this is an action research design, there are no a priori design of the nurse-led model of care coordination or nursing interventions required. However, as both the model and the interventions will be developed in collaboration with *real-world* clinical practice and the health care literature, it will be important to ensure concordance between both. No control or comparator will be included within the model assessment, but survey participants who attended the outpatient department prior to commencement of the nurse-led service will be examined. The service setting is geographically limited since it is located at only one site; however, it is anticipated that the setting will be adaptable and applicable to geographically diverse locations. Electronic record and patient data systems vary across health sectors and can pose access and consistency issues. These will be addressed through the highly pragmatic nature of the study, which will focus on relationship building [47] and regular and consistent communication across health sectors as part of the nursing interventions.

Acknowledgments

This protocol is part of KMD's PhD studies.

Authors' Contributions

KMD was responsible for the literature review and study design, along with drafting the initial manuscript and its revised versions. GEC contributed significantly to the drafting and preparation of the manuscript and contributed to the study design. MCE, SS, ADH, JH, and GS contributed to the drafting and preparation of the manuscript and to the study design.

Conflicts of Interest

None declared.

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Abbreviations

ACIC: Assessment of Chronic Illness Care
APRD: The Advanced Practice Nursing Role Delineation Questionnaire
CALHN: Central Adelaide Local Health Network
EQ-5D: European Quality-of-Life Five-Dimension Scale
EQ-5D-3L: European Quality-of-Life Five-Dimension Three-Level Scale
EuroQol: European Quality-of-Life Scale
HREC: Human Research Ethics Committee
MACS: Multidisciplinary Ambulatory Consulting Service
NCQ: Nijmegen Continuity Questionnaire
PHC: primary health care
PROSPERO: international prospective register of systematic reviews

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Protocol

Characteristics, Opportunities, and Challenges of Osteopathy (COCO) in the Perceptions of Osteopaths in Germany, Austria, and Switzerland: Protocol for a Comprehensive Mixed Methods Study

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Abstract

Background: Currently, the importance of osteopathy within the health care system is controversial. The training structures and the acknowledgment of the occupational profile strongly differ in the German-speaking territory.

Objective: This study aims to examine the characteristics of the osteopathic profession as well as the possibilities and challenges for osteopaths in Germany, Austria, and Switzerland.

Methods: This study adopted a mixed methods design. The research topic will be examined based on qualitative and quantitative partial studies that will be conducted in parallel as well as sequentially. By applying different research methods and sample testing and by using standardized, validated measurement methods, we expect to be able to gain new insights into the work area of osteopathy.

Results: In November 2018, we started the research and data collection. Currently, we are conducting the first two partial studies. The planned duration of each of the partial study is 6-9 months. The project is scheduled to be completed in 2021.

Conclusions: This study will examine how osteopaths define themselves in comparison with professionals from other occupational profiles and how they describe the characteristics of their work. The identification of central issues is expected to help clarify the issues and define the profession. As such, the results might contribute to the conservation and improvement of the quality of osteopathic treatment.

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KEYWORDS

osteopath; osteopathic medicine; health occupations; occupational profile; mixed methods

Introduction

Background

The treatment method of osteopathy and the occupational profile of osteopaths have been discussed more often in recent times. However, there is still no uniform international regulation on who is allowed to practice as an osteopath and what qualification he or she requires. Osteopathy has been defined by the European Committee for Standardization as a whole-person, patient-centered, manual health care discipline that emphasizes on the interrelationship of structure and function of the body and facilitates the body's innate ability to heal itself [1].

An increasing number of European countries, such as Italy and Luxembourg, are developing professional regulations for

osteopaths [2]. Thus far, eight countries in Europe (England, Finland, France, Iceland, Lichtenstein, Malta, Portugal, and Switzerland) have legal regulations concerning osteopathy [3].

