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Effects of a Novel, Transdiagnostic, Hybrid Ecological Momentary Intervention for Improving Resilience in Youth (EMIcompass): Protocol for an Exploratory Randomized Controlled Trial

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Abstract

Background: Most mental disorders first emerge in youth and, in their early stages, surface as subthreshold expressions of symptoms comprising a transdiagnostic phenotype of psychosis, mania, depression, and anxiety. Elevated stress reactivity is one of the most widely studied mechanisms underlying psychotic and affective mental health problems. Thus, targeting stress reactivity in youth is a promising indicated and translational preventive strategy for adverse mental health outcomes that could develop later in life and for improving resilience. Compassion-focused interventions offer a wide range of innovative therapeutic techniques that are particularly amenable to being implemented as ecological momentary interventions (EMIs), a specific type of mobile health intervention, to enable youth to access interventions in a given moment and context in daily life. This approach may bridge the current gap in youth mental health care.

Objective: This study aims to investigate the clinical feasibility, candidate underlying mechanisms, and initial signals of the efficacy of a novel, transdiagnostic, hybrid EMI for improving resilience to stress in youth—EMIcompass.

Methods: In an exploratory randomized controlled trial, youth aged between 14 and 25 years with current distress, a broad Clinical High At-Risk Mental State, or the first episode of a severe mental disorder will be randomly allocated to the EMIcompass intervention (ie, EMI plus face-to-face training sessions) in addition to treatment as usual or a control condition of treatment as usual only. Primary (stress reactivity) and secondary candidate mechanisms (resilience, interpersonal sensitivity, threat anticipation, negative affective appraisals, and momentary physiological markers of stress reactivity), as well as primary (psychological distress) and secondary outcomes (primary psychiatric symptoms and general psychopathology), will be assessed at baseline, postintervention, and at the 4-week follow-up.

Results: The first enrollment was in August 2019, and as of May 2021, enrollment and randomization was completed (N=92). We expect data collection to be completed by August 2021.

Conclusions: This study is the first to establish feasibility, evidence on underlying mechanisms, and preliminary signals of the efficacy of a compassion-focused EMI in youth. If successful, a confirmatory randomized controlled trial will be warranted. Overall, our approach has the potential to significantly advance preventive interventions in youth mental health provision.

Trial Registration: German Clinical Trials Register DRKS00017265; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00017265

International Registered Report Identifier (IRRID): DERR1-10.2196/27462

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KEYWORDS

experience sampling methodology (ESM); ecological momentary assessment (EMA); mobile intervention; at-risk individuals; smartphone training; blended care; mental health; stress reactivity; mobile phone

Introduction

Background

Youth is a critical life period, and most mental disorders have their onset before the age of 25 years [1]. In the early stages of psychopathology, subthreshold expressions of symptoms may occur, reflecting an extended phenotype in the general population that is often transdiagnostic in nature, spanning from subthreshold expressions of anxiety, depression, and mania to psychotic experiences [2-4]. This extended transdiagnostic phenotype may, in turn, be associated with a range of subsequent psychopathological outcomes or exit syndromes later in life [2,3]. On the basis of emerging evidence on the transdiagnostic dimensions of psychopathology [5-10], dimensional classification systems with transdiagnostic high-order spectra that place individuals on a continuum of mental ill-health have recently been proposed, including the Hierarchical Taxonomy of Psychopathology [11-14], and clinical staging models have been proposed considering the overlapping and nonspecific nature of early psychopathology [15-18]. For example, Hartmann et al [16] in their clinical staging model, distinguish three stages of early mental health problems, that is, current psychological distress (stage 1a), a broad Clinical High At-Risk Mental State (CHARMS) with attenuated symptoms of psychosis, mania, or depression (stage 1b), and a first episode of severe mental disorder (stage 2). Moreover, mental disorders in youth aged 10-24 years have been reported to be the leading cause of disease burden in high-income countries [19], underlining the importance of early intervention and prevention. However, access to care remains deficient, with only 1 in 5 youth with mental health problems having access to mental health services [20,21]. Thus, there is a strong need for easily accessible, low-threshold, preventive interventions in the provision of youth mental health services.

Recent rapid advances in digital technologies have led to the development of novel mobile health (mHealth) assessment and intervention techniques, of which ecological momentary assessments (EMAs) [22,23] and ecological momentary interventions (EMIs) [23-28] are, arguably, among the most powerful [26,28]. EMIs such as Acceptance and Commitment Therapy in Daily Life [29,30], recently also referred to as just-in-time adaptive interventions [31], provide a unique opportunity to deliver youth-friendly, adaptive, personalized, real-time transfer of intervention components to individuals' daily lives. EMIs enable youth to access interventions tailored to what a young person needs in a given moment and context through interactive sampling and administration of specific training components [26,27,32]. To this end, EMIs build on real-time data acquired through EMA, a structured digital diary technique that measures moment-to-moment fluctuations in experience, behavior, and—when coupled with electrocardiography (ECG) and actigraphy sensors—physiological markers in daily life to offer training components that are adapted to the person, moment, and context based on EMA data. Therefore, EMIs are amenable to enhancing access to mental health services for youth depending on their needs and preferences. Indeed, youth—as the generation of digital natives—already make regular use of mHealth apps and are more likely to do so when experiencing psychological distress [33]. However, most mHealth apps that are currently available in major app stores are not evidence-based, often use problematic data sharing and privacy practices, and sometimes contain harmful content [34-36]. As reviewed recently, there is evidence on the effectiveness of mindfulness-based EMI for stress reduction [37] and reduction of psychotic experiences [30,38,39]. Furthermore, there is evidence for higher compliance and greater effectiveness of hybrid interventions that include both digital and face-to-face intervention components with research staff or clinicians [40,41].

Underlying transdiagnostic mechanisms may be important intervention targets in youth to prevent transition to and incidence of severe mental disorder. The most widely studied transdiagnostic mechanisms are (1) elevated stress reactivity (ie, more intense emotional reactions to minor stressors in daily life), (2) heightened interpersonal sensitivity, and (3) enhanced threat anticipation. There is evidence that stress reactivity is elevated in individuals with higher familial or psychometric risk, individuals with an ultrahigh risk state for psychosis, first-episode psychosis, severe and enduring psychosis [42-45], as well as with depressive disorder [46-48], mania, and bipolar disorder [49-51]. Moreover, some evidence suggests that differential reactivity to momentary stressors may reflect a risk and resilience mechanism [44,52-54]. Heightened interpersonal sensitivity is another putative transdiagnostic psychological mechanism that has been characterized by an enduring sense of feeling vulnerable in the presence of others [43,55]. Interpersonal sensitivity has been previously reported as a relevant psychological mechanism in individuals with ultrahigh risk, paranoia, and psychotic disorders [55,56] as well as in

individuals with affective disturbances, including depression, anxiety, and bipolar disorder [57-59].

Furthermore, our recent EMA findings extended beyond elevated interpersonal and socioenvironmental sensitivity and, consistent with previous research on psychotic, depressive, and anxiety disorders [60-65], also indicated that enhanced anticipation of threat might be an important mechanism in the development of psychosis [43,44]. These mechanisms have been implicated in a range of adverse mental health outcomes, which we have found to overlap considerably [2,5,6,66] and, as noted above, often manifest at a developmentally early stage in adolescence. Thus, developing EMIs targeting these candidate mechanisms underlying a dimensional transdiagnostic and extended phenotype of psychosis, mania, depression, and anxiety in youth is a promising indicated strategy [67] for preventing transition to, and incidence of, severe mental disorders, which, if effective, will be associated with substantial public health gains.

Compassion-focused interventions are third-wave cognitive behavioral therapy (CBT) approaches that use a wide range of innovative therapeutic techniques for enhancing emotional resilience by activating emotion regulation systems related to self-compassion, self-acceptance, and positive affect rather than those related to stress, threat, anxiety, and depression [68-70]. Indeed, there is meta-analytic evidence on compassion-focused interventions treating various conditions [71-73], such as depression and anxiety [74], psychosis [75], and general distress [76]. Compassion-focused interventions involve the use of techniques that seek to access emotion regulation processes through imagery rather than rational understanding [68,69]. In doing so, compassion-focused interventions aim to enhance emotional resilience by developing specific affective regulation patterns and, thereby, reduce reactivity to stress, hypervigilance for threat, interpersonal sensitivity, and negative affective appraisals. Experimental evidence indicates that compassion-focused intervention techniques can reduce negative affect and paranoia in moments of high stress [77,78]. Therefore, compassion-focused interventions are particularly promising for targeting these putative transdiagnostic mechanisms. Building on these pieces of evidence, we have recently developed a novel, accessible, transdiagnostic, compassion-focused, hybrid intervention to enhance resilience in youth with early mental health problems—the EMIcompass intervention [53], which consists of an EMI plus face-to-face training sessions. Although there is preliminary evidence on the feasibility and initial therapeutic effects of the EMIcompass intervention from an uncontrolled pilot study [53], robust evidence on the underlying mechanisms, feasibility, and initial signals of efficacy of EMIcompass from an exploratory trial is pending.

Objectives

Against this background, this study will aim to examine the clinical feasibility, underlying mechanisms, and initial signals of efficacy of EMIcompass for improving resilience in an exploratory, randomized controlled trial (RCT) of youth with current psychological distress, a broad CHARMS, or a first episode of severe mental disorder. The EMIcompass intervention will be administered in addition to treatment as usual (TAU) in the experimental condition compared with a control condition of TAU only. Specifically, this study's aims are as follow:

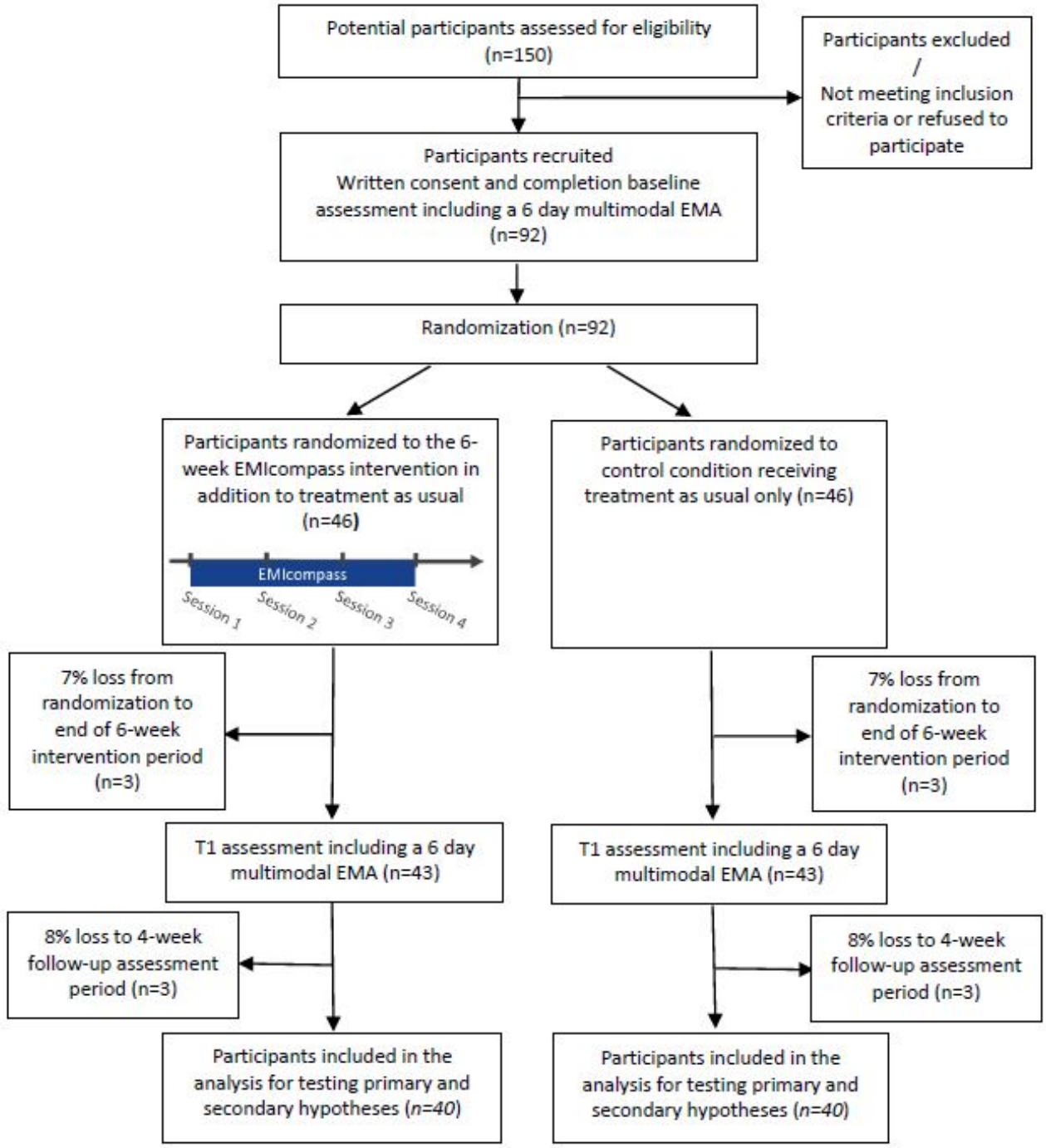
1. to establish the clinical feasibility of the trial methodology and deliver the EMIcompass intervention to youth with early mental health problems (based on successful recruitment, assessment of inclusion criteria, randomization, retention in the assessment of outcomes, fidelity of delivering the intervention, compliance with the intervention protocol, satisfaction, and acceptability);
2. to detect initial signals of the efficacy of the EMIcompass intervention in reducing psychological distress (candidate primary outcome), primary (ie, psychotic, manic, anxiety, or depressive) symptoms, and general psychopathology (candidate secondary outcomes) at postintervention and 4-week follow-up;
3. to test the effects of the EMIcompass intervention on reducing stress reactivity (primary candidate mechanism), threat anticipation, interpersonal sensitivity, negative affective appraisals, resilience, self-compassion, emotion regulation, and physiological markers of stress reactivity (secondary candidate mechanisms) at postintervention and 4-week follow-up; and
4. to explore whether the effects of the EMIcompass intervention on psychological distress, primary (ie, psychotic, manic, anxiety, or depressive) symptoms, and general psychopathology are mediated via pathways through stress reactivity, threat anticipation, interpersonal sensitivity, negative affective appraisals, resilience, self-compassion, and emotion regulation.

Methods

Study Design

In an exploratory RCT, youth aged 14-25 years will be randomly assigned to the EMIcompass intervention in addition to TAU (experimental condition) or a control condition of TAU only, which will include routine mental health care. Participants will be recruited from mental health services in Mannheim, Germany, and via advertisements on the institute's webpage, Facebook, and Instagram and via local registries. Candidate mechanisms and outcomes will be assessed before randomization (at *baseline*), at the end of the 6-week intervention period (*postintervention*), and at the 4-week follow-up (ie, 4 weeks after completing the intervention period) by blinded assessors (Figure 1). Randomization will be conducted by an independent researcher using a computer-generated sequence. The assessment of outcomes and statistical analyses will be blinded to the treatment allocation.

Figure 1. Study flowchart. EMA: ecological momentary assessment, collected eight times per day on 6 consecutive days (including self-reported and activity or electrocardiography sensor); n denotes the total number of participants.



Participants

We will recruit and randomize 92 individuals with current psychological distress, CHARMS or a first episode of severe mental disorder based on a modified version of the clinical staging model by Hartmann et al [16]. Individuals presenting to mental health services at the Central Institute of Mental Health (CIMH), Mannheim, will be approached by a clinician who will provide initial information about the study. If the individual agrees, their treating clinician will pass on their contact details to the research team. In addition, individuals from the general population, who do not seek help from mental health services at CIMH, will be recruited for example, via social media or local registries. All participants will then be contacted by the research team, and initial information about the study will be provided. Following this, individuals will be fully informed about the study, and written informed consent will be obtained by researchers with a master's degree in psychology (including parents or legal guardians for minors), which can be withdrawn at any time without any negative consequences. Eligibility will then be assessed in an interview using observer-rated measures (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [79]; Comprehensive Assessment of At-Risk Mental State [80] completed by the researcher; and self-reported measures using the Kessler Psychological Distress Scale [1,81]).

All participants will be reimbursed for their time and travel expenses at the end of the study.

Ethics Approval and Consent to Participate

The study, titled *Efficacy of a novel, accessible, transdiagnostic, compassion-focused ecological momentary intervention for help-seeking youth (EMIcompass)*, has received ethical approval from the local ethics committee of the Medical Faculty Mannheim Heidelberg University (2017-602N-MA, date: September 7, 2017). Ethical approval was granted before funding was obtained, given that this is a requirement for project grants by the German Research Foundation. All participants and, in the case of individuals aged <18 years, parents or legal guardians will provide written informed consent before inclusion in the study. The sponsor has an insurance, which covers accidents on the journeys to the study appointments. However, no insurance covers harm from study participation, as this is expected to be of low risk.

Inclusion and Exclusion Criteria

Textbox 1 provides an overview on the inclusion and exclusion criteria, and Table 1 defines the inclusion criteria in more detail.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age between 14 and 25 years
- Meeting criteria for one of the following stages (based on a modified version of the clinical staging model by Hartmann and colleagues [16]): individuals with current psychological distress (stage 1a), that is, a score of 20 or above on the Kessler Psychological Distress Scale [1,81], but no Clinical High At-Risk Mental State (stage 1b) or first episode of severe mental disorder (stage 2); individuals who meet criteria for a Clinical High At-Risk Mental State (stage 1b); individuals, who meet criteria for a first episode of psychotic disorder, bipolar disorder, severe depressive disorder or severe anxiety disorder according to according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (stage 2)
- High emotional reactivity assessed with a two-item self-report measure (instruction: “Please think of the most unpleasant event in the last week: (1) How sad, disappointed or angry have you been? (2) Have you been sad, disappointed or angry because of your feelings?”) rated on a 7-point Likert scale (ie, a score of ≥3 indicating high reactivity) or by the interviewer-rated Comprehensive Assessment of At-Risk Mental State subscale [80] rated on a 7-point Likert scale (ie, with a rating of ≥3 indicating high reactivity)
- Reduced positive affect (ie, a mean positive affect score below 3.19 for men and 3.05 for women based on normative scores from a representative sample of the German population [82]) or increased negative affect (ie, a mean negative affect score above 1.81 for men and 1.75 for women [82]) assessed using the Positive Affect and Negative Affect Scale [83]
- Willingness to participate in the EMIcompass intervention
- Ability to provide written informed consent (or consent by parents in the case of minors)

Exclusion criteria

- A primary diagnosis of alcohol or substance abuse or dependence, assessed using the Structured Clinical Interview for DSM-5 [79]
- Evidence that symptoms are precipitated by an organic disease
- Insufficient command of German so that the intervention cannot be followed, and outcomes cannot be reasonably assessed in German
- Diagnosis of a learning disability according to case records
- Current suicidal ideation (indicated by a score>4 in the Comprehensive Assessment of At-Risk Mental State [80])

Table 1. Inclusion criteria and transdiagnostic sample characteristics based on a modified version of the clinical staging model by Hartmann et al [16].

Stage and criteria	Measure
1a (distressed individuals)	
• Psychological distress (K10[a] score ≥20) but not fulfilling criteria of stage 1b or 2	• K10
1b (CHARMS[b])	
Psychosis trait vulnerability	
• First degree relative with psychosis and SOFAS[c] < 50 in the last 12 months or • Or SOFAS 30% below the past level	• Family risk • SOFAS
Psychosis trait vulnerability	
• Schizotypal personality and SOFAS <50 in the last 12 months or • Or SOFAS 30% below the past level	• SCID II[d] • SOFAS
Bipolar trait vulnerability	
• Depressed mood or diminished interest or pleasure for at least 1 week as well as two additional criteria of depression: weight loss, sleep disorder, psychomotor disturbances, loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate or indecisiveness, suicidality • And mood swings for at least 6 months in the lifetime (not symptom-free for a longer period than 2 months consecutively) and at least three symptoms: decreased need for sleep, increased energy, inflated self-esteem or grandiosity, increase in goal-directed activity, restlessness, increased talkativeness, unusual ideas, risky behavior, inappropriate humor (does not have to equal loss of function!) • Or first degree relative with bipolar disorder	• SCID-5[e] • Family risk
Attenuated psychotic symptoms	
• CAARMS[f] global rating score of 3-6 and frequency of 3-6 on the subscales: unusual thought content, nonbizarre ideas, perceptual abnormalities, disorganized speech • Or global rating score of 6 and frequency of 3 on the subscales: unusual thought content, nonbizarre ideas, perceptual abnormalities, disorganized speech	• CAARMS
Attenuated hypomanic symptoms	
• Elevated, expansive or unusually irritable mood on at least 2 consecutive days • And 2 (or in case of only irritable mood 3) additional criteria: inflated self-esteem or grandiosity, decreased need for sleep, increased talkativeness, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity or psychomotor agitation, unusual ideas, increased involvement in activities that are pleasurable in short time but have a high potential for long-term damage • For a duration of 3 days maximum if 3 or more (or in case of only irritable mood 4 or more) additional criteria are met and there are functional disturbances or others notice the mood or functional disturbances • For a duration of 6 days maximum if 3 or more (or in case of only irritable mood 4 or more) additional criteria are met or there are functional disturbances or others notice the mood or functional disturbances • Exclusion: hospitalization, severe impairment in social or professional functioning, no psychotic elements	• CAARMS
Moderate (attenuated) depression	
• Mild or moderate depression (current or lifetime), that is, at least 1 cardinal symptom, 5 additional symptoms • And HAM-D[g]>17 (cutoff)	• SCID-5 • HAM-D
BLIPS[h]	
• Global rating of 6 on the subscales: unusual thought content or nonbizarre ideas • Or global rating of 5 or 6 on the subscale perceptual abnormalities • And/or global rating of 6 on the subscale disorganized speech present for less than a week • And frequency of 4-6 on all above mentioned scales	• CAARMS

Stage and criteria	Measure
Anxiety	
• Mild or moderate panic disorder /agoraphobia (current or lifetime) • Or not fully meeting criteria for GAD[i], that is, symptoms for less than 6 months or less than four symptoms met • Or mild or moderate social phobia (current or lifetime) • And HAM-A[j]>9 (cutoff)	• SCID-5 • HAM-A
2 (first treated episode)	
Psychosis	CAARMS
Severe major depression (current or lifetime)	SCID-5
Mania or hypomania	SCID-5
Severe anxiety disorder (current or lifetime); eg, agoraphobia, GAD	SCID-5

[a]K10: Kessler Distress Scale [81].

[b]CHARMS: Clinical High At-Risk Mental State.

[c]SOFAS: Social and Occupational Functioning Assessment Scale [84].

[d]SCID II: Structured Clinical Interview for DSM-IV Axis II Personality Disorders,

[e]SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [79].

[f]CAARMS: Comprehensive Assessment of At-Risk Mental State [80].

[g]HAM-D: Hamilton Depression Rating Scale [85].

[h]BLIPS: brief limited intermittent psychotic symptoms.

[i]GAD: Generalized Anxiety Disorder.

[j]HAM-A: Hamilton Anxiety Rating Scale [86].

Interventions

Control Condition: TAU

Participants allocated to the TAU control condition will continue to receive all the treatment they received before the start of the study. This will include good standard care delivered according to local and national service guidelines and protocols by their general practitioner, psychiatrist, and other providers of (mental) health care. Service contacts will be assessed for the duration of the trial using the Client Service Receipt Inventory [87] to monitor variation in the delivery of, and engagement with, mental health services.

Experimental Condition: EMIcompass Intervention Plus TAU

The EMIcompass intervention will be delivered by trained psychologists within a 6-week period in addition to TAU to individuals allocated to the experimental condition. TAU consists of all the treatment individuals received before inclusion in the study, including their general practitioner, psychiatrist, and clinical psychologist, except for treatment using elements of third-wave CBT. The manualized EMIcompass intervention consists of four biweekly sessions (three training sessions and one review session) with a duration of 45-60 minutes administered face-to-face or using a certified and encrypted video conferencing system and a 6-week compassion-focused EMI. An optional on-demand session will be offered if participants are unable to complete tasks between sessions or report acute psychological distress so that a scheduled session cannot be followed as per the manual. The EMI, which translates the training from the intervention sessions into individuals' daily lives, will be administered through a smartphone-based app (movisensXS, movisens GmbH) running on dedicated study smartphones. The first three sessions are based on elements of compassion-focused therapy [68]. In line with our pilot study [53], compassion-focused therapy principles and techniques are introduced in these guided sessions. The first session aims to familiarize the participants with the app offering EMI. Further, practical tasks to activate the soothing system, as a key emotion regulation system in compassion-focused therapy, are presented and trained together with the psychologist, as described elsewhere [88]. Face-to-face sessions also offer the opportunity to reflect on the progress and problems participants face with EMI. In the last session, progress with all tasks will be reviewed and subjective improvement in, compliance and satisfaction, and acceptance of the EMIcompass intervention will be assessed.

The app will offer EMI tasks according to three types of delivery schemes: (1) enhancing, (2) consolidating, and (3) interactive EMI tasks that aim for ecological translation of therapeutic principles and techniques to daily life. Participants will be asked to complete one *enhancing task* per week, practicing new compassion-focused tasks such as self-compassionate writing, experiencing emotions as a wave, and discovering their own compassionate self. Furthermore, participants will be offered *consolidating tasks* covering components of *enhancing tasks* from previous days. The components of *consolidating tasks* will be extended each time an *enhancing task* has been presented until all components are covered. In addition, participants will be offered to complete a brief EMA of momentary stress, affective disturbance, and threat anticipation six times per day, 3 days per week. On the basis of these EMAs, *interactive* tasks will be offered if participants score high on momentary stress or negative affect. The threshold for triggering interactive tasks

will be either high momentary negative affect operationalized as a score of 4 or higher (on a 7-point Likert scale ranging from 1-7) on items of established and validated EMA measures of negative affect (Textbox 2) or high momentary stress based on items of established and validated measures of EMA of event-related, activity-related, or social stress (ie, a score <0 on a bipolar scale ranging from −3 to 3).

Participants will be instructed in detail in the semantic meaning of the 7-point Likert and bipolar scales and encouraged to carefully observe moment-to-moment variation in, and make use of the full range when rating, these scales on EMA items that have been previously used and validated to measure moment-to-moment variation in stress or negative affect. Given that a crucial element of compassion-focused therapy is for individuals to use compassionate imagery in moments of high stress or negative affect, these interactive tasks reflect an important component of the EMIcompass intervention. Participants can decline the EMI tasks in each delivery scheme. After completing the intervention period, participants will return the study devices and will no longer have access to the app.

Textbox 2. Ecological momentary assessment domains and measures.

Momentary stress

Momentary stress was operationalized as unpleasant events, activities, and social situations in daily life. In line with previous research, we distinguished three different types of stress, that is, event-related stress, activity-related stress, and social stress [43,89]. Participants will be asked to report the most important event that happened in the time since the last assessment. This event will be subsequently rated on a 7-point Likert scale (−3=very unpleasant, 0=neutral, 3=very pleasant) comprising the event-related stress measure. Activity-related stress will be assessed by asking participants to report their current activity and then judge the valence of the activity ("This is...") using a 7-point Likert scale (1=very unpleasant, 7=very pleasant). Further, social stress will be measured by asking participants to evaluate the social context when other people were present as well as when they were alone by answering the items "I am taking care of myself"/"I am taking care of somebody" and "I would rather be alone"/"I would prefer to have company" using two 7-point Likert scales and the item on social valence ("This is..." rated on the 7-point Likert scale from 1=very unpleasant to 7=very pleasant)

Negative affect

Six items will be used to assess negative affect (anxiousness, loneliness, insecurity, anger, annoyance, and feeling down), using 7-point Likert scales ranging from "not at all" (rating of 1) to "very much" (rating of 7)

Negative affective appraisals

In case participants report negative affect (ratings >3), two items on how they cope with their negative affect will be displayed: "I want to change my negative feelings" and "I would like to get rid of my negative feelings" using two 7-point Likert scales

Positive affect

Positive affect will be assessed by four items (cheerfulness, satisfaction, enthusiasm, and feeling relaxed) using 7-point Likert scales ranging from "not at all" (rating of 1) to "very much" (rating of 7)

Aberrant salience

The ecological momentary assessment measure comprises three items in line with [43]. The items will be rated on a 7-point Likert scale (ranging from 1 ["not at all"] to 7 ["very much"]): "Everything grabs my attention right now," "Everything seems to have meaning right now," and "I notice things that I haven't noticed before"

Self-esteem

Three items will be rated on a 7-point Likert scale ranging from "not at all" (rating of 1) to "very much" (rating of 7): "I feel guilty," "I doubt myself," "I feel disappointed about myself"

Self-compassion

Three items will be rated on a 7-point Likert scale ranging from "not at all" (rating of 1) to "very much" (rating of 7): "I like myself," "I feel safe," "I feel benevolent"

Psychotic experiences

Psychotic experiences will be assessed using eight items on thought problems and hallucinations ("I see things that aren't really there," "I hear things that aren't really there," "I feel suspicious," "It's hard to express my thoughts in words," "I feel unreal," "My thoughts are influenced by others," "I can't get these thoughts out of my head," "I feel like I am losing control") that will be rated on 7-point Likert scales ranging from "not at all" (rating of 1) to "very much" (rating of 7)

Resilience

If participants indicate that there was a negative event (valence −3 or −2), then the item "I had difficulties to recover" will be rated on a 7-point Likert scale

Threat anticipation

In line with previous research, we will ask participants to rate the likelihood of negative events happening to them in the future [43]. They will be asked to think of what might happen in the next few hours and to rate the item "I think that something unpleasant will happen" on a 7-point Likert scale from "not at all" (rating of 1) to "very much" (rating of 7)

Disturbance

"This prompt disturbed me" will be rated at the end of each assessment on a 7-point Likert scale from "not at all" (rating of 1) to "very much" (rating of 7)

Clinical Feasibility, Acceptability, Treatment Adherence, and Intervention Fidelity

Clinical feasibility will be assessed in relation to the trial methodology and the delivery of the EMIcompass intervention to youth with early mental health problems. The feasibility of the trial methodology will be assessed based on the following criteria: (1) successful recruitment of at least 96 participants during the study period; (2) assessment of inclusion criteria in 95% of potential participants after obtaining written consent; (3) successful randomization of at least 92 participants after completion of eligibility and baseline assessment; and (4) a retention rate of at least 85% for assessment of outcomes at least at one of the two time points at postintervention and 4-week follow-up. In addition, the following criteria will be used for establishing the feasibility of delivering the EMIcompass intervention, including its acceptability, intervention adherence, and intervention fidelity: (1) satisfaction with the EMIcompass

intervention in general, ease of use, accessibility and comprehensiveness of various components of the intervention in a debriefing questionnaire [30,90], and the subjective quality of EMIcompass using the mobile application rating scale [91]; (2) compliance with, and adherence to, the EMIcompass intervention protocol based on a satisfactory level of session attendance, an adherence checklist covering all core components [29,30,92], and adherence to EMI tasks (ie, mean number of consolidating/interactive EMI tasks completed per week); and (3) fidelity to the EMIcompass intervention protocol based on independent ratings of a random selection of audio recordings of three face-to-face sessions, including fidelity to session protocol (ie, independent rating of core components delivered by trained psychologist), ability to model and embody the spirit of compassion, and the use of microskills in compassion-focused therapy assessed by the Compassion Focused Therapy-Therapist Competence Rating Scale [93].

Candidate Mechanisms and Outcomes

Overview

After obtaining written informed consent, all eligible participants will be assessed on candidate mechanisms and outcomes before randomization (*baseline*, t_0), after the 6-week intervention period (*postintervention*, t_1) and after a 4-week follow-up period (*follow-up*, t_2) by blinded assessors (Figure 1 and Multimedia Appendix 1). Research Electronic Data Capture (REDCap) [94], a secure, web-based software platform hosted at the CIMH servers, will be used for data collection.

Primary Candidate Mechanism

The primary candidate mechanism is a reduction in stress reactivity acquired by EMA from baseline to postintervention for the experimental condition compared with the control condition. EMA will include eight assessments per day, scheduled at random within set blocks of time, for 6 consecutive days at baseline, postintervention, and follow-up [43,95]. Momentary stress will be assessed using established and validated EMA measures of event-related stress, activity-related stress, and social stress (Textbox 2) [43,89]. We will compute a composite momentary stress measure (ie, the mean score of event-related, activity-related, and social stress) in line with the literature [52,96,97] and the EMIcompass pilot study [53]. Negative affect will be assessed using an established and validated EMA measure of negative affect [43]. Stress reactivity as the primary candidate mechanism will be computed in linear mixed models with composite momentary stress as the independent variable and negative affect as the outcome variable [43,89,95].

Secondary Candidate Mechanisms

Secondary candidate mechanisms (Multimedia Appendix 1 and Textbox 2) measured using EMA include threat anticipation, negative affective appraisals, emotional resilience to stress (operationalized as attenuated recovery in positive affect in response to minor stressors), and elevated stress reactivity (ie, increased negative affect) in response to event-related, activity-related, and social stress using subscale scores of the EMA stress measure. Threat anticipation will be additionally assessed using the Threat Anticipation Measure [62], asking participants to estimate the future likelihood of a list of negative, neutral, and positive events happening to themselves and other people [61-63]. Interpersonal sensitivity will be assessed using the Interpersonal Sensitivity Measure [98] in addition to EMA. Resilience will be measured using the Connor-Davidson Resilience Scale [99] and the Resilience Scale [100]. Furthermore, the Self-Compassion Scale [101], the Fife Facet Mindfulness Questionnaire [102], and the Cognitive Emotion Regulation Questionnaire [103] will be used to assess self-compassion and emotion regulation. In addition, we will assess physiological markers of stress reactivity using a sensor for ambulatory ECG and actigraphy (movisens ECGmove4) during the 6-day EMA at baseline, postintervention, and at follow-up.

Candidate Primary Outcome

The candidate primary outcome of this exploratory RCT is psychological distress measured using the well-validated Kessler Psychological Distress Scale [81]. The 10 items are rated on a 1 (never) to 5 (always) Likert scale focusing on psychological distress in the last month. Strong psychometric properties have been reported with a reliability of Cronbach α>.90 [81].

Candidate Secondary Outcomes

Secondary outcomes include primary (ie, psychotic, manic, anxiety, or depressive) symptoms and general psychopathology. These will be assessed using the following observer-rated measures: the Brief Psychiatric Rating Scale [104], including the Comprehensive Assessment of At-Risk Mental State [80], the Young Mania Rating Scale [105], the Hamilton Depression Rating Scale [85] and the Hamilton Anxiety Rating Scale [86]. On the basis of these measures, we will assess the transition to another clinical stage (according to a modified version of the clinical staging model by Hartmann et al [16]; see above). In addition, the following self-report measures will be used: the Brief Symptom Inventory [106], the Beck Depression Inventory [107], and the Prodromal Questionnaire [108]. Secondary outcomes further include quality of life measured using the WHO-Quality of Life assessment [109].

Other Measures

Other study parameters will include basic sociodemographic characteristics, familial risk factors for psychopathology, and other parameters (including age, sex, alcohol or substance use, and childhood trauma [110]). The Client Service Receipt Inventory [87] will be used to record patients' contacts with mental health services, monitor variation in the delivery of TAU, and model economic outcomes for a definitive trial. The Working Alliance Inventory [111,112] will be used to assess the relationship between practitioners and patients.

Sample Size

A formal sample size calculation is not essential for this exploratory trial, which primarily seeks to establish feasibility, effects on candidate mechanisms, and initial signals of efficacy. In planning, we aimed to determine the sample size in such a way as to establish the feasibility of the methodology for conducting an RCT and delivering the EMIcompass intervention to youth with early mental health problems and initial signals

of the efficacy of EMIcompass in reducing psychological distress as a candidate primary outcome (see Statistical Analysis Plan [113] for further detail) as a basis for a future definitive trial. For the latter, previous studies of third-wave CBT [72,114], including compassion-focused interventions [68,77], suggest that these types of interventions may yield clinically meaningful reductions in psychological distress of moderate to large effect size. This is consistent with the initial findings from an uncontrolled phase I pilot study [53]. However, even if the effect size for the main effect of condition on psychological distress (primary outcome) in this exploratory RCT is small, a power simulation in the R environment indicated that a sample size of N=80 participants (40/40, 50% experimental, 40/40, 50% control condition) would be sufficient to detect a small effect size of 0.3 across the postintervention 4-week follow-up with a power of 81% when testing at α=.05 for the effect of condition (experimental vs control condition) on psychological distress using linear mixed modeling, which will be tested using a Wald-type test of no difference between the two conditions across both time points against the two-sided alternative hypothesis that the conditions are, on average, different across the two follow-up time points (given the exploratory nature of this trial), while controlling for baseline psychological distress and group status. At the 4-week follow-up, we expect an attrition rate of 15%, resulting in a loss to follow-up of approximately 6 individuals per condition on average (Figure 1). Therefore, we will randomize a total of 92 participants at baseline, leaving 80 participants at follow-up to detect a small effect size of 0.3 at this time point. This sample size is also sufficient to test the criteria for establishing feasibility. Simulation studies on power and accuracy for multilevel mediation models with continuous variables [115] and our recently completed multilevel moderated mediation analysis of EMA data [42] suggest very little bias in parameter estimates with samples of this size (and 40 repeated measures, on average, per participant).

Randomization and Blinding

Participants will be randomized at a 50:50 ratio to the experimental or control condition at the level of the individual participant after completion of the baseline assessment. Block randomization in blocks of four will be performed by an independent research assistant through a computer-generated sequence, with stratification for the three stages (ie, stages 1a, 1b, and 2). The assessors will be blind to the allocation of participants when assessing outcomes at postintervention and follow-up. Any data specific to the intervention group (eg, clinical feasibility) will be stored in a separate database. Breaks in masking will be documented, and another (blinded) researcher will repeat the assessment to maintain masking.

Assessment of Safety

Serious adverse events (SAEs) will be monitored throughout the entire study period and reported to the accredited Medical Ethics Review Committee, the Data Monitoring and Ethics Committee (DMEC), and, where required, the Trial Steering Committee (TSC). SAEs are any serious incidents that result in death, persistent or significant disability or incapacity that require hospitalization, or life-threatening situations. SAEs are not expected to occur as a result of the intervention. If there are doubts about safety or ethical concerns, the TSC will terminate the trial. The DMEC will advise on safety and ethical concerns, monitor evidence for harm by the intervention (eg, SAEs) in the experimental condition, and review whether these events are in line with expectations. If deemed necessary, the DMEC can recommend to the principal investigator (PI) and TSC for interim analyses to be conducted and the trial to be terminated prematurely.