In Germany, however, *osteopathy* is not an independent profession. Currently, three different professional groups are practicing osteopathy: physicians, natural health professionals, and physiotherapists [4]. However, there is no legal basis for practicing osteopathy and for its rank in health care treatment. Hence, different jurisdictions and the interpretation of osteopathy during the past years have, in practice, resulted in confusion among professionals practicing osteopathy. The Higher Regional Court Düsseldorf, for example, prohibited a physiotherapist from practicing osteopathy at his facility, as long as the treating person had not been appointed as a physician or had received permission to practice healing arts pursuant to § 1 HeilPrG (German law on natural health professionals) [5]. In contrast, in the course of another matter, the Higher Regional Court Frankfurt decided that practicing healing arts will only be reserved for physicians and natural health professionals if the patient's health is at risk. Such an indirect risk for the patient resulting from an osteopathic intervention could, however, be excluded by order of the treating physician [6].

Austria does not have any current legal regulation for the occupational profile either. Physicians trained in osteopathy and physiotherapists are practicing osteopathy in Austria [7]. During a complete survey in the framework of a master's thesis, the Austrian *standard osteopath* was described as being female, aged between 30 and 49 years, and primarily qualified as a physiotherapist. Moreover, 77.8% of the interviewees indicated that they did not practice osteopathy exclusively, but mostly in combination with their original profession [8].

In contrast, the term *osteopath* has been protected in Switzerland since 2013 and was acknowledged as a medical profession in 2016 [9].

Objective

Research concerning the effectiveness of osteopathic treatment methods has advanced lately [10-12]; however, there is only little research about the profession as an osteopath. Therefore, the Characteristics, Opportunities, and Challenges of Osteopathy (COCO) study is supposed to provide clarification on how osteopaths define themselves in comparison with other occupational profiles. The COCO study will examine the characteristics of the osteopathic profession, in addition to the possibilities and challenges, for osteopaths in Germany, Austria, and Switzerland.

Comparable research has already been conducted in other countries. In the framework of the study "Challenges and opportunities for Australian osteopathy: A qualitative study of the perceptions of registered osteopaths," published in 2018 in the *International Journal of Osteopathic Medicine*, Blaich et al [13] interviewed osteopaths, questioning them about the osteopathic profession. The authors concluded that future osteopathic research and uniform training can strengthen the profession's position within the health care system. They classified their results as being mostly specific for the Australian context; the results may not transfer to other countries. The qualitative study design is formulated as a potential restriction because the results were acquired from a small sample. With respect to a German-speaking country, this study might be a typical example of a qualitative partial study in the framework of the COCO study. The results of the study by Cerritelli et al [14] provide essential insights into the osteopathic profession in Italy. On the basis of a Web-based survey, the professional profile of an Italian osteopath could be described as that of a freelance, young, and male adult working on his own and having received his training part-time; his original profession is in the fields of sport science or physiotherapy. Concerning the implementation of a license or registration procedure in their country, the authors have pointed out that the different types of professional training must especially be accounted for. This study might be a typical example of a quantitative partial study in the framework of the COCO study.

If we consider both of the indicated studies more closely, the combination of different study designs appears to make sense; therefore, we will be able to examine any data acquired within the intended examination directly with respect to their generality.

The objective of the COCO study is to examine how osteopaths define themselves in comparison with other occupational profiles and how they describe the characteristics of their work.

As the intended research project is very comprehensive, superordinate planning will be required. The objective of this study is to prepare a detailed study design for the more extensive comprehensive study.

Methods

Study Design

This study employed a mixed methods design. The research topic will be examined based on qualitative and quantitative partial studies that will be conducted in parallel as well as sequentially.

The parallel form comprises several partial studies during the same period, which will be evaluated subsequently. In contrast, different studies are finally conducted in a sequential form. Thus, evaluation of the qualitative studies will influence the later implementation of the quantitative studies in the planned study: Technically, this is an exploratory design. First, hypotheses can be developed on the grounds of the results from the qualitative study projects, which are then examined in a second step on the generality of the projects. This kind of sequential planning allows for differentiated questioning. In contrast, a parallel design allows for implementation of different study designs without reciprocal influence [15].

Procedure

Before the study, intensive literature research was conducted. We searched databases for publications referring to the research topic. On the basis of an overview of the current research situation, qualitative partial studies will be implemented as a first step, for example, interviews with osteopaths in Germany, Austria, and Switzerland. Following analytical evaluation of the study contents, questionnaires will be developed with the resulting data. In the second step, the quantitative partial studies

will be conducted by standardized questionnaires. These will be filled in by osteopaths working in Germany, Austria, and Switzerland. After conclusion of the survey, meta-integration of the qualitative and quantitative study results will be conducted in a separate partial study. At the end of the integrative work, a quantitative study will be performed to evaluate the entire study project.

Literature Research

We primarily looked for osteopathic final papers describing the work area of osteopathy in the broadest sense. A search was performed using the internet search engines *Google* and *Google Scholar* as well as via the portals *Osteopathicresearch.com*, *Ostemed-dr*, *Pubmed*, *EMBASE*, and *Pedro*. Keywords used for the search were, for example, *Abschlussarbeit Osteopathie*, *Fragebogen Osteopathie*, *Berufsbild Osteopathie*, *dissertation/thesis osteopathy*, *questionnaire osteopathy*, and *occupational profile osteopathy*. In addition, we particularly searched for papers published on the websites of individual training institutions and universities offering osteopathic education.

Inclusion and Exclusion Criteria of Available Literature

To avoid falsifying the current situation of osteopathy by inclusion of older surveys, only studies published ≤10 years ago have been accounted for. In addition, the full text of the used studies must be available to the authors.

Inclusion and Exclusion Criteria of Participants

All participants of the individual qualitative and quantitative studies must have attended at least 4 years of training as osteopaths and must be practicing as osteopaths (for humans). Participants are enrolled via the lists of therapists of the professional associations or interest groups. As such, it is guaranteed that the criterion of a comprehensive training in osteopathy will be fulfilled; otherwise, the participants cannot be members of such associations.

Another criterion for the entire group of participants is a balanced gender distribution (as balanced as possible). In addition, participants in the individual countries should be subject to a topographic spread as wide as possible, so that district-specific phenomena can be excluded. In Germany and Austria, osteopathy is not an independent profession; therefore, different professional groups practicing osteopathy in both countries should be represented among the participants of the study.

Description of the Partial Studies

For the partial studies, each study is conducted by an individual study co-ordinator who has access to the literature, the study protocol, and the datasets resulting from other partial studies.

Qualitative Partial Studies—Osteopaths in Germany, Austria, and Switzerland

These partial studies include the planning and conduct of interviews with osteopaths working in Germany, Austria, and Switzerland separately. Subsequently, there will be a qualitative content analysis, according to Mayring [16], to achieve a first overview of the research topic. To acquire representative results, 10-12 interviewees in each country will be questioned per study [16].

Quantitative Partial Study—Osteopaths in Germany, Austria, and Switzerland

In the framework of this partial study, a questionnaire survey is planned with closed-ended questions. In Germany, Austria, and Switzerland, there are approximately 10,000, 1000, and 1040 practicing osteopaths, respectively; therefore, we intend to enroll 370, 278, and 281 cases, respectively (95% CI for the respective number of practicing osteopaths), for the questioning to acquire representative results [17-20].

Meta-Integration Partial Study

This partial study includes a meta-integration of the results of the individual qualitative and quantitative partial studies.

Quantitative Partial Study: Evaluation of the Entire Study Project

In the framework of this partial study, an evaluation of the entire COCO study is planned from a scientific point of view and from the point of view of the participating persons.