Statistical Analysis

The primary objective of this exploratory RCT is to establish the feasibility of the trial methodology and intervention delivery and initial signals of efficacy on the candidate primary outcome (ie, psychological distress) as a basis for a future definitive trial. In addition, this trial seeks to obtain parameter estimates (95% CI) for the effects on primary and secondary candidate mechanisms and candidate secondary outcomes. A detailed Statistical Analysis Plan [113] has been agreed with the DMEC and the TSC and has been preregistered and published on the Open Science Framework. It was registered while collecting the data before study completion and accessing the locked database. Descriptive statistics will be used, and CIs will be constructed as appropriate to compute basic sample characteristics and address the primary aim of establishing the feasibility of the trial methodology and intervention delivery based on the criteria described above and in further detail in the Statistical Analysis Plan using three categories (in line with a traffic light system): (1) feasibility fully established (green), (2) feasibility established, but study procedures need to be modified (yellow), and (3) feasibility not established (red) [113]. The analysis of candidate mechanisms and initial signals of efficacy has been described in detail in the Statistical Analysis Plan [113] and will be an intention-to-treat analysis or an available case analysis following intention-to-treat principles, with data from all participants entered into the analysis, including those who have low adherence to or who will drop out from the intervention. We will make every effort to assess all participants at postintervention and 4-week follow-up. Linear mixed modeling in Stata 16 will be used to compare candidate mechanisms and outcomes between experimental and control conditions at postintervention and 4-week follow-up. The primary candidate outcome of psychological distress measured at postintervention and 4-week follow-up will be entered as the dependent variable and psychological distress measured at baseline, group status (3-level factor), time (2-level factor), and condition (2-level factor) as independent variables. The main effect of condition on psychological distress will be parameterized so that it reflects the difference between the two conditions at the two follow-up time points (ie, postintervention and 4-week follow-up), which will be tested (at α=.05) by a Wald-type test with df=1, which tests the joint null hypothesis of no difference at both follow-up time points against the alternative hypothesis that there is, on average, a difference across the two follow-up time points. In addition, given the exploratory nature of this trial, with the main goal of establishing feasibility and obtaining parameter estimates for a future definitive RCT, 95% CI for the two time-specific contrasts of a time×condition interaction term will be inspected to obtain estimates for the differences across conditions at each of the

two time points, with a time × condition interaction and a baseline psychological distress×time interaction added as independent variables to the previous model. Within-subject clustering of repeated measures (postintervention and 4-week follow-up) will be taken into account by including a level-2 random intercept and allowing the models' level-1 residuals to be correlated with a completely unstructured error variance-covariance matrix. The model will be fitted using restricted maximum likelihood estimation. The analysis of secondary candidate outcomes and primary and secondary candidate mechanisms will, in principle, follow the same steps, focusing on 95% CIs (rather than P values at $\alpha<.05$). Multilevel moderated mediation analysis of EMA data will be used to explore whether the effects of condition on primary (ie, psychotic, manic, anxiety, or depressive) symptoms are mediated via stress reactivity, threat anticipation, negative affective appraisals, and interpersonal sensitivity [42]. As participants will be randomly assigned to experimental and control conditions, no differences across conditions are expected in other study parameters (sociodemographic characteristics, alcohol or substance use, and childhood trauma). No statistical tests will be performed on these study parameters at baseline.

Results

Overview

The trial is ongoing. It started recruitment on July 15, 2019, and the first enrollment was conducted in August 2019. We are currently working with trial protocol version 5 (June 24, 2020). The last changes to the protocol were related to adaptations because of the COVID-19 pandemic, such as introducing the option of using video conferencing systems. As of May 2021, enrollment and randomization were completed (n=92 participants). Assessment of outcomes at postintervention and follow-up is still ongoing, with the last assessment for the last participant being scheduled for August 2021. Data will then be entered, checked, and the database locked (by September 2021). We expect results to be published in 2022.

Research Governance

The CIMH is the trial sponsor. The study has received ethical approval by the local ethics committee (EC) of the Medical Faculty Mannheim, Heidelberg University (2017-602N-MA). Amendments to the study protocol will be submitted to the EC and sent to the DMEC, TSC, and study sponsor. The trial is registered at the clinical trial register, and changes to the protocol will be updated. Deviations from the protocol will be documented in the study folder using a breach report form and will be reported to the TSC. The trial does not involve the collection or storage of biological samples. All data will be handled confidentially and will be coded using a number according to the order of study entry. Data will be securely stored in line with the European General Data Protection Regulation. Personal data will be kept separately from pseudonymized data. The PI has overall responsibility for the trial. The trial research team will meet regularly and will be chaired by the PI. It will manage the day-to-day running of the study, monitor the progress of the trial (ie, recruitment and assessment), and oversee the preparation of presentations and reports to EC, TSC, and DMEC. The TSC will meet biannually and provide independent overall supervision, monitor the progress of the trial (eg, recruitment, data completion rates, and adherence to the protocol), and approve the protocol and any amendments. The DMEC will meet at least once per year, advise on ethical or safety concerns, monitor SAEs and other evidence of intervention harm and whether this is in line with expectations. If deemed necessary, the DMEC can recommend that the PI and TSC are granted access to all trial data, to perform interim analyses and to terminate the trial prematurely.

Discussion

Transdiagnostic mechanisms implicated in the development of severe mental disorders are important targets for prevention and early intervention. Ecological translation of compassion-focused intervention components to individuals' daily lives through an EMI offers new avenues for tangible prevention strategies delivering real-world and real-time interventions that are easily accessible by youth [36]. Findings from a recent, nationally representative survey suggest that psychological distress, social isolation, lack of company, and worrying during the COVID-19 pandemic were highly prevalent in youth and, interestingly, associated with the current use of and a positive attitude toward digital interventions [33]. EMIs are also amenable to enhancing access to mental health services for youth depending on their needs and preferences, for instance, by delivering low-threshold interventions by frontline mental health staff [116-118] as a component that can be rolled out across adolescent and adult mental health services and link in with what is urgently needed, that is, a wider youth mental health reform that aims to provide seamless coverage of mental health care with smooth transitions from adolescence to mature adulthood at an age of approximately 25 years [20]. Furthermore, EMIs allow for investigating the strength of the evidence in support of several causal criteria (ie, association, temporality, sole plausibility, and ecological validity) as part of the ecological interventionist causal model approach that targets candidate underlying psychological mechanisms in daily life to achieve sustainable change under real-world conditions [27]. However, robust, trial-based evidence on EMIs and other mHealth interventions remain very limited [26,27,29,36,116,119]. A key next step is to examine the efficacy of youth-friendly, accessible, interactive, real-time interventions targeting candidate mechanisms underlying the transdiagnostic phenotype of psychosis, mania, depression and anxiety and thereby, help preventing adverse outcomes later in life. While, in the current study, we use EMA items that have been previously used and validated to measure moment-to-moment variation in stress/negative affect, with considerable within-person variability having been observed for these items in several EMA studies [43,89,120], inter-individual differences in within-person variability as well as general response tendencies may influence the number of triggered EMI tasks and hence, further research is needed to optimize and personalize the assignment of EMI components, eg, by using methods of artificial intelligence, recurrent neural networks (RNNs) in particular [121]. For example, we currently aim to apply recurrent neural networks in an ongoing study of personalized digital mental health promotion and prevention in

youth [33]. In addition, clinical staging models of severe mental disorders require further scrutiny, including heterogeneity in phenomenology, course, and outcome within individual stages [5,122,123].

The present exploratory RCT is the first to establish feasibility, evidence on underlying mechanisms, and preliminary signals of efficacy of a compassion-focused, hybrid EMI for reducing stress reactivity (EMIcompass) in youth at different clinical stages. Preliminary evidence from a pilot study of the EMIcompass intervention in help-seeking youth showed reductions in clinical symptoms and stress reactivity [53]. If this exploratory trial is successful, a confirmatory RCT will be warranted. Overall, our approach has a scalable potential to prevent the transition of early mental health problems to severe and enduring mental disorders not only in individuals at risk of developing psychosis but transdiagnostically and across clinical stages and, thereby, significantly advance preventive interventions in youth mental health provision.

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Authors' Contributions

UR designed the study, is the PI, and has managerial responsibility for the successful completion of the study. JB is the trial statistician. BB provides supervision for the trained psychologists who deliver the intervention. AS, UR, CR, and IP drafted the manuscript. All authors were involved in writing, reading, and approving the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for International Trials (SPIRIT) figure.
[DOCX File , 28 KB - resprot_v10i12e27462_app1.docx]

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Abbreviations

CBT: cognitive behavioral therapy
CHARMS: Clinical High At-Risk Mental State
CIMH: Central Institute of Mental Health
DSM-5: Diagnostic and Statistical Manual of Mental Disorders
DMEC: Data Monitoring and Ethics Committee
EC: ethics committee
ECG: electrocardiography
EMA: ecological momentary assessment
EMI: ecological momentary intervention
mHealth: mobile health
PI: principal investigator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SAE: serious adverse event
TAU: treatment as usual
TSC: Trial Steering Committee

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Protocol

The Communicating Narrative Concerns Entered by Registered Nurses (CONCERN) Clinical Decision Support Early Warning System: Protocol for a Cluster Randomized Pragmatic Clinical Trial

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Abstract

Background: Every year, hundreds of thousands of inpatients die from cardiac arrest and sepsis, which could be avoided if those patients' risk for deterioration were detected and timely interventions were initiated. Thus, a system is needed to convert real-time, raw patient data into consumable information that clinicians can utilize to identify patients at risk of deterioration and thus prevent mortality and improve patient health outcomes. The overarching goal of the COmmunicating Narrative Concerns Entered by Registered Nurses (CONCERN) study is to implement and evaluate an early warning score system that provides clinical decision support (CDS) in electronic health record systems. With a combination of machine learning and natural language processing, the CONCERN CDS utilizes nursing documentation patterns as indicators of nurses' increased surveillance to predict when patients are at the risk of clinical deterioration.

Objective: The objective of this cluster randomized pragmatic clinical trial is to evaluate the effectiveness and usability of the CONCERN CDS system at 2 different study sites. The specific aim is to decrease hospitalized patients' negative health outcomes (in-hospital mortality, length of stay, cardiac arrest, unanticipated intensive care unit transfers, and 30-day hospital readmission rates).

Methods: A multiple time-series intervention consisting of 3 phases will be performed through a 1-year period during the cluster randomized pragmatic clinical trial. Phase 1 evaluates the adoption of our algorithm through pilot and trial testing, phase 2 activates optimized versions of the CONCERN CDS based on experience from phase 1, and phase 3 will be a silent release mode where no CDS is viewable to the end user. The intervention deals with a series of processes from system release to evaluation. The system release includes CONCERN CDS implementation and user training. Then, a mixed methods approach will be used with end users to assess the system and clinician perspectives.

Results: Data collection and analysis are expected to conclude by August 2022. Based on our previous work on CONCERN, we expect the system to have a positive impact on the mortality rate and length of stay.

Conclusions: The CONCERN CDS will increase team-based situational awareness and shared understanding of patients predicted to be at risk for clinical deterioration in need of intervention to prevent mortality and associated harm.

Trial Registration: ClinicalTrials.gov NCT03911687; https://clinicaltrials.gov/ct2/show/NCT03911687

International Registered Report Identifier (IRRID): DERR1-10.2196/30238

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KEYWORDS

nursing documentation; prediction; early warning system; deterioration; clinical trial; clinical decision support system; natural language processing

Introduction

Background

Every year, more than 330,000 inpatient deaths resulting from cardiac arrest and sepsis occur [1,2], which could otherwise have been avoided if those patients' risk for deterioration was detected earlier and meaningful interventions were provided. While clinicians strive to provide the best quality care, suboptimal interprofessional communication between nurses and physicians can lead to delays in patient care [3-6]. Nurses often observe subtle yet concerning changes in their patients even before physiological conditions start to deteriorate. When they do, they tend to increase surveillance among those patients and documentation within the electronic health record (EHR) [3,7-9]. However, owing to systemic problems within hospital settings, such as physicians frequently needing to round between multiple units or not having substantial time to review nurses' documentation, physicians and nurses may have different understandings of a patient's situation. A lack of shared situational awareness can inhibit the care team's ability to deploy early interventions directed at deterioration prevention, placing patients at greater risk for deterioration. Real-time processing and conversion of raw patient data into consumable information, displayed using "smart" visualizations, are therefore needed within EHRs to ameliorate these deficiencies and ensure that hospitalized patients at high risk for deterioration are rapidly identified with equal understanding by all members of the care team.

Implementing an early warning system (EWS) within EHRs would provide users with a tool to communicate nurses' emerging concerns about changes in patient states to the interprofessional team. EWSs have assisted clinicians in detecting patients' risk of deterioration since the 1990s [10]. In the past, EWS algorithms were often built using clinicians' consensus [11]. Recently, as we reported previously, approaches to EWS algorithms have shifted to become more data-driven [11], which can reveal hidden relationships that are difficult to detect by humans. Today's EWS algorithms, therefore, more commonly leverage vast numbers of variables available in the EHR, such as vital signs, level of consciousness, and laboratory data.

The COmmunicating Narrative Concerns Entered by RNs (CONCERN) study is developing and evaluating the impact of a new EWS that predicts and provides clinical decision support (CDS) when patients are at increased risk of deterioration. Compared to existing EWSs, the CONCERN CDS system defined a new source of predictive data, analyzing nursing documentation patterns that reflect nursing surveillance and indicate nurses' changing levels of concern. Our preliminary study using the aforementioned approach has demonstrated that using nursing documentation patterns as an EWS predictor performed similarly to the Modified Early Warning Score (MEWS), one of the most widely used EWSs in clinical settings, which leverages the actual recorded values (eg, a heart rate of 60 BPM) as its predictors [12]. However, CONCERN was able to detect patient deterioration 42 hours earlier than the MEWS [13]. CONCERN's earlier detection capabilities therefore create a more advantageous window of opportunity for clinicians to anticipate and appropriately react to impending patient deterioration.

This study proposes the CONCERN intervention trial design, a multiple time-series intervention evaluating the system's implementation through efficacy evaluation to understand how the CONCERN CDS system performs in the clinical setting.

Study Objectives

Primary Objective

This multi-site cluster randomized pragmatic clinical trial study [14] (between New York Presbyterian and Mass General Brigham) will assess quantitative CDS usage and monitoring data to evaluate the effectiveness of implementing the CONCERN CDS system to decrease hospitalized patients' negative health outcomes on acute and critical care units.

Secondary Objectives

This study's secondary objectives are to evaluate qualitative CONCERN CDS system usage and to conduct usability surveys focused on the following topics: (1) perceived understandability of the CONCERN CDS app, (2) perceived technical competence of the CONCERN CDS app, and (3) trust in the CONCERN CDS app (as influenced by understandability and technical competence).

CONCERN CDS System Development

The CONCERN CDS system will be triggered on the basis of analytics of nursing documentation through NLP, which indicates the recognition of and concerns about negative patient changes [13,15]. Testing of the predictive model underlying the CONCERN CDS has been conducted on retrospective data and

findings have been published, including those that previously highlighted that CONCERN performs similarly to the MEWS with an improved lead time of 42 hours [13,15]. The CONCERN CDS app will alert the interprofessional care team to the patients entering "risky states" to increase team-based situational awareness of these patients and support them as they perform early clinical interventions.

Conceptual Framework

A Healthcare Process Modeling Framework to Phenotype Clinician Behaviors for Exploiting the Signal Gain of Clinical Expertise (HPM-ExpertSignals) was used as the fundamental conceptual framework of the CONCERN model [13]. This model identifies features from user interaction with clinical systems, which are patterns of clinical behaviors that can be interpreted as proxies of individuals' decisions, knowledge, and expertise. These proxies, in turn, can be used in predictive models to identify associations with outcomes. In developing the CONCERN early warning score, increased surveillance beyond the standard of care was used as an indicator of acute concern about patient deterioration.

Development: CONCERN CDS Scoring Engine

The development of the CONCERN CDS scoring engine was separated into three stages: (1) feature selection and preprocessing, (2) feature modeling, and (3) assignment of colors and postprocessing. Expert consensus, clinician feedback, and evaluation of machine learning performance were used in each stage to develop and assess the engine. Initial features selected from prior research [7], vital signs and vital sign comments frequency, were combined with features selected by experts and were thought to be signals of clinical concern. Additional added features including pro re nata (PRN) medications that were administered, medications of any type that were withheld, frequency of nursing notes being written, and nursing note content were also included in the model, along with the times that those actions were performed [13]. Features were iteratively aggregated over the past 12 hours. Final features used in the algorithm are informed by our cumulative qualitative and quantitative analyses over the years. These features were combined using machine learning techniques (NLP, decision trees, and logistic regression) with proxies for clinical deterioration such as rapid response, cardiac arrest, sepsis, unanticipated intensive care unit (ICU) transfer, and death as the outcomes. A logistic regression–based model was chosen for implementation because focus group with clinicians indicated that model explainability was important. In addition, based on the existing information technology (IT) infrastructure at Mass General Brigham's (MGB) hospital, logistic regression models were the most feasible to implement. The weights derived from machine learning were used to combine the features into a single score that was reflective of clinical concern for patient deterioration. Color coding of the score and other postprocessing was carried out to incorporate feedback from clinicians, adjust for demographic disparities, and retain the signals obtained from machine learning. We specifically evaluated our model to identify and mitigate any racial disparities and have presented those results here [13,15]. The resulting CONCERN score is a color-coded score representative of changes in surveillance patterns indicative of a patient's degree of risk for deterioration. A red score signifies a high CONCERN level, which implies that the patient is actively showing signs of deterioration. A yellow score is arguably the most important, which implies that the patient is at increased risk for deterioration, but not yet showing signs of active deterioration. A green score represents a low CONCERN level, which implies that the patient is at low risk for deterioration. All patients will have a CONCERN level of gray (nonscore) until they have 12 hours of history under acute care. To minimize alert fatigue and based on our analysis of historical data, we configured the predictive model to targeted specific percentiles of patients in the units with the following scores: 2%-3% are red and 20%-25% are yellow.

Development: Iterative, Participatory Approach to Design the CONCERN CDS App

A multi-method approach, consisting of user-centered design sessions, focus group interviews, and simulation testing sessions with nurses and physicians, was used to facilitate participatory design of our CONCERN CDS app. The design was updated iteratively after each stage on the basis of feedback collected from the participants.

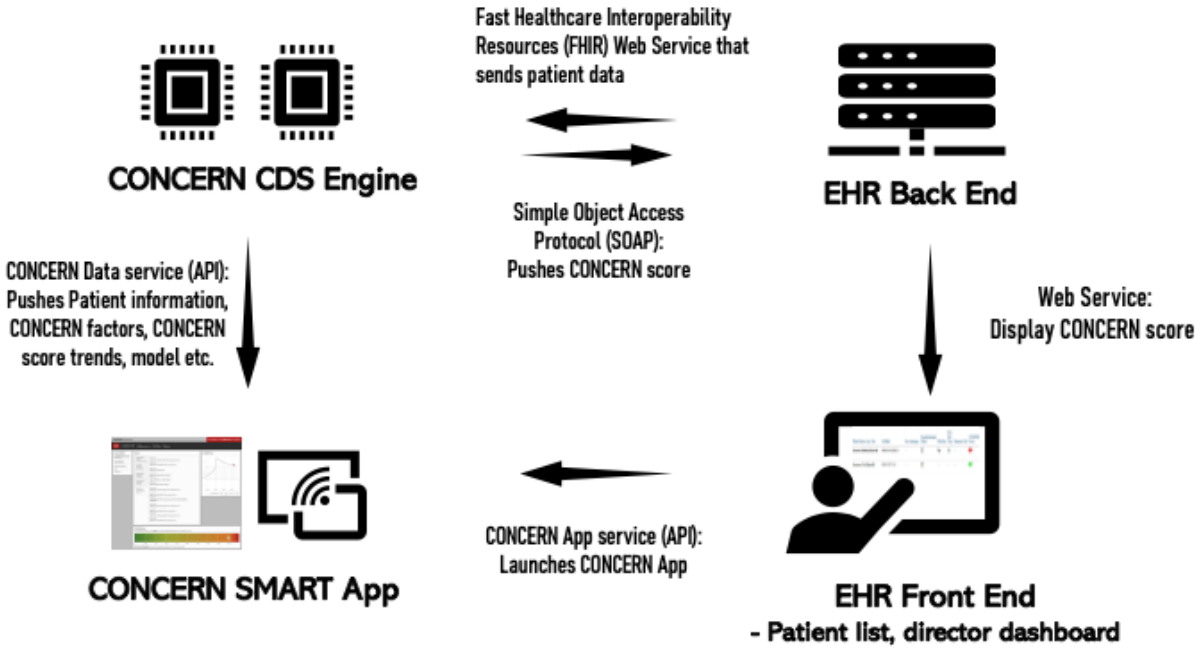
User-centered design sessions were conducted to evaluate the preliminary design of the CONCERN CDS app. Participants were probed about features of CDS tools they used in their practice, which they perceived as useful. Then, focus groups were conducted, during which the results of the preliminary data analysis were presented in addition to mockups of the front-end design of the CONCERN CDS app integrated into the EHR system. Clinicians were asked to provide their opinions on the clinical significance of our findings and their perceptions of the front-end design. The last stage of the participatory process was simulation testing. We used a web-based, functional CONCERN CDS prototype to assess the tool's usability and functionality within existing end user workflow.

Development: CONCERN CDS Technical Architecture

The CONCERN CDS app currently runs outside of the EHR (Figure 1). The process is as follows: (1) Fast Healthcare Interoperability Resources (FHIR) webservices (a combination of FHIR and Epic web services are being used at one site) pull data from the EHR backend into the CONCERN CDS engine. (2) The patients' demographics, clinical notes, and app logging information are retrieved, and the CONCERN score is computed in the engine and pushed back to the EHR backend using a Simple Object Access Protocol (SOAP) service. (3) Then, the CONCERN level, corresponding color, and description to CONCERN score are displayed to the clinicians in their EHR's patient list and to nursing directors in their EHR's unit dashboard. (4) Double-clicking the CONCERN level icon in the EHR front end will seamlessly bring the user to the CONCERN web app, which provides detailed information about the CONCERN model, including factors that contribute to each patient's specific CONCERN level and CONCERN level trendline over 72 hours. Users can click on a specific factor and that data from the patient's chart will be readily available. Given that the control and intervention groups of this study include inpatient acute and intensive care units, the color indicators are

integrated into the existing EHR patient list and will only be visible for inpatients in these units.

Figure 1. Technical architecture of the COmmunicating Narrative Concerns Entered by Registered Nurses (CONCERN) clinical decision support (CDS) app. API: application programming interface; EHR: electronic health record.



Methods

CONCERN Intervention Trial Design

The CONCERN intervention trial design will be a cluster randomized pragmatic clinical trial with a multiple time-series intervention [14] (Figure 2). The trial has received institution review board approval at Columbia University and Mass General Brigham. A multiple time-series intervention is used to assess the impact of the CONCERN CDS system because it allows for periodic evaluation and model optimization (ie, we can refine our models on the basis of continuous data monitoring). Randomization will occur at the cluster level; we define the cluster as the clinical unit (ie, clinical ward) that the patients in our trial are admitted to. There will be a total of 86 intervention and control units across all sites, with the intervention and control groups randomly assigned using a random number generator. Study units include nonspecialty acute and intensive units. Randomization does not occur at the individual patient or clinician level in order to mitigate potential cross-over between control and intervention groups owing to clinician movement throughout the hospital. Baseline data will be collected prior to the intervention. Silent release mode (no CDS viewable to the end user) will be used in nonequivalent control units and as a postintervention unit control to evaluate whether notifying clinicians can decrease rates of negative clinical outcomes. Silent mode is a functionality that allows the CDS logic to actively run within the system and log its activity for later analysis, but not display any information or alerts to the user.

The primary outcomes are in-hospital mortality and length of stay; and secondary outcomes are cardiac arrest, unanticipated ICU transfers, and 30-day hospital readmission rates.

Three phases will be conducted through a 1-year period, and CONCERN CDS will be updated between each phase on the basis of the latest findings. Phase 1, the “burn-in” phase, will evaluate adoption of, and adaptation to, our algorithm. In the case of the Mass General Brigham site, the burn-in phase will be separated into two processes: pilot testing and trial testing. Phase 2 will activate the optimized versions 2 and 3 of the CONCERN CDS, which will be optimized based on experience from the burn-in phase 1. In the final phase, phase 3, the system will be set to silent release mode where no CONCERN levels are displayed within the patient list.

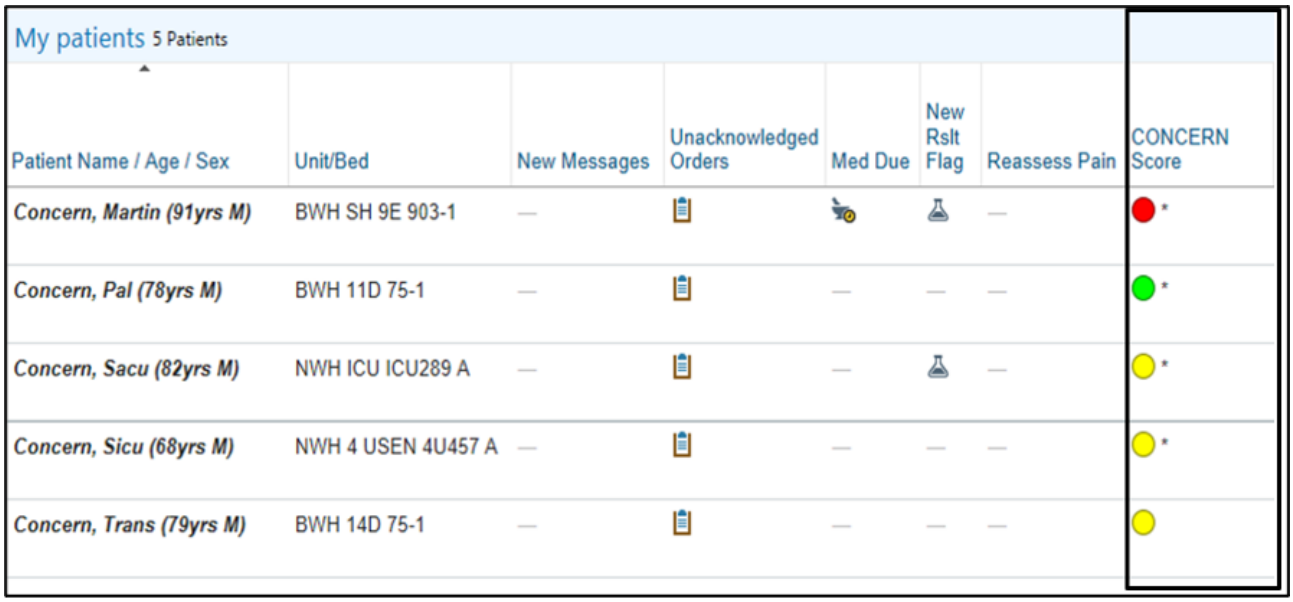
Figure 2. Cluster randomized pragmatic trial design with multiple time-series intervention. B: Baseline data; MGB: Mass General Brigham; NYP: New York Presbyterian; Silent: CONCERN CDS will function but will not display to clinician; Active: CONCERN CDS will display to clinician; V1: version 1, refined on the basis of continuous monitoring of data; V2: version 2, refined on the basis of continuous monitoring of data; V3: version 3, refined on the basis of continuous monitoring of data.

<table>
<tr><th>Group</th><th>Study Site</th><th>Pre-intervention (6 months)</th><th></th><th colspan="2">Phase 1 (3 months) [burn-in phase]</th><th></th><th>Phase 2a (3 months)</th><th>Phase 2b (3 months)</th><th></th><th>Phase 3 (3 months)</th><th></th></tr>
<tr><td rowspan="2">Control Group</td><td>MGB</td><td>B</td><td rowspan="4">End-User Training & Education</td><td colspan="2">V1 silent</td><td rowspan="4">System Evaluation</td><td>V2 silent</td><td>V3 silent</td><td rowspan="4">System Evaluation</td><td>V3 silent</td><td rowspan="4">System Evaluation</td></tr>
<tr><td>NYP</td><td>B</td><td colspan="2">V1 silent</td><td>V2 silent</td><td>V3 silent</td><td>V3 silent</td></tr>
<tr><td rowspan="2">Intervention Group</td><td>MGB</td><td>B</td><td>V1 active (Pilot testing 2 month)</td><td>V1 active (3 months)</td><td>V2 active</td><td>V3 active</td><td>V3 silent</td></tr>
<tr><td>NYP</td><td>B</td><td colspan="2">V1 active</td><td>V2 active</td><td>V3 active</td><td>V3 silent</td></tr>
</table>

CONCERN Intervention

Nurses and physicians who work on intervention units will have the CONCERN Score column integrated into their EHR patient list. The color-coded CONCERN score icon (red, yellow, green, and gray), which indicates the level of patient risk for deterioration, will be displayed in this column (Figure 3). The control units will not contain the CONCERN score column. Even if control group participants manage to manually add the CONCERN score column to their patient list view by themselves, only gray color (nonscores) will be displayed since their units and patients are excluded from the model.

Figure 3. COmmunicating Narrative Concerns Entered by Registered Nurses (CONCERN) Score column in Mass General Brigham's Epic patient list. Epic screen shot used with approval by 2021 Epic Systems Corporation. © 2021 Epic Systems Corporation.



Clinician Training

A training period will be conducted with nurse and physician end users from the intervention units prior to implementation to promote effective use of the CONCERN CDS app. The training plan was established with physician and nursing leaders who participated in user-centered design, focus group interviews, and simulation sessions. The training curriculum will last approximately 30 minutes and will be executed in groups or individually in consideration of each clinician's schedule. In addition, educational materials such as informative posters,

pocket reference cards, and CONCERN tip sheets will be distributed on intervention units before and throughout the trial.

Study Setting

The CONCERN CDS system will be integrated into the EHR at New York Presbyterian's Columbia University Medical Center (NYP-CUMC) and the Allen Hospital (NYP-Allen), Mass General Brigham's Brigham and Women's Hospital (MGB-BWH), and Newton-Wellesley Hospital (MGB-NWH). Our system will be implemented in 21 intervention and control units (721 beds) at NYP-CUMC, 5 intervention and control units (147 beds) at NYP-Allen, 55 intervention and control units (663 beds) at MGB-BWH, and 5 intervention and control units (153 beds) at MGB-NWH, yielding a total of 86 intervention and control units across all sites. Clinical unit room and bed counts are known to fluctuate slightly as a result of continuous updates in hospital operations, including in response to the COVID-19 pandemic. Therefore, the counts listed are subject to change.

Study Participants

All patients over 18 years of age admitted to one of our 86 study units will be enrolled in the trial. Hospice and palliative care patients will be excluded. All nurses and physicians at our study sites will be eligible to participate in a usability survey. All clinicians are expected to be above the age of 21 years of age. Minors will be excluded from participating in the study.

Data Collection and Analysis

Qualitative Evaluation

The individual and group interviews will be conducted with nurses and physicians who have used the CONCERN CDS app. They will mainly focus on the following: (1) assessing perceived understandability of the CONCERN CDS app, (2) evaluating perceived technical competence with the CONCERN CDS app, and (3) gauging trust in the CONCERN CDS app (as influenced by understandability and technical competence). Participation will be voluntary, and all recruitment materials—including emails, flyers, and information sheets—will reflect that fact. The interviews will be conducted and recorded using Zoom (a Health Insurance Portability and Accountability Act [HIPAA]–compliant Zoom account will be used for all interviews) or in person, transcribed using a HIPAA-compliant professional service, and coded using NVivo software.

Quantitative Evaluation

Quantitative CONCERN intervention trial data collection and analysis includes the collection of pre- and postintervention data during the 6 months before and 12 months after implementation. Prior to conducting hypotheses tests, descriptive statistics will be used to describe outcome variables and key confounding variables. We propose a generalized linear mixed model to examine the impact of the CONCERN system on each of the two primary outcomes: in-hospital mortality and length of stay. This model is used to deal with combined data from multiple sites and can account for changes over time. It also allows different baselines and trajectories to account for the contrasting ICU and non-ICU settings and can include both patient-level and unit-level covariates. We will include a variable for closed versus open units in our analysis. We will estimate statistical power for the comparison of mortality rates between the intervention and nonintervention periods and between silent- and active-model periods.

All power calculations will be based on 2-sided tests with Cronbach α=.05. Using hospitalized patients' statistics, we expect at least 2000 total admissions per month (ranging from 38 to 270 admissions in different units) with a mean length of stay of approximately 6 days. Each intervention period (pre- and postintervention periods) will be 6 months; therefore, we expect approximately 12,000 patients in each period. For length of stay outcome analysis, we will have at least 80% statistical power to detect a relative difference of 2% in the length of stay. Based on hospitalized patients' statistics, mean mortality rates of 37.5 (range 11.9 to 48.8) deaths per 10,000 inpatient days were obtained. Using a conservative number of total 50,000 inpatient days in each intervention period, we will have at least 80% statistical power to detect a relative difference of risk ratio of 0.76 in mortality rates.

There is no consensus regarding the best method for analyzing length of stay. Length of stay has been analyzed using both Poisson models (or negative binomial [NB] models or other related models such as Zero-truncated Poisson models) and survival models (such as Cox proportional hazard models) [16]. Both approaches will be applied to the length of stay, and the better predictive performing model, measured by the average squared error (ASE) for individuals from a testing data set, will be retained. Secondary outcomes include 30-day hospital readmission, cardiac arrest, and unanticipated transfers to the ICU, as well as analytics of CONCERN system log-files for clinician usage metrics.

Results

This trial has been approved by the institutional review boards at Columbia University Medical Center (protocol AAAR1389) and Mass General Brigham (IRB protocol 2015P002472). Data collection and analysis are expected to conclude by August 2022. The CONCERN CDS system is expected to have a positive impact on patient health outcomes (ie, reduced mortality and shorter hospital stays).

Discussion

Expected Findings

The CONCERN CDS leverages our predictive algorithm to determine and assign each patient a "CONCERN Level" (red, yellow, or green), representing a patient's risk level for deterioration. The CONCERN CDS has the potential to impact yellow-coded patients most significantly, as greater care team awareness, increased surveillance, and early interventions can help prevent these vulnerable patients from deteriorating. Generally speaking, CONCERN will be less impactful on patients who receive a red CONCERN level because they are likely actively deteriorating to such an extent that clinicians will already be aware of those declining health statuses.

Reduce CDS Alarm Fatigue

CDS alarm fatigue has been reported as a threat to patient safety [17]. We have explored this phenomenon in user-centered design and focus group interviews and found that clinicians do not want interruptive alarms, as these contribute significantly to alarm fatigue. Therefore, the CONCERN CDS app was integrated into the existing EHR patient list function and was designed to only display colored circle icons to easily communicate the degree of deterioration risk without interrupting clinician workflow. In addition, an asterisk (*) will appear next to the CONCERN level icon any time the score's color has recently changed (eg, a score that has changed from green to yellow, red to green, etc, within the past hour).

We also addressed CONCERN CDS scoring sensitivity in our algorithm development. If the scores are too sensitive, and the system designates too many patients as at above-average risk, over time they could cause users to perceive the tool as meaningless, especially in the ICU. The distributions of risk scores present at any given time are therefore controlled by our algorithm, limiting the number of patients who receive yellow and red scores to simply 10% and 2%, respectively. Score sensitivity is further controlled on the basis of unit type (ICU versus non-ICU), as ICU patients at baseline tend to be in more critical health states and require more attention and extreme treatment measures than non-ICU patients.

Risks and Discomforts

Because the core function of the CONCERN CDS app is to aid clinicians recognizing and taking measures to quickly and effectively treat patients at risk for deterioration, there are no anticipated physical risks in the study. Moreover, the CONCERN CDS will initially be deployed in "silent" mode, allowing for adequate evaluation and validation that it is functioning properly before it is activated for clinicians providing patient care. The CONCERN CDS app will be monitored closely with manual and automated review of log-files to ensure it is suitable for patient care. If any critical issue with the system should arise, which negatively impacts or impedes patient care, it will be immediately turned off, while diagnostic measures, such as retracing the software development lifecycle steps, are to be performed and solutions would be found. Then, only after thorough testing of the updated system, specifications, and fixes to the software reliably demonstrate that the solutions have addressed those issues, will the system be reactivated.

Integration Within Workflow

Implementation of the CONCERN CDS app is focused on integrating the tool within the users' existing workflow as seamlessly as possible. To best complement established clinical environments and cultures, the CONCERN implementation training strategy was constructed with physician and nursing leaders. The first step of this strategy is selecting champions among the professional development managers and nurses in charge from intervention units. The champions play an integral role in ensuring that integration of the CONCERN CDS app into their units' workflows is carried out harmoniously and in facilitating communication channels between the tool's end users and study team. Champions will also be trained as CONCERN "superusers," who in turn will train and support clinicians on the processes and rationale for using the app through all facets of the pre-, mid-, and postimplementation periods. Similarly, the CONCERN team will provide champions with educational material (eg, posters and pocket cards), maintain constant contact, and remain easily accessible to assist them in these training efforts whenever and however needed.

Study Limitations

As with all EWS models, clinical outcomes may underrepresent the impact of an EWS intervention on "at-risk" patients who receive timely and successful interventions and therefore do not experience a negative outcome. Additionally, the impact of clinician expertise and team coherence on patient outcomes has been considered and should be studied. However, quantifying information about the quality of the nurse and physician relationship into actionable CDS for predictive validity is not currently feasible and is beyond the scope of this study. The interplay of personality, temperament, and other factors in addition to work history would be pertinent for such an analysis. SCR's work at MGB and NYP [5,6,18,19] validated that care teams consistently leverage verbal conversations for decision-making while referencing CDS and other EHR information. Therefore, the extent to which expertise of one care team member or trainee has influenced a decision and the team's dynamic is either not consistently recorded in the EHR, or if recorded is likely not documented in real time [19]. Thus, it is not practicable to perform real-time predictive analytics of these types of care team dynamics. However, by designing the CONCERN CDS algorithm to utilize data over 12 hours for hourly calculations, we are able to capture and use any documentation that is delayed and is not in real time. Another potential limitation is that the CONCERN system might cause clinicians to overlook patients with a green CONCERN level because of perceived low risks. Nonetheless, during training, clinicians are encouraged to use the tool as an additional feature that helps them with CDS rather than a definitive tool to guide their decisions. We shall obtain a better understanding of the effect of the CONCERN CDS and its impact on clinician behaviors during outcome evaluation.

Conclusions

Our study defined a new source of predictive data by analyzing the types and frequencies of nursing documentation indicative of nurses' developing concerns about their patients, and subsequent increased surveillance, to build an early warning score system—the CONCERN CDS system. The CONCERN CDS system will be released and evaluated in 2 different health care systems through a multiple time-series trial protocol that consists of 3 phases. The impact on health outcomes and the usability of the CONCERN CDS by the end users will be evaluated through a mixed methods (quantitative and qualitative) approach. We expect the CONCERN CDS will increase team-based situational awareness, shared understanding of the patient situation, and timely recognition of patients predicted to be at risk for deterioration to influence rapid intervention that prevents mortality and associated harm.

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Conflicts of Interest

None declared.

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Abbreviations

ASE: average squared error
CDS: clinical decision support
CONCERN: COmmunicating Narrative Concerns Entered by Registered Nurses
EHR: electronic health record
EWS: early warning system
FHIR: Fast Healthcare Interoperability Resources
HIPAA: Health Insurance Portability and Accountability Act
ICU: intensive care unit
MEWS: Modified Early Warning Score
MGB: Mass General Brigham's
MGB-BWH: Mass General Brigham's Brigham and Women's Hospital
MGB-NWH: Mass General Brigham's Newton-Wellesley Hospital
NB: negative binomial
NLP: natural language processing
NYP-CUMC: New York Presbyterian's Columbia University Medical Center
PRN: pro re nata
SOAP: Simple Object Access Protocol

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Protocol

Validation of a Musculoskeletal Digital Assessment Routing Tool: Protocol for a Pilot Randomized Crossover Noninferiority Trial

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Abstract

Background: Musculoskeletal conditions account for 16% of global disability, resulting in a negative effect on millions of patients and an increasing demand for health care use. Digital technologies to improve health care outcomes and efficiency are considered a priority; however, innovations are rarely tested with sufficient rigor in clinical trials, which is the gold standard for clinical proof of safety and efficacy. We have developed a new musculoskeletal digital assessment routing tool (DART) that allows users to self-assess and be directed to the right care. DART requires validation in a real-world setting before implementation.

Objective: This pilot study aims to assess the feasibility of a future trial by exploring the key aspects of trial methodology, assessing the procedures, and collecting exploratory data to inform the design of a definitive randomized crossover noninferiority trial to assess DART safety and effectiveness.

Methods: We will collect data from 76 adults with a musculoskeletal condition presenting to general practitioners within a National Health Service (NHS) in England. Participants will complete both a DART assessment and a physiotherapist-led triage, with the order determined by randomization. The primary analysis will involve an absolute agreement intraclass correlation (A,1) estimate with 95% CI between DART and the clinician for assessment outcomes signposting to condition management pathways. Data will be collected to allow the analysis of participant recruitment and retention, randomization, allocation concealment, blinding, data collection process, and bias. In addition, the impact of trial burden and potential barriers to intervention delivery will be considered. The DART user satisfaction will be measured using the system usability scale.

Results: A UK NHS ethics submission was done during June 2021 and is pending approval; recruitment will commence in early 2022, with data collection anticipated to last for 3 months. The results will be reported in a follow-up paper in 2022.

Conclusions: This study will inform the design of a randomized controlled crossover noninferiority study that will provide evidence concerning mobile health DART system clinical signposting in an NHS setting before real-world implementation. Success should produce evidence of a safe, effective system with good usability, potentially facilitating quicker and easier patient access to appropriate care while reducing the burden on primary and secondary care musculoskeletal services. This rigorous approach to mobile health system testing could be used as a guide for other developers of similar applications.

Trial Registration: ClinicalTrials.gov NCT04904029; http://clinicaltrials.gov/ct2/show/NCT04904029

International Registered Report Identifier (IRRID): PRR1-10.2196/31541

(JMIR Res Protoc 2021;10(12):e31541) doi:10.2196/31541

KEYWORDS

mHealth; mobile health; eHealth; digital health; digital technology; musculoskeletal; triage; physiotherapy triage; validation; mobile phone

Introduction

Background

Musculoskeletal disorders (MSDs) are the leading contributors to years lived with disability worldwide and have shown an increase in disease burden over the past decade [1-3]. Musculoskeletal conditions can affect as many as 1 in 4 adults and are set to continue rising, being associated with decreased life expectancy and reduced activity [4,5]. MSDs are prevalent throughout the life span and associated with early work retirement and reduced ability to participate socially [5]. In developed countries, they present the most significant proportion of lost productivity in the workplace, leading to a significant impact on the gross domestic product and health care costs [6,7].

In the United Kingdom, this poses a financial and societal challenge, costing >£4.76 billion (US $6.35 billion) of the UK National Health Service (NHS) resources and using up to 30% of primary care physician visits annually [8,9]. A freedom of information request has revealed that the average waiting time for NHS musculoskeletal outpatient physiotherapy services exceeded 6 weeks in the year to April 2019, with some patients waiting 4 months for routine appointments [10]. Longer waiting times can result in delays to physiotherapy services, with potentially detrimental effects on pain, disability, and quality of life [11,12]. The increasing proportion of burdens on public health services because of MSDs has highlighted the need for a targeted policy response [3,13].

Access to the *right person, right place, first time* is considered a key factor in improving musculoskeletal condition outcomes and reducing unwarranted variation in clinical pathways, such as unnecessary secondary care consultations and investigations [14]. Musculoskeletal triage as a single point of access is effective across various outcome measures, including user satisfaction, diagnostic agreement, appropriateness of referral, and reduction in patient waiting times [15]. Importantly, triage has also shown a reduction in costs across the musculoskeletal pathway, which is particularly crucial in overburdened health care systems, where triage can be performed effectively via several methods and by a range of clinicians [16-18].

Remote triage services such as telephone and video consultations or web-based or digital applications have the potential to reduce waiting times and musculoskeletal caseload [15,19]. Direct access to these services with initial assessments by physiotherapists may be a viable, cost-effective solution for managing the growing burden of MSD demand and workloads [19-22], with recent advances being made in digital primary care triage applications [23,24]. Some research has suggested that physiotherapy-led telephone triage is shown to be clinically as effective as usual care [21,25] and broadly acceptable to patients with MSDs seeking early physiotherapy advice [26]. However, barriers include the time required to reach a triage outcome, limited patient and professional trust, and interoperability problems. It should also be noted that comparisons between studies are hampered by variations in outcome measures and lack of randomization and statistical power, making any generalizations across health care settings problematic.

Mobile health (mHealth) technology has been proposed as a cost-effective solution for improving health care delivery [27,28]; however, this requires robustly tested and validated web-based triage platforms to signpost patients with MSDs to an appropriate level of care [19,29]. Standards and guidance for safe and effective implementation of mHealth apps have been published by several national and international organizations, all specifying a requirement for evidence of clinical safety and effectiveness [30-38]. A UK evidence standards framework specifically requires as the best practice standard a high-quality randomized controlled study or studies done in settings relevant to the UK health and social care system, which compare the digital health technology with a relevant comparator and demonstrate consistent benefits, including clinical outcomes in the target population [30].

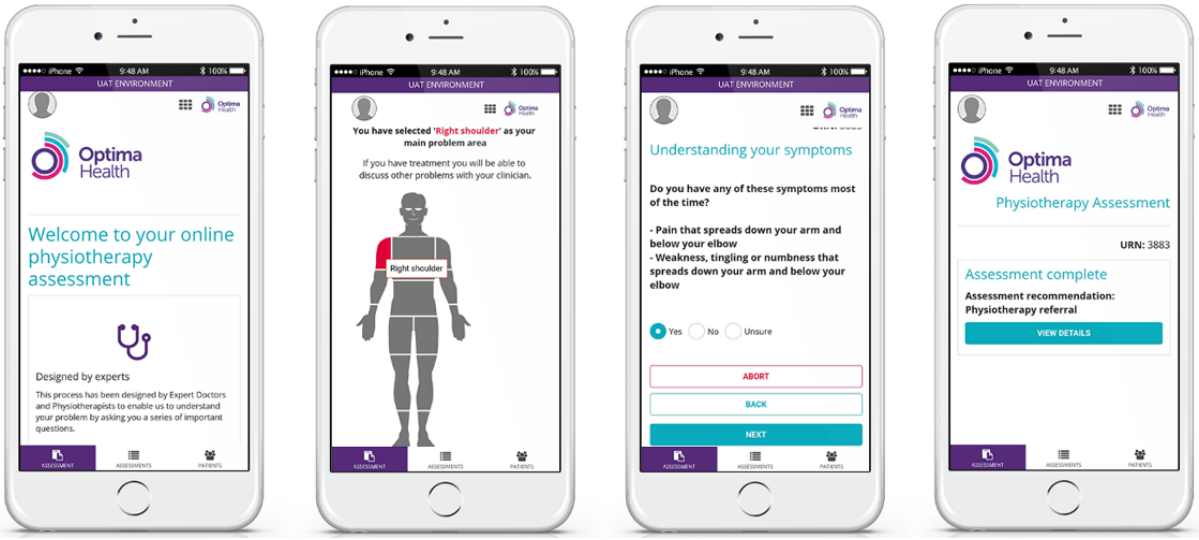
To date, there is limited evidence regarding the use of web-based or digital triage platforms for MSDs specifically, and most investigations have focused on the performance of generic symptom checkers, covering a wide range of clinical presentations. However, the evidence from these studies concerning clinical- and cost-effectiveness, signposting to appropriate services, patient compliance, and safety was found to be weak or inconsistent [29]. A review of 36 primary care generic diagnostic and triage symptom checkers on web-based or mobile platforms found that appropriate triage advice was given for only 49% of the 688 vignette cases, with appropriate triage advice being given most frequently for emergency (63%) or urgent care (56%) and nonurgent care being accurate in only 30% of cases [39]. This finding is consistent with previous literature that evaluated web-based generic symptom checkers for self-diagnosis and triage [40]. A systematic review of generic health digital and web-based symptom checkers found algorithm-based triage to be inferior and more risk averse in providing appropriate triage advice compared with doctors and health practitioners [29]. Although most system developers consider this to be a safe approach, incorrect or unnecessary clinical escalations have been shown to adversely affect user trust and system adoption [41]. It is proposed that the digital assessment routing tool (DART) may overcome the limitations of existing generic symptom checkers and triage platforms by narrowing the scope of the tool and refining clinical algorithms to specifically address MSD presentations. The potential to improve triage efficiency and timely signposting of patients with MSDs to an appropriate level of care is potentially significant.

DART Overview

DART (Optima Health) is the first contact mHealth system designed specifically for the management of MSDs. The clinical algorithms are configured to provide the patient with a

recommendation for the correct intervention level. The patient can self-assess using a computer, tablet, or smartphone. Alternatively, the content can be delivered by a remotely situated clinician or nonclinical administrator by telephone or video call. Once the affected body region has been selected, the patient is presented with a varying number of questions, depending on the nature of their symptoms and previous responses. Serious pathology is screened for, and appropriate signposting is given at the start of the assessment, with less urgent medical referrals being identified as the patient passes through the questioning. Algorithms are configured to match the provider's clinical services based on evidence-based practice and sector-specific referral criteria. DART can be applied across any number of health care systems, including public and private services, and typically signposts to emergency or routine medical assessment, specific condition specialists, physiotherapy, self-management programs, or psychological support services. DART has an integral reporting function that allows the analysis of individual and amalgamated patient data to assess the system and clinical pathway performance (Figure 1).

Figure 1. Digital assessment routing tool mobile health system.



Previous Work

This pilot study is part of a larger project, bringing DART from concept to implementation through a series of clinical and academic research work packages.

To assess the algorithm's clinical validity, 2 reports were commissioned by Optima Health and undertaken by a panel of 5 consultant clinicians experienced in the musculoskeletal field, which comprised a consultant rheumatologist, a consultant orthopedic surgeon, a consultant sports and exercise physician and senior clinical lecturer, an honorary general practitioner (GP) in emergency care, and a consultant physiotherapist and academic lead. The first round of desktop evaluation comprised the panel inputting symptoms from 100 clinical scenarios (including red flags and complex presentations) into DART. The DART recommendation was then assessed by the panel as being correct, arguably correct, or disagree. Feedback from the panel was incorporated into a new iteration, leading to improved DART accuracy during the second review. On the basis of their opinion, the panel recommended that clinical validity was sufficient to allow DART to proceed to further research studies.

Real-world usability testing has been completed using an iterative convergent mixed methods design incorporating patient and public involvement [42], the results of which will be reported later in 2021. This study optimized usability in the final DART iteration that will be used in this pilot study and subsequent main trial.

Research Aims and Objectives

The aim of this study is to facilitate the delivery of a future trial by exploring key aspects of trial methodology, assessing the procedures, and collecting exploratory data to inform the design of a definitive, randomized, crossover, noninferiority trial to assess DART safety and effectiveness in an NHS primary care setting.

Primary Objective

The primary outcome measure is to collect exploratory data about the agreement of triage decisions made by the DART system and physiotherapy-led triage, which will provide a variance (SD) estimate required for the sample size calculation in the main trial.

Secondary Objectives

The secondary outcome measures are as follows:

1. Evaluate the number of people who sign up and are retained, with a dropout rate and identification of when dropouts happen
2. Evaluate the systems for randomization and data collection (effectiveness, process of implementation, allocation concealment, and bias)
3. Identify the burden on the patient and therapist (treatment delay, DART procedure complexity, and additional questions)
4. Identify barriers in the proposed intervention delivery processes

Methods

Design

A pilot randomized, single-blinded, crossover, noninferiority trial will be conducted to compare the safety and efficacy of DART signposting with physiotherapy-led triage outcomes in an NHS primary care setting. This preliminary study was designed in accordance with the CONSORT guidelines for pilot and feasibility trials [43], CONSORT guidelines for equivalence and noninferiority randomized trials [44], and the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [45]. Moreover, the trial design will not influence the care or triage decisions made by the usual care clinicians. Participants will complete both a DART assessment and a physiotherapy-led triage assessment on the same day, with randomization determining the order in which this is done (Figure 2).

The outcomes available to the physiotherapist will be matched by those available within the DART, allowing direct comparison between the 2 assessment outcomes (Table 1). Following their DART assessment, the participant will use a web-based questionnaire to complete the system usability scale (SUS) [46] to measure user satisfaction.

Figure 2. Study design and participant flowchart. DART: digital assessment routing tool; MSD: musculoskeletal disorder; NHS: National Health Service.

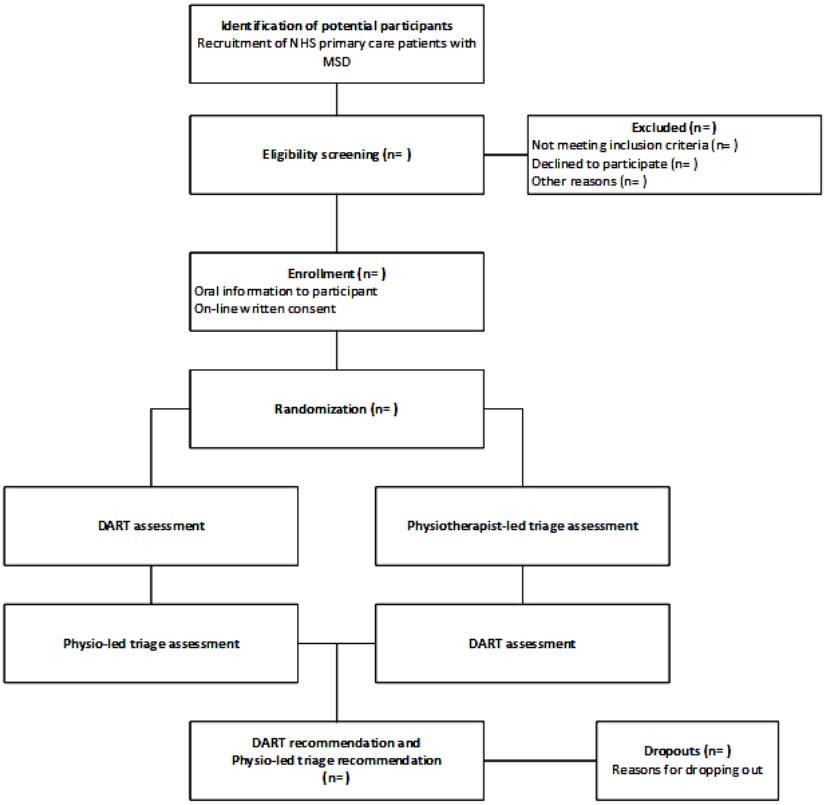


Table 1. All possible outcomes and suboutcomes from the digital assessment routing tool and physiotherapist-led triage assessment.

Medical care	FCP[a] physiotherapist	Physiotherapy care	Remote self-management
Emergency care (accident and emergency referral/NHS111)	N/A[b]	Post fracture or surgery physiotherapy	Supported self-management
Urgent primary care physician (GP[c])	Urgent FCP	Urgent physiotherapy referral	Continue self-management advice
Routine primary care physician (GP)	Routine FCP	Routine physiotherapy referral	Web-based support material
Consultant review	N/A	Physiotherapy referral plus psychosocial support	Digital self-management

[a]FCP: first contact practitioner.

[b]N/A: not applicable.

[c]GP: general practitioner.

Recruitment

A total of 76 participants will be recruited for this pilot study using purposive sampling from a single NHS general practice. Monthly MSD referral volumes far exceed the number required for the study, which should support the completion of data collection within the anticipated study timescale. Patients with an MSD wishing to access support from the practice, either from a GP or physiotherapist, will be recruited into the study using an advert on the practice website, posters and leaflets in the GP waiting room, and by invitation from the practice administrators if the patient telephones in to make an appointment. Interested patients will be able to access the participant information sheet on the web or through hard copies available in practice, which will provide the researcher's contact details and a request to contact them if they wish to participate (Multimedia Appendix 1). The researcher will make contact, answer any further questions, complete eligibility screening, and gain initial verbal consent. An appointment will then be made for the next available study clinic.

Inclusion Criteria

The study participant inclusion criteria were as follows: (1) aged >18 years, (2) able to speak and read English, (3) registered as a patient at the primary care practice, (4) having a current musculoskeletal condition for which they are seeking treatment, and (5) able to access the internet either by themselves or with the help of a family or friend.

Exclusion Criteria

The study participant exclusion criteria were as follows: (1) cognitive impairments or learning disabilities that limit a participant's ability to follow study-related procedures, (2) unwillingness or inability to follow protocol-related procedures, and (3) Optima Health or Queen Mary University of London employees.

Informed Consent

Each participant will receive the participant information sheet (Multimedia Appendix 1), which outlines the purpose of the study and the nature of their participation. This includes information about the format of the interaction, potential risks, confidentiality and protection of their personal data, the anonymity of study findings, and their right to withdraw at any time without prejudice. The participant will be given the opportunity to raise any questions with the researcher during the formal consenting process when they attend the practice. Formal written consent will be completed by the researcher with the patient in the practice waiting room using a web-based form. Failure to provide consent will result in the participant receiving a usual care physiotherapy-led triage without a DART assessment.

Randomization and Blinding

Participants will be randomized to either (1) a DART assessment followed by a physiotherapist-led triage assessment or (2) a physiotherapist-led triage assessment followed by a DART assessment. This is to account for the order effects in the crossover design (Figure 2). This will be achieved by block randomization with permuted blocks of random size and without stratification factors to avoid selection bias and unequal arms [47-49]. After gaining consent, the researcher will open a sealed envelope that contains the randomization to be used for the participant. Allocation will be performed using a computer-generated list of random numbers, which will lead to a randomization sequence in Microsoft Excel 2020. The allocation ratio between the arms will be 1:1.

Blinding in this study will be ensured at 3 different points: (1) the physiotherapist leading the triage will be blinded to group allocation and DART assessment outcomes; (2) participants will be blinded to the DART assessment outcome and the physiotherapist triage outcome until they have completed both assessments and the SUS; and (3) the analysis and interpretation of the study results will be conducted by researchers blinded to the intervention group allocation.

To minimize potential bias created during the physiotherapist assessment, the physiotherapist will be required to minimize any information or advice they give to the participant until after they have completed their subjective assessment and arrived at a provisional management recommendation. This will include discussing any possible diagnoses or giving any condition management advice. Once the participant has completed both assessments and data collection is complete, they will return to the physiotherapist, who will then complete the objective assessment and continue with normal care.

Data Collection

Physiotherapy-Led Triage

Participants will receive a usual care physiotherapy-led triage assessment from a first contact practitioner (FCP). An FCP physiotherapist is a qualified autonomous clinician who can assess, diagnose, treat, and discharge a patient without a medical referral, where appropriate. They have completed additional postgraduate training to provide expert assessment, check for red flags, and provide advice on self-management. If needed, they prescribe medication, order investigations, refer for physiotherapy, or provide onward referral to secondary care services such as rheumatology or orthopedics [50]. As such, the FCP physiotherapist will provide a rigorous comparator against which to measure DART signposting recommendations.

The physiotherapist-led triage assessment will be completed within a 20-minute appointment. The management pathways available to the FCPs are matched by those that can be generated by DART to allow an objective comparison (Table 1). Participants may seek help elsewhere or opt out of the study at any point, which will not affect their usual physiotherapy-led care.

DART Assessment

Participants will access DART using a tablet device in a treatment room or a quiet area in the practice waiting room. The researcher will log onto DART and enter the participant study number but will have no further contact with the participant until they have completed their DART assessment. The DART assessment will be completed either before or after their appointment with the physiotherapist, depending on their randomization allocation. A unique reference ID will be

generated in the DART system and linked to the participant's study number. The participant will complete the DART assessment, which will result in a signposting outcome. This will not be visible to the participant but will be stored in the DART system for later retrieval and analysis. Thereafter, the participant will complete a web-based version of the SUS, capturing their experience of using DART. All participants will be given the physiotherapist triage assessment outcome by the physiotherapist, who will complete any associated management actions or referrals. Both assessments will be completed on the same day in close succession to reduce variations in clinical presentation.

Panel Assessment

An independent panel comprising 3 experts in musculoskeletal physiotherapy and general practice qualified to the consultant level will provide consensus on all disagreements between DART and physiotherapy-led triage that would yield a safety concern (Textbox 1). In addition, a random sample of cases will be assessed by the panel to decide which they consider to be the correct outcome based on the patient's presentation from the physiotherapist's clinical record of their assessment. The panel decision will provide the definitive *gold standard* outcome against which the physiotherapist outcome will be compared. The triage outcomes that are amended by the panel will be deemed the most appropriate outcome in preference to those from the physiotherapy assessment and will provide the outcome against which DART is compared.

Textbox 1. Adverse triage outcomes in medical care, physiotherapy care, and self-management that would yield a safety concern, including a delay in intervention likely to result in a poor outcome.

Adverse triage outcomes that would yield a safety concern

- Physiotherapy or self-management when it should have been urgent medical care (accident and emergency/NHS111 referral or urgent general practitioner)
- Self-management when it should have been physiotherapy, first contact practitioner, or medical care
- Routine care when it should have been urgent care

Clinical Signposting Outcomes

The primary outcome measure will be assessment outcomes from physiotherapy-led triage and DART assessments (Table 1). These decisions are classified into 4 categories (medical care, FCP, physiotherapy care, and remote self-management), with further suboutcomes in each category. This allows for precise comparisons within each category and subcategory and is based on usual care signposting approaches in musculoskeletal clinical practice. Adverse triage outcomes that could yield safety concerns will also be identified (Textbox 1). Our aim for the pilot data is to explore the agreement rate between DART and physiotherapy-led triage across assessment outcomes, with additional analysis of suboutcomes. This will inform the suitability of the outcome measure and analysis for the future main trial. Additional data will be collected from DART and the physiotherapist. Demographic variables include age and gender. Clinical characteristics include the musculoskeletal pathway related to the body site.

Process Outcomes

The process outcomes will help to determine whether the implementation of the main trial design is feasible. Anonymized data will be collected, including the proportion of participants who showed interest in participating against those who were recruited into the study. Participant dropout rates at each stage of the trial (and, where possible, reasons for dropping out) will be collected. System process outcomes include errors reported in randomization, allocation concealment, blinding, or data collection. Any evidence for selection bias or other sources of bias will be explored. Other outcomes include the overall time burden: average times from initial participant contact to the first assessment, along with any treatment delay because of the additional time required to perform the research procedures. Technical problems with DART or other comments from the physiotherapist or participants that pose a barrier to intervention delivery or trial procedures will be explored.

Study Duration

Following ethics approval, 3 months will be allocated for the collection of data from the required 76 participants. The exact duration will be dependent on the volume of physiotherapy referrals entering the physiotherapy service and recruitment uptake.

Data Analysis

Calculation of Main Study Sample Size

As the nature of this pilot trial is to explore trial design and feasibility, a formal power-based sample size calculation will not be conducted. Our sample size is based on the estimated stepped rules of thumb from Whitehead et al [51] to demonstrate an extra small standardized effect size (σ<0.1) at a 90% powered main trial. The obtained variance estimate of the outcome measures from the pilot data will allow sample size calculation for the main trial using the noncentral T-distribution approach from Julious and Owen [52]. Our plan is to recruit a total of 76 participants over a 3-month period in this trial.

Primary Outcome

The primary analysis will involve an absolute agreement intraclass correlation (A,1) estimate with 95% CIs between DART and the clinician on triage outcomes with recommended management pathways, which will be calculated using SPSS, version 23 (IBM Corporation) and based on a single rating, 2-way mixed-effects model [53,54]. The analysis includes intention-to-treat and per-protocol analyses, with a subanalysis of categories (medical care, physiotherapy care, and

self-management) and adverse triage outcomes. A predefined margin of correlation with an intraclass correlation ≥0.90 will be set and based on both clinical recommendations and the literature in which a correlation was demonstrated in clinical management decisions taken between telehealth and face-to-face physiotherapy [55]. In addition, diagnostic properties (sensitivity, specificity, and predictive values) will be calculated for DART and reported with 95% CI [56]. A descriptive summary of the variables includes the mean, SD or CI, median, and IQR as appropriate. The amalgamated SUS score will be reported as a mean and used to calculate a percentile score to allow benchmarking of the DART system usability against other systems [57].

Evaluation of Participant Recruitment and Retention

The number of participants referring to physiotherapy will be reported, including the proportion that meets the eligibility criteria, shows initial interest, and consents to participate in the trial. Participants who show initial interest in participating but do not consent will also be reported (and, where possible, reasons for not participating). Participants who opt out of the trial at any stage, such as between interventions, will also be reported. Differences in dropout rates between the intervention groups will be compared. As recruitment rates vary in randomized controlled trials [58], a conservative margin will be set. Dropouts seem unlikely to occur as there is only a single visit that will coincide with the physiotherapy appointment. Thus, a predefined criterion of 50% and 95% will be considered satisfactory for the proportion of identified participants recruited and retained, respectively.

Evaluation of Randomization, Allocation Concealment, Blinding, Data Collection, and Bias

Any underpinning errors in systems responsible for procedural randomization, allocation, blinding, or data collection will be reported. Baseline characteristics will be compared between the intervention groups (DART-physiotherapy-triage and physiotherapy-triage-DART) using analysis of variance for continuous variables or chi-square tests for categorical variables. Homogeneity between groups will indicate successful randomization and minimized risk of selection bias. Discrepancies in allocation concealment or unblinding of participants or therapists will be further compared between intervention groups and reported. Unsuccessful blinding is considered when physiotherapists become unblinded to group allocation or DART assessment advice.

Identification of Trial Burden and Barriers to Intervention Delivery

Administrative and physiotherapist burden in terms of additional time required to administer the study process will be assessed and extrapolated to understand the implications for the main study. Feedback from the service administrators and participating physiotherapists will also be recorded and reported.

Bias

This study is funded by Optima Health, the developers of DART, and therefore, is at risk of bias. The lead researcher (CL) is an employee of Optima Health and enrolled in a PhD program at the Queen Mary University of London. To mitigate bias, participants will be excluded if they are employees of Optima Health or the Queen Mary University of London. Participants will not have previously seen or used DART. Recruitment is through promotion directly to the medical center patients and not by the researcher contacting them using a database. There is no financial reward offered to people to participate in the study. After gaining of formal consent and ensuring that the participant has logged on to DART, the researcher has no further contact with participants, with data being collected through DART, by the physiotherapist, or the SUS web-based questionnaire. The expert panel will comprise senior musculoskeletal clinicians who are not employed in any form by Optima Health.

Risks and Benefits

There will be no form of physical intervention during this study, and participants will have no extra travel in addition to that required for their physiotherapy appointment. Normal care, as determined by the triage physiotherapist, will be followed in all cases, and participants will have full access to all existing clinical pathways available to them. Participants will not be given the DART signposting recommendation, so there will be no conflict with the recommendation given by the physiotherapist.

Data Management

Participants will have the right to withdraw from the study at any time. If they do, data collected up to the point they withdraw will be retained but not added to. Electronic and paper data will be managed and stored securely in accordance with the general data protection regulations. Study data will be collected outside the NHS firewall. Personal data collected in DART will be confined to age and sex at birth and linked to other research data using a DART system unique reference number. The data inputted by the participant during the DART assessment will be generated entirely by them, and no data will be extracted from their NHS records. DART system information security and data protection will be covered by Optima Health's certification and compliance with Cyber Essentials Plus and ISO 27001. Data collected by the physiotherapist will comprise physiotherapist assessment recommendations and study numbers only. The web-based SUS questionnaire will only contain the participant's study number. Research data will be stored separately to personal data and linked by a unique reference number that is only accessible to the researchers. Access to the participant's physiotherapy assessment record forms a part of the study consenting process; however, only the assessment completed as a part of the study will be reviewed by the panel and no other part of the NHS record. The data collected during this pilot may be reused for a later definite randomized noninferiority trial in a deidentified format.

Results

Ethics approval was submitted in June 2021. This study has been registered at ClinicalTrial.gov NCT04904029. Recruitment will commence early 2022, and data collection is anticipated to last for up to 3 months. The results will be reported in a follow-up paper in 2022.

Discussion

Overview

The demand for an mHealth system to correctly assess and signpost patients with MSDs has been demonstrated. Research into the patterned use of generic symptom checkers indicates that MSDs are among the most common reasons for accessing web-based or digital triage applications in primary care [59,60]. Studies regarding the effectiveness of generic symptom checkers have shown variable levels of system validity [23,24,29,40], and it cannot be assumed that these research findings translate to an mHealth system with a well-defined scope, such as DART with MSDs. To date, there are no published studies providing a proven methodology for evaluating the real-world validity of similar musculoskeletal mHealth systems. This pilot trial will explore the feasibility and study design for a future large-scale, noninferiority trial determining whether DART's efficacy and safety are noninferior or *not unacceptably worse* to FCP physiotherapist-led triage, a usual practice comparator. During earlier DART development, the desktop validity of DART clinical algorithms was appraised as being good by an expert panel using vignettes; however, this is not representative of the real-world validation required for safe and effective implementation into routine clinical practice [61]. DART has demonstrated good usability through an iterative convergent mixed methods study, leading to the version to be used in this pilot trial. This pilot study protocol will give a greater understanding of how to assess the validity of an mHealth system such as DART within an NHS setting and provide a template for other researchers and developers to use across triage and referral mHealth systems.

Methodological Limitations

The purpose of this pilot is to validate or provide information for improvement in the study design to underpin the successful completion of the subsequent main trial. The crossover design can create a delay in the participant receiving normal care, albeit only a few minutes, and there is an increase in the amount of service administration time required. The most common errors in crossover trials are failure to adapt stratification in the order of treatments and analysis of the group rather than separately between sequence groups [62]. This is accounted for by the permuted block randomization and the independent analysis of results per group. A washout period between interventions is normally recommended to prevent carryover effects; however, there is no therapeutic effect from either DART or the physiotherapy-led assessment. The physiotherapist being asked to refrain from giving management advice as they assess the patient may be a change in normal practice for some clinicians but should not affect their signposting recommendation. Carryover effects may involve the participant becoming primed to answer questions about their health differently after gaining more insight into their health problem from having completed the previous assessment. Data analysis comprises assessing clinical agreement between the physiotherapist and DART system management recommendations. This study is not designed to examine the impact of differing DART recommendations on individual patient management and how this may positively or negatively affect care complexity, case duration, or cost. This would form the basis of a future implementation study to assess these factors across the entire MSD pathway.

Methodological Strengths

The findings from this pilot trial will constitute the design of a future noninferiority trial, as well as provide preliminary data on DART safety and effectiveness. The key benefit of a crossover design using the same participant for both arms is that differences in clinical presentation as a confounder are minimized. The large variety of MSD symptomology, patients' general health, and psychosocial status means that using a study design where different participant results are compared, such as in a parallel study, would require an unacceptably large sample size. Assessing the participant twice within minutes reduces the risk of a change in symptoms that could lead to a different signposting recommendation between the physiotherapist and DART assessments. The use of real-world NHS participants rather than clinician testing using vignettes supports patient and public involvement, a crucial component of testing for any system designed to be used with patients. Piloting within the NHS ensures that DART is tested across a wide range of clinical presentations and patient demographics, including varying socioeconomic status, eHealth literacy, fluency of English speaking, age, and employment status.

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Authors' Contributions

CL conceived the study topic and wrote the protocol, with input from HHS and DM. CL and HHS will perform data analysis. CL drafted the manuscript with input from HHS, which was reviewed by DM, WM, and HHS before submission.

Conflicts of Interest

Optima Health has developed the DART system and is the owner of the associated intellectual property. The principal investigator (CL) is an employee of Optima Health and a PhD Research Student at Queen Mary University of London. HHS is employed by Optima Health to work as a research assistant on this study.

Multimedia Appendix 1
Patient information sheet.
[DOCX File , 65 KB - resprot_v10i12e31541_app1.docx]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DART: digital assessment routing tool
FCP: first contact practitioner
GP: general practitioner
mHealth: mobile health
MSD: musculoskeletal disorder

NHS: National Health Service
SUS: system usability scale

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Protocol

Accuracy and Cost-effectiveness of Technology-Assisted Dietary Assessment Comparing the Automated Self-administered Dietary Assessment Tool, Intake24, and an Image-Assisted Mobile Food Record 24-Hour Recall Relative to Observed Intake: Protocol for a Randomized Crossover Feeding Study

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Abstract

Background: The assessment of dietary intake underpins population nutrition surveillance and nutritional epidemiology and is essential to inform effective public health policies and programs. Technological advances in dietary assessment that use images and automated methods have the potential to improve accuracy, respondent burden, and cost; however, they need to be evaluated to inform large-scale use.

Objective: The aim of this study is to compare the accuracy, acceptability, and cost-effectiveness of 3 technology-assisted 24-hour dietary recall (24HR) methods relative to observed intake across 3 meals.

Methods: Using a controlled feeding study design, 24HR data collected using 3 methods will be obtained for comparison with observed intake. A total of 150 healthy adults, aged 18 to 70 years, will be recruited and will complete web-based demographic and psychosocial questionnaires and cognitive tests. Participants will attend a university study center on 3 separate days to consume breakfast, lunch, and dinner, with unobtrusive documentation of the foods and beverages consumed and their amounts. Following each feeding day, participants will complete a 24HR process using 1 of 3 methods: the Automated Self-Administered Dietary Assessment Tool, Intake24, or the Image-Assisted mobile Food Record 24-Hour Recall. The sequence of the 3 methods will be randomized, with each participant exposed to each method approximately 1 week apart. Acceptability and the preferred 24HR method will be assessed using a questionnaire. Estimates of energy, nutrient, and food group intake and portion sizes from each 24HR method will be compared with the observed intake for each day. Linear mixed models will be used, with 24HR method and method order as fixed effects, to assess differences in the 24HR methods. Reporting bias will be assessed by examining the ratios of reported 24HR intake to observed intake. Food and beverage omission and intrusion rates will be calculated, and differences by 24HR method will be assessed using chi-square tests. Psychosocial, demographic, and cognitive factors associated with energy misestimation will be evaluated using chi-square tests and multivariable logistic regression. The financial costs, time costs, and cost-effectiveness of each 24HR method will be assessed and compared using repeated measures analysis of variance tests.

Results: Participant recruitment commenced in March 2021 and is planned to be completed by the end of 2021.

Conclusions: This protocol outlines the methodology of a study that will evaluate the accuracy, acceptability, and cost-effectiveness of 3 technology-enabled dietary assessment methods. This will inform the selection of dietary assessment methods in future studies on nutrition surveillance and epidemiology.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12621000209897; https://tinyurl.com/2p9fpf2s

International Registered Report Identifier (IRRID): DERR1-10.2196/32891

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KEYWORDS

24-hour recall; Automated Self-Administered Dietary Assessment Tool; Intake24; mobile food record; image-assisted dietary assessment; validation; controlled feeding; accuracy; dietary measurement error; self-report; energy intake; adult; cost-effectiveness; acceptability; mobile technology; diet surveys; mobile phone

Introduction

Background

Dietary intake surveillance enables monitoring of diet-related health and nutritional status of populations and provides vital data to inform public health nutrition policies and programs [1]. Therefore, accurate assessment of dietary intake is important to assist effective government decision-making on dietary advice and programs by defining the extent of the problem and possible solutions. The 24-hour dietary recall (24HR) is the current standard and preferred method for large-scale population surveillance to assess absolute dietary intakes [2-6]. Technology-assisted 24HR offers the potential to improve accuracy and reduce participant and researcher burden. However, the relative accuracy, acceptability, and cost of various technology-assisted methods are unclear. Population dietary surveillance studies typically include thousands of participants. As such, cost and personnel requirements are major determinants of the feasibility of a dietary assessment method. However, information on the cost of method administration has rarely been collected or published. This information would contribute to the feasibility assessment by researchers and decision makers.

A 24HR method is designed to capture detailed information on foods and beverages consumed on the previous day or during the previous 24 hours and is traditionally conducted as a structured face-to-face interview [7]. The 24HR method is a complex process involving numeracy, perception, memory, and the conceptualization of that memory [8]. The benefits of 24HR methods over less burdensome methods, such as food frequency questionnaires, include the detailed accounting of all foods and beverages consumed and information on context (eg, meal timing). This information allows the examination of questions related to different dietary components, dietary patterns, and meal patterning [9].

Various methods have been developed to enhance recall and reduce errors in reported intake. For example, the National Health and Nutrition Examination Survey in the United States includes an interviewer-administered Automated Multiple-Pass Method (AMPM) 24HR [3] as does the Australian Health Survey [2]. AMPM is a web-based interface designed for surveillance, typically implemented in-person by a trained interviewer, which adds to the cost of undertaking large-scale surveys. The AMPM provides a structured interview format with specific probes in 5 structured sets *or passes*: a quick list, forgotten foods pass, time and occasion pass, detail pass, and final review [10]. Portion size estimation is addressed using a food model booklet. More recently, web-based interfaces have been developed to enable self-administration of the 24HR method by participants, removing the need for trained interviewers and reducing study costs.

Automated web-based, self-administered 24HR methods begin with a quick list. Details are collected using a sequence of

probes, and standard images of foods or models are used to help participants estimate portion sizes. The format and number of images are informed by user testing [11,12]. These methods include the US-developed Automated Self-Administered Dietary Assessment Tool (ASA24) and the UK-developed Intake24. ASA24 is an adaptation of AMPM and was developed by the United States National Cancer Institute based on input from stakeholders in an external working group, along with cognitive and usability testing [13]. Intake24 was developed by Newcastle University, United Kingdom, using 4 cycles of user testing, with modification after each cycle, in adolescents and young adults [12,14]. Similar levels of measurement error have been observed in web-based self-administered 24HR methods (Intake24 and ASA24) and in interviewer-administered methods as determined by objective measures of energy intake using doubly labeled water [15,16]. This suggests that the additional costs associated with interviewer-administered methods in the form of trained interviewers and coders may not translate to improved accuracy. However, to date, no study has evaluated the differences in accuracy between Intake24 and ASA24.