Data Evaluation

Phases

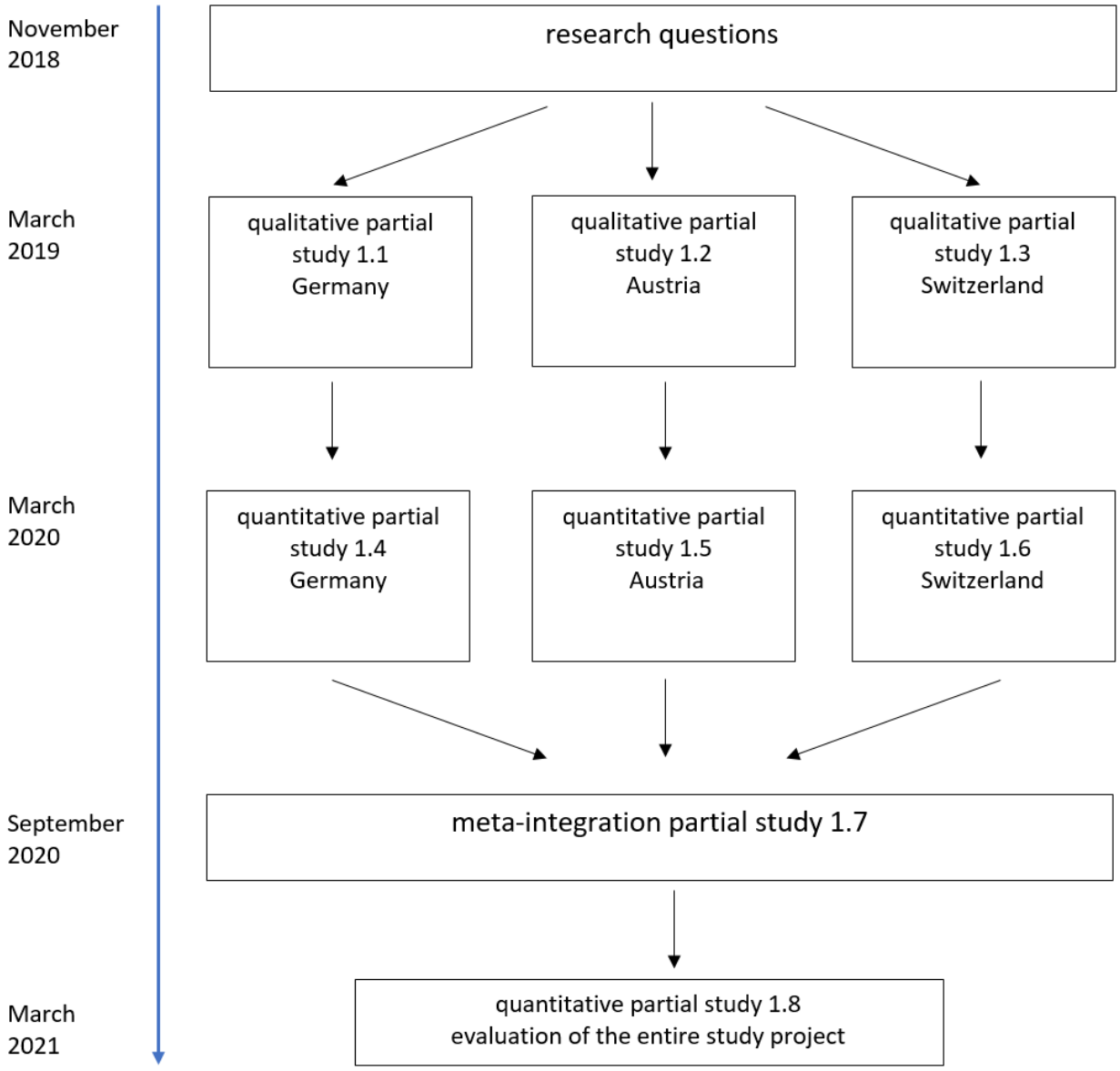
In the following paragraphs, individual phases of the described study procedure will be explained in detail. Currently, three evaluation phases are planned:

- Phase 1: Planning and implementation of the qualitative partial studies
- Phase 2: Planning and implementation of the quantitative studies
- Phase 3: Meta-Integration of the different partial studies and evaluation of the project

Phase 1: Planning and Implementation of the Qualitative Partial Studies

This phase includes reading and evaluation of the available studies to obtain a first overview of the state of research. The studies will be categorized according to the survey period, the type of collected data, and the country of origin. To keep the results as up to date as possible, the studies should be weighted according to their year of publication. For example, studies can be categorized and evaluated according to the periods of 2019-2017, 2016-2013, and 2013-2009, similar to the process used in another mixed methods study by Carsons-Stevens et al [21]. Subsequent to the evaluation of the available literature, an interview guideline will be developed with respect to the research topic. The country-specific questionnaire of participants and the qualitative content analysis are conducted by one study co-ordinator, according to the first three planned partial studies (Figure 1).

Figure 1. Design of the Characteristics, Opportunities, and Challenges of Osteopathy (COCO) study as a flowchart.



The objective is to reduce the material by the subsequent content analysis in such a way that essential content can be filtered out and the research topic can be better understood [22]. A system of categories will be developed to interpret the results of the qualitative partial studies, where the resulting data can be categorized. This system of categories makes the interpretation of the data comprehensible for the readers [22]. On this basis, it will be possible to develop a questionnaire with closed-ended questions in the framework of the following partial studies and to conduct larger surveys.

Phase 2: Planning and Implementation of the Quantitative Studies

The results of the partial studies (studies 1.1, 1.2, and 1.3 in Figure 1) will be compiled. The quantitative studies are implemented with the objective of reviewing the results of the qualitative partial studies with respect to the population. By sampling, we will examine how often statements or categories stemming from the qualitative studies occur within the population. As a measuring tool, a standardized questionnaire is developed. The survey will again be implemented in three partial studies that are conducted by one study co-ordinator (studies 1.4, 1.5, and 1.6 in Figure 1). The results will be conveyed in a descriptive manner by preparing schemes in the form of spreadsheets and graphics for the individual items. Before comparison of the individual groups, the data are tested with respect to normal distribution. During the planning of a study, assumptions concerning normal distribution may be based on the results of pilot studies, for example, the studies by Rochon et al and Shuster [23,24]. The visual assessment of a histogram and the Q-Q or P-P plots, as well as the Shapiro-Wilk test, may also be indicated as possible alternatives [25]. The distributions will then be examined with the help of Chi-square and Fisher exact tests. In addition, group comparisons may be conducted using the *t* test or the Wilcoxon-Mann-Whitney test.

Phase 3: Meta-Integration of the Different Partial Studies and Evaluation of the Project

The data resulting from the qualitative and quantitative partial studies will be compiled, and the entire study project will be evaluated subsequently. Integration and reflection will be performed after data collection has been completed. It is the objective of the integration to examine which results from the qualitative research can be generalized by the quantitative study by using questionnaires. To compare the data and results, a spreadsheet or concept map will be compiled. As such, it will be possible to evaluate individual items or categories with the respective questions as opposed to entire questionnaires [15].

Recommendation for Questionnaires

Several aspects must be accounted for with regard to the conception of the measuring instruments. For example, the questions should be short and concrete and formulated in simple words. Hypothetic or leading questions should be avoided [26]. To review the questionnaires developed later with respect to comprehensibility and unambiguity of the questions, as well as concerning the completeness of the possible answers, the execution of a pretest is recommended [27]. The basis of a representative result is also a questionnaire response rate as high as possible. In the case of questionnaire administered in writing, a response rate of 52% (SD 24%) is expected [28]. To increase the motivation of the study's potential participants, it is possible to offer shopping vouchers or any similar incentive to the study participants.