Using image-assisted methods to supplement the 24HR method has the potential to reduce recall bias, with images used to assist food identification and portion size estimation. In recent reviews, image-assisted approaches, including 24HR methods, resulted in greater accuracy of self-reported dietary intake when compared with the accuracy of methods without images supplied by participants [17-19]. The Image-Assisted mobile Food Record 24-Hour Recall (mFR24) is a mobile app developed by Purdue University. Participants are instructed to take *before* and *after* images of all food and beverages consumed and to include a fiducial marker (an object of known shape, size, and color) [20] in each image to aid in portion size verification. The content of the images is confirmed either by a human trained analyst or by automated methods using computer vision and machine learning (eg, deep learning) techniques [21-23]. In contrast to other image-assisted 24HR methods in which the image review occurs toward or at the end of the interview [24-28], the image review in mFR24 begins at the start of the interview based on participant feedback from pilot testing. This novel approach has yet to be evaluated for its accuracy and acceptability. Furthermore, the accuracy and acceptability of the mFR24 has not been compared with either the web-based self-administered ASA24 or Intake24 in the same study population.

To continue to improve upon dietary assessment, there is an urgent need for studies that enable the understanding and mitigation of measurement errors [29]. The error in dietary intake estimation can be identified by comparing reported intake with recovery biomarkers, such as doubly labeled water as a measure of true energy intake [30]. However, such methods are limited to energy or single nutrients and do not identify specific foods and beverages that are omitted or inaccurately reported. Controlled feeding studies allow for the examination of measurement errors at the level of foods and beverages. Studies with measures of known food and beverage intake enable the understanding of factors contributing to misreporting, such as omission of particular types of foods, intrusions, inaccurate portion size estimation, and incorrect food descriptions [31-35]. For example, Kirkpatrick et al [33] found that more intrusions (items not consumed) were present with the use of a web-based self-administered 24HR method than in an interviewer-administered 24HR method. Widaman et al [35] found no statistically significant differences between estimated and observed intake of grain foods using web-based self-administered 24HR methods, although all other food groups were overestimated. These findings illustrate how controlled feeding studies can provide insights into the mechanisms of dietary intake measurement errors that would otherwise remain unknown.

Various psychosocial factors have been associated with misreporting, including social desirability traits, restraint, disinhibition, fear of negative evaluation, and body weight and body image perceptions [36-38]. In a study conducted in the United States, measuring an array of psychosocial and demographic factors, Tooze et al [37] found that although these factors cumulatively accounted for 20% of the variability in misreporting in interviewer-administered 24HR methods, 80% remained unaccounted for. Clearly, other constructs associated with misreporting, psychosocial or otherwise, need to be identified, and it has been recommended that future research focuses on this [37,39]. For example, it is frequently stated that visual perception and conceptualization of memory are involved in reporting of intake [8], but these factors are not typically assessed in studies evaluating participant reporting accuracy. Furthermore, a better understanding of how psychosocial and cognitive factors map to various sources of error (eg, omissions and intrusion) could potentially help to minimize measurement error. To the best of our knowledge, no controlled feeding studies have evaluated the associations of psychosocial or cognitive factors in food and beverage reporting accuracy.

Social factors may also contribute to misreporting. Individual work patterns and lifestyles have rapidly changed with the increased use of screen-based work and leisure activities [40,41]. In a survey of over 12,000 households in Australia, 75% people reported that they always, often, or sometimes felt rushed or pressed for time [42]. With these rapid shifts in day-to-day life, the demands for traditional dietary assessment methods may be misaligned with people's daily lives and expectations and may be viewed as inconvenient. Technology-based self-report dietary assessment methods enable remote completion using laptops or mobile devices and have been indicated as more acceptable to participants than traditional face-to-face methods [43-45]. For example, research conducted in the United States demonstrated that 70% preferred the ASA24 over the AMPM [46]. The acceptability of dietary assessment methods has important implications, especially in large-scale population studies, as it can impact response rates and therefore the representativeness and generalizability of the study sample [47,48]. Image-assisted 24HR methods, such as the mFR24, are yet to be fully evaluated for consumer acceptability and comparison with other technology 24HR methods such as Intake24 and ASA24.

Objectives

This research protocol will compare 3 leading technology-assisted dietary assessment methods. Using a

controlled feeding study design with healthy adults aged 18 to 70 years, this study will (1) compare the accuracy, acceptability, and cost-effectiveness of 3 technology-assisted 24HR methods (ASA24, Intake24, and mFR24) relative to observed intake for 3 meals on 1 day; (2) test the accuracy of automated methods for determining food and beverage intake using food images and image analysis, computer vision, and machine learning techniques; and (3) assess associations between reporting errors and demographic, psychosocial, and cognitive factors.

Methods

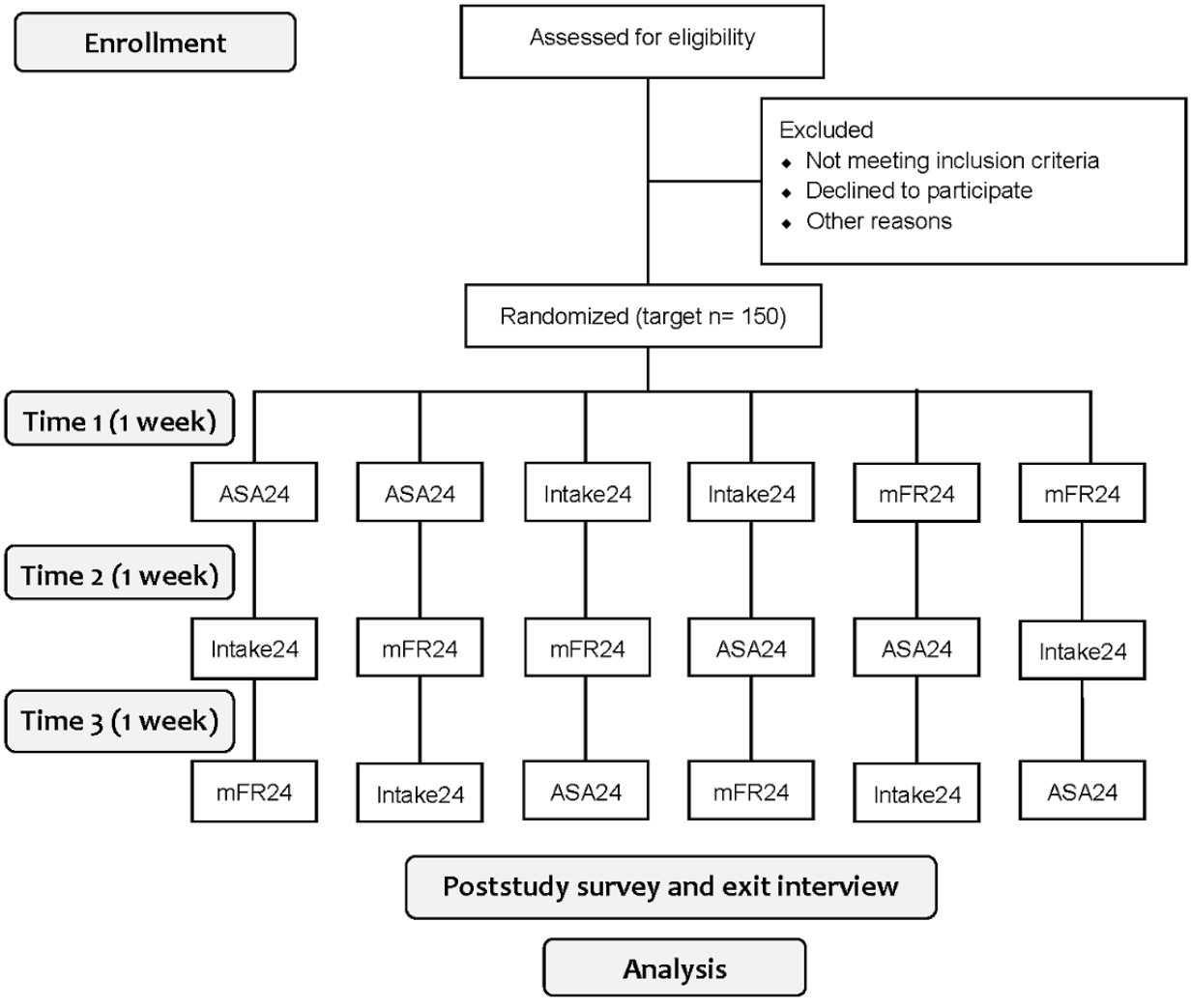
Sample and Recruitment

The sample will be selected from adults aged 18-70 years residing in Perth, the capital city of Western Australia, Australia, and recruited via the electoral roll by selecting postcodes that provide representation across socioeconomic status. Other recruitment methods will include advertising on the Curtin University website and a snowball methodology (eg, email newsletter and referrals from friends or colleagues). A final sample of 150 randomized participants (allowing for a 20% dropout) will allow for 90% power at a 5% significance level when the true difference between any 2 mean differences between estimated and observed dietary energy intake is 0. Quota sampling will be used to ensure that equal numbers of men and women are recruited. To be included in the study, participants must be able to attend in-person feeding sessions on 3 separate days and have access to a computer and a smartphone (running iPhone operating system or Android operating system) with a data plan. Exclusion criteria include serious illnesses or medical conditions, pregnancy, special dietary requirements, or dietary restrictions because of food allergies or intolerances or dieting to lose weight.

Study Design

A controlled feeding study with a crossover design will compare the accuracy of 3 technology-assisted methods of assessing 1 day of dietary intake: ASA24, Intake24, and mFR24. The sequence of the 3 dietary assessment periods will be randomized for each participant, with a 1-week washout period between each feeding session (Figure 1). Therefore, each participant will be exposed to each of the 3 methods at different periods. The crossover design, a repeated measurement design, will allow both between-group and within-group method comparisons. This design yields a more efficient comparison of treatments than a parallel design because fewer participants are required in the crossover design to attain the same level of statistical power or precision as a parallel design.

Figure 1. Accuracy, acceptability, and cost-effectiveness of technology-assisted dietary assessment study flowchart on enrollment, randomization, and study design. ASA24: Automated Self-Administered Dietary Assessment Tool; mFR24: Image-Assisted mobile Food Record 24-Hour Recall.



Ethics approval from the Curtin University Human Research Ethics Office has been obtained (approval number: HRE2019-0222). Reciprocal ethics approval from the Department of Health Western Australia Human Research Ethics Committee has also been obtained (approval number: 201909.06), and the trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000209897). All research design, practices, and reporting of studies conducted in Australia will be aligned with the Australian Code for the Responsible Conduct of Research. Participants will receive a maximum of Aus $60 (US $42) as a token of appreciation for their involvement in the study.

Research Study Database

A purpose-built research study database will be developed using a database platform (Microsoft Office Professional Plus 2016, Microsoft Pty. Ltd) to manage, contact, and track the progress of the study participants throughout the study. The database will send autogenerated emails containing study information and personalized links to remind participants of upcoming appointments and complete applicable surveys beforehand. Email and SMS text messaging prompts will be sent directly from the study database using *Email to SMS* technology. The study database will automatically update the participant status with respect to their study compliance. The system will prompt reminders via email and SMS text messaging for participants who have not yet completed their tasks.

Randomization

At the first face-to-face session, eligible participants will be randomized using a random number generator and stratified by gender. The order in which the participant completes the three 24HR methods will be randomly allocated to ensure no order effect. Allocation will be concealed using sealed opaque envelopes. A statistician, not involved in data collection, will generate the randomization sequence. This will ensure adequate allocation concealment from the research team involved in recruitment and data collection.

Procedures

Each participant will complete a web-based screening and provide informed consent. If eligible, they will be directed to complete web-based baseline demographic and psychosocial surveys (taking approximately 30 minutes) and cognitive tests (taking approximately 20 minutes) before attending 3 feeding days at the Curtin University School of Population Health food laboratory. Demographic characteristics, including age, gender, and highest education attainment will be recorded. Physical activity levels will be assessed using the International Physical Activity Questionnaire, short form 7-day self-administered format [49]. Table 1 presents a brief description of the questionnaires and the tests. Figure 2 shows a conceptual framework of the role of demographic, psychosocial, cognitive, and dietary factors in misreporting, synthesized from previous literature and adapted from existing frameworks [8,36,37,39,50-52].

Figure 2. Conceptual framework for assessment of factors that may be associated with 24-hour dietary recall reporting accuracy. 24HR: 24-hour dietary recall.

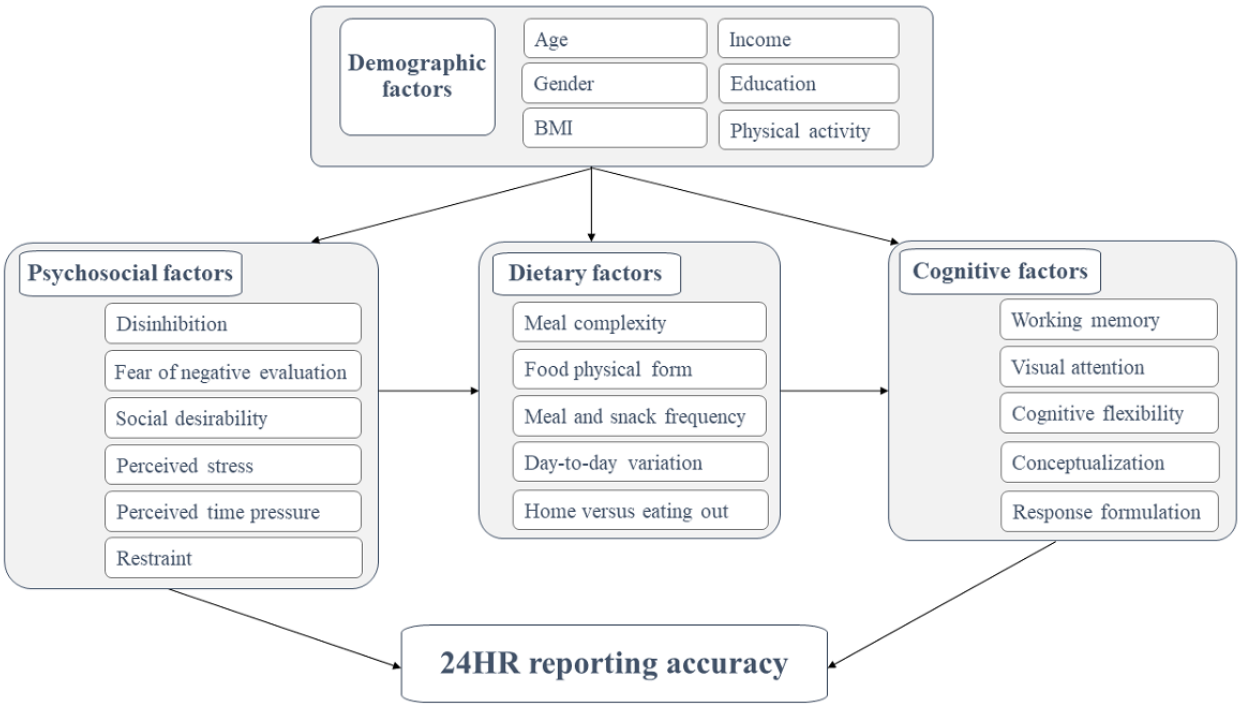


Table 1. Baseline study questionnaire and test descriptions in Accuracy and Cost-effectiveness in Technology-Assisted Dietary Assessment.

Questionnaires and tests	Description of content	Study
Demographic and personal characteristics	11 items: gender, age, educational level, employment, country of birth, ethnicity, smoking, alcohol use, and socioeconomic and financial status	__[a]
Physical activity	8 items: International Physical Activity Questionnaire (short form)	[49]
Psychosocial measures		
Three-factor eating	51 items measuring factors associated with eating behavior: cognitive restraint of eating, disinhibition, and hunger	[53,54]
Social desirability	13 items: true-false statements measuring social approval and acceptance	[55]
Fear of negative evaluation	12 items: 5-point scales to assess concern about being perceived unfavorably by others	[56]
Time pressure	7 items: assesses the competing perceived time pressure	[57]
Perceived Stress Scale	5 items: assesses perception of external environmental stressors; short version of the original Perceived Stress Scale-14	[58]
Weight loss history	2 items: assesses frequency and magnitude of previous weight loss.	[59]
Cognitive measures		
Visual digit span (forward and backward)	Assesses working memory by asking participants to recall spans of digits in 14 trials. Participants will see digit sequences on a computer or mobile phone screen and must recall them by selecting the recalled digits from a circle of digits with the mouse or their finger.	[60]
Vividness of visual imagery questionnaire	16 items: 5-point scale administered twice to assess conceptualization of visual memory. Participants imagine people and scenes and rate the vividness of these mental images (first with eyes open and then with eyes closed).	[61]
Trail making test	Assesses visual attention and task switching. Participants are asked to draw lines in specific, predetermined sequences from node to node on a screen as quickly and as accurately as possible.	[62]
Wisconsin card sorting test	Assesses cognitive flexibility and executive function. Participants are asked to sort cards into 4 different "categories." No instructions are given regarding the categorization rules. Participants are informed whether each selection was correct or incorrect. The cards to sort into these piles have similar designs and vary in color (4 variants), shape (4 variants), and number of shapes (4 variants). Categorization rules change midtask without warning.	[63]

[a]Question items devised by authors.

Feeding Days

The participants will attend the food laboratory on 3 separate days. On day 1, they will receive a brief introduction to the study (with the objective described as finding better ways to assess what people eat) and be randomized. They will have their height and weight measured using standard protocols [64]. At the food laboratory, participants will consume 3 meals ad libitum (breakfast, lunch, and dinner) on the same day and will leave the laboratory between meals. No restrictions will be placed on consuming food and beverages outside of the laboratory meals. The participants will select from a menu and will not have access to the weight of their food and beverage selections. Menu items will be selected based on a combination of the top 100 most commonly consumed meals and snacks in Australia (Australian Bureau of Statistics, personal communication, 2020).

Each participant will enter the food laboratory one at a time to consume their meal. In accordance with the COVID-19 protocols issued by the Western Australia Government Department of Health, participants will be separated by screens and physically distanced from each other, with a maximum of 8 participants at any one time. This may change if restrictions are eased. All food and beverage items will be inconspicuously weighed using Kelba KHX-3 bench scales (Kelba) with a 0.1-gram resolution in a separate laboratory space before being served on the participant tray. Before delivering the tray to each participant, the researcher will inconspicuously take an image of the tray using a researcher version of the mFR24 app that allows insertion of a unique user ID for each image. When finished eating, each participant's tray will be collected and an *after image* with the researcher mFR app will be taken. Plate waste will then be weighed to determine the amount of each item consumed. The amount consumed will be determined by subtracting the weight of the food plate waste from the weight of the served amount. Weighing will be conducted in duplicate, and a third measure will be taken if the first 2 measures differ by >0.5 grams. The average of the 2 closest measures will be recorded.

24-Hour Dietary Recall Interview Methods

Each day subsequent to the feeding day, the participants will complete a 24HR interview remotely, each time via a different technology-assisted dietary assessment method (ASA24, Intake24, or mFR24), the order of which will be randomized.

Automated Self-Administered Dietary Assessment Tool (2016)

Participants will be emailed a weblink and a username and password to access the ASA24 interface. A consortium of Australian Universities adapted the ASA24 by incorporating Australian food composition tables [65]. Participants will be

asked to (1) report everything they had to eat and drink the previous day from midnight to midnight by selecting an eating occasion and time, then searching for matching food and beverage items, and reviewing any gaps in consumption of more hours; the database contains >4800 foods and beverages from Australian food composition tables (AUSNUT 2011-2013); (2) provide additional details of each food and beverage item (eg, form, preparation method, additions, and amount consumed); food images in ASA24 will assist in portion size estimation; (3) review and edit all the foods and beverages they selected; (4) add any commonly forgotten foods and beverages that they consumed after being prompted and directed back to the food list; and (5) confirm that they have recorded all of the food and beverages from the previous day [13]. Participants can add food and beverages that are not in the database via a *missing foods* tool incorporated in a bespoke spelling correction system to address misspelled food names. In previous studies, participants completed the ASA24 in 17 to 34 minutes [66].

Intake24

Participants will be emailed a weblink to access the Intake24 interface. A short instructional video is provided for the participants to watch before commencing the 24HR interview. Participants will be asked to (1) key in all the foods and beverages consumed the previous day between waking up and going to sleep as free text; (2) select items from a database and match each item consumed; the database contains >2800 foods and beverages by incorporating Australian food composition tables (AUSNUT 2011-2013) [67]; participants will be able to add food and beverages not included in the database via a *missing foods* tool incorporated in a bespoke spelling correction system to address misspelled food names; participants can add their own personal recipes, sandwiches, and salads; (3) estimate the portion sizes of the items consumed using images and standard serving sizes; (4) review all the foods and beverages they have selected and edit if necessary; and (5) add any missing items associated with the foods they have already selected after being prompted to do so [12]. Previous studies indicate an average completion time of 20 minutes.

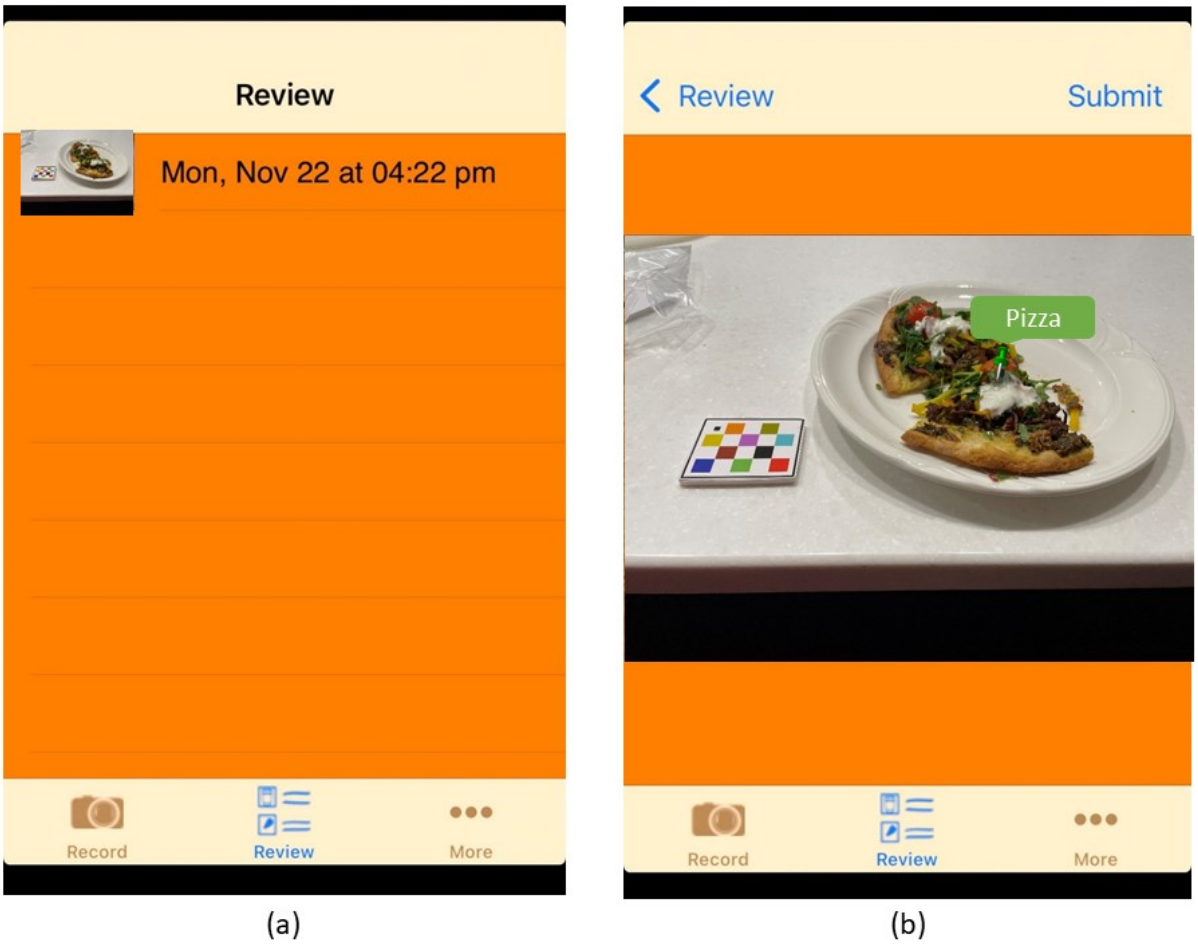
Image-Assisted Mobile Food Record 24-Hour Recall

Overview

The mFR24 app, an image-based dietary assessment system [20,22,23,68], will be adapted as an image-assisted 24HR method for this study. The system consists of a mobile food record app (mFR24), which runs on a mobile device (iPhone or Android smartphone) and a dedicated cloud-based server for the storage of images, metadata, and food image processing and analysis. Using the mFR24, participants will take pictures of their food and beverages before and after eating. The images will be automatically uploaded to the cloud-based server via Wi-Fi or the 4G or 5G network. The content of the images will then be confirmed by the participant in a process known as user confirmation. A researcher version and a participant version of the app will be used in this study. The researcher version will be installed on various devices and used to take before and after images of each participant tray. These images will be uploaded to a researcher folder on the server. The participant version of the app will include additional features.

When allocated to the mFR24, the participants will install the mFR24 (participant version) on their smartphones and be shown how to use the mFR24 app on the feeding day by a research assistant. They will be instructed to take a *before* and *after* image of all meals, beverages, and snacks consumed from the first meal served at the study center until midnight and include a fiducial marker (a colorful checked object of known size, color, and shape that assists in food and beverage recognition and quantification) in each image. mFR24 has an automated feature to detect the presence of the fiducial marker and alert participants if the fiducial marker is missing from the image. An angle-detection algorithm assists participants in taking the image at the correct angle (between 45° and 60° from the horizontal plane). Once captured and confirmed by the participant, the images will no longer be accessible to the participant until the user confirmation step (Figure 3). At the dinner session, participants will receive training on how to label their images for user confirmation the following day.

Figure 3. Screenshots of the mFR24 application interface showing the steps in the review process and viewing an eating occasion. (a) image list with time and date stamp displayed (b) viewing a labeled eating occasion with colored pins and labels identifying the food and beverages. The image also shows the inclusion of the fiducial marker.



User Confirmation

The mFR24 app includes a feature known as the *user confirmation step*, where once midnight has lapsed, the images are returned to the participant for labeling with food and beverage names. On the day following the feeding day, participants will select and label each image from the review function in the mFR24 app (Figure 3). To label a food or beverage, the participant will tap on the item, and a pin will appear with *tap to edit*. Tapping the pin again will take the participant to the food list *search function*. When the participant starts typing the word, a list of foods will appear where they can select from the list. The food list consists of 372 food and beverage items. The food list has been adapted so that a *mini label* and *short description* are displayed to the participant. These labels link to a food composition database (not visible to the participant) with the food code, detailed description, and energy and nutrient composition (AUSNUT 2011-2013 nutrient database). If the participant cannot locate their food item in the list, typing *food not listed* will allow a free text entry. Once confirmed, the image with the confirmed pins is automatically sent to the server and disappears from the app. Participants will be asked to complete this task before the mFR24 interview. Researchers will be able to view the participant's annotated images on a secure server.

mFR24 Interview

A trained researcher will conduct a 24HR interview following an adapted multiple-pass approach [69] outlined in Table 2. This 24HR process will enable the estimation of the total intake of food and beverages consumed during a 24-hour period. The recall process will be assisted by the labeled food and beverage images taken by the participant using the mFR24 app. The interview will be conducted via a video call on the day following the controlled feeding day. The interview structure is based on the AMPM developed by the United States Department of Agriculture [10]. Briefly, the original 5 steps include the collection of a quick list of foods and beverages consumed, a check for commonly forgotten foods, time and occasion, details and review, and a final probe. In the adapted version used in this study, the quick list and time pass will be completed by researchers before the interview using the participant labeled images, which will be viewed on a secure server.

Table 2. Adaptations of the United States Department of Agriculture Automated Multiple-Pass Method in the interview structure for the Image-Assisted mobile Food Record 24-Hour Recall interview.

Automated Multiple-Pass Method steps	Aim	Image-Assisted mobile Food Record 24-Hour Recall steps	
		When image is taken	When image is not taken
Step 1: quick list	The purpose of the quick list pass is to obtain a quick report of foods and beverages consumed in the past 24 hours without interrupting the respondent and to introduce the respondent to the concept of 24-hour recall.	Taken from the mini label and image provided by the participant; participant is asked to list any foods and beverages consumed that are not shown in images.	Participant is asked to list all foods and beverages consumed that are not shown in images.
Step 2: forgotten foods list and additions	The forgotten foods list prompts the respondent's memory and collects other foods or beverages that are not reported in the quick list.	Participants are asked if they consumed items from a list of commonly forgotten foods.	Participants are asked if they consumed items from a list of commonly forgotten foods.
Step 3: time and occasion	The time and occasion of food or beverages consumed are recorded.	This does not require a separate pass. Time of eating is taken from the image metadata.	Ask participant to recall time and occasion of forgotten foods when item is reported.
Step 4: detail cycle	The aim of this step is to collect specific descriptive information about each food item and beverage reported and record quantities and any additions made to the food.	Clarify only nonidentifiable food and beverage items; follow the Australian Health Survey food model booklet to confirm amounts consumed; and check the after image for leftovers.	Use food-specific probes to obtain details; follow the Australian Health Survey food model booklet to confirm amounts consumed; and probe leftovers.
Step 5: final probe	This is the last opportunity for the respondent to remember any new foods and beverages.	Read out the list of food and beverage items.	Read out the list of food and beverage items.

The video call interview will consist of a quick list of any foods or beverages for which an image was not taken, a probe for commonly forgotten foods, a detail cycle, and a final probe. The researcher will use a screen-sharing function to enable both the researcher and participant to view each image simultaneously. During the detail cycle, participants will be asked to provide food and beverage details when these are unclear from the images. The participants will also be asked to describe the amount of each item consumed, using the standard food model booklet used in the Australian Health Survey [70]. Household measures such as metric teaspoons or pieces will also be used to describe amounts not available in the booklet and may, in some instances, be the preferred method of portion size description by the participants. During the final probe, the researcher will confirm all foods and beverages, descriptions, and portion sizes reported by the participant. The researcher conducting the 24HR interviews will not have access to the observed intake data and will not be present on the feeding day. Following the interview, data will be entered into a nutrition analysis software (FoodWorks 10, Xyris Software) linked to the AUSNUT 2011-2013 nutrient database to estimate food, energy, and nutrient intake for the 24-hour recall period.

Automated Image Analysis

Automated methods using computer vision and machine learning (eg, deep learning) techniques will also be undertaken [21-23] using the images collected with the mFR24. The study will test the accuracy of automated methods using computer vision and machine learning techniques to estimate true intake. These methods include food identification [71], food segmentation [72], and volume estimation (for food portion size estimation) [73]. In recent years, there has been rapid proliferation in the use of artificial intelligence and machine learning techniques in image analysis, particularly the use of deep learning methods based on neural networks [74]. The authors (EJD and FZ) from Purdue University have recently developed several deep neural network approaches for food image analysis and will modify these methods for use in this study. This will include generating ground truth images to train the deep neural networks using a series of standard images of the food and beverage items to be served at each meal with known food weights. As deep learning methods require a large amount of training data, we will investigate the use of data augmentation methods, particularly using generative adversarial networks [75], to aid in training. Trained models will then be used to recognize the food types, estimate the food portions, and compare the automated methods with the true intake. Standard metrics of precision and recall will be used in the computer vision and machine learning fields to determine the performance of the automated techniques.

Poststudy Acceptability Questionnaire

The participant's perceptions of the acceptability of the 24HR method will be asked at the end of the study via a web-based survey using both open and closed questions. Their perceptions of each method will be asked about one at a time in a randomized order. Participants will be asked what device they used to complete each method and then be asked questions using a 5-point Likert scale to rate their agreement with statements including how easy it was to find and remember foods and remember amounts and whether they would be willing to use the method again. Open-ended questions will explore the participant's likes and dislikes about each method. Finally, participants will be asked which of the methods, if any, they preferred and why.

Exit Interviews

A qualitative methodological approach using in-depth interviews and reflexive thematic analysis [76] will explore and describe perceptions and beliefs regarding each of the dietary assessment methods. Approximately 10% (20/150) of the recruited sample (participants stratified by age and gender) will be invited to participate in a semistructured in-depth interview. The script will include questions regarding what would motivate participants to take part in studies assessing dietary intake, barriers and enablers to participation, retention, and most-favored incentives to diet research participation (eg, dietary feedback and financial incentives). Questions will also be asked about the acceptability of the mFR24 method and features (eg, labeling of images). Interviews will be audio-recorded, transcribed verbatim, and reviewed for accuracy by the participant and researcher before analysis. Transcripts will be managed using transcription software (NVivo 12.6, QSR International). Sampling and analysis will continue until pragmatic saturation is reached [76].

Cost and Cost-effectiveness of Measures

Both financial and time costs for participants to use each of the methods will be assessed. The time spent by researchers and participants in the administration of each 24HR method will be recorded for each participant. This includes time spent training individuals to take the mFR24 images, time spent completing the 24HR interview, and any time spent supporting individuals to complete their 24HR interviews. The time spent by researchers coding the mFR24 data will also be recorded. Both ASA24 and Intake24 have the capability to collect time stamp data to identify how much time the participants spend inputting data. All other time data, including time spent cleaning the data, will be manually collected by researchers.

Financial costs, such as server space for digital data storage, will be recorded. After converting the time data to a financial cost, the total cost data will be considered in parallel with the measures of accuracy derived for the 3 methods. The primary accuracy measure for cost-effectiveness is the absolute percentage error in energy intake. Comparing costs with accuracy will identify whether any of the 3 methods are dominated by another (ie, is more expensive and less accurate). If not, the cost per person to reduce absolute misreporting by 1% point will be estimated.

Data Analyses

Energy Intake Estimation Accuracy

The participant feeding days with at least two meals eaten at the food laboratory will be included in the analyses. Daily energy intake from each 24HR method and the controlled feeding sessions will be calculated, excluding any items reportedly consumed outside of the food laboratory. Outlier checks will be conducted to identify any obvious keying errors or food composition data anomalies, which will be corrected before proceeding. Bland-Altman plots will be used to test for agreement between the 24HR values and controlled feeding measures at the individual and group levels. Repeated measurements will be analyzed using the linear mixed models procedure using SPSS version 25, accounting for age, gender, and BMI, with 24HR method and method order as fixed effects, to assess whether there are statistically significant differences by 24HR method. Misreporting will be assessed by examining the ratio of reported 24HR intake to observed intake, with the lowest tertile considered to indicate underreporting. The proportion of underreporters in each 24HR method will be compared using chi-square tests and logistic regression. Among underreporters, the total energy misestimation will also be compared using regression models adjusted for age, gender, and BMI.

Food Groups and Misreporting

Foods and beverages consumed during the controlled feeding sessions will be matched to the food codes from Australian food composition tables (AUSNUT 2011-2013) using a nutrition analysis software (FoodWorks 10, Xyris Software). The measured quantities of the foods and drinks consumed in the food laboratory will be coded. The observed intake of the provided food groups will be calculated. In ASA24, Intake24, and mFR24 data sets, foods and drinks that were reportedly consumed outside of the food laboratory (eg, snacks) will be removed before analysis based on the reported eating occasions and time.

The 24HR data on food and beverage intake from each method will be compared with the observed weight and daily intake of food and beverages to identify 4 types of misreporting, that is, omissions, intrusions, misclassifications, and portion misestimations. The following 5 steps will be used:

1. Matches between reported and observed intake will be identified by comparing the assigned food codes. Food codes correspond to a food grouping hierarchy in which the first 2 digits indicate the major food groups (eg, dairy, meat, and vegetables), the first 3 digits indicate the submajor food groups (eg, milk products and dishes), and the first 5 digits indicate the minor food groups (eg, dairy milk, yogurt, and cheese) [77]. Food codes of reported and observed intake data will be considered an exact match if they belong to the same minor food group. Foods codes from the same submajor food group will be considered a close match, whereas foods from the same major food group will be considered a far match.
2. Omissions, which are items that were consumed but are not reported, will be identified, and omission rates at each food group level will be calculated using the formula:
   sum of omissions / (sum of omissions + sum of all matches) × 100%.
   Omission rates of mixed meals, single items, and condiments will be calculated. Differences in omission rates by 24HR method will be assessed using chi-square tests.
3. The proportion of misclassifications, which are incorrect descriptions of consumed items, will be defined as close or far matches. Differences in the proportion of misclassifications within food groups by the 24HR method will be assessed using chi-square tests.
4. Intrusions, which are items that are reported but were not consumed, will be identified, counted by food group, and expressed in kilojoules.

5. Misestimation of portion size will be assessed by comparing the intake of food item matches in grams for each 24HR method with observed intake using a paired samples statistical test.

Correlates of Energy Misestimation

Psychosocial, demographic, and cognitive factors associated with omission and intrusion rates and with energy misestimation on each 24HR method will be evaluated using chi-square tests and multivariate logistic regression. The effects of factors will be reported as odds ratios and associated 95% CIs. Some dietary factors in the Accuracy and Cost-effectiveness of Technology-Assisted Dietary Assessment study are standardized because of the controlled feeding methodology (meal frequency and eating location), but it is hypothesized that food and meal complexity and physical form will affect reporting accuracy via an interaction with cognitive factors. P<.05 will be considered statistically significant in all analyses.

Acceptability

Differences in acceptability among methods indicated by the rating and proportions of participants agreeing with each of the ease-of-use statements will be assessed using chi-square tests. Demographic correlates of a preference for a particular method will be explored using multivariable logistic regression, adjusting for method order.

Cost-effectiveness

Both participant and researcher time costs will be multiplied by standard staff costs (including on-costs) to estimate the financial cost of using each method on a per-person basis. Differences in time cost and total financial cost will be compared across methods using a repeated measures analysis of variance test. P<.05 will be considered statistically significant. If statistically significant differences exist, differences in cost-effectiveness will be assessed using the same procedure. Cost-effectiveness will be defined as the cost per person to reduce the absolute misestimation of energy intake by 1% point.

Results

Participant recruitment commenced in March 2021 and will end in December 2021. Ethics approval for this study was granted by the Institutional Review Board in April 2019. Participant recruitment commenced in March 2021. As of August 2021, 68 participants had enrolled in the study. Data collection will conclude at the end of December 2021. Data analysis will commence in 2022, and results are expected to be published in late 2022.

Discussion

Overview

This study will provide outcome results in 3 main areas. It will evaluate (1) the accuracy, user acceptability, and administration cost of 3 technology-assisted dietary assessment tools, which have never been compared in a single study; (2) the accuracy of novel automated image analysis technology; and (3) the association of reporting accuracy of participants with a range of cognitive and psychosocial factors.

The results of this research will provide additional information on the feasibility, accuracy, and cost to aid the selection and further development of 3 technology-assisted 24-hour recall methods for application in large-scale dietary assessment. The use of a controlled feeding study design for comparing multiple technology-based dietary assessment methods is novel and will allow comparison among methods relative to observed intake. The results will also elucidate the correlates of dietary intake misreporting, which will be useful in developing error mitigation strategies.

Comparison With Previous Work

Measuring the cost of the 3 technology-assisted dietary assessment methods is a unique feature of this study. The costs of interviewer-administered pen and paper–based 24HR in 2013 ranged from US $178 per participant in South Asia to US $774 per participant in the Middle East and North Africa [78]. However, there is little published information on the operational costs of technology-assisted dietary assessment [79], although researchers have noted that staff costs persist despite substantial savings on data collection and entry [80]. Quantifying and comparing the costs of technology-assisted dietary assessment will provide essential information to aid decisions in planning population surveillance and large-scale epidemiological studies that aim to enroll thousands of individuals.

Elucidating the correlates of and developing methods for addressing misreporting in dietary data collection and analyses is relevant to the global research community involved in studies that assess dietary intake. It has been claimed that the measurement errors in dietary assessment are so great that the data hold no value [81,82]. A comprehensive refutation of this assertion argued that besides further developing and evaluating assessment methods, studies should be conducted to understand and manage measurement errors [29].

To date, studies evaluating the role of psychosocial factors in dietary reporting accuracy have focused on dietary energy misestimation, with energy expenditure as a reference measure [37,51,83-86]. Studies with measures of known food and beverage intake aid the understanding of how misreporting occurs, that is, the distributions of omissions, intrusions, incorrect portion sizes, and incorrect food descriptions [87-89]. However, to our knowledge, no such study has measured psychosocial and cognitive factors, and thus the associations with various food and beverage error types; this study aims to address this gap.

Strengths and Limitations

This study has several strengths and limitations. A strength of this study is the collection of observed food and beverage intake using a controlled feeding study design. Many criterion validation studies use biomarkers of energy expenditure, which indicate the magnitude of misreporting, but do not help to understand differential misreporting of food and beverage items nor the underlying mechanisms. For example, certain food types may be more frequently omitted from reporting, or certain food portion sizes may be frequently misestimated. Another strength

is the crossover design of the study, which allows for between- and within-group comparisons. Few studies have compared 24-hour recall methods with reference methods using a within-group comparison, and those studies did not use technology-based methods [90,91]. Studies assessing multiple technology-based 24HR methods have included different participants completing each method [33,46]. In such studies, between-person differences in dietary intake and recall biases may have contributed to the observed differences. The within-group comparison of the 3 dietary assessment methods in our study will enable a comparison not subject to confounding by between-person variation. This is an important strength of this study, as it will also allow the evaluation of consumer acceptability of these methods. The uniqueness of this study is the evaluation of the cost-effectiveness of the 24HR methods. This will provide valuable data for policy makers and researchers planning large-scale surveys.

A limitation of this protocol study is that the limited number of foods offered may facilitate a better chance of a match between reported and observed intakes than if the study was conducted in a free feeding environment. Another limitation of this study is the self-selecting sample, meaning that the findings may not be fully generalizable to the wider population, as study participants who volunteered may be more motivated to complete dietary assessment methods because of their own interest in dietary intake. Recruitment through the electoral roll is an important aspect of the study design that facilitates a wide and diverse recruitment. In addition, randomization by gender aims to recruit equal proportions of men and women across the groups so that gender differences can be assessed.

Conclusions

The 24HR dietary assessment is a widely used method for population-wide nutrition surveillance and epidemiology globally [92]. By assessing the accuracy of dietary intakes, acceptability, and cost-effectiveness, this study will comprehensively evaluate 3 technology-assisted dietary assessment methods, which are administered remotely. The study will also determine if such methods can provide a cost-effective, efficient, and timely approach to large-scale data collection, which may translate to lower costs and improvements in scale, frequency of dietary intake surveillance, and better precision regarding food consumption.

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Authors' Contributions

DAK, CJB, CEC, BM, MER, SSD, RN, EJD, FZ, SIK, PA, and CMP conceived the research question and overall design of the study. DAK, CJB, CEC, MER, TAM, JDH, CW, JLW, and CRG planned and compiled measurement tools and protocols. BM provided expertise on psychosocial and cognitive measures. RN provided expertise on cost and cost-effectiveness measures. DAK, JDH, SSD, SAM, and CW planned the data management and analysis. The paper was drafted by CW. The paper was revised for intellectual content by all authors who approved the final content of the paper.

Conflicts of Interest

None declared.

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Abbreviations

24HR: 24-hour dietary recall
AMPM: Automated Multiple-Pass Method
ASA24: Automated Self-Administered Dietary Assessment Tool
mFR24: Image-Assisted mobile Food Record 24-Hour Recall

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Protocol

Exploring the Effects of In-App Components on Engagement With a Symptom-Tracking Platform Among Participants With Major Depressive Disorder (RADAR-Engage): Protocol for a 2-Armed Randomized Controlled Trial

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Abstract

Background: Multi-parametric remote measurement technologies (RMTs) comprise smartphone apps and wearable devices for both active and passive symptom tracking. They hold potential for understanding current depression status and predicting future depression status. However, the promise of using RMTs for relapse prediction is heavily dependent on user engagement, which is defined as both a behavioral and experiential construct. A better understanding of how to promote engagement in RMT research through various in-app components will aid in providing scalable solutions for future remote research, higher quality results, and applications for implementation in clinical practice.

Objective: The aim of this study is to provide the rationale and protocol for a 2-armed randomized controlled trial to investigate the effect of insightful notifications, progress visualization, and researcher contact details on behavioral and experiential engagement with a multi-parametric mobile health data collection platform, Remote Assessment of Disease and Relapse (RADAR)–base.

Methods: We aim to recruit 140 participants upon completion of their participation in the RADAR Major Depressive Disorder study in the London site. Data will be collected using 3 weekly tasks through an active smartphone app, a passive (background) data collection app, and a Fitbit device. Participants will be randomly allocated at a 1:1 ratio to receive either an adapted version of the active app that incorporates insightful notifications, progress visualization, and access to researcher contact details or the active app as usual. Statistical tests will be used to assess the hypotheses that participants using the adapted app will complete a higher percentage of weekly tasks (behavioral engagement: primary outcome) and score higher on self-awareness measures (experiential engagement).

Results: Recruitment commenced in April 2021. Data collection was completed in September 2021. The results of this study will be communicated via publication in 2022.

Conclusions: This study aims to understand how best to promote engagement with RMTs in depression research. The findings will help determine the most effective techniques for implementation in both future rounds of the RADAR Major Depressive Disorder study and, in the long term, clinical practice.

Trial Registration: ClinicalTrials.gov NCT04972474; http://clinicaltrials.gov/ct2/show/NCT04972474

International Registered Report Identifier (IRRID): DERR1-10.2196/32653

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KEYWORDS

app; engagement; major depressive disorder; remote measurement technologies; research; mobile phone

Introduction

Background

The last decade has seen a significant increase in the use of mobile technology in health care (mobile health [mHealth]) research and clinical practice [1]. One such application of mHealth is the use of remote measurement technologies (RMTs), which provide real-time, longitudinal health tracking using a combination of smartphone apps for active symptom reporting tasks (active RMT [aRMT]) and mobile or wearable sensors for passive data collection (passive RMT [pRMT]) [2]. Multi-parametric RMT data have the potential to inform about current clinical state by reflecting patients' daily experiences in situ. They may also offer predictions by detecting subtle shifts in physiological, behavioral, or environmental variables that occur before a change in clinical state [3,4].

RMTs may be particularly relevant in recurrent conditions. Major depressive disorder (MDD) is a mental health disorder characterized by persistent low mood and anhedonia, often following a trajectory of remission and relapse over time [5]. The economic burden of MDD is currently estimated at US $326 billion [6], with increased risks of comorbidities and health care use associated with high relapse rates [7]. RMTs can collect information about a wide range of factors associated with MDD (mood variability, sociability, activity, cognition, and sleep) [2]. Raw, passive sensor data can be translated into low-level features, higher-level behavioral markers, and ultimately clinical state [8]. Previous work has found ambulatory self-reporting of mood symptoms [9] and multi-parametric RMT measures of location, device use, and sleep across a 30-day period [10] to be clinically valid assessments of individual depression trajectories.

The benefits of using RMTs for MDD symptom tracking are 2-fold. First, given the suggested biases [11] toward mood-congruent information in symptom reporting in depression, such data present a more accurate picture of symptom variability. Second, continuous monitoring of symptom recurrence could provide the temporal resolution needed to detect indicators of future depressive episodes [4]. Therefore, the use of RMTs in MDD could hold great potential for understanding current and predicting future depressive states.

Remote Assessment of Disease and Relapse in MDD

Remote Assessment of Disease and Relapse in MDD (RADAR-MDD) is a longitudinal, multi-site, prospective cohort study that is investigating the feasibility and predictive validity of RMT data in identifying predictors of MDD relapse [2]. It is part of the wider RADAR-CNS program [12] and uses the open-source mHealth platform, RADAR-base [13], to collect aRMT data (fortnightly tracking of mood, self-esteem, and speech using an active smartphone app), pRMT data (GPS, Bluetooth interactions, and ambient noise and light using a passive smartphone app and heart rate and step count from a wrist-worn wearable), and 3-monthly outcome assessments (web-based) in participants with MDD. The core research team provided the initial enrollment session and support throughout the 2-year remote follow-up period. Data were collected from 623 participants across the London, Amsterdam, and Barcelona sites, and the study was concluded in April 2021. The results will explore whether multi-parametric RMTs can feasibly provide clinically relevant information and, if so, pave the way for translation of the platform into routine clinical practice and self-management of MDD.

Engagement With RMTs in Research

The promise of research such as RADAR-MDD depends heavily on user engagement. Engagement with mHealth technologies can be defined as (1) a behavioral construct measured by objective completion statistics and (2) an experiential construct measured by focused attention and interest when interacting with the technology [14]. Qualitative studies suggest that service users endorse the use of RMTs in mental health care [15,16]. Successful recruitment into the RADAR-MDD study also suggests widespread interest in using remote symptom tracking for research [17]. However, past studies have reported varying rates of behavioral engagement during follow-up. Studies using app-based symptom tracking in cohorts with depression have reported low rates of data completion [18,19]. A wider review of RMT for health management found large variations in aRMT and pRMT use times [20]. Preliminary data from RADAR-MDD indicate that participants completed a median of 21 (IQR 9-31) out of a possible 52 aRMT questionnaires, and 52.3% (326/623) provided wearable data for over 75% of the participating days [21]. Iterative work on the RADAR-base platform has also addressed the challenges of deciphering between low user engagement and technical issues with the technology [22].

Behavioral engagement with RMTs in research is vital in reducing data missingness and bias and enhancing quality [23,24]. However, an understanding of experiential engagement with RMTs and the act of symptom tracking itself could prove of equal benefit for data completeness and long-term adherence. In a study using multi-parametric RMTs in bipolar disorder, experiential engagement measures (self-awareness of emotional

health and learning about symptoms) positively correlated with increased behavioral engagement with symptom tracking using a smartphone app and Fitbit [25]. A holistic approach to measuring engagement is necessary for understanding the current lack of and promoting future engagement with RMT studies.

Several methods are available to promote engagement within the RMTs themselves. In addition to the presence of a contactable research team, which has been previously associated with increased engagement [17,24], in-app components work remotely within the technology. Push notifications are prompts that appear on the smartphone screen and can vary according to content and timing [26]. Following the Fogg behavioral model [27], notifications provide a trigger to perform a behavior, such as completing tasks on a manual food logging app [28]. Adding theoretically informed notification content, such as insights or tips for using self-monitoring, can further motivate the completion of mood scales [29]. The effects of notification frequency on engagement show mixed results [26,30,31]. Data visualization is a common technique used in mood monitoring apps [32]. Visually displaying data completion allows users to revisit progress and may prompt the *action* of continued data input [33]. This might be especially effective given that anticipatory pleasure is thought to predict motivation for reward in individuals with depression [34]. It is unclear which combination of in-app features can promote behavioral and experiential engagement with a multi-parametric symptom-tracking app in depression. Findings in this field would provide scalable solutions for engagement in RMT studies, higher quality results, and applications for implementation in clinical practice.

Study Aims and Objectives

This study aims to test the effect of in-app components in a multi-parametric RMT platform on engagement with active and passive symptom tracking in MDD. A 2-armed randomized controlled trial will be used to compare the RADAR-base active app with an adapted app with insightful notifications and progress visualization aimed at promoting behavioral and experiential engagement. Engagement will be measured as provision of symptom tracking data collected through RMT over the 12-week study period and the degree to which participants feel experientially engaged with symptom tracking via the platform. It is hypothesized that participants using the adapted app will be better engaged in monitoring their symptoms, as measured by both behavioral engagement (completion of mood questionnaires) and experiential engagement (measures of attention, aesthetic appeal, and self-awareness). Process evaluation measures will also reveal participant experience with the engagement strategies used.

Methods

Ethics Committee Approval

This study was approved by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee at King's College London (reference number: RESCM-20/21-21083) and registered as a clinical trial (reference number: NCT04972474).

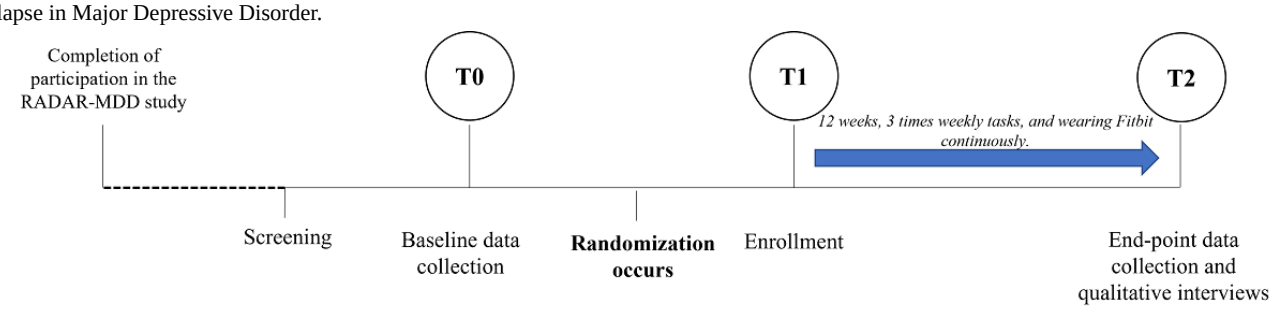
Study Design

This study is a 12-week, 2-arm randomized controlled trial with 1:1 randomization. A summary of the study design is presented in Figure 1. A 12-week period was chosen to align with the original structure of the RADAR-MDD study [2]. Participants will be recruited from RADAR-MDD, will provide baseline data (T0), and will be randomized at enrollment (T1) to 1 of 2 arms: an adapted app that includes insightful notifications and progress visualization (active arm) or active app as usual (control arm). Both the control and active arms will be delivered through the RADAR-base active app, which collects data in combination with a passive data collection app and a Fitbit Charge device [13]. In both arms, participants will be asked to complete 3 tasks each week via the app and wear the Fitbit device throughout the study. The primary outcome is the percentage of weekly tasks completed over 12 weeks of follow-up.

Upon completion of the study, 20 participants (n=10 from each arm) will also be randomly invited to complete a qualitative interview about their experience of participating.

The study will be conducted using a combination of the RADAR-base platform, including the management portal web application [13] and REDCap (Research Electronic Data Capture) [35]. Owing to the COVID-19 pandemic, participation will be fully remote.

Figure 1. Study design from screening to follow-up end point, including time points 0, 1, and 2. RADAR-MDD: Remote Assessment of Disease and Relapse in Major Depressive Disorder.



Eligibility Criteria

Inclusion Criteria

Participants will be included if they (1) participated in RADAR-MDD and gave consent for future research contact, (2) experienced at least one episode of MDD in the 2 years preceding RADAR-MDD enrollment, (3) are willing and able to continue to use an Android smartphone and Fitbit Charge device for a 12-week period (both provided for use in RADAR-MDD), and (4) feel comfortable completing an enrollment session remotely either via email instructions or video calls.

Exclusion Criteria

Participants will be excluded if they have been diagnosed with a comorbid psychiatric disorder since their enrollment into RADAR-MDD: bipolar disorder, schizophrenia, psychosis, schizoaffective disorder, or dementia. This will be checked with the participant via email during the recruitment process.

Recruitment

Participants will be recruited through the RADAR-MDD database of the London site. Contact details will be extracted from the RADAR-MDD REDCap system for those who have provided consent to be contacted for future research. This will include any participant who enrolled in the study during the 31 months of recruitment (November 2017 to June 2020; n=345).

Participants will be invited to participate via an email that will explain the study and provide the participant information sheet. Interested participants will respond via email. They will then be asked the eligibility questions via email. If eligible, participant details will be entered into the study REDCap system, which will initiate the sending of a personalized link to the web-based consent form and baseline questionnaires (T0). Once these have been completed, the participant will receive a second link to a web-based booking system, where they can book a time slot for an enrollment session. Enrollments will be conducted between April and May 2021. On the day of enrollment, participants will receive an email (or a video call, depending on their preference) outlining instructions for downloading the study apps and unique QR codes to register them to the platform (T1).

Interventions

Overview

Upon enrollment into the study, participants will be asked to complete 3 tasks per week via the active app, allow the passive app to run in the background on their smartphones, and wear the Fitbit device as much as possible. The active app tasks are as follows: (1) Patient Health Questionnaire-8 (PHQ-8) [36], an 8-item questionnaire assessing the variability of depressive symptoms over the last week; (2) Rosenberg Self-Esteem Scale [37], a 10-item questionnaire assessing variations in self-esteem; and (3) a speech task, during which the participant records themselves reading aloud a short paragraph.

In both arms, the weekly questionnaire tasks, the passive app, and the Fitbit device remain the same. The study is designed such that the enrollment process is identical for both arms to ensure that participants do not prime to the study arm that they are assigned and that both arms are comparable with RADAR-MDD.

Control Condition

Participants in the control arm will receive one notification at the 9 AM, 10 AM, and 11:30 AM time points on the day that a questionnaire task is due, which reads “Questionnaire Time. Won’t usually take longer than 3 minutes.” They will not be able to view any data aside from that through the Fitbit app.

Active Condition

Development of the Adapted App

The design of RADAR-MDD, including the active app, was heavily informed by service user involvement [38]. This study used behavior change theory and further patient public involvement work to inform its design.

To establish how best to promote the behavior of symptom tracking, it is useful to draw on theories and models of behavior change. The Behavior Change Wheel [39] presents a framework for the development of strategies to promote a target behavior. Previous work was used to identify key health-, user-, and technology-related barriers to engaging with symptom tracking in MDD [15,20,38] (Figure 2). Following the COM-B model, *psychological capabilities*, such as lack of symptom insight and perceived utility of the research, *automatic motivations* related to motivational difficulties and low mood, and *physical opportunities*, such as inability to answer questionnaires at a specific time and unsure if the data have been logged, presented the most pertinent barriers. Following the Behavior Change Wheel, suitable intervention functions thus included education, incentivization, and enablement [39]. Therefore, it was decided that an engaging app should include reminder notifications with information on the potential impacts of symptom tracking from a credible source. It should also include incentivizing feedback on behavior in the form of data visualization. Finally, users should be provided with researcher contact details to report technical issues or receive support.

The progress visualization component was further informed by service user involvement [40] (Figure 2). Simple, clear graphical representations of data were preferred, presented on a white background with colored data points. Users expressed an interest in positive reinforcement based on reaching achievements, for example, step count goals or simply the entering of data, coupled with a visual representation of completion, for example, a change in color. They also requested the choice to view or hide visualizations. Therefore, the visualization component was designed to comprise a separate section of the app that users can choose to view with a simple, colored graph showing completion or noncompletion at each weekly time point. Completion is denoted by a green dot and noncompletion, by a red dot.

Figure 2. Service user involvement in the design of the adapted app. RMT: remote measurement technology.

Barriers to RMT use	Facilitators of RMT use
Lack of motivation (health-related)	**Perceived utility, for example, raising awareness, sense of control, and thinking more positively (user-related)**
Poor insight into health status (health-related)	**Perceived success of the research (user-related)**
Perceived costs, for example, increased anxiety, time, and effort (user-related)	Ability to visualize data (tech-related)
Notifications at inconvenient timings, incompatibility with daily routine (tech-related)	**Clarity of information (tech-related)**
Irrelevant questions or symptoms tracked (user-related)	**Presence of notifications (tech-related)**
Technical malfunctions (tech-related)	**Availability of practical support (tech-related)**
	Motivational feedback, for example, virtual rewards, motivational texts, and learning about real-time activity (tech-related)

Data visualization preferences:

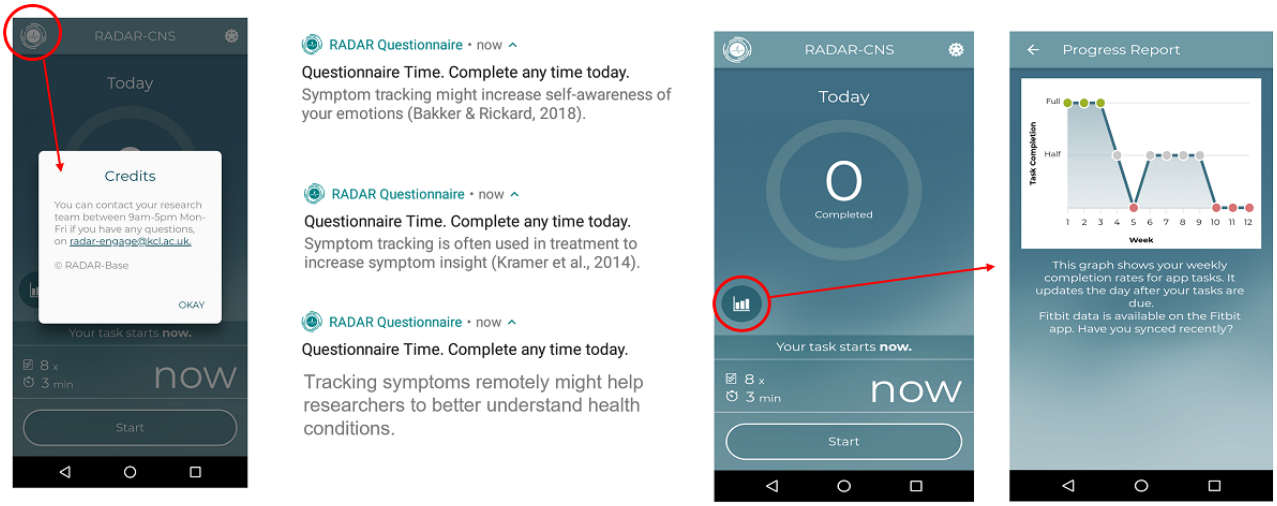
- Images rather than text.
- **Bar graphs and simple charts with dots or lines.**
- **White background with coloured data.**
- **Choice to view data or not**.
- Graphical representations preferred, for example, line, bar, or pie charts.
- No *harsh* colors, for example, red. **Bright colors, in general, but more muted when acutely depressed.**
- **Do not emphasize lack of progress.**
- **Option to add contextual information.**
- Customization: what to visualize, how to visualize it, and how often to access it.

In-App Components

Participants in the active arm will receive notifications at the same time points as those in the control arm, along with the following additional content (Figure 3):

1. Theoretically informed notifications: additional sentences included in the notifications covering the proposed benefits of remote symptom monitoring for emotional self-awareness, clinical practice, and research, along with a reminder that the questionnaire can be completed *any time today.*
2. Progress visualization: participants will be able to view their questionnaire task completion through the app visualized as a graph that is accessible from the main app home page.
3. Research team contact details: additional text on the app home page will provide a contact phone number, email address, and contact times for the research team.

Figure 3. Screenshots of the in-app components included in the adapted app.



(1) Research team contact details, accessible through an icon on the homepage.

(2) Theoretically-informed notifications alternating between 3 phrases.

(3) Progress visualization, accessible through an icon on the homepage, displaying full, half, or non-completion of weekly tasks for each of the 12 weeks.

Data Collection and Follow-up Procedure

A summary of measures and data collection time points is outlined in Table 1.

Table 1. A summary of measures and data collection points across the 12-week follow-up period.

Measures	Baseline (T0)	End point (T2)	Weekly	Continuously
REDCap[a] survey				
Consent	✓			
Contact information	✓			
Study devices	✓			
Sociodemographics	✓			
Social environment	✓			
Medical history	✓			
Lifetime Depression Assessment Self-report [41]	✓			
Inventory of Depressive Symptomatology [42]	✓	✓		
The World Health Organization Composite International Diagnostic Interview Short-Form [43]	✓	✓		
Generalized Anxiety Disorder-7 [44]	✓	✓		
Work and Social Adjustment Scale [45]	✓	✓		
Brief Illness Perception Questionnaire [46]	✓	✓		
Life events [47]	✓	✓		
Client Service Receipt Inventory [48]	✓	✓		
User Engagement Scale (adapted for mHealth[b] use) [49]	✓	✓		
Emotional Self-Awareness Questionnaire [50]	✓	✓		
mHealth App Usability Questionnaire [51]	✓	✓		
Active app measures				
Patient Health Questionnaire-8 [36]			✓	
Rosenberg Self-Esteem Scale [37]			✓	
Speech task			✓	
Passive app measures				
GPS, Bluetooth, and ambient noise and light				✓
Fitbit				
Heart rate and step count				✓
Process evaluation				
App use metrics				✓
Qualitative interviews		✓[c]		

[a]REDCap: Research Electronic Data Capture.

[b]mHealth: mobile health.

[c]Only a select few participants will be asked to interview.

Baseline questionnaires will comprise questions on contact information, sociodemographics, recent service use, physical and mental health history, and comorbidities, including the presence of depression and recent life events. The research team will also manually pull data pertaining to participation in RADAR-MDD for each participant, for example, participation length and completion rates. At the 12-week postbaseline follow-up, participants will receive a personalized link to repeat several baseline questionnaires. Responses received more than 3 weeks after baseline or follow-up will not be recorded.

The principal investigator (KMW) will monitor incoming data streams to ensure that the app is functioning correctly. Participants will not be contacted by the team once enrollment is complete, aside from a check-in email at the 6-week point to ensure that the app is functioning correctly. Participants will not be withdrawn from the study based on nonengagement; however, participants will be made aware that they can withdraw at any point.

Suicidal ideation will also be monitored at baseline (T0) and at follow-up (T2). Participants who report ideation or intent at either time point will be contacted via phone call, advised to

contact their treating physician, and emailed a list of appropriate signposts.

Upon completion of the study, participants will view a debriefing page explaining that the study aimed to test the effectiveness of notifications and progress visualizations on engagement with the platform. Both arms will be outlined, identifying arm assignments and end point instructions.

Outcome Measures

Primary Outcome Measure

The primary outcome measure will be the behavioral engagement with the RADAR-base system. This will be measured as the percentage of weekly PHQ-8 questionnaires completed over the 12-week follow-up period. Completion of 1 PHQ-8 task is defined as the completion of the 8 questions.

Secondary Outcome Measures

Secondary outcome measures will be as follows:

1. Experiential engagement with the RADAR-base platform measured with the User Engagement Scale (UES) [52] adapted to mHealth use [49]. The UES is a 30-item questionnaire measuring 4 factors of experiential engagement with mHealth apps: focused attention, perceived usability, aesthetic appeal, and reward. The UES has been widely adopted and shows good reliability and construct validity [53].
2. Experiential engagement with the RADAR-base platform measured by the Emotional Self-Awareness Questionnaire (ESQ) [50]. The ESQ is a 33-item questionnaire measuring recognition, contextualization, and decision-making in relation to one's own emotions. The ESQ has a reliability of 0.92 and shows significant positive correlations with the Emotional Intelligence Test [50].
3. System usability measured using the mHealth App Usability Questionnaire (MAUQ) for stand-alone apps used by patients [51]. This will be assessed at T2 only, asking participants to reflect solely on their experiences over the last 12 weeks. The MAUQ comprises 18 questions relating to the immediate and long-term usability of the app, including health care management (overall Cronbach α=.914).
4. Combined adherence to active and passive (Fitbit) components of the system will be measured as follows: adherence rate for the active app measured as the proportion of participants with over 50% of completed data across all 3 weekly questionnaire tasks and adherence rate for the passive Fitbit measured as the proportion of participants with over 50% of study days with any recorded data. These measures were chosen to align with data availability reporting in RADAR-MDD [21], previous literature [25], and the minimum amount of data sufficient for performing predictive analyses.

Additional Data Collection

Passive data through the RADAR-base passive app will also be collected; however, these will not be analyzed as part of this trial. This additional data will be collected for 2 reasons: (1) to emulate the RADAR-MDD as closely as possible and (2) for use in future analyses. The passive app collects information on phone location, battery level, Bluetooth devices, and background noise and light. Participants can opt out of using any of the study apps during their participation.

Process Evaluation Measures

Process evaluation measures will also be collected to further understand the interaction with the RADAR-base system. Quantitative measures will be obtained regarding app use: notification interaction, app initialization, specific module viewing, and viewing time. These will be available from the back end of the RADAR-base platform.

At the end of the follow-up period, 20 participants will be randomly invited to participate in a semistructured telephone interview with a member of the research team, discussing their experiences of participating in the study. Discussions will comprise perceptions of the arm to which the participant was randomized, experiences of the in-app techniques used, suggestions for further improvements for engagement with the system, and views on engagement with RMT systems for symptom tracking in research, clinical care, and self-management (Multimedia Appendix 1).

Sample Size

Power calculations were performed based on preliminary data from the RADAR-MDD. A total of 132 participants are required to detect a difference of 25% completion of PHQ-8 tasks between the control and active arms, with 80% power and 95% CI at the 12-week end point. Allowing for 10% attrition (based on previous research [21] but accounting for a much shorter follow-up period in this study), we will aim to recruit 140 participants. A total of 345 participants will be available to be contacted from the RADAR-MDD study cohort; assuming 50% acceptance of invitation (given the recruitment from a previously motivated cohort), a target of 140 participants should be feasible.

Randomization

Randomization will occur after baseline data collection when the REDCap randomization module initiates the generation of a QR code from the RADAR-base management portal assigned to the participant identifier. Each participant will be randomly allocated at a 1:1 ratio to either the control or the active arm. Simple randomization will be used, in which an allocation table with a random sequence of 1,2 will be generated and uploaded to REDCap. This will be carried out by a team member external to the core research team (YR) and therefore be concealed from the principal investigator (KMW) before enrollment.

Blinding

Individual participants will have previously used the RADAR-MDD app and therefore cannot be blinded because they might recognize new features of the app. However, arm assignments will not be explicitly revealed to the participants until the study debrief.

The principal investigator (KMW) will be unblinded to allocation to ensure that remote enrollments have been carried out correctly. All measures are conducted using the app or web-based REDCap system to avoid detection bias in assessments [54]. The trial data manager (DL) will be blind to

arm allocation. No other individuals will have access to the data set for data monitoring or analysis purposes; all tasks will be carried out by the principal investigator (KMW).

Data Management

All data collected via the Fitbit device and smartphone apps will be encrypted and uploaded to a secure server maintained by King's College London in accordance with the process cited by Ranjan et al [13]. The REDCap system sits on the King's College London Rosalind server. Only members of the RADAR-Engage team will have access to identifiable data. Qualitative interview data will be temporarily stored on the King's College London server, transcribed anonymously, and subsequently deleted.

Statistical Analysis: Plan

Overview

All data, including those from withdrawn participants (unless they request for their data to be deleted) will be included in the final analysis. Demographic and clinical characteristics at baseline and follow-up will be summarized by arm using appropriate summary statistics, for example, mean and SD for continuous variables and counts and percentages for categorical variables. Data completeness for all measures and outcomes will be summarized.

The primary outcome will be analyzed using 2-sample *t* tests (2-tailed) to assess whether the mean percentage of PHQ-8 completion in each arm is statistically different.

For the secondary outcomes, experiential engagement (as measured by the UES and ESQ) will be collected at T0 and T2 and will thus be calculated as a change from baseline. This will be assessed using repeated measures mixed modeling to explore whether experiential engagement is statistically different between the 2 arms. App usability scores (MAUQ) and overall system adherence rates will also be compared. Complete case analyses will be used; if <20% of responses to each questionnaire are missing, mean imputation will be used to provide a total score.

All analyses will be conducted using the intention-to-treat principle. The threshold for statistical significance was set at P=.05.

Process Evaluation Analyses

Qualitative interviews will be transcribed and coded using NVivo software [55]. Grounded theory thematic analysis will provide an exploration of participant experiences across the 2 arms and with the additional in-app components. Descriptive statistics will be reported for app use statistics.

Dissemination

This study will be reported following the CONSORT (Consolidated Standards of Reporting Trials) checklist [56]. The results of this study will be discussed via publication.

Results

This study will begin recruiting and enrolling participants in April and May 2021. Data collection will be completed by September 2021. Data analysis will commence in 2022. The results of this study will be communicated via publication in mid-2022.

Discussion

Principal Findings

The use of RMTs for symptom tracking in MDD research holds great potential for relapse prediction and personalized health care. Understanding current and promoting future engagement with RMTs in research studies is of utmost importance for producing high-quality results, and this is only amplified by the shift to remote health care monitoring during the COVID-19 pandemic [57-59]. Although previous studies have explored the impact of specific in-app components in encouraging data completion [25,26,32,33], to our knowledge, this study is one of the first to explore the promotion of engagement with a multi-parametric RMT system for MDD symptom tracking. Within the framework of the RADAR-base system, this study uses the questionnaire app as a participant-facing conduit to promote behavioral and experiential engagement with active and passive RMT in a large-scale research study incorporating theoretical notifications and progress visualization.

The findings of this study will, first, provide some understanding about how best to promote engagement in subsequent rounds of the RADAR-MDD study. The ability to collect sufficient data remotely by relying less heavily on a core research team while also minimizing burden on the user is a highly valuable asset for RMT research. This study also represents the first attempt to recruit and follow up with participants completely remotely using RADAR-base and, if successful, will pave the way for fully remote recruitment across a range of conditions. Second, this work sheds light on experiential engagement with RMT symptom tracking. The findings here could uncover new methods for measuring and promoting engagement in MDD research. Third, studying behavioral and experiential engagement in a research context can act as a proxy for understanding engagement in a clinical context [60]. Taken together, these findings could have wider implications for RMT research studies across health conditions, alongside the implementation of RMT data collection in clinical settings.

Strengths and Limitations

A key strength of this study is its grounding in a previous research project, using a system that has already been well-documented, designed, and developed for the purpose of RMT data collection [21,61,62]. It also takes an additional theory-driven and user-centered approach to adapting components of the system to promote optimal user engagement. However, this study has 3 main limitations. First, our ability to recruit and retain a sufficient number of participants for power analysis may be hindered by participation fatigue, given that many will have completed up to 2 years in the previous study. The effects of the COVID-19 pandemic on participants' willingness to engage in research studies are unclear. Second, it should be considered that recruiting from an existing study cohort with prior understanding of the system could create a ceiling effect for engagement, such that participants are already highly motivated to engage in symptom tracking. App literacy

has also been noted as a key facilitator of mHealth app engagement [63]. Nonetheless, there is good reason to believe that the new in-app components can encourage engagement over and above the moderate data availability reported in RADAR-MDD [21]. Third, although concerted efforts were made to include health-, user-, and technology-related barriers to engagement in the app development process, we acknowledge that this is not all-encompassing. Certain aspects of depressive symptomatology, for example, low mood or motivation [34], could affect engagement with the RADAR-base system in ways that might not be mitigated by theoretical notifications or progress visualization. Therefore, we have also included process evaluation measures to further understand how participants interact with the components and gain insight for future improvements.

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Conflicts of Interest

MH is the principal investigator of the RADAR-CNS consortium, a private-public pre-competitive consortium with research funding from Janssen, UCB, MSD, Biogen and Lundbeck. No further conflicts are declared.

Multimedia Appendix 1
Semistructured qualitative interview schedule (N=20).
[DOCX File , 28 KB - resprot_v10i12e32653_app1.docx]

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Abbreviations

aRMT: active remote measurement technology
CONSORT: Consolidated Standards of Reporting Trials
ESQ: Emotional Self-Awareness Questionnaire
MAUQ: mHealth App Usability Questionnaire
MDD: major depressive disorder
mHealth: mobile health
PHQ-8: Patient Health Questionnaire-8
pRMT: passive remote measurement technology
RADAR-MDD: Remote Assessment of Disease and Relapse in Major Depressive Disorder
REDCap: Research Electronic Data Capture
RMT: remote measurement technology
UES: User Engagement Scale

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Protocol

Evaluation of a Healthy Relationship Smartphone App With Indigenous Young People: Protocol for a Co-designed Stepped Wedge Randomized Trial

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Abstract

Background: We co-designed a smartphone app, Harmonised, with taitamariki (young people aged 13-17 years) to promote healthy intimate partner relationships. The app also provides a pathway for friends and family, or whānau (indigenous Māori extended family networks), to learn how to offer better support to taitamariki.

Objective: The aim of our taitamariki- and Māori-centered study is to evaluate the implementation of the app in secondary schools. The study tests the effectiveness of the app in promoting taitamariki partner relationship self-efficacy (primary outcome).

Methods: We co-designed a pragmatic, randomized, stepped wedge trial (retrospectively registered on September 12, 2019) for 8 Aotearoa, New Zealand, secondary schools (years 9 through 13). The schools were randomly assigned to implement the app in 1 of the 2 school terms. A well-established evaluation framework (RE-AIM [Reach, Effectiveness, Adoption, Implementation, Maintenance]) guided the selection of mixed data collection methods. Our target sample size is 600 taitamariki enrolled across the 8 schools. Taitamariki will participate by completing 5 web-based surveys over a 15-month trial period. Taitamariki partner relationship self-efficacy (primary outcome) and well-being, general health, cybersafety management, and connectedness (secondary outcomes) will be assessed with each survey. The general effectiveness hypotheses will be tested by using a linear mixed model with nested participant, year-group, and school random effects. The primary analysis will also include testing effectiveness in the Māori subgroup.

Results: The study was funded by the New Zealand Ministry of Business, Innovation, and Employment in October 2015 and approved by the Auckland University of Technology Ethics Committee on May 3, 2017 (application number: 17/71).

Conclusions: This study will generate robust evidence evaluating the impact of introducing a healthy relationship app in secondary schools on taitamariki partner relationship self-efficacy, well-being, general health, cybersafety management, and connectedness. This taitamariki- and indigenous Māori–centered research fills an important gap in developing and testing strengths-based mobile health interventions in secondary schools.