Ethical Considerations

Participation in all the studies conducted within this project will be voluntary. Participants will be informed about their right to refuse participation [29]. Participation based on remuneration will also be excluded. For participants of questionnaires administered in writing, this information can be handled, for example, by including the conditions of participation in an annex of the questionnaire, which the participants approve by sending back the survey. All the interview partners will be informed and must have expressed their consent in writing. The anonymity of all the participants will be guaranteed at all times.

Results

In November 2018, we started the research and data collection. The planned duration of each of the partial studies is 6-9 months. Qualitative study projects are being conducted in parallel and evaluated. Currently, we are running the first two partial studies, 1.1 and 1.2.

Upon conclusion of the qualitative partial studies toward the end of the year 2019, all results will be collected during a period of 2-3 months to plan the following quantitative partial studies. After the development of a questionnaire as a standardized measuring instrument, the provisional start of questioning is planned for March 2020 within the parallel partial studies 1.4, 1.5, and 1.6. Subsequent to the questioning, the research results will be summarized finally in a meta-integration in the form of autonomous study 1.7, which will begin in September 2020. After the expected conclusion of the research project in March 2021, the study will be evaluated with the last partial study 1.8. From the current point of view, the overall results of the project will be published at the end of the year 2021.

Discussion

This will be the most extensive analysis on the profession of osteopaths in the German-speaking territory. By applying different research methods and sample testing and by using standardized, validated measurement methods, we expect to be able to gain new insights into the work area of osteopathy.

During evaluation of the results, topics concerning the situation of osteopathy in general practice will be identified primarily. The resolution of these central issues is expected to help identify the characteristics of the work area. Delimitation concerning other professional groups will also be possible. Thus, the results may contribute to the conservation and improvement of the quality of osteopathic treatment. Blaich et al [13] highlighted the necessity of advancement in osteopathic education and research through their qualitative study design.

Increased interdisciplinary cooperation between different professional groups can help us achieve a target-oriented and responsible collaboration between osteopaths and other medical professions during the planning and implementation of patients' treatment. Comparable results were provided by Cerritelli et al [14] who did not only describe the profile of osteopaths practicing in the country but also provided new insights into the cooperation of different medical professions in the health care system [14].

The issue of different professional situations in the countries to be examined should also be mentioned. Currently, there is no legal basis for practicing osteopathy in Germany and Austria, whereas in Switzerland, *osteopathy* is an acknowledged profession. We will observe whether data can be collected to allow for any conclusions on the reasons of the respective professional situations in these countries. Thus, topics primarily concerning improvements in practice and the professional situation may be identified. Notably, different professional situations in the countries surveyed may limit the comparability of the results. Nonetheless, we believe that we will be able to compare the groups to a certain extent because in all three countries, physiotherapists are the ones who mainly practice osteopathy, even if in Germany, many osteopaths additionally have passed an examination as a Heilpraktiker for legal reasons [30-32]. The final results and recommendations will be summarized to be distributed and made available for politics, professional associations, universities, and training institutions. Thus, the results can be used to improve specific and professional education, training, and advanced training possibilities. Tasks and possibilities of the profession will be presented to extend the task profile and increase autonomy.

Owing to the partially parallel design, studies are conducted simultaneously in the framework of the COCO project, particularly in the qualitative research area. These parts may vary with respect to the selection of methods for the questionnaire of participants. Hence, the qualitative content analysis may become potentially more difficult. The chronological order of the individually designed partial studies

may also be considered critically. Owing to the sequential design, the evaluation of the results of the qualitative studies must be concluded before the questionnaires can be started. As the different parts of this study need to be coordinated and conducted in a chronological order, the dataset may be falsified between evaluation and review by sampling. Therefore, subsequent studies will be considered to observe any future modifications of the osteopathic profession. The results will consequently also serve as a basis of further development and testing by future research projects. Through a planned questionnaire of all the study co-ordinators, improvement measures may also be revealed within the COCO study.

Conflicts of Interest

None declared.

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Abbreviations

COCO: Characteristics, Opportunities, and Challenges of Osteopathy

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