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KEYWORDS

indigenous; Māori; young people; relationships; school; mHealth; smartphone app; mobile phone

Introduction

Study Rationale

Abuse in intimate partner relationships is a human rights violation and a social and public health problem [1,2]. In Aotearoa, New Zealand, 1 in 3 women experience physical or sexual violence by a partner, with rates higher for indigenous Māori (58%) compared with New Zealand European (34%) women [3,4]. For many, their first experience of relationship abuse is during adolescence (13-18 years) [5-9]. Relationship abuse may include psychological, physical, sexual, or cyber abuse threats [10-12]. There is a small but growing body of literature examining relationship abuse prevalence, prevention, and intervention during this critical period of adolescence, when individuals transition from childhood to adulthood [13-15]. Comprehensive, accessible, innovative, and cost-effective interventions are required to prevent intimate partner abuse among young people. However, frequently, research programs appear to be done *on* rather than *with* young people, and few studies provide an indigenous lens. Given the significant health and social inequities of indigenous Māori in Aotearoa, New Zealand, we embarked on a program of co-designed research to develop and evaluate a personalized healthy relationship smartphone app using a *taitamariki*- (young person) and Māori-centered approach. The RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework, including qualitative and quantitative data collection methods, was used to examine the adoption and implementation of the app in 8 pilot secondary schools in New Zealand [16,17]. In this paper, we present a trial protocol for testing the effectiveness of the app.

Taitamariki-Centered Approach

As a team, we are committed to including the voice of young people in our work, consistent with their right to express opinions freely and have these considered in any matter that affects them [18,19]. We will convene *taitamariki* advisory groups (TAGs) to enable young people to cocreate the app using participatory research principles [20] and cocreation processes [21,22]. Before the formal trial, Māori team members experienced in child advocacy and focus group methodology (ME, TD, and TWBU) recruited and facilitated 2 cohorts of TAGs. TAG members and their parents provided written consent to participate in this research project. The initial *tuakana* (older) TAG included 7 *taitamariki* from 1 New Zealand region. At recruitment, they ranged in age from 15 to 17 years and included both *taitamatane* (boys; n=4) and *taitamahine* (girls; n=3); 5 of the 7 *taitamariki* self-identified as Māori. As the app was developed and trial was planned, meetings were convened *kanohi-ki-te-kanohi* (face-to-face), supplemented with communication via a private Facebook group. The second *teina* (younger) TAG members are recruited from our pilot schools across New Zealand and include 15 *taitamariki* (boys, n=4; girls, n=11). Communication includes *kanohi-ki-te-kanohi* meetings, videoconferencing, and interaction on Instagram. TAG members participated in project branding, app development, and trial design. The project branding *Harmonised* was chosen by the TAG. The TAG members will participate in the implementation, interpretation of findings, and dissemination.

Māori-Centered Approach

As a team, together with our community advisors, we are committed to a Māori-centered approach. At our first team *hui* (meeting), we specified our purpose, *kaingākau* (values), *tikanga* (right way of doing things in a Māori worldview), and *whanongapono* (principles) to guide our *mahi* (work). A Māori-centered approach is premised on the bicultural relationship between Māori as *tangatawhenua* (indigenous people of the land) and *tauiwi* (nonindigenous people) [23]. This research privileges a Māori worldview, ensuring that processes and outcomes are beneficial for Māori, inclusive of Māori values, expectations, and needs, and cedes control to protect Māori interests.

Early in the development of this research program, we took a philosophical turn from the mainstream deficit-based approach of reducing violence to a Māori well-being and strengths-based approach of promoting healthy relationships. From that point, we problematized our processes and decisions. For example, we identified that available validated measures focused on measuring adolescent relationship abuse (or *dating violence*) rather than measuring healthy relationships—the core focus of the research. In addition, identified measures were predominantly developed for adults and *modified* for young people, often without input from young people themselves. Finally, we could identify no measures for our variables of interest that represented a Māori or indigenous youth perspective. Therefore, in many respects, we are traveling uncharted territory, balancing cross-disciplinary and cross-cultural bodies of knowledge.

Why Mobile Health?

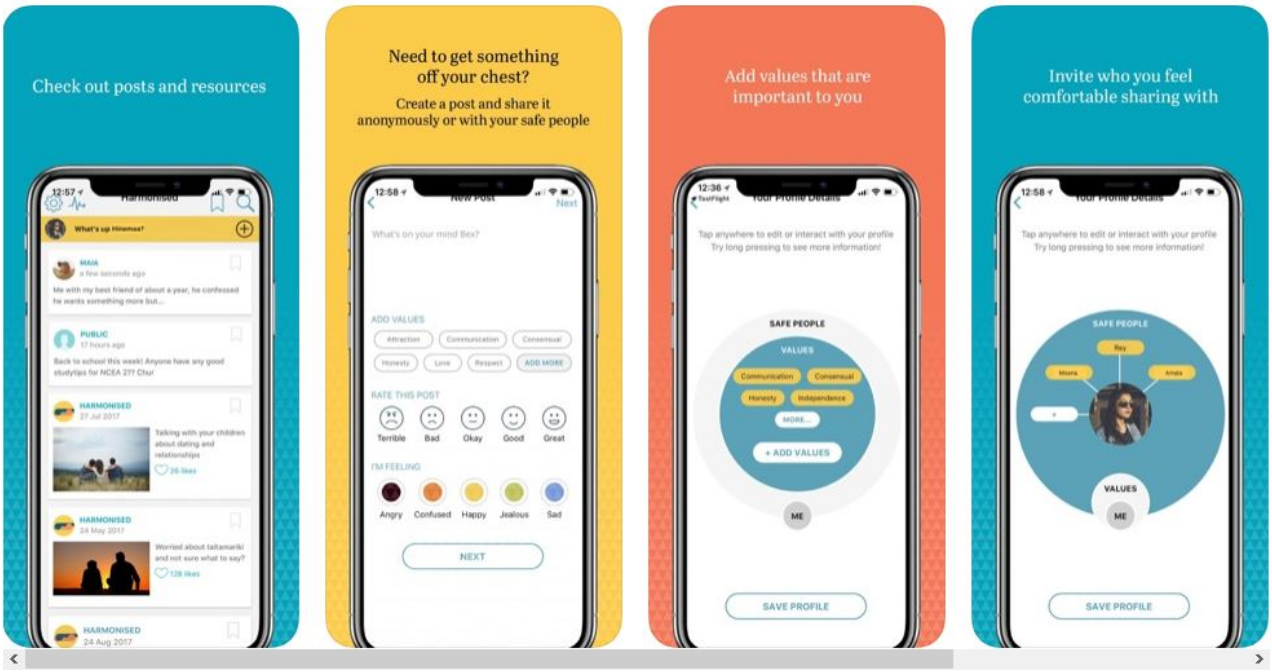
As people are increasingly seeking health information from the internet [24,25], mobile health interventions offer promise for improved health and well-being across the life span [26,27]. There is also evidence of value in the development of mobile health interventions aligned with indigenous frameworks [28-30]. In research with *taitamariki* Māori in Northland New Zealand about healthy and unhealthy *intimate relationships*, *taitamariki* expressed a need for more information and more effective support from friends and whānau [31,32]. However, rather than being *lectured to or given advice when they haven't asked for it*, they suggested *safe, easily accessible social media and web-based tools to use privately* [33]. The Harmonised app is meant to address this information need identified by *taitamariki* Māori. The intent is to develop a resource that would supplement, rather than replace, other healthy relationship learning in schools, whānau, or families or communities. New

Zealand secondary schools have a range of digital technology devices [34] and a Ministry of Education–funded Chrome Education License [35].

Harmonised Healthy Relationship App

The Harmonised healthy relationship smartphone app was developed consistent with our *taitamariki*- and Māori-centered approach. Development was iterative, involving repeated cycles of *taitamariki* input, app development, and testing. Our software engineer and app developer worked together in applying the specifications identified by *taitamariki* in focus groups, usability testing, and by our TAG members (Figure 1). *Taitamariki* specified their desire for an interactive, private social network that allows *taitamariki* users to (1) create their own relationship profile and choose their relationship values, (2) learn about common relationship issues (healthy relationship information and skill resources), and (3) post issues or comments about their relationships with others. *Taitamariki* control whether to make posts private (sharing only with selected *safe people*) or public (shared anonymously). Responding to the *taitamariki* desire for better support from their friends and whānau, the Harmonised app supports 2 user types: (1) primary users are *taitamariki*, with access to all app functions, and (2) secondary users are friends, whānau, or family and community who have access to healthy relationship information resources only, unless invited as a primary user's *safe person* to comment on a specific post.

Figure 1. Screenshot from the Apple App Store (version 1.8.3; August 2019).



A Harmonised moderation protocol guides safe practices for all posts (posts and comments), minimizing the risk of harm to primary app users, harmful use of the app, and harm to the platform. The protocol is aligned with best practice safety and security measures from Netsafe [36], Technology Safety [37], and others [21,38]. The moderation protocol includes automated (inappropriate language block and suicidality or self-harm automated message), human (daily review by the research team with the ability to block posted comments or individual users), community-based (users' report inappropriate content), and reputation-based moderation. An escalation pathway identifies procedures, should moderators have a safety concern. The safe and responsible use of the app is communicated to all users. The protocol is aligned to the New Zealand Harmful Digital Communications Act 2015.

Healthy relationship resources are collated by a Harmonised resource working group to provide *taitamariki* with the information they have requested. The topics covered include, for example, communication, consent, dealing with anger, and how to talk with your parents or children about healthy relationships and sexuality. The working group followed a protocol for resource selection, modification, and permission for use. Resources include links to videos, quizzes, brief articles, and stories from a range of open-access sources. Where to get help is a *recommended* resource for all users. New Zealand and Māori resources were prioritized.

Following a beta test version available in June 2017, version updates continued with bug *fixes* and enhancements. In some cases, changes were made in response to requests by school staff (eg, ability for persons to accept or not accept a *safe person's* invitation). As a prevention intervention, there is also

attention to promoting the app for all *taitamariki*, regardless of relationship status. For example, presenting the interactive selection of relationship values as a requirement before advancing to the app *feed* allows all *taitamariki* to participate in the healthy relationship values exercise. We also use gender-diverse language, sensitive to the minority (estimated at 3.8%) of Aotearoa young people attracted to others of the same sex or both sexes [21,39,40].

The hybrid app in English and Te Reo Māori (translation by a certified Māori language interpreter) is available across the digital ecosystem, including mobile devices (smartphones and tablets), laptops, and desktop computers. The app was first published in June 2018 in the Apple App Store, Google Play Store, and web browser by the Auckland University of Technology Enterprises Ltd. To increase privacy, the app is personal identification number code–protected to keep information safe once a user moves away from the screen. To reduce the risk of harm from *nontaitamariki* inappropriately posting (eg, trolling), the posting function is limited to students enrolled at participating schools and validated during app registration against email lists provided by the schools.

Methods

Trial Purpose and Hypotheses

We are investigating the adoption and implementation of the interactive, personalized healthy relationship Harmonised app in 8 pilot secondary schools in New Zealand using the well-established RE-AIM evaluation framework [16,17]. Mixed method data sources include a quantitative web-based *taitamariki* survey, focus groups with *taitamariki* and school stakeholders (persons identified by schools who are involved in their response to *taitamariki* health and well-being), app use data, school engagement notes, and itemized costs (Table 1). In this paper, we present the trial protocol for testing the effectiveness of the Harmonised app using a quantitative web-based *taitamariki* survey.

We hypothesize (primary analysis) that implementation of the app (compared with before implementation) will (1) increase *taitamariki* relationship self-efficacy (RSE; primary outcome) and (2) increase *taitamariki* well-being, general health, cybersafety management, and connectedness (secondary outcomes). We will also conduct (3) primary analyses limited to Māori participants (subgroup analyses). Other measures include school and student characteristics and *taitamariki* help-seeking and barriers to getting help.

Table 1. Harmonised evaluation data sources guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework.

Implementation	Quantitative data sources	Qualitative data sources
Engage with schools to adopt the Harmonised app	• Number of schools agreeing to participate, number of schools invited, and proportion of invited schools agreeing to participate	Drivers of and barriers to school participation: • School engagement log • School engagement notes • Preimplementation school information forms • Preimplementation focus groups
The app is implemented in schools	• Number of schools implementing in accordance with random assignment • Costs of implementation (time and money)	Understanding implementation: • School implementation plans • Implementation run sheets • Postimplementation stakeholder focus groups • Postimplementation taitamariki focus groups
The app reaches the target population	• Number and proportion of students in participating schools and others that download and use the app: • App download data (Firebase reports) • App use assessed in taitamariki survey postimplementation	Drivers of and barriers to app access and use: • Open-ended query in survey reason for not downloading • Postimplementation focus groups with taitamariki • Postimplementation focus groups with stakeholders • Whānau interviews
The app is effective at improving relationship and well-being outcomes	• Primary and secondary outcomes assessed in web-based survey completed by taitamariki at 5 school terms over 18 months	Impacts of the app: • Postimplementation focus groups with taitamariki
Maintenance of the Harmonised app beyond the implementation period	• App use data posttrial (Firebase)	Understanding long-term impacts and app retention: • Postimplementation hui (meeting)

Trial Design

A pragmatic, stepped wedge, cluster randomized (one-directional crossover) trial in 8 pilot secondary schools tests the effectiveness of the Harmonised app. Secondary schools in New Zealand include years 9 through 13 (5 years of high school, generally young people aged 13 to 17 years). In the stepped wedge design, the app is implemented in all 8 schools in one of 2 school terms, with the order of implementation determined at random [41-44]. There are 5 assessments (web-based surveys) per school and 2 time steps over a 15-month trial period (Table 2). Our protocol description follows the CONSORT (Consolidated Standards of Reporting Trials) stepped wedge, cluster randomized trial extension [44]. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619001262190) on September 12, 2019.

Table 2. Stepped wedge implementation design plan.

School ID Number	Year and school term				
	Year 1				Year 2, T1[a]
	T1[a]	T2[a]	T3[a]	T4[a]	
8	CC[b]	CC	TP[c]	IC[d]	IC
7	CC	CC	TP	IC	IC
6	CC	CC	TP	IC	IC
5	CC	CC	TP	IC	IC
4	CC	TP	IC	IC	IC
3	CC	TP	IC	IC	IC
2	CC	TP	IC	IC	IC
1	CC	TP	IC	IC	IC

[a]T1 to T4 are the terms for the implementation of the design plan.

[b]CC: control condition.

[c]TP: transition period.

[d]IC: intervention condition.

Eligibility for Clusters: School Selection

Overview

The New Zealand Ministry of Education website provides school characteristics, including type of school, gender, ethnicity proportion, and other characteristics [45]. The 366 state schools in New Zealand include a mix of coeducational and boys- or girls-only schools across years 9 to 13. Although there are National Certificate of Educational Achievement unit standards for healthy relationships, their integration into secondary school curricula varies. Our inclusion criteria includes secondary or composite schools that had a school roll >175 (based on average class sizes for each year) and ≥16% Māori (proportion of Māori in the population; StatsNZ). This left 194 eligible schools. In this *taitamariki*- and Māori-centered study, we added 6 schools to the eligibility list that had a high proportion of Māori students and had participated in earlier *kaupapa* Māori research in the Ngāpuhi tribal boundaries within the Northland region of New Zealand [33].

School Recruitment

From the list of eligible schools, we will purposefully invite schools until we achieve our desired sample of 8 schools. We aim to balance girls-only, boys-only, and coeducational schools. We also aim for a balance of schools that have and have not participated in specialized healthy relationship curricula such as Mates and Dates (Accident Compensation Corporation) that are being piloted [46,47]. Finally, we will consider the geographic diversity and travel feasibility.

Implementation Conditions

The intervention consists of the implementation of the Harmonised app in each participating secondary school. An app implementation plan is being developed jointly with each school following a stakeholder focus group. A one-off single-period (40-50 minutes) implementation delivery occurs within individual classrooms or during school assembly. Participating schools may elect for app implementation sessions to be school-led or researcher-led. A hard-copy training resource designed specifically for the study supports implementation and includes instructions regarding app navigation and function. Researcher-led training includes demonstrations of app functions. Students are led through the process of registration, creation of user profiles, and creation of posts. Strategies to support app adoption include the use of posters and school newsletters. The intended frequency and duration of use of the app beyond the initial guided implementation is at the students' discretion. The tailored nature of the implementation limits the evaluation of fidelity.

Comparison Condition

The comparison period includes school terms before app implementation from the clustered one-directional crossover design. In the preimplementation comparison period, researchers engage with an identified school liaison, convene a

preimplementation focus group, and confirm the school's pathway for referral of students needing health and well-being services, including social workers, counselors, and health providers. No control period activities that affect school students will be undertaken.

Survey

Eligibility for Survey Participants: Student Selection Within Schools

Student eligibility criteria includes being enrolled in one of the pilot schools as a year 9-13 student and able to consent and complete a web-based survey. For schools with a roll <100, all students of years 9-13 are eligible to participate. For schools with a larger roll, all students in 1 class in a given subject for each year (9-13) are selected. Class selection is negotiated with the school liaison and prioritizes the inclusion of Māori students. A new class of year 9 (aged 13 years) is selected in each school in year 2, term 1 of the study.

Student Recruitment and Retention for the School Survey

We will attend selected classrooms during class time and invite eligible students to participate in the research by completing 5 web-based surveys over 5 school terms. Students are asked to share their understanding of what is being asked of them. During data collection sessions, there are discreet options available for students choosing not to participate. Consenting students complete the baseline survey on school digital devices during class time, with researchers available to respond should *taitamariki* have any questions as they complete the survey. Sandwiches are provided to all students at the end of class time. Students can exit the survey and complete it later. The remaining 4 surveys are completed independently by students in response to email and text nudges. Nudges are sent during week 5 of the subsequent 4 terms. Students are free to withdraw at any time by emailing the project. Survey data are exported into a secure server at the Auckland University of Technology.

Survey Development and Pilot-Testing

In preparation for the trial, the survey was pilot-tested in 2 schools (based on convenience) with approximately 60 students. This provided information on the time to complete the survey and identified the technical issues. Focus groups with students who completed the survey will be conducted to assess acceptability, comprehension, and appropriateness. Survey refinements will be made as indicated. Demographic characteristics include age, year in school, gender, ethnicity, internet exposure, and mobile phone access.

Outcomes

Students will complete web-based surveys at baseline (school term 1, year 1), 12 weeks (term 2, year 1), 24 weeks (term 3, year 1), 36 weeks (term 4, year 1), and 47 weeks (term 1, year 2). In selecting outcomes, the team considered the following: (1) positive, strengths-based measures (rather than deficit-based); (2) instruments developed with young people (rather than adult measures *modified* for young people); (3) instruments developed with indigenous young people; and (4) instruments developed with *taitamariki* Māori. At the time of study planning, there were no validated strengths-based measures developed with *taitamariki* Māori. The overwhelming majority of instruments used with young people measured *dating* or adolescent violence and had been modified from adult instruments.

Table 3 presents the final selection of the primary and secondary outcomes. All primary and secondary outcomes are assessed in each of the 5 surveys. Our primary outcome of interest is taitamariki RSE and includes 2 measures: confidence to talk about or seek help for themselves (RSE-self) and confidence to help others (RSE-others). The self-efficacy items are modeled on the Self-efficacy to Deal with Violence Scale [48,49]. In total, 2 items address RSE-self (How confident are you that you could check if parts of your relationship are ok, if you are not sure and How confident are you that you could seek help when your boyfriend or girlfriend has done something that's not ok), and 2 items address RSE-others (How confident are you that you could help or support a friend or whānau member if they were not sure about parts of their relationships and How confident are you that you could help or support a friend or whānau member whose boyfriend or girlfriend has done something that's not ok).

Table 3. Harmonised outcome measures.

Outcomes	Sources and modifications	Scales and subscales (number of items)	Response options	Possible score (range)
Primary outcomes				
RSE[a]	Items modelled on Self-efficacy to Deal with Violence Scale [48,49]	• RSE-self (2) • RSE-others (2)	• 0=not at all confident • 3=very confident	• 0-6 • 0-6
Secondary outcomes				
WB[b]	World Health Organization-Five Well-Being Index [50] used in children [51,52] and in New Zealand youth [53,54]. Modified "I have felt active and vigorous" to "I have felt active and full of energy"	• WB (5)	• 0=at no time to 5=all the time	• 0-25
General health	Single 5-point Likert scale to rate respondent's general health	• General health (1)	• 0=poor to 4=excellent	• 0-4
Connectedness	Retained 2 subscales from Hemingway Measure of Adolescent Connectedness [55] with language regionalized and negatively worded items not scored	• Connectedness-family or whānau (5) • Connectedness-friends (5)	• 0=not at all true • 4=very true	• 0-20 • 0-20
Cybersafety	15-item questionnaire began with a scenario modified from the Coping with Cyberbullying Questionnaire [56]; items are from original research with young Māori women [57]	• Cybersafety–being safe (7) • Cybersafety–taking action (8)	• 0=definitely not • 3=definitely yes	• 0-21 • 0-24

[a]RSE: relationship self-efficacy.

[b]WB: well-being.

The Cyber-Safety questionnaire was developed from original research on young Māori women [57]. The 15-item questionnaire begins with a scenario modified from the Coping with Cyberbullying Questionnaire [56], as follows:

> *Imagine that for a few weeks, you have been receiving nasty and threatening text messages. Aside from that, you found out that embarrassing pictures of you are being spread around.*

Taitamariki then respond how likely they would be to use each of the 15 strategies to keep yourself safe on the internet (eg, I would talk to my friends about it, I pay attention to who has access to my data). Other secondary outcomes include well-being, general health, and connectedness (Table 3).

The baseline data (preimplementation of the intervention acquired in all schools before the transition period) will be extensively analyzed, leading to a full analytical design. In particular, exploratory factor analysis of the outcomes will lead to the creation or confirmation of subscores, making RSE, connectedness, and cybersafety bivariate outcomes.

Randomization

Schools are stratified by size (small or large). Large schools are further stratified by ongoing standardized delivery of a healthy relationship program (HRP). Within each stratum, the school labels are randomly ordered using a computer-generated sequence of pseudovariates. They are then assigned in this random order to the first sequence period (year 1, term 2: 2 small schools, 1 large school with HRP, and 1 large school with no HRP), and then the second sequence period (year 1, term 3: 1 small school, 2 large schools with HRP, and 1 large school with no HRP).

Analysis

The data will be kept stratified within the clusters by gender, Māori versus non-Māori ethnicity (hereafter identified as ethnicity), and year-group. The year-group (years 9-13) is defined as usual for the first 4 periods and crosses over to the next nominal year-group in the fifth period, so that each year-group defines a subcohort followed over time. The year 9 group from period 5 is identified as a separate year-group. The analysis sets consist of intention-to-treat, as-treated, and adopter (students reporting app use) sets. All primary analyses will take place in the intention-to-treat set. General effectiveness hypotheses will be tested using a linear mixed model with nested participant, year-group, and school random effects. All models will initially be fitted with the function *lme* from the R package *nlme* [58]. If the results fail to converge or otherwise display poor numerical behavior, PROC MIXED from SAS/STAT version 9.4 (SAS Institute Inc) will be used instead.

To ensure the overlap of the intervention and control in the design, data will be collected during the transition periods and included in the analysis, assuming an intervention effect half the size of that in the posttransition periods. This approach is nonstandard but necessary in this instance and broadly plausible under the conditions of implementation and the nature of the intervention.

Māori subgroup analyses are planned. They will consist of all primary analyses limited to Māori participants. Subgroup analyses will take place in the intention-to-treat and as-treated sets. It will extend to all outcomes covered by primary analyses.

A blind review of the data will take place (before allocation unblinding) to determine whether any transformation is necessary, to settle on the final models, and to determine whether any missing covariate or outcome data require multiple imputation, and generally to finalize the statistical analysis plan. All tests will be performed at a 5% significance level against 2-sided alternatives. There are no circumstances in which unblinding is permissible.

Sample Size

Recruitment of 8 schools and data collection over 5 terms is judged feasible, with app implementation (the intervention) scheduled at 2 time points (terms 2 and 3, respectively, in the first year). We assumed roughly equal numbers of participants from each school. We use the method of Hussey and Hughes [59] to compute the power for different effect sizes under a model including the primary outcome (RSE), school-related random effect, and fixed effect associated with the term. The sample size computation was programmed in R version 3.x (R Foundation for Statistical Computing) by the study statistician in accordance with the analysis plan, including the specification that the intervention effect is assumed to be halved during the transition period. Other covariates may be included in the model, as decided during the blind review of the data.

Assuming an attrition of 35% (conservatively applied to all assessment time points postbaseline) and using a school-specific intraclass correlation of 0.07, evidenced in a bullying study in New Zealand schools [60], we estimate that recruiting 600 students is sufficient for detecting an effect size of 0.25 with 83% power and an effect size of 0.30 with 94% power. These correspond respectively and approximately to a change of 0.75 and 0.9 in the mean score of either component of the RSE score, based on the baseline data.

Ethics and Safety

The trial protocol was approved by the Auckland University of Technology Ethics Committee (application number: 17/71), approved on May 3, 2017. All schools have a pathway for students needing health and well-being services, including social workers, counselors, and health providers. Consent to participate is provided by each school's principal and Board of Trustees. Schools follow their processes for sharing information about the study with parents and gaining parental consent (information and consent forms provided by researchers). Students choosing to participate in the survey provide consent in the introduction to the web-based survey that details confidentiality. Students were identified using a randomized code number. All communication and visits with schools are documented by the research staff and reviewed by senior investigators as contextual data and to audit trial conduct. Our Harmonised ethical research practice and data sharing protocol provides a process for accessing Harmonised data aligned with our Māori-centered approach, available on request. Guided by our *tikanga*, we will prioritize *taitamariki*, schools, and whānau to disseminate our findings.

Results

The study was funded by the New Zealand Ministry of Business, Innovation, and Employment in October 2015 and approved by the Auckland University of Technology Ethics Committee on May 3, 2017 (application number: 17/71). A total of 8 schools were recruited, and data were collected over 5 school terms.

Discussion

Principal Findings

The Harmonised trial will generate robust evidence to evaluate the impact of introducing a healthy relationship app into secondary schools. Importantly, this strengths-based *taitamariki*- and Māori-centered research counters the dominant adult-focused and deficit-based intimate partner violence literature. Working with *taitamariki* and community advisors, we have created the Harmonised brand focusing on what young people have told us about healthy partner relationships. The Harmonised app provides a safe digital network with resources for *taitamariki* to consider the values that are important to them for a healthy intimate partner relationship.

Conclusions

This pragmatic trial offers an opportunity and challenge to understand whether a healthy relationship digital resource can be embedded in the secondary school environment and whether the resource benefits *taitamariki*, particularly Māori. Secondary schools are busy places that are typically underresourced to meet all the complex needs to support students and families to flourish. Our Harmonised study guided by explicit *tikanga* and using mixed methods guided by the RE-AIM framework will make an important contribution to understanding drivers of and barriers to conducting research in this unique setting. Our trial measures will identify whether the introduction of the app improves *taitamariki* partner RSE, well-being, general health, cybersafety management, and connectedness.

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Authors' Contributions

JKM is the principal investigator; she conceived the study with DW, ACV, ME, SNR, and TD. ACV contributed their statistical expertise in the trial design and analysis plan. DW, ME, TD, MR, and TWBU contributed to the study of the indigenous Māori

caucus. All authors contributed to study protocol refinement and the interpretation of the findings. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
HRP: healthy relationship program
RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance
RSE: relationship self-efficacy
TAG: taitamariki advisory group

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Protocol

A Modern Flexitarian Dietary Intervention Incorporating Web-Based Nutrition Education in Healthy Young Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: The trend of flexitarian eating patterns is on the rise, with young adults among the biggest adopters claiming health and environmental reasons to reduce red meat intake. Nutrient-dense meat and animal products are often the lynchpin of these diets, even when consumed only occasionally and in moderate amounts. Red meat provides forms and concentrations of essential proteins, lipids, and micronutrients that are scarce in exclusively vegetarian regimens.

Objective: The aim of this study is to consider the effects of moderate consumption of lean red meat as part of an otherwise vegetarian balanced diet and its impact on biomarkers of sustained health and well-being.

Methods: A cohort of healthy, young (20-34 years old, n=80) male and female participants will take part in a 2-arm, parallel randomized controlled trial (RCT) for a duration of 12 weeks, with a 3-month posttrial follow-up. The trial will commence with a 2-week assessment period followed by allocation to the intervention arms. The intervention will include the consumption of red meat or meat alternatives 3 times per week for 10 weeks. Blood samples of the participants will be collected to measure changes in erythrocyte fatty acid distribution, circulating amino acids, neurotransmitters, markers of mineral status, and inflammatory markers. Questionnaires to assess well-being and mental health will be undertaken every 2 weeks. Body composition, physical function, and blood parameters will be assessed at allocation (t_0), week 5 into the intervention (t_5), and post intervention (t_{10}).

Results: The protocol has been developed using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist and the outcomes will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The trial was approved by the New Zealand Ministry of Health's Health and Disability Ethics Committees (protocol 20/STH/157). The results of this study will be communicated via publication.

Conclusions: To our knowledge, this is the first RCT investigating the overarching health consequences of consuming pasture-fed red meat or no meat as part of a healthy diet.

Trial Registration: ClinicalTrials.gov NCT04869163; https://clinicaltrials.gov/ct2/show/NCT04869163

International Registered Report Identifier (IRRID): PRR1-10.2196/30909

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KEYWORDS

protein; meat; vegetarian; eating patterns; diet; nutrition; dietary restrictions; biomarkers; health; well-being; macronutrients; micronutrients

Introduction

Although not always labeled so, "flexitarianism" is the default lifestyle for much of the world, whereby plant-derived foods provide the bulk of a person's calories [1,2]. Nutrient-dense meat and animal products can be an important pillar of these diets, even when consumed only occasionally and in moderate amounts [1]. They provide high-quality protein, essential fatty acids, and micronutrients that are limited in concentration or bioavailability in exclusively plant-based diets, notably including vitamin B_{12}, iron, zinc, and long-chain omega-3 fatty acids (LCn3) [3]. However, production of meat is resource-intensive and widely censured for its environmental impacts [4]. As a consequence, the trend of meat-rich dietary patterns in Western consumers may not be sustainable.

The role of meat in the diet is under debate, not only from sustainability and ethical considerations, but also from a health perspective based on evidence that habitual consumption increases the risk of some metabolic diseases and cancers [5]. However, much of that research has been retrospective and reliant on food recall, which is known to yield equivocal results and oversimplified recommendations (eg, not distinguishing between intact red meats and processed, cured, or preserved meats) [6]. Randomized trials have more control over diet composition but have tended to feed relatively high levels of meat [5,7] that exceed those recommended by the World Cancer Research Fund guidelines [8]. These trials, which do not consider the potential of moderation, are yielding increasingly contradictory outcomes.

Individuals might choose to avoid or limit meat intake entirely for reasons of personal preference, ethical stance, culture, religion, or health [9]. Vegetarianism has been reported to reduce mortality on account of diverse protective effects [10]. However, research results are inconsistent, the underlying reason for which is yet undefined and the observed health benefits may be confounded by "lifestyle" factors associated with socioeconomic status, such as adequate levels of physical activity [5,11-13]. The association between meat eating and disease tends to be higher in North American [14] than in Asian cohort studies [15], indicating the presence of lifestyle bias, a meat dose effect, and nutritional differences in the meat produced in certain regions [2,16].

Diet is more than just adequate nourishment. Eating well can be a pleasure and a challenge that affects many aspects of well-being and quality of life. A Scandinavian study that compared teenage omnivores versus low-meat consumers found that symptoms of depression and anxiety were considerably worse among the latter [17]. This may have been related to the absence of meat or because the adolescents adhering to the low-meat diets did not also follow other typical lifestyle health choices. A broader review of the psychological health of omnivores and meat-abstainers also found that those who avoided meat consumption had significantly higher rates or risk of depression, anxiety, or self-harm behaviors [18]. The components of red meat that may be beneficial for mental health include fatty acids, phospholipids, cholesterol, niacin, vitamin B_6, and vitamin B_{12}, while saturated fat is considered detrimental to cognitive function [19]. In particular, the essential LCn3 are valued for their roles including lipid-lowering properties, mitigation of platelet aggregation and inflammation, and improvements in cognition and mood [20]. In the context of Western diets where seafood is a minor constituent, the contribution of red meat to total LCn3 intake can be substantial [21].

Evidence suggests that young adults are the largest age group who adopted a flexitarian diet [2,16]. Despite the long-lasting impacts of diet during young adulthood, this is an age group not frequently researched in the meat and nonmeat consumption literature, particularly those focusing on their subjective experience to the diet [2]. To our knowledge, no randomized controlled trial (RCT) has investigated aspects of physiological and psychological well-being concurrently, nor in young adults.

The objective of this trial is to compare the physiological and psychological effects of consuming moderate amounts of pasture-raised lean red meat or vegetarian analogues in the context of a balanced diet for 10 weeks. We will measure changes in markers of nutritional status and indices of longer-term health and mental well-being, with the hypothesis that lean red meat will confer benefits related to the presence, concentration, and bioavailability of nutrients which are typically not matched in vegetarian analogues [7,19,22]. The study is part of a larger program to understand the human and environmental implications of consuming pasture-raised (ie, grass-fed) beef and lamb.

Methods

Study Design and Setting

The study is a parallel RCT comprising a 2-week preintervention assessment, a 10-week intervention period, and a 22-week posttrial follow-up. Participants will all be maintained on a balanced vegetarian basal diet and be randomized to also consume either red meat ("Flexitarian" arm) or a meat substitute ("Vegetarian" arm). The meat will be pasture-raised beef and lamb butchered and packaged in accordance with our specifications in New Zealand, while the meat substitute will be commercially available plant-based products (Multimedia Appendix 1). The SPIRIT guidelines were followed when designing the research [23].

Recognizing that there are many interpretations of the terms, "vegetarian" and "flexitarian," in this study we define vegetarian as ovo-lacto vegetarian and flexitarian as "a vegetarian diet with moderate amounts of red meat." Both arms can consume eggs and dairy products, but not chicken, pork or fish, and no red meat other than that supplied by the researchers.

The study is designed around pairs of young adult consumers who share meals and are therefore likely to engage over the values and challenges of developing a healthy lifestyle. Couples/household units (see *Recruitment*) will be randomized to the same intervention arm. Depending on their allocation, the couple will receive regular allotments of either frozen red meat or meat-analogue, which will be sufficient to provide 3 meals (approximately 350-500 g of cooked meat or vegetarian alternative per person per week) [8,24,25]. We will evaluate changes in objective and self-assessed subjective health variables between the 2 intervention arms. These include physical function, body composition, metabolic health biomarkers, and psychological well-being.

Recruitment

We will recruit pairs of individuals (spouses, partners, or companions) who cohabitate and typically share evening meals. Participants will be GenZ (18-23 years old) and millennial (23-34 years old) individuals. This population demographic has the greatest variation in meat intake [8]. Recruitment will be advertised with posters placed around the University of Auckland and using social media websites and tools.

Potential participants will meet with researchers responsible for recruitment in person, where eligibility will be confirmed, and details of the study will be discussed with opportunity for questions to be clarified. At this in-person screening visit, participants will provide written informed consent (Multimedia Appendix 2).

Eligibility Criteria

All participants are required to be considered omnivores if, in the last 2 months, they consumed at least 2-3 meals per week which included meat of any description (red or white fleshed meat, including fish). They must be willing to consume both red meat and meat analogues for the purposes of the trial. Those with chronic health conditions, obesity (BMI≥30 kg/m^2), hyperlipidemia, disordered eating patterns, history of anosmia and ageusia (issues with smell and taste), use of medications (except for occasional nonsteroidal anti-inflammatory drugs and antihistamines), or recreational drugs, or those who smoke tobacco will be excluded from participating. Potential participants who use dietary supplements were asked to abstain for the month prior to the beginning of the study. Participants must own a mobile phone with a camera and be proficient with using Facebook and Facebook messenger. Women must confirm they are neither pregnant nor intending to become pregnant during the trial.

Participants will complete a web-based eligibility screening, which includes the Three-Factor Eating Questionnaire (TFEQ-R18), a Self-Efficacy questionnaire, a Food Frequency questionnaire, and a health survey. Participants with a TFEQ score greater than 75% will be excluded on the basis that their perception of food is potentially influenced by underlying psychological issues or that they demonstrate disordered eating patterns. Given the routine monitoring of food intake and subjective experience to food required in this research, this cut-off was deemed clinically relevant for the purpose of this study by the research team, including psychologists and registered dietitians [26]. Participants must own a mobile phone with a camera. Women must confirm they are not pregnant, nor intending to become pregnant during the trial.

Participants will be monitored for their adherence to the study guidelines through the dietary recording smartphone app *Easy Diet Diary* and were prompted for adherence via emails, social media, and SMS text messages. They will have the right to withdraw from the study at any time without any explanation. The principal investigator (PI) will have the right to discontinue participants' involvement if they become ineligible or when any significant protocol deviations occur in the study. The data of participants who withdraw will be retained and might be used in exploratory analyses, unless the participant requests data to be deleted.

Sample Size Calculation

The primary biomarker for calculating the sample size is the concentrations of LCn3 in erythrocyte membranes, and a sample size of 63 will provide sufficient power to detect changes in fatty acids, which might be due to the intervention. Published data indicate a change of 3.01 µg/mL (SD 1.1 µg/mL) in erythrocyte fatty acid composition (20:5) following a 2-week dietary intervention and crossover meat trial among young adults [27-29]. The Cohen effect size of 0.2 (small) of the variability in erythrocyte fatty acids was used to consider the smallest worthwhile effect. To allow for dropouts, a total of 80 participants will be recruited.

Randomization and Blinding

The 80 participants (self-organized as 40 couples/household units) will be randomized evenly to the vegetarian or flexitarian arm, with a random allocation sequence (1:1 ratio) generated using Random.org. Researchers responsible for participant recruitment will be blinded to allocation until participants begin their 2-week lead-in period. Owing to the nature/form of the food provided, participants will not be blinded to their intervention; nonetheless, they will not be aware of this until the intervention begins.

Couples will be further organized into "teams," which are groupings of 5 couples who consume the same diet. There will be 4 such teams per intervention arm. A team serves as another layer of structure and mutual support during the intervention period. Team members will engage virtually through social media, which was explained to participants during recruitment.

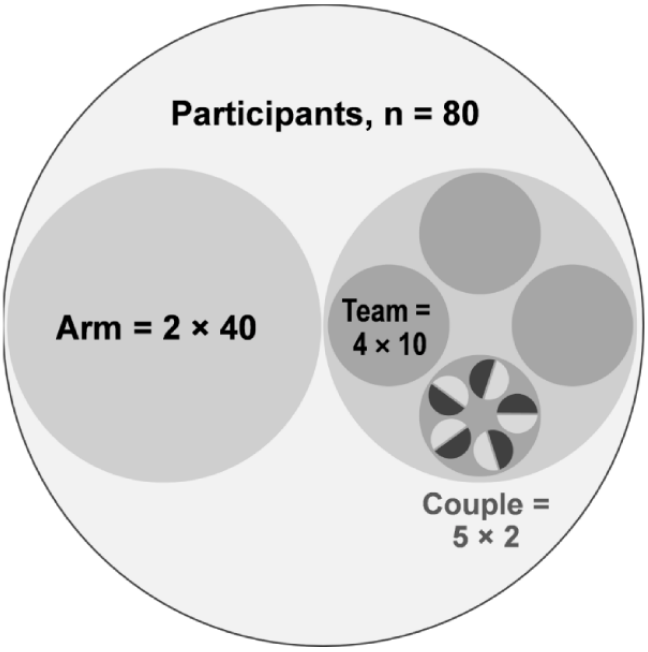
Ethics and Dissemination

The designed intervention has been assessed by a nutrition expert panel. The trial was approved by the New Zealand Ministry of Health's Health and Disability Ethics Committees (protocol 20/STH/157). The investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, with relevant institutional regulations. Results arising from this study will be submitted for publication in scientific journals and presented at meetings. Authorship will be determined in accordance with the guidelines of the International Committee of Medical Journal Editors.

Study Overview

Each participant will be coupled with another participant within a team in each arm (Figure 1). The trial commences with a 2-week preintervention period when participants consume their usual diet. Following allocation, couples will begin to receive allotments of either meat or the meat alternative (3 meals per week) and weekly vegetarian meal kits plus (additional 3 meals per week). The dietary intervention continues for 10 weeks.

Figure 1. Participation grouping within the 2 intervention arms.



At intervals during the trial, participants will take part in assessments of nutritional status and mental well-being in accordance with the schedule shown in Table 1. A follow-up evaluation (on the internet or in person) at week 22 will conclude the study.

Participants will visit the University of Auckland Clinical Research Centre and a blood testing facility in Auckland on three occasions: at baseline (t_0), midway through intervention at week 5 (t_5), and at the end of intervention at week 10 (t_{10}). A blood sample will be collected from an antecubital vein by a trained phlebotomist following an overnight fast. Body weight, blood pressure, grip strength, and body composition will be measured as described below. Participants will wear a wristband accelerometer for the duration of the study to estimate their level of physical activity and sleep patterns. All participants will complete the suite of mental health questionnaires on up to 7 occasions either on the internet or in person, which takes approximately 15 minutes. From t_0 to t_{10}, participants will record their dietary intake using Easy Diet Diary. Two members of the research team will be responsible for participant recruitment, clinic visit assessments, and nutrition education delivery via the web-based platform. Participants will also be in contact with technical staff at the blood testing facility.

Table 1. Schedule of enrolment, interventions, and assessments.

	Study period							
	Enrollment	Preintervention	Intervention					Close-out
Timepoint (week)		$-t_2$	t_0	$t_{2.5}$	t_5	$t_{7.5}$	t_{10}	t_{22}
Enrollment								
Eligibility screening	X							
Informed consent	X							
Allocation		X						
Interventions								
Vegetarian[a]			X	X	X	X	X	X
Flexitarian with pasture-raised beef and lamb[a]			X	X	X	X	X	X
Assessments								
Easy Diet Diary monitoring[b]		X	X	X	X	X	X	X
Activity/sleep monitor[b]		X	X	X	X	X	X	X
MFSI-SF[c]/WHO-5[d]/ PES[e]/DASS-21[f] questionnaires		X	X	X	X	X	X	X
University of Otago Food Frequency Questionnaire		X			X		X	X
Body composition (dual x-ray absorptiometry)			X				X	
Grip strength/blood pressure/weight			X		X		X	
Erythrocyte/plasma fatty acids			X		X		X	
Inflammatory markers			X		X		X	
Minerals (Fe and Zn)			X		X		X	
Vitamins (A, D, E, and K)			X		X		X	
Insulin/glucose/high-density lipoprotein cholesterol/low-density lipoprotein cholesterol			X		X		X	
Amino acids and 1-carbon nutrients/metabolites			X		X		X	
Neurotransmitters			X		X		X	
Self-efficacy questionnaire	X							
End of intervention survey							X	X

[a]Continuous monitoring from t_0.

[b]Continuous monitoring from $-t_2$.

[c]MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form.

[d]WHO-5: World Health Organization–Five Well-Being Index.

[e]PES: Positive Eating Scale.

[f]DASS-21: Depression Anxiety Stress Scales-Short Form.

Dietary Intervention

Household units will receive regular deliveries of either red meat or vegetarian analogues sufficient for 3 evening meals per week. The quantity of meat will provide 350-500 g cooked weight per person per week, which conforms to the latest international recommendations for maximum intake [8] and the reported typical frequencies of red meat consumption [24,25].

The meat alternatives are commercially available soy protein–based products which been selected on the basis of similar quantities (350 g cooked weight), form (“beef” mince and patties which can be interchanged in recipes between red meat and vegetarian groups), macronutrient composition with a focus on total protein and fat, as well as taking product availability in the local food supply into account (Table 2).

Table 2. Comparison of red meat and vegetarian analogue nutritional profiles.

Nutrients, per 100 g	Beef[a]	Lamb[b]	Vegetarian mince[c]	Vegetarian patties[c]
Energy (kJ)	615	551	974	950
Protein (g)	20.9	20.9	18.0	14
Fat (g)	7	5.3	12.0	14.2
Saturated fat (g)	2.5	2	8.2	8.6
Carbohydrates (g)	0	0	11.0	8.9
Sugar (g)	0	0	3.6	2.0
Sodium (mg)	47	75	368	311

[a]Beef, hindquarter sirloin, separable, lean, and raw.

[b]Lamb, hindquarter double loin, separable lean, and raw.

[c]Provided on the nutrition information panel.

Participant's background diet can affect the physiological and psychological outcomes of interest. Efforts have been made to align participants' diets with healthy eating guidelines and to increase consistency between intervention arms, while still providing a realistic examination of the effects of consuming moderate amounts of red meat compared rather than its vegetarian analogue. To achieve this, household units will receive a weekly vegetarian meal kit delivery (Woop Ltd) containing complete ingredients and recipe cards for cooking 3 evening meals, which will be matched across all participants. Beyond the protein and meal kit provided, participants do have a degree of choice within their diet but are provided with a cookbook and web-based nutrition support package to facilitate healthy meal choices and preparation (see *Nutrition Education*). Collectively, the objective is to ensure that participants are meeting local recommendations for servings of core food groups consumed each day (fruits/vegetables, wholegrains, protein/alternatives, and dairy/alternatives), and minimizing the intake of discretionary foods (eg, takeaways and fizzy drinks) [30].

A secondary outcome of this study is the subjective ease, compliance, and satisfaction of following a prescribed healthy eating pattern with or without red meat. This aligns with the trial objective of understanding the psychological response to following a diet with moderate amounts of red meat or vegetarian analogues.

Nutrition Education

We have designed a web-based nutrition education package specifically for young adults, following a literature review and focus group needs assessments. The nutrition package was developed and reviewed by expert registered dietitians in the team, who are appropriately placed to ensure the accuracy and quality of information provided. The Nine Principles framework, incorporating behavioral theory and user-centered design, was used to guide its development [31]. The aim of the package is to (1) support young adults' adoption and maintenance of healthy dietary behaviors, such as those outlined in the Eating and Activity Guidelines for New Zealand Adults [30], and (2) support adherence to respective dietary arms. Each team will have a private Facebook page and messenger chat which will be utilized to deliver evidence-based nutritional information and meal ideas. Behavior change techniques used in this study include goal-setting, behavior demonstration, and setting graded tasks. The nutrition package content and delivery will be standardized across arms to encourage consistency in the adoption of healthy dietary behaviors. Participants will only be prompted to engage with nutrition education by way of notifications through Facebook and Facebook messenger as posts are made in accordance with a predetermined schedule. eHealth use will be monitored in accordance with participant's having viewed messages in the Facebook messenger chat, and engagement will be monitored in accordance with their "likes" and comments on Facebook messages and posts.

Dietary Intervention Compliance

Participants will be emailed a link to register for Easy Diet Diary (Xyris Software Pty Ltd) at $-t_2$. This app enables researchers to see all data entered in real time, allowing compliance to be routinely monitored during the intervention. Instructional support on using the app will be provided at $-t_2$ and t_0. From t_0, participants are required to record all dietary intake manually through text insertion into the app 2 days a week (Sunday and Monday). For the remaining 5 days of the week (Tuesday to Saturday), participants are required to enter intake through a choice of photographs or manual text insertion to monitor participant compliance with consuming all red meat or meat analogues provided each week. Participants will receive regular text reminders to complete their diaries. Compliance to dietary recording and the dietary intervention will be monitored twice a week (every 3-4 days). Adequate dietary recording is defined as entering at least 1 full day (ie, 3 meal occasions) per 3-4–day period. If participants are noncompliant with recording or the dietary intervention within a 3-4–day period, they will be sent a reminder through SMS text message. If they are noncompliant for 3 consecutive periods, the pair will be contacted and will discontinued from the study if adherence is not improved.

Outcomes

Primary Outcome Variable

- Change in concentrations of polyunsaturated fatty acids (18:2 n-6, 18:3 n-3, 20:4 n-6, 20:5 n-3, 22:5 n-3, and 22:6 n-3) in erythrocyte membranes post the intervention.

Secondary Outcome Variables

- Change in plasma markers of cardiovascular disease risk (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides).
- Change in plasma amino acids and 1-carbon nutrients/metabolites and their posttranslational modifications.
- Change in fat-soluble vitamins (A, D, E, and K).
- Change in plasma neurotransmitters and related metabolites.
- Change in plasma inflammatory markers (tumor necrosis factor-α, interleukin [IL]-1, IL-6, IL-8, IL-10, IL-13, high-sensitivity C-reactive protein).
- Change in blood hemoglobin and iron and zinc status.
- Change in physical health status including body composition, physical activity, and muscle strength.
- Change in psychological and mental well-being, including scores on the Multidimensional Fatigue Symptom Inventory-Short Form (MSFI-SF) [32], the Depression Anxiety Stress Scales-Short Form (DASS-21) [33], the World Health Organization–Five Well-Being Index (WHO-5) [34], and the Positive Eating Scale (PES) [35].
- Subjective experience to the diets, including eating experiences (PES), adherence to the intervention, ease of following a prescribed healthy eating pattern and satisfaction of the diet (end of intervention only).
- Adverse events.

Outcome Measurements

Dietary Intake

On completion of the intervention, the data manually entered into the Easy Diet Diary will be analyzed by FoodWorks Professional (Xyris Pty Ltd), which are aligned with those in the New Zealand food composition database (New Zealand FOODfiles 2018). This will allow for analysis of the nutritional composition of participant's diets during the intervention and to obtain insight into the dietary behaviors of participants. In addition, the Otago Food Frequency Questionnaire-Short Form will be used at t_{-2}, t_5, t_{10}, and t_{22}. It has been validated in New Zealand to assess overall nutrient intake over a 3-month period [36].

Psychological Well-being

Psychological well-being will be self-assessed at intervals during the study using the MSFI-SF [32], the DASS-21 [33], the WHO-5 [34], and the PES [35]. Together, these scales capture well-being status related to mental health, physical vitality, flourishing, and satisfaction/pleasure in eating.

Physical Activity and Sleep Monitoring

All participants will wear a Huawei Band 4 Pro fitness wristband for the duration of the study. The device has an accelerometer and optical heart beat detector that will be set to continuous monitoring, and a sleep tracker which will be enabled. Participants will be asked to download the Huawei Health smartphone app (Huawei Device Co, Ltd) before the intervention. At t_5 and t_{10} clinic visits, a weekly average number of steps and sleep duration will be collected for the previous 5 weeks from this app.

Body Composition

Body weight and height will be measured at each laboratory visit. Additionally, full body composition will be analyzed using dual x-ray absorptiometry (DEXA) at t_0 and t_{10}. Each DEXA scan is 6-9 minutes long, and measures percent body fat, percent body lean mass, and bone mineral density.

Muscle Strength

Grip strength will be assessed with a handheld dynamometer at 3 laboratory visits.

Blood Erythrocyte, Plasma, and Serum Analyses

Whole blood samples will be coagulated at room temperature for 15 minutes prior to centrifugation and serum separation, which will be stored at –80°C until analysis. Erythrocytes and plasma from whole blood containing anticoagulant will be harvested and stored at −80°C until analysis.

In erythrocytes, the fatty acid composition will be analyzed using the fatty acid methyl esters assay and through lipidomics as previously described [28,37].

In plasma, glucose and cholesterol (total, LDL, HDL cholesterol) and triglycerides will be measured using a Roche Cobas c311 through the enzymatic colorimetric assay, and insulin will be measured with an electrochemiluminescence immunoassay using the Roche E411 autoanalyzer.

Free amino acids and 1-carbon metabolites will be analyzed using ultraperformance liquid chromatography in accordance with previously published methods [38,39].

Fat-soluble vitamin extraction procedures and analysis will follow a liquid chromatography–mass spectrometry (LC–MS) method [40].

Neurotransmitters and related compounds will be measured through mass spectroscopy. These include phenylethyl amine, 3,4-dihydroxyphenylalanine, dopamine, 3-methoxytyramine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, norepinephrine, 3,4-dihydroxyphenylglycol, 3-methoxy-4-hydroxyphenylglycol, normetanephrine, epinephrine, metanephrine, vanillylmandelic acid, tryptophan, kynurenine, 5-hydroxytryptophan, serotonin, 5-hydroxyindoleacetic acid, α-aminobutyric acid, and γ-aminobutyric acid. The methodology utilizes a mass spectrometry probe and a stable isotope coding LC–MS method developed by AgResearch and has been optimized for plasma samples. The method is in accordance with previously published protocol data [41].

Inflammatory markers will be analyzed using the Invitrogen Inflammation 20-Plex Human ProcartaPlex Panel (catalogue number: EPX200-12185-901). Briefly, 25 µL of plasma and internal controls are incubated with magnetic beads prior to a series of wash steps. In total, 25 µL of detection antibody will be added and incubated for 30 min before adding 50 µL of Streptavidin-PE. The 96-well plate will be analyzed using the

Bio-Plex 200 system (BioRad) with inflammatory markers being measured in pg/mL.

Serum iron status biomarkers (iron, unbound iron capacity, ferritin, transferrin, and soluble transferrin receptor) and whole blood hemoglobin will be analyzed using a Roche Cobas c311 by enzymatic colorimetric assay. Serum zinc concentration will be analyzed using a commercial fluorometric probe kit (Ab176725, Abcam).

Self-efficacy and End of Intervention Questionnaires

The self-efficacy questionnaire will be distributed at eligibility screening. The questionnaire asks participants to indicate their levels of confidence with adherence to healthy eating behaviors, adherence to the flexitarian or vegetarian food patterns, and cooking skills.

The end-of-intervention questionnaire will include closed and open-ended questions regarding the satisfaction, ease of compliance, and likelihood of continuing the food pattern in the future.

Adverse Events

Psychological assessments will be monitored by a psychology scientist, and those who raise concerns will be referred to counseling services, with participant permission. Serious adverse events will be reported to the Health and Disability Ethics Committee.

Results

This study will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist. Our results will be communicated via publication. The trial is registered with ClinicalTrial.gov (unique identifier NCT04869163).

Discussion

Limitations

Using a free-living, mixed meal approach has its advantages in real life applicability of study findings but may hinder the clarity in outcomes. A key aim was to compare the health effects of red meat and alternatives in combination with a healthy diet, using a clearly planned nutrition education and adherence strategy. However, we acknowledge that compliance is voluntary, and the degree to which participants comply will impact the outcomes. To address this, daily food intake will be assessed using images based or mobile phone app technology and stop-go strategies in place to best support the participants in adhering to the dietary intervention and provide confidence in participant compliance [42,43].

Scientific and Industry Benefits

Concurrent analysis of physiological and psychological well-being provides an extraordinary opportunity to understand the broad benefits of a healthy diet. If the inclusion of pasture-raised red meat improves compliance, enjoyment, and measures of mental and physical health, then this can be communicated to markets and demographics that are important to industries in New Zealand. A sequence of scholarly publications will underpin, and be a prerequisite for, any marketing messages.

Data Management Committee and Availability of Data and Material

The PI is responsible for project coordination and will oversee the operational aspects of the trial. A scientific advisory group will regularly monitor study implementation, as well as data generation, documentation, and reporting. The PI will communicate protocol amendments to the ethics committee and clinical trial registration. Access to data will be granted to appropriate members of the research team and to authorized representatives from the host institution to monitor or audit the study and ensure compliance with regulations. Data will be made available to external academics on reasonable request.

Acknowledgments

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Conflicts of Interest

EB has received funding from the Meat Industry Association to investigate the nutrient composition of NZ beef. EB has received funding from meat companies (eg, First Light Foods) to study the health impacts on consuming red meat products (ACTRN12618001022257). There are no other conflicts to declare.

Multimedia Appendix 1
SPIRIT checklist.
[DOCX File , 14 KB - resprot_v10i12e30909_app1.docx]

Multimedia Appendix 2
Copy of informed consent form.
[DOCX File , 22 KB - resprot_v10i12e30909_app2.docx]

Multimedia Appendix 3
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1186 KB - resprot_v10i12e30909_app3.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DASS-21: Depression Anxiety Stress Scales-Short Form
DEXA: dual x-ray absorptiometry
HDL: high-density lipoprotein
LC–MS: liquid chromatography–mass spectrometry
LCn3: long-chain omega-3 fatty acids
LDL: low-density lipoprotein
MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form
PES: Positive Eating Scale
PI: principal investigator
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TFEQ-R18: Three-Factor Eating Questionnaire
WHO-5: World Health Organization–Five Well-Being Index

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Protocol

A Venomics Approach to the Identification and Characterization of Bioactive Peptides From Animal Venoms for Colorectal Cancer Therapy: Protocol for a Proof-of-Concept Study

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Abstract

Background: Cancer is the third leading cause of death in the United Arab Emirates (UAE), after cardiovascular diseases and accidents. In the UAE, colorectal cancer (CRC) is the first and fourth most common cancer in males and females, respectively. Several treatment modalities have been employed for cancer treatment, such as surgery, radiotherapy, chemotherapy, hormone replacement therapy, and immunotherapy. These treatment modalities often elicit adverse effects on normal cells, causing toxic side effects. To circumvent these toxicities, there has been an increased impetus towards the identification of alternate treatment strategies. Animal venoms are rich sources of pharmacologically active polypeptides and proteins.

Objective: In this proof-of-concept study, we will apply a high-throughput venomics strategy to identify and characterize anticancer bioactive peptides (BAPs) from 20 different animal venoms, specifically targeting CRC. We chose to focus on CRC because it is one of the foremost health issues in the UAE.

Methods: In the initial study, we will screen 2500 different peptides derived from 20 different animal venoms for anticancer activity specifically directed against 3 CRC cell lines and two control cell lines employing the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay for cytotoxicity. Of the 20 venoms, 3 that exhibit specific and potent anticancer activity directed against the 3 CRC cell lines will be selected; and from these 3 venoms, the specific peptides with anti-CRC activity will be isolated and characterized.

Results: This study is at the protocol development stage only, and as such, no results are available. However, we have initiated the groundwork required to disseminate the proposed study, which includes culturing of colorectal cancer cell lines and preparation of venom screens.

Conclusions: In summary, the proposed study will generate therapeutic leads to manage and treat one of the leading health issues in the UAE, namely, CRC.

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KEYWORDS

animal venoms; colorectal cancer; bioactive peptides; high-throughput screening; venom; cancer; colorectal; peptide; screening; treatment; conceptual; characterize; development; therapy

Introduction

Background

Cancer is the third leading cause of death in the United Arab Emirates (UAE) after cardiovascular diseases and accidents. In the UAE, colorectal cancer (CRC) is the first and fourth most common cancer in males and females, respectively [1]. Numerous modalities have been employed for cancer treatment, such as surgery, radiotherapy, chemotherapy, hormone replacement therapy, and immunotherapy [2]. These treatment modalities often elicit adverse effects on normal cells, causing toxic side effects such as neurotoxicity, hepatotoxicity, and nephrotoxicity [3]. To circumvent these toxicities, there has been an increased impetus to identify alternate treatment strategies.

Animal venoms are veritable gold mines of pharmacologically active polypeptides and proteins. In fact, proteins and peptides with anticancer properties have been identified and characterized from venoms of snakes, bees, scorpions, wasps, ants, spiders, and caterpillars [4,5]. One case in point is contortrostatin, a disintegrin isolated from the venom of *Agkistrodon contortrix contortrix* (southern copperhead); although it is not cytotoxic to breast cancer cells, it inhibits angiogenesis induced by breast cancer in vivo [6]. Similarly, gonearrestide, a scorpion-derived peptide, inhibits the growth of primary colon cancer cells and solid tumors by triggering cell cycle arrest in G1 phase through inhibition of cyclin‐dependent kinase 4 and by the upregulation of the expression of cell cycle regulators and inhibitors—cyclin D3, p27, and p21 [7]. Furthermore, conopeptides derived from *Conus inscriptus* have been shown to possess prospective anticancer activity, specifically against cervical cancer [8].

In summary, animal venoms comprise a mix of bioactive peptides (BAPs), many of which exhibit anticancer activity against specific types of cancer mediated by one of the following four mechanisms: (1) induction of cell cycle arrest, growth inhibition, and apoptosis; (2) inhibition of angiogenesis; (3) inhibition of invasion and metastasis; and (4) blocking of specific transmembrane channels [9].

In this proof-of-concept study, we will apply a high-throughput venomics strategy to identify and characterize anticancer peptides from 20 different animal venoms, specifically targeting colorectal cancer. We chose to focus on colorectal cancer because it is one of the foremost health issues in the UAE.

The proof-of-concept study will address two specific aims.

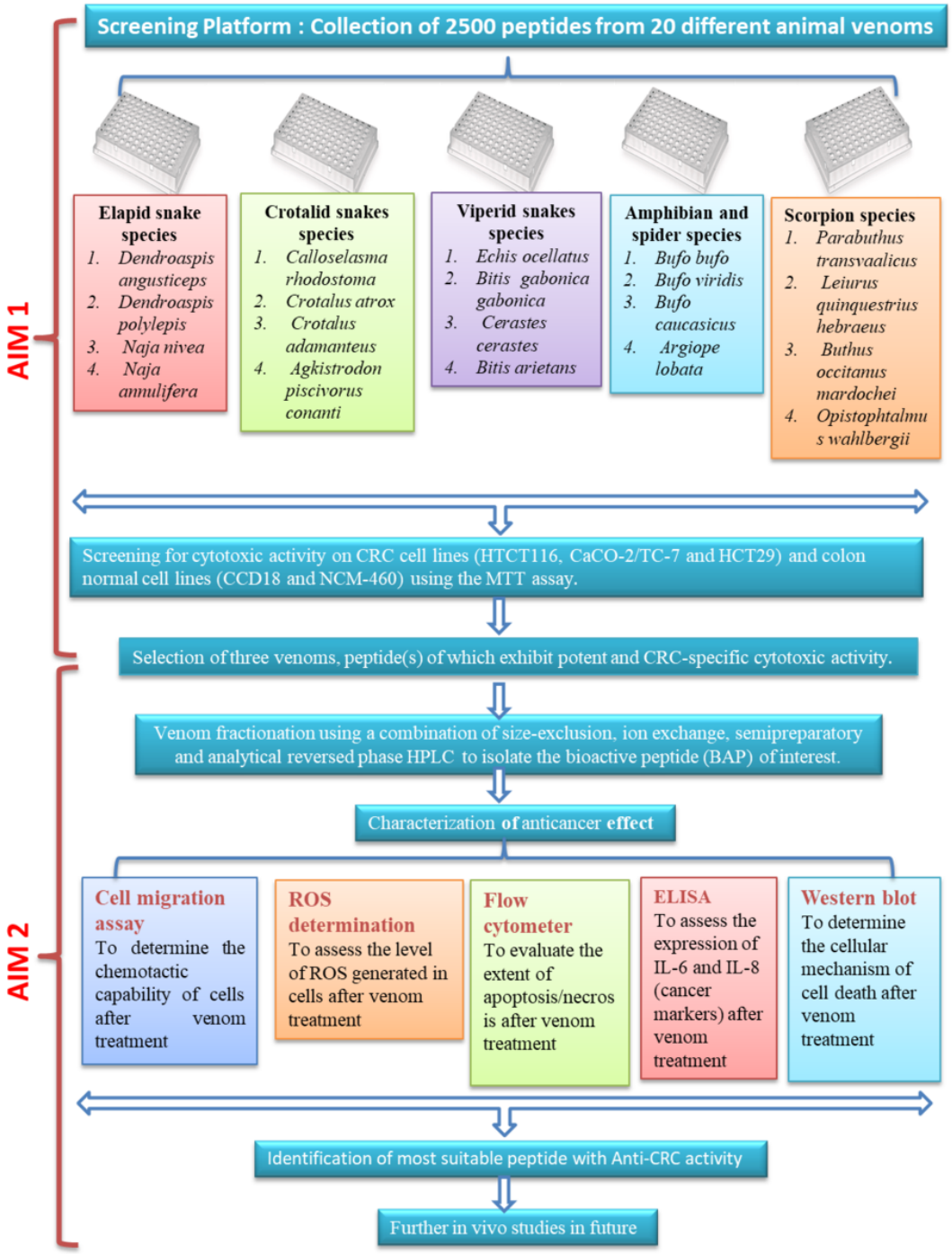
In Aim 1, we will screen 2500 different peptides derived from 20 different animal venoms for anticancer activity specifically directed against 3 CRC cell lines and 2 control cell lines employing the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay for cytotoxicity.

In Aim 2, 3 venoms of the 20 screened in Aim 1 that exhibit specific and potent anticancer activity directed against the 3 CRC cell lines will be selected; from these 3 venoms, the specific peptides with anti-CRC activity will be isolated and characterized.

Methods

The dissemination plan for the proposed research corresponding to Aim 1 and Aim 2 is shown in Figure 1.

Figure 1. Dissemination plan for the proposed research. CRC: colorectal cancer; HPLC: high-performance liquid chromatography; ROS: reactive oxygen species.



Aim 1: Dissemination

Aim 1 of the study is directed to the identification of three animal venoms which exhibit potent and specific cytotoxic activity on CRC cell lines (HCT116, Caco-2/TC-7, and HT29) and normal colon cell lines (CCD18 and NCM-460).

Preparation of the Venom-Derived Peptide Screen

This step of the project will be pursued in collaboration with Latoxan (Valence, France), a leading producer of animal venoms, with whom we have engaged in previous research collaborations. Briefly, a library of venom peptides will be created in 96-well plates. Venoms will be first cleared from molecules over 8500 Da (cytolytic enzymes). On the basis of high-performance liquid chromatography (HPLC), each venom will be split into 20 fractions. Each fraction is expected to contain 5 to 10 peptides at a 10 µmolar concentration in a volume of 100 µl. The strength of this strategy is that the separation of peptides using HPLC facilitates the identification of the active peptide once a hit (specific cytotoxic activity on CRC cell lines) is detected. Each 96-well plate will be filled with the fractions derived from 4 venoms, equaling 80 fractions and approximately 500 different peptides in total. Therefore, the entire screen contains 2500 venom-derived peptides separated in 400 lyophilized fractions from 20 different animal

venoms (refer to Figure 1 for details of the species that will be included in the screen).

Cell Culture

Human colorectal cancer cell lines (HCT116, Caco-2/TC-7, and HT29) and normal colon cell lines (CCD18Co and NCM-460) will be purchased from American Type Culture Collection. For cell culturing, RPMI 1640 (Sigma-Aldrich) medium will be used, supplemented with 10% fetal bovine serum (Sigma-Aldrich) and 1% penicillin/streptomycin antibiotic cocktail (Sigma-Aldrich). The culture flasks (T25/T75) will be incubated in a 5% CO_2 humidified incubator at 37 ºC. After reaching 70% to 80% confluency, the cells will be split using 1% trypsin–ethylenediaminetetraacetic acid (EDTA) solution (Sigma-Aldrich).

Cytotoxicity on Normal and CRC Cell Lines

High-throughput screening of 400 lyophilized venom fractions from 20 different animal species will be executed by measuring the cytotoxic activity of the fractions on CRC cell lines (HCT116, Caco-2/TC-7, and HCT29) and normal colon cell lines (CCD18 and NCM-460) using the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Merck Millipore) using the methods depicted in [10,11]. First, the lyophilized fractions will be diluted in dimethyl sulfoxide (DMSO) for further experiments. Secondly, 3000 to 4000 cells/well will be grown in 96-well plates, and after 24 hours, the cells will be introduced to 2 µM concentrations of venom fractions in complete culture medium, maintaining a blank (no venom) as a negative control and 5-fluorouracil as a positive control. After 72 hours of incubation, the cells will be incubated with 10% MTT, followed by 3 hours of incubation in dark in a 5% CO_2 humidified 37 ºC incubator. The purple formazan formed will be dissolved in DMSO (Sigma-Aldrich), and the plates will be quantified by measuring the absorbance at 570 nm using a microplate reader (Hidex). The percent viability of the cells will be calculated as:

> [(absorbance of experimental sample) – (absorbance of blank sample)] / [(absorbance of untreated sample) – (absorbance of blank sample)] × 100

IC_{50} values and statistical significance will be determined using one-way analysis of variance.

Expected Results

For 3 animal venoms, fractions (containing peptides) that exhibit specific and potent cytotoxic activity on CRC cell lines will be selected and used for subsequent studies, as depicted in Aim 2. We aim to focus on peptides; therefore, during the preparation of the screen, we will eliminate the cytolytic enzymes in the venoms.

Aim 2: Dissemination

Purification of BAPs With CRC Cell Line–Specific Cytotoxic Activity From the 3 Venoms Identified in Aim 1

The 3 venoms identified in Aim 1 will be procured in bulk from Latoxan. BAPs with CRC cell line–specific cytotoxic activity will be purified from the venoms using a combination of size exclusion, ion exchange, and semipreparatory and analytical reverse-phase high-performance liquid chromatography on an AKTA Avant multidimensional chromatography system (GE Healthcare Systems) that is available in our laboratory. The purification strategy will be similar to that described by Banerjee et al [12,13]. At each step of purification, we will check for cytotoxic activity, employing the MTT assay to identify the fraction in which the BAP is present. The purified BAP fractions will be collected, lyophilized, and stored at −20 °C until further use.

Under Aim 1, once we have screened all the venom fractions, we will analyze the hits that we have achieved. For this part of the project, we will be focusing on the hits for which cytotoxic activity is specifically observed against HT-29 cells. We will select the 3 venoms corresponding to the peptides that exhibit the most potent cytotoxic activity specifically against HT-29 cells. The remaining information corresponding to the peptides that exhibit cytotoxic activity will be used to create a biobank of active peptides, which will be the focus of later studies.

Therefore, under Aim 2 of the study, we will focus on purifying BAPs from the 3 venoms that we have selected following the screening process. These BAPs will be purified to homogeneity using a combination of chromatographic techniques (as indicated above). These purified peptides will be further characterized to identify the molecular mechanism by which they mediate the anticancer activity. Because the characterization phase will require BAPs in significant quantities, we also will use fluorenylmethoxycarbonyl (Fmoc) solid phase peptide synthesis for bulk synthesis of the BAPs. In a later phase of the study, we will establish a bacterial expression system for the mass production of the BAPs identified and characterized in Aim 2 using the methodology depicted in [14].

Determination of the Molecular Weight of the BAPs

The homogeneity and molecular weight of the BAPs will be determined by electrospray ionization mass spectrometry using a PerkinElmer Life Sciences API-300 liquid chromatography/tandem mass spectrometry (MS) system at the MS facility at SGS (Geneva, Switzerland). Typically, reverse-phase HPLC fractions will be directly used for analysis. The ion spray, orifice, and ring voltages will be standardized for analysis. Nitrogen will be used as a nebulizer and curtain gas. A LC-10AD pump (Shimadzu) will be used for solvent delivery (40% acetonitrile in 0.1% trifluoroacetic acid) at a flow rate of 50 µl/min. BioMultiview software (PerkinElmer Life Sciences) will be used to analyze and deconvolute the raw mass spectra.

Reduction and Pyridylethylation

The purified BAPs will be reduced and pyridylethylated using procedures described previously. Briefly, BAPs (0.5 mg) will be dissolved in 500 µl of denaturant buffer (6 m guanidine hydrochloride, 0.25 m Tris-HCl, and 1 mm EDTA [pH 8.5]). After the addition of 10 µl of β-mercaptoethanol, the mixture will be incubated under vacuum for 2 hours at 37 °C. 4-Vinylpyridine (50 µl) will be added to the mixture, and it will be maintained at room temperature for 2 hours. The

pyridylethylated BAPs will be purified on a Jupiter C18 analytical column (4.6×250 mm) using a gradient of acetonitrile in 0.1% (volume/volume) trifluoroacetic acid at a flow rate of 0.5 ml/min.

N-Terminal Sequencing

N-terminal sequencing of the native and S-pyridylethylated BAPs will be performed by automated Edman degradation using a pulsed liquid-phase sequencer (PerkinElmer Life Sciences Model 494, Procise) with an online Model 785A phenylthiohydantoin derivative analyzer (Applied Biosystems).

Characterization of the Anticancer Properties of the BAPs

Using a combination of different in vitro experiments, the anticancer properties of the BAPs will be characterized. The experimental protocols and the rationale for pursuing these experiments are indicated below.

Cell Migration Assay

Cell motility is a very important parameter in determining the survival and progression of cancer. Augmented cancer cell motility is the root cause of end-stage organ damage causing mortality [15]. The cell motility assay will be performed according to a procedure recommended by Rodriguez et al [16]. Briefly, CRC cells will be grown in a 60 mm Petri dish until they reach 80% confluency; then, a fine scratch will be made with the aid of a sterile pipette tip, and the scratch will be immediately photographed at hour 0. Next, cells will be supplemented with complete medium to allow them to grow. After 24 hours, the migration of the cells from the scratched area will be monitored microscopically. The width of the scratch at 0 and 24 hours will be measured, and the percentage of the gap covered by the cells will be calculated.

Determination of Reactive Oxygen Species Levels

Cancer metastasis involves a slight elevation in the production of reactive oxygen species (ROS). Cancer cells appear to thrive on high levels of ROS compared to their normal counterparts, as cancer cells have developed augmented antioxidant systems [17]. ROS generation in CRC cells and normal cells after in the presence and absence of BAPs will be assessed using 2,7-dichlorofluorescein diacetate (DCFH-DA) (Sigma-Aldrich) using the manufacturer's protocols. Briefly, CRC cells and normal cells will be plated in 6-well plates (0.3 million cells/well), and subsequently, subconfluent cells will be treated with BAPs for half an hour. Afterwards, the cells will be trypsinized and plated in new black 96-well plates, followed by incubation with 10 µM DCFH-DA for 4 hours at 37 °C. The fluorescence measurements will be performed in a Hidex microplate reader (Turku) at an excitation and emission wavelength of 485 nm and 538 nm, respectively.

Investigating Apoptosis Using Flow Cytometric Experiments

The extent of apoptosis caused by BAP will be evaluated on a FACSAria III flow cytometer (BD Biosciences) using an annexin V and 7-aminoactinomycin D (7-AAD) apoptosis detection kit (BioLegend). Cells at a concentration of 0.3 M will be seeded in a 6-well plate and incubated in a 37 ºC 5% CO_2 humidified incubator. After 24 hours, the cells will be treated with benzopyrene and 5-fluorouracil (positive control) for 24 hours. Cells will be stained with annexin V and 7-AAD in the dark for 20 minutes according to the manufacturer's protocols. FlowJo 10.7.1 software (BD Biosciences) will be used to analyze the data.

Enzyme-Linked Immunosorbent Assay

Elevated levels of vascular endothelial growth factor, IL-6, and IL-8 are proven biological markers indicating cancer progression [18,19]. Taking into consideration the proactive character of these cytokines (IL-8 and IL-6) in cancer, we will assess their expression in CRC cell lines and normal cell lines following BAP treatment using the method described by Duffy et al [18]. Briefly, 0.3 million cells will be seeded in complete culture medium containing 1% bovine serum albumin (BSA) and incubated in a 37 ºC 5% CO_2 humidified incubator for 6 hours. Purified BAPs will be introduced to the cells, followed by incubation for 24 hours. After 24 hours, the cell culture media will be collected and centrifuged to remove the cell debris. The adherent cells will be collected after trypsinization and will be counted to normalize the cytokine concentration. The assay will be executed as per the manufacturer's guideline on enzyme-linked immunosorbent assay (ELISA) plates (ExtraGene) precoated with human IL-6 and IL-8. The colorimetric intensity will be measured on a microplate reader (Hidex) at 450 nm.

Western Blot Analysis

RhoC is a metastatic protein that is found to be constitutively active in many types of cancers, including CRC [20]. We will check the expression level of RhoC and the phosphorylation of its downstream targets, ERK1/2, JNK, and P38, in BAP-treated cells to investigate the disruption of the signaling mechanisms. Equal amounts of proteins extracted from control and BAP-treated cells will be loaded on 12% sodium dodecyl sulfate-polyacrylamide gel using a Mini-PROTEAN system (Bio-Rad Laboratories). Proteins will be transferred to nitrocellulose membranes using an iBlot 2 gel transfer device (Thermo Fisher Scientific). The membranes will be incubated with RhoC, ERK1/2, JNK, P38, and GAPDH antibodies (Abcam) after blocking of the membranes with 3% BSA. After the membranes are incubated with secondary antibodies, the bands will be visualized on a ChemiDoc MP Imaging System (Bio-Rad Laboratories) with enhanced chemiluminescence detection reagents.

Statistical Analysis

Statistical analyses will be accomplished using the Student *t* test in Stata (StataCorp LLC). The mean values will be reported with standard deviations. *P* values ≤.05 will be considered significant for differences.

Results

This study is at the protocol development stage, and as such, no results are available. Experimental procedures in this study will be conducted in vitro and will not involve the use of animal

models or samples, patient samples or data, or recruitment of human subjects. Therefore, research conducted as part of this study poses minimal risk and fits one of the exempt review categories as defined by institutional review board (IRB) regulations at Mohammed Bin Rashid University (MBRU). Further clarification and information can be obtained from the MBRU IRB at irb@mbru.ac.ae. We received funding for this study following review of our proposal. The funding ID for our research is MBRU-CM-RG2021-08. Additionally, we have initiated the groundwork for this study, which includes the purchase of CRC cell lines and preparation of the venom screen kit in collaboration with Latoxan.

Discussion

Animal venoms are cocktails of pharmacologically active polypeptides and proteins. Therapeutic leads from venom have been successfully developed into drugs, such as the following examples.

Captopril

This drug [21] was developed based on the therapeutic lead of teprotide, identified and characterized from the Brazilian arrowhead viper (*Bothrops jararaca*). Captopril is a potent hypotensive agent used to manage/treat hypertension.

Tirofiban

This peptidomimetic drug [22] was first approved for therapeutic use in 1998; the original peptide lead was isolated and characterized from the venom of the African saw-scaled viper (*Echis ocellatus*). Tirofiban is commonly prescribed to patients recovering from heart attacks or experiencing angina.

Ziconotide

Ziconotide [23] is a peptidomimetic drug sold under the brand name Prialt; the original peptide was identified and characterized from the venom of *Conus magus*. Ziconotide is injected into spinal fluid to prevent pain signals from reaching the brain.

Our studies will identify novel BAPs with anti-CRC activity. These BAPs will act as therapeutic leads for the development of peptidomimetics; in the initial stages, we will apply a similar strategy to that depicted by Al-Amri et al [24] for the development of the peptides, which will have future potential for commercialization. Therefore, in the proposed study, we will attempt to develop a sufficient and resilient infrastructure capable of supporting anticipated economic growth in the UAE. Additionally, through the dissemination of this project, we will endeavor to train 7 undergraduate students and 1 graduate student in the niche of biomedical research. This aspect attests to the development of a highly skilled productive research workforce in the UAE.

Several studies are available in the literature in which the anticancer properties of animal venoms specifically targeting CRC have been investigated. However, these studies mostly focus on the anticancer properties of the whole venom rather than on the isolation and characterization of BAPs mediating the anticancer effect. For example, in the study by Al-Asmari et al [25], the anti-colorectal cancer properties of three scorpion venoms, *Androctonus bicolor*, *Androctonus crassicauda*, and *Leiurus quinquestriatus*, were assessed, but the study fell short of identifying the specific BAPs that mediated the anticancer activity. Although such studies are of biochemical research interest, they are not therapeutically viable, as whole venom cannot be administered for treating patients with CRC. Our study, on the other hand, presents a rational approach in which we will first screen for anti-CRC of specific venom, followed by isolation and characterization of those BAPs that exhibit these activities with high potency. Therefore, the strategy applied in this study can also be adopted for similar studies intending to isolate and characterize BAPs from different animal venoms.

Conflicts of Interest

None declared.

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Abbreviations

7-AAD: 7-aminoactinomycin D
BAP: bioactive peptide
BSA: bovine serum albumin
CRC: colorectal cancer
DCFH-DA: 2,7-dichlorofluorescein diacetate
DMSO: dimethyl sulfoxide
EDTA: ethylenediaminetetraacetic acid
ELISA: enzyme-linked immunosorbent assay
Fmoc: fluorenylmethoxycarbonyl

HPLC: high-performance liquid chromatography
IRB: institutional review board
MBRU: Mohammed Bin Rashid University
MS: mass spectrometry
MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
ROS: reactive oxygen species
UAE: United Arab Emirates

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Protocol

Effects of Prosthetic Rehabilitation on Temporomandibular Disorders: Protocol for a Randomized Controlled Trial

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Abstract

Background: Loss of teeth or occlusal imbalance is one of the proposed dental risk factors for temporomandibular disorders (TMDs). Losing some non–free-end teeth cause the original occluding tooth/teeth to supraerupt from the original upright position and causes neighboring tooth/teeth to shift in an angle, causing biomechanical imbalance on the mandible. Based on these sequelae, rehabilitation of missing teeth is the first step in managing TMD in edentulous patients. Even though the prevalence of TMD in association with edentulism and in rehabilitated patients has been increasing, proper guidelines for the management of such cases have not been established. This study describes the protocol to analyze the effect of prosthetic rehabilitation on patients with TMD.

Objective: This study aims to determine the effectiveness of prosthetic rehabilitation in the reduction of pain in edentulous patients with TMD and to determine the effect of the span of edentulism, the number of quadrants involved, pathological migration, the type of Kennedy classification, and the prosthetic status on temporomandibular joint dysfunction signs and symptoms.

Methods: In this randomized controlled trial, 300 patients diagnosed with TMD will be grouped into one of the three interventional groups based on the type of their edentulous state. The interventional groups are (1) partially edentulous arch: Kennedy Class I and II (prosthetic rehabilitation without splint); (2) partially edentulous arch: Kennedy Class III and IV (prosthetic rehabilitation with a splint); and (3) completely edentulous arches (prosthetic rehabilitation without splint). All three of the mentioned interventional groups have corresponding control groups that will receive symptomatic treatment and comprehensive counseling. The measured primary outcomes are pain and electromyogram, and the secondary outcomes include pain drawing, Graded Chronic Pain Scale, Jaw Functional Limitation Scale, Oral Behaviours Checklist, depression, physical symptoms, and anxiety. The outcome measurements will be recorded at baseline and at the end of 24 hours, 7 days, 28 days, and 3 months.

Results: Ethical approval was obtained from the Institutional Review Board of Amrita Institute of Medical Sciences, Kochi, India. Study participants' recruitment began in May 2021 and is expected to conclude in March 2023. This clinical trial protocol was developed based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement.

Conclusions: The purpose of this study is to gather data on prosthetic rehabilitation as a treatment for TMD. Obtaining this goal will aid in the development of evidence-based therapy protocols for prosthetic rehabilitation in TMD management.

Trial Registration: Clinical Trials Registry - India CTRI/2020/06/026169; http://ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=42381

International Registered Report Identifier (IRRID): DERR1-10.2196/33104

(JMIR Res Protoc 2021;10(12):e33104) doi:10.2196/33104

KEYWORDS

orofacial pain; joint pain; prosthesis, edentulism; TMD; temporomandibular disorder; prosthetic rehabilitation

Introduction

Background

Temporomandibular disorders (TMDs) are defined by the American Academy of Orofacial Pain as "a collective term that embraces a number of clinical problems that involve the masticatory muscles, the temporomandibular joint, and the associated structures" [1]. TMDs are characterized by clinical signs such as muscle and/or temporomandibular joint tenderness; temporomandibular joint sounds (clicking, popping, or grating) while opening or closing the mouth or while chewing; and restriction, deviation, or deflection of the mouth while opening or closing [1].

The sum or exacerbation of these signs and symptoms eventually limits or even disables individuals in their physiological activities [2]. Between 40% to 75% of the population has at least one TMD sign such as noise in the temporomandibular joint, and 33% have at least one symptom, facial pain, or temporomandibular joint pain [3]. Between 65% to 85% of humans experience some symptoms of temporomandibular joint dysfunction at some time during their life, and 5% to 7% of the whole population requires treatment to decrease the symptoms of TMD [4]. Due to the high variability in the presentation of this disorder, TMD is diagnosed by its associating signs and symptoms [5,6].

TMD have been identified as a major cause of orofacial pain of nondental origin [7]. The World Health Organization has emphasized the importance of being free of chronic orofacial pain as a clear prerequisite for oral health as well as the negative effect of functional problems, such as chewing and eating, on the individual's well-being and daily living, making them determinants of oral and general health [8]. Individuals with TMD symptoms have been found to seek different care providers and use the health care system to a greater degree as well as being more frequently on sick leave than people without these conditions [9]. Patients with TMD consequently experience a considerable negative effect on their quality of life [10].

TMDs have a complex and multifactorial etiology. One contributing factor that has been debated for years is the "occlusal condition" of the patient [10]. Loss of teeth or occlusal imbalance is one of the proposed dental risk factors for TMD. These dental factors include posterior crossbite, overjet/overbite greater than 5 mm, centric relation/maximum intercuspal sliding greater than 2 mm, edge-to-edge bite, sagittal relation class III, anterior open bite, and missing teeth [11,12]. Teeth are the most important components of the masticatory system with a close relationship with the temporomandibular joint and masticatory muscles. Any change to their normal functioning can induce pathological changes in the temporomandibular joint. *Missing posterior teeth* has been shown to have varied effect on the incidence of TMD [13-15].

Loss of teeth without replacement, especially at an early age, often causes the original occluding tooth/teeth to supraerupt from the original upright position and causes the neighboring tooth/teeth to shift in angle. Once the tooth/teeth begin to shift in angle, the vector of force tends to increase tooth-/teeth-tilting, thus imposing a different biomechanical effect on the mandible [16]. There is gender predilection, wherein the female mastication system may have less ability to withstand harmful stimulation from abnormal occlusion compared to counterparts, and thus, females may be more susceptible to TMD than men [17].

Little has changed in terms of study designs for temporomandibular joint research in the last decade, and treatment for patients with severe TMD remains controversial [18]. Following loss of occlusion due to tooth loss, there are secondary changes in the temporomandibular joint, which may accentuate further signs and symptoms [19]. The scientific community is uncertain about occlusion as the dominant cause of TMD nor do they justify prosthetic rehabilitation as the primary treatment modality for the management of TMD. The irony is that even though there is lack of evidence for loss of occlusion as a cause of TMD, the standard protocol in the management of TMD with edentulism is prosthetic rehabilitation.

There are still disagreements over the most effective and cost-effective treatment approach that can be widely distributed and used [20]. It is based on the clinical experience that, as the teeth are the most important components of the masticatory system and as they have a close relationship with the temporomandibular joint and masticatory muscles, any change to their normal functioning can induce pathological changes in the temporomandibular joint. Although prosthetic rehabilitation is the primary step in managing TMD, it is hardly justified with the evidence in the literature. With these gaps in knowledge regarding occlusion as a causative factor for TMD in the literature, we designed this trial to generate evidence regarding prosthetic rehabilitation for the management of TMD. Achieving this objective will help to develop the evidence for a treatment protocol for prosthetic rehabilitation in the management of TMD.

There are 3 intervention groups and their corresponding 3 control groups. The study has prosthetic rehabilitation with or without a splint (intraoral appliance) as the intervention. The comparator agent is symptomatic treatment and comprehensive counselling. If the patient is diagnosed with jaw joint disorder and has missing teeth, and if they are willing to take part in the study, they will be grouped into one of the three interventions or one of the three control groups based on the type of the toothless condition.

Objectives

Research Question

Can prosthetic rehabilitation of edentulous patients with TMD decrease the pain symptoms of TMD?

Hypothesis

Prosthetic rehabilitation of edentulous patients will reduce pain symptoms of TMD as compared to patients without rehabilitation.

Primary Objective

The primary objective is to determine the effectiveness of prosthetic rehabilitation in the reduction of pain in edentulous patients with TMD.

Secondary Objective

The secondary objective is to determine the effect of the span of edentulism, the number of quadrants involved, pathological migration, the type of Kennedy classification, and the prosthetic status on temporomandibular joint dysfunction signs and symptoms.

Trial Design

This trial is designed as randomized, as controlled, with a parallel arm, as blinded for outcome measurement, and with adaptive trial design.

Methods

Study Setting

The trial will be conducted at Amrita School of Dentistry, AIMS, Kochi and Amrita Urban Health Centre, Kaloor, Kochi, Kerala, India.

Study Population

Partially and fully edentulous individuals reporting to the centers for routine dental care will be recruited for the study with their consent. Patients belonging to any gender, with/without prosthetic rehabilitation, and with/without any complaint of TMD with varied edentulous span will be included in the study.

Clinical Definition

Patients presenting with pain in the jaw or temple area, pain or stiffness in the jaw, or pain on functional movements of the jaw (International Classification of Diseases, Tenth Revision, Clinical Modification Code M26.60). These symptoms are evaluated by the TMD screening questionnaire. Individuals giving a positive to any of the 3 screening questions in relation to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) will be recruited to the study. The TMD pain screener has showed high sensitivity and specificity for detecting TMD pain [21].

Eligibility Criteria

Inclusion Criteria

The following inclusion criteria will be used:

- Individuals within an age limit of 20-80 years
- Individuals completely or partially edentulous for a minimum period of 0-10 years
- Completely or partially nonrehabilitated edentulous individuals
- Patients who show signs and symptoms of myalgia of facial muscles
- Individuals who understand the importance of prosthetic rehabilitation and oral splints for TMDs
- Individuals who are willing to report at the required intervals for evaluation

Exclusion Criteria

The participant may not enter the trial if *any* of the following apply:

- TMD associated with macrotrauma of the head
- TMD associated with inflammatory/infectious/congenital disorders of the temporomandibular joint
- Individuals with Class II, Class III, or transverse malocclusion
- Individuals who refuse dental treatment
- Individuals with skeletal or dental developmental abnormalities and serious chronic medical conditions
- Any other significant disease or disorder that, in the opinion of the investigator, may either put the participants at risk because of participation in the trial or may influence the result of the trial or the participant's ability to participate in the trial

Patient Selection

Partially and fully edentulous individuals reporting to the centers will be recruited for the study with their consent. Patients belonging to any gender, with/without prosthetic rehabilitation, and with/without any complaint of TMD with varied edentulous span will be included in the study. After obtaining an informed consent, these patients will be screened using the DC/TMD screener questionnaire. The patients who are screened positive and satisfy the inclusion/exclusion criteria will be recruited to the study. They will undergo detailed oral examination and the TMD examination using the DC/TMD Axis I and Axis II questionnaire. The electromyography (EMG) reading of these patients will also be recorded. These patients will be allocated to the specific arms of the study based on their dentulous state.

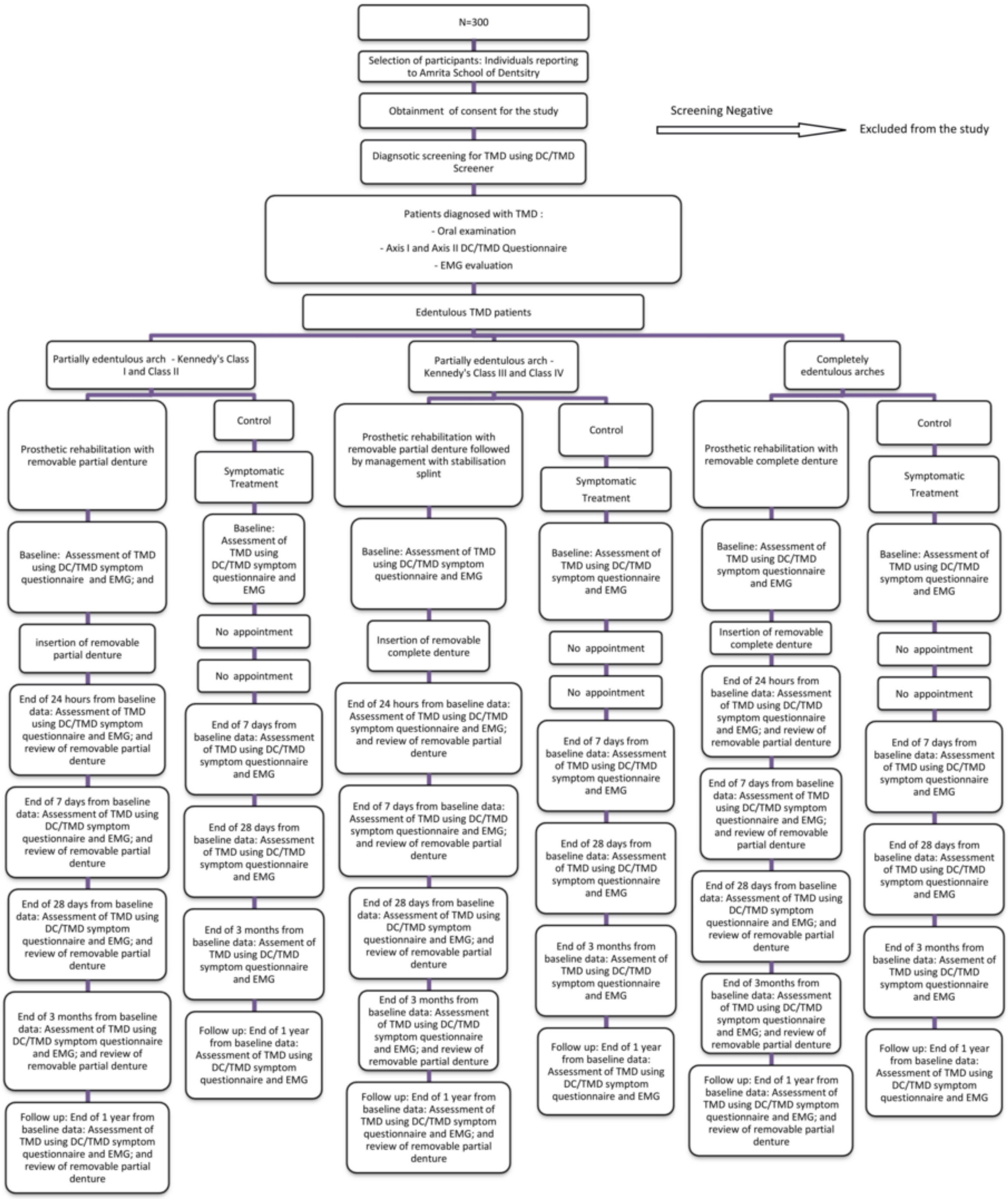
Interventions

The participants will be grouped into 3 interventional and 3 control groups based on their state of edentulism (Figure 1; higher-resolution version in Multimedia Appendix 1). The interventional groups are:

1. Partially edentulous arch—Kennedy Class I and Class II: Kennedy Class I describes a patient who has edentulous areas bilaterally, posterior to the remaining natural teeth. Kennedy Class II describes a patient who has a one-sided edentulous area, posterior to the remaining natural teeth. The participants of this group will receive mouth preparation, prosthetic rehabilitation with removable partial denture, and comprehensive counseling (n=50).
2. Partially edentulous arch—Kennedy Class III and Class IV: In Class III the edentulous area has teeth located both anteriorly and posteriorly to it. In Class IV, there will be a single but bilateral (crossing the midline) edentulous area located to the anterior of the remaining natural teeth. The participants of this group will receive mouth preparation and prosthetic rehabilitation with removable partial denture followed by management with stabilization splint and comprehensive counseling (n=50).
3. Completely edentulous arches: The participants of this group will receive prosthetic rehabilitation with removable complete denture and comprehensive counseling (n=50).

Each of the 3 mentioned interventional groups will have their corresponding control groups with 50 participants in each control group. The participants in all the 3 control groups will receive symptomatic treatment and comprehensive counseling.

Figure 1. Flowchart showing study design. DC/TMD: Diagnostic Criteria for Temporomandibular Disorders; EMG: electromyography; TMD: temporomandibular disorder.



Outcomes

The outcome measurements will be made by an examiner calibrated according to the guidelines of DC/TMD criteria. The DC/TMD instruction video has been peer-reviewed and published [22]. Self-study guidelines and description of supervised skill development have also been described. The outcome measurements will be made at baseline and at the time points of 24 hours, 7 days, 28 days, and 3 months.

Primary Outcome Measurements

Pain

Pain will be measured using the visual analog scale (VAS) for pain. The pain VAS is a unidimensional single item measure of pain intensity [23], which has been widely used in diverse adult populations. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the

"no pain" anchor and the patient's mark, providing a range of scores from 0 to 100 [24].

For pain intensity, the scale is most anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100 on a 100-mm scale). The following cut points on the pain VAS will be used: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm) [25].

Electromyography

The EMG of the masseter and the temporalis will be recorded with the individuals seated with their heads guided in the Frankfurt horizontal plane. The masseter and temporal anterior muscles will be examined with surface electrodes at an interelectrode distance of 20 mm positioned on the muscle bellies parallel to the muscle fibers ("temporal anterior: vertically along the anterior muscular margin around the coronal suture; masseter: parallel to the muscle fibers, with the upper pole of the electrode at the intersection between the tragus-labial commissure and the exocanthion-gonion lines") [26]. Reference electrodes will be applied in positions "inferior and posterior to the right ear" [27].

Secondary Outcome Measurements

Pain Drawing

The pain reported in distinct body regions, especially if related to known regional disorders (eg, headache, back pain, pelvic pain, or neck pain), can be summarized as a count variable. Extent of pain can be computed as percent of the body area [28].

Graded Chronic Pain Scale, Version 2.0

This scale [29] includes three items for pain intensity, four items for function, and one item for number of days of pain. *Characteristic pain intensity* is the computed mean of items 2 to 4 (pain right now, worst pain, average pain) multiplied by 10. The *interference score* is the computed mean of items 6 to 8 (daily activities, social activities, work activities) multiplied by 10. The total disability points are the sum of points for disability days + points for interference score. Based on the scores, chronic pain is graded as 0 (none), I (low-intensity pain, without disability), II (high-intensity pain, without disability), III (moderately limiting), and IV (severely limiting).

Jaw Functional Limitation Scale

This scale [30] with 20 items is used to calculate a single global score of "jaw functional limitation" by computing the mean of the available items. Subscale scores for each type of functional limitation are computed as follows:

- Mastication: mean of items 1 to 6
- Mobility: mean of items 7 to 10
- Verbal and nonverbal communication: mean of items 13 to 20

Oral Behaviours Checklist

Scoring can be computed as the sum of the number of items with nonzero response. Based on comparison of individuals with chronic TMD versus those without TMD, an Oral Behaviours Checklist summary score of 0 to 16 appears to represent normal behaviors, while a score of 17 to 24 occurs twice as often in those with TMD, and a score of 25 to 62 occurs 17 times more often. As a risk factor for TMD, only a score in the 25 to 62 range contributes to TMD onset [31].

Patient Health Questionnaire-9: Depression

The Patient Health Questionnaire (PHQ)-9 [32] is comprised of 9 items assessing depressed mood. A total sum score is computed. Scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe, and severe depression, respectively.

Patient Health Questionnaire-15: Physical Symptoms

The PHQ-15 [33] is comprised of 15 items and assesses nonspecific physical symptoms, also referred to as functional symptoms or medically unexplained symptoms. Items are scored by adding the individual responses. A total sum score is computed. Scores of 5, 10, and 15 represent cut points for low, medium, and high physical symptoms, respectively.

General Anxiety Disorder-7: Anxiety

The General Anxiety Disorder-7 [34] is comprised of 7 items assessing anxious mood and behavior. A total sum score is computed. Scores of 5, 10, and 15 represent cut points for mild, moderate, and severe anxiety, respectively.

Participation Timeline

Each eligible patient will be participating in the trial for 3 months, 1 year from their visit (baseline). The total number of visits will depend on the study arms to which the participants are allocated, but the outcome measurements will be recorded at 5 visits (baseline, 24 hours, 1 week, 28 days, and 3 months; Figure 2 and Table 1).

Figure 2. Schedule of enrollment, interventions, and assessment. DC/TMD: Diagnostic Criteria for Temporomandibular Disorders; EMG: electromyography.

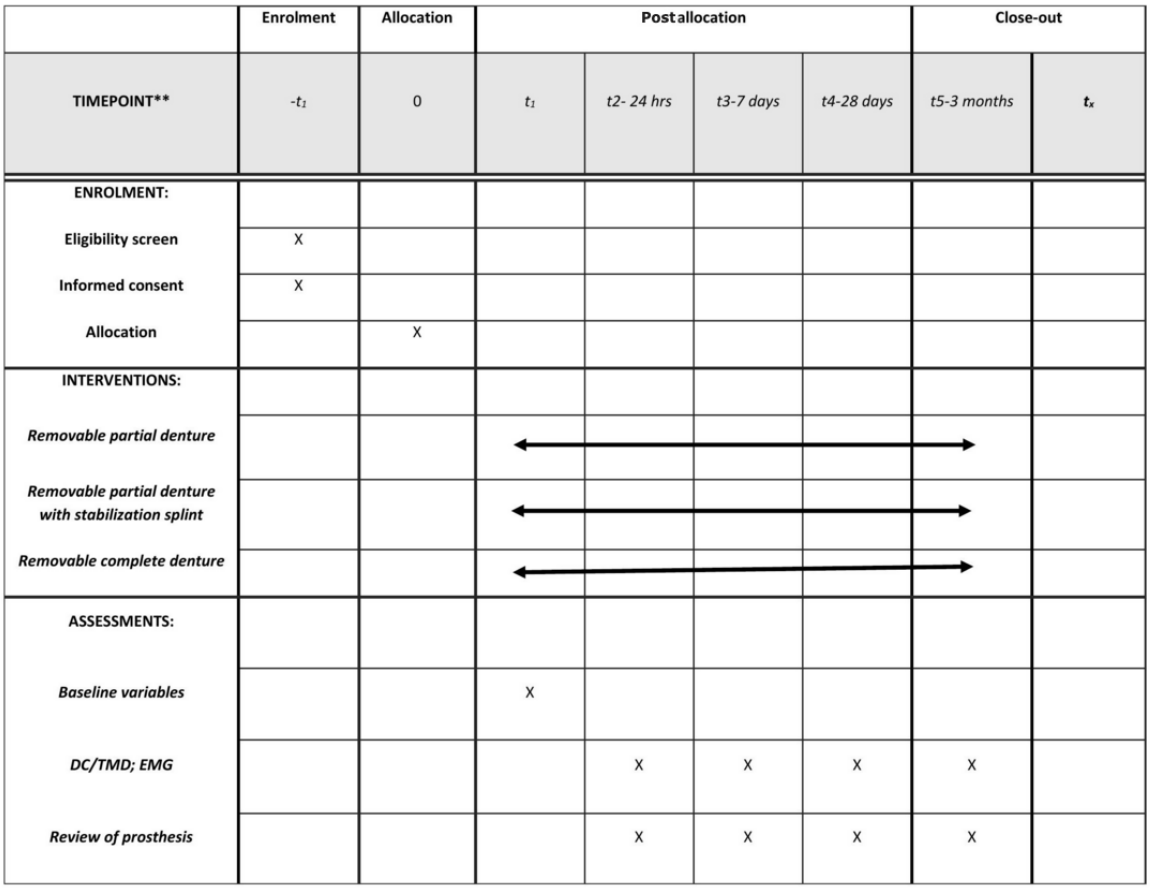


Table 1. Participation timelines.

Procedures	1[a] (0 weeks)	2[b] (2 weeks)	3 (24 hours)	4 (7 days)	5 (28 days)	6 (3 months)
Prescreening consent	Yes	No	No	No	No	No
Informed consent	Yes	No	No	No	No	No
Oral examination	Yes	No	No	No	No	No
Eligibility assessment	Yes	No	No	No	No	No
Allocation to study arms	Yes	No	No	No	No	No
Prosthetic intervention						
Group 1	No	Yes	Yes	Yes	Yes	Yes
Group 2	No	Yes	Yes	Yes	Yes	Yes
Group 3	No	Yes	Yes	Yes	Yes	Yes
Compliance	Yes	No	No	No	No	No
Assessment of DC/TMD[c], EMG[d], review of prosthesis	Yes	Yes	Yes	Yes	Yes	Yes
Adverse event assessments	No	Yes	Yes	Yes	Yes	Yes

[a]It may be single or multiple based on patient-informed consenting process.

[b]It may be multiple based on the type of prosthesis being delivered.

[c]DC/TMD: Diagnostic Criteria for Temporomandibular Disorders.

[d]EMG: electromyography.

Sample Size

The activity of masticatory muscle (mean and SD) while chewing, estimated by EMG, reflects the TMD in a patient [35]. With a power of 80%, alpha error of .05, and effect size of 0.77, the minimum sample size estimated for each group was 22. Considering attrition and the inclusion of various variables (edentulousness location, etc), we increased the sample to 50 for each interventional group. The sample size of 50 will have a minimum of 20 patients with edentulous maxilla and 20 patients with edentulous mandible for intervention groups 1 and 2. The total sample size for the study is 300 with 150 for the interventional group and 150 for the control group. Please refer to Table 2 for the sample breakdown.

Table 2. Sample size breakdown.

	Group 1: removable partial denture, n	Group 2: removable partial denture with stabilization splint, n	Group 3: removable complete denture, n	Total, n
Intervention	50	50	50	150
Patients with edentulous maxilla	20	20	20	
Patients with edentulous mandible	20	20	20	
Total	40	40	40	
Females	20	20	20	
Males	20	20	20	
Total	40	40	40	
Control	50	50	50	150
Patients with edentulous maxilla	20	20	20	
Patients with edentulous mandible	20	20	20	
Total	40	40	40	
Females	20	20	20	
Males	20	20	20	
Total	40	40	40	
Sample per group	100	100	100	300

Recruitment

The adults visiting for routine dental care prosthodontics, Amrita School of Dentistry or at Amrita Urban Dental Health Centre will be recruited for the study. On examination, if the patient is found to satisfy the inclusion criteria, then they will be given options for the management of TMD by prosthetic rehabilitation or by splints. If the patient opts for prosthetic rehabilitation, then an option of participation in the trial will be explained, and the consenting process is followed. In case the patient declines to participate in the trial, the missing teeth will be managed according to the standard protocol of the department.

Sequence Generation

The selected patient for trial will be randomly allocated to either the intervention arm or the control arm of their group, as per computer-generated randomization, schedule stratified, based on the type of group it belongs. The selected individuals will be allocated in equal probabilities to the intervention and control groups by stratified randomization. Stratified randomization is achieved by performing a separate randomization procedure within each of the two strata of participants. This will ensure that the numbers of participants receiving each intervention are closely balanced within each stratum. Treatment assignments are then made from separate randomization lists created in advance of the trial for each stratum.

Allocation Concealment Mechanism

Allocation concealment will be ensured, the randomization code will not be released until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed. The randomized codes, kept in a sealed cover at each clinic, will assign the patient to the intervention at baseline visit. The statistician will design the randomization schedule.

Implementation

The randomization will be conducted by a statistician to manage the data, and the statistician will be blind against the study condition. The randomization list will remain with the doctoral committee for the whole duration of the study. Thus, randomization will be conducted without any influence of the dentist and hygienist.

Blinding

Due to the obvious nature of the treatment, neither the treating dentist or patients are blinded; patients are only randomly allocated to the intervention. However, the data analyst or statistician will be blinded during the statistical process.

Data Collection Methods

Each personnel will be trained centrally for the study requirements, standardization of examination and assessment

of the outcomes and counselling for adherence, and the eliciting of information from study participants in a uniform reproducible manner. The data to be collected and the procedures to be conducted at each visit will be reviewed in detail. Each of the data collection forms and the nature of the required information will be discussed in detail on an item-by-item basis. Entering data forms, responding to data discrepancy queries, and general information about obtaining research quality data will also be covered during the training session. Once an individual is enrolled or randomized, the study site will make every reasonable effort to follow the individual for the entire study period of 12 months. It is projected that the rate of loss-to-follow-up on an annual basis will be at most 5%.

Retention

Everyone has the right to withdraw from the trial at any time. In addition, the treating dentist may discontinue an individual from the trial at any time if they consider it necessary for any reason, including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant noncompliance with treatment regimen or trial requirements
- An adverse event that requires discontinuation of the trial or results due to inability to continue to comply with trial procedures
- Disease progression that requires discontinuation of the trial or results due to inability to continue to comply with trial procedures
- Withdrawal of consent
- Loss of follow-up

Participants also may be withdrawn if the regulatory authorities terminate the study prior to its planned end date. If the participant is withdrawn due to an adverse event, the treating dentist will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilized.

Compliance With Trial Treatment

The follow-up visits of the individual are important for the trial. Compliance to visit the dental clinic at designated intervals is done by telephonic and email reminders to the individuals. If the individual has missed the appointment or wants to reschedule, then it is rescheduled within +/– 2 days. If the individual misses two rescheduled appointments, then it is referred as noncompliance. The individual will be withdrawn from the study. However, if the individual completes 6 months and becomes noncompliant for the next 6 months, the person's time of participation in the trial will be counted and will be used for analysis.

Data Forms and Data Entry

This may be done at a center or at the participating site where the data originated. Original study forms will be entered and kept on file at the participating site. Participant files are to be stored in numerical order and stored in a secure and accessible place and manner. Participant files will be maintained in storage for a period of 3 years after completion of the study.

All forms related to study data will be kept in locked cabinets. Access to the study data will be restricted. All reports will be prepared such that no individual patient can be identified. The study sites will send 6-month email reports with information on missing data, missing forms, and missing visits.

Statistical Methods

The effectiveness of pain reduction within each arm and between each group will be analyzed using analysis of variance. The details of the analysis are explained in Table 3.

Table 3. List of proposed analysis for trial results.[a]

Variable/outcome	Hypothesis	Outcome measure	Methods of analysis
Effectiveness of reduction of pain: within each arm	Intervention improved outcome from baseline to 12 months	Per person reduction of VAS[b] score and GCPS[c] (proportion or mean)	Chi-square methods or ANOVA[d]
Effectiveness of reduction of pain: between group 1, group 2, and group 3	Intervention improved outcome from baseline to 12 months	Per person reduction of VAS score and GCPS (proportion or mean)	Chi-square methods or ANOVA
Subgroup analysis			
Effectiveness of reduction of pain: between group 1, group 2, and group 3	Intervention improved outcome from baseline to 12 months	Per person reduction of VAS score and GCPS (proportion or mean)	Regression methods with appropriate interaction term
Between posterior teeth rehabilitation vs anterior teeth rehabilitation	Number of teeth affects effectiveness of outcome	Per person reduction of VAS score and GCPS (proportion or mean)	Chi-square methods
Upper vs lower teeth	Position of edentulism affects the effectiveness outcome	Per person reduction of VAS score and GCPS (proportion or mean)	Chi-square methods
Duration of edentulism	Duration of edentulism affects pain outcome	Per person reduction of VAS score and GCPS (proportion or mean)	Chi-square methods
Number of quadrants	Number of quadrants affects the effectiveness outcome	Per person reduction of VAS score and GCPS (proportion or mean)	Chi-square methods

[a]In all analyses, results will be expressed as coefficient, SEs, corresponding 95%, and associated *P* values. Goodness of fit will be assessed by examining the residuals for model assumptions and chi-square tests for goodness of fit.

[b]VAS: visual analog scale.

[c]GCPS: Graded Chronic Pain Scale.

[d]ANOVA: analysis of variance.

Analysis Population and Missing Data

We will report reasons for withdrawal for each randomization group and compare the reasons qualitatively. The effect that any missing data might have on results will be assessed via sensitivity analysis of augmented data sets. Dropouts will be included in the analysis by using multiple imputation methods for missing data. Excluding patients from the analysis who violated the research protocol (did not get their intended treatment) can have significant implications that impact the results and analysis of a study. If the attrition loss is less than 15%, a per protocol analysis will be carried out; otherwise, “intention to treat” will be performed.

Data Monitoring

An interim analysis is performed on the primary end point (reduction in pain) when 50% of patients have been randomized and have completed the 12-month follow-up. The interim analysis will be performed by an independent statistician, blinded for the treatment allocation.

Research Ethics Approval

This clinical trial protocol has been approved by the Institutional Review Board (IRB) of Amrita Institute of Medical Sciences, Kochi, India. The investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki. The protocol, site-specific informed consent forms (speaking language), participant education and recruitment materials, and other requested documents—and any subsequent modifications—will be reviewed and approved by the IRB. The chief investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice. The chief investigator shall submit once a year throughout the clinical trial, or on request, an annual progress report to the IRB. In addition, an end of trial notification and final report will be submitted.

Consent to Participate

A trained trial coordinator will introduce the trial to patients who will be shown a video regarding the main aspects of the trial. Patients will also receive information sheets. They will discuss the trial with patients considering the information provided in the video and information sheets. Patients will then be able to have an informed discussion with the participating consultant. The participant will be detailed on no less than the exact nature of the trial, what it will involve for the participant, the implications and constraints of the protocol, and the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

They will obtain written consent from patients willing to participate in the trial. Information sheets and consent forms are provided for all participants involved in the trial. All information sheets, consent forms, and the video transcript will be in speaking language. Written and verbal versions of the participant information and informed consent will be presented to the patient. They will be allowed as much time as wished to consider the information and have an opportunity to question the treating dentist to decide whether they will participate in

the trial. Written informed consent will then be obtained by means of a participant dated signature and dated signature of the person who presented and obtained the informed consent. A copy of the signed informed consent will be given to the participant. The original signed form will be retained at the trial site.

Protocol Amendments

Any modifications to the protocol that may impact the conduct of the study or potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will be notified to the IRB for approval.

Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database. All documents will be stored securely and only accessible by trial staff and authorized personnel. The trial will comply with the Data Protection Act, which requires data to be anonymized as soon as it is practical to do so. Source documents are where data are first recorded and from which participants' case report form (CRF) data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents other than the signed consent, the participant will be referred to by the trial participant number/code, not by name. The participants will be identified by a unique trial specific number or code in any database.

Results

Ethical approval was obtained from the IRB of Amrita Institute of Medical Sciences, Kochi, India. Informed consent will be obtained from all participants before recruiting to the study. Recruitment began in May 2021.

Discussion

Overview

There have always been controversies regarding occlusion as a causative factor for TMD. The effect of partial/total edentulism and their rehabilitation on temporomandibular joint has not been documented in any long-term clinical trials. To better understand this phenomenon, long-term studies that evaluate both edentulism as a cause of TMD and prosthetic rehabilitation as a prevention or cure of TMD must be conducted. Even though the prevalence of TMD in association with edentulism and in rehabilitated patients has been increasing, proper guidelines for the management of such cases have not been established. Any attempt to identify and symptomatically treat to relieve such patients from pain also means improvement of their quality of life.

Strengths and Limitations of This Study

This study has the following strengths and limitations:

- The study design (RCT) will provide evidence of prosthetic rehabilitation on the TMD.
- Patients with TMD are grouped based on their edentulous state as completely or partially edentulous, and partially edentulous patients are classified further based on the Kennedy classification. This ensures that the effect of different types of edentulism on TMD are assessed.
- EMG reading for recording the muscle activity is an additional quantitative outcome evaluation used to assess and evaluate the TMD.
- As the study has a follow-up period of 3 months after the intervention, we expect some amount of attrition.

Conclusion

This protocol has input from a study that we conducted on a tribal population to find out the prevalence of TMD. The study found out that there is a relation between the type of edentulism and TMD. The research question was developed based on this research experience and understanding that there is a lack of well-designed trials to evaluate the effects of prosthetic rehabilitation on TMDs. The study has been designed by grouping edentulous patients to different strata based on the types of edentulism.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Higher-resolution version of Figure 1.
[PNG File , 3767 KB - resprot_v10i12e33104_app1.png]

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Abbreviations

CRF: case report form
DC/TMD: Diagnostic Criteria for Temporomandibular Disorders
EMG: electromyography
IRB: Institutional Review Board
PHQ: Patient Health Questionnaire
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TMD: temporomandibular disorder
VAS: visual analog scale

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Protocol

Optimizing a Just-in-Time Adaptive Intervention to Improve Dietary Adherence in Behavioral Obesity Treatment: Protocol for a Microrandomized Trial

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Abstract

Background: Behavioral obesity treatment (BOT) is a gold standard approach to weight loss and reduces the risk of cardiovascular disease. However, frequent lapses from the recommended diet stymie weight loss and prevent individuals from actualizing the health benefits of BOT. There is a need for innovative treatment solutions to improve adherence to the prescribed diet in BOT.

Objective: The aim of this study is to optimize a smartphone-based just-in-time adaptive intervention (JITAI) that uses daily surveys to assess triggers for dietary lapses and deliver interventions when the risk of lapse is high. A microrandomized trial design will evaluate the efficacy of any interventions (ie, theory-driven or a generic alert to risk) on the proximal outcome of lapses during BOT, compare the effects of theory-driven interventions with generic risk alerts on the proximal outcome of lapse, and examine contextual moderators of interventions.

Methods: Adults with overweight or obesity and cardiovascular disease risk (n=159) will participate in a 6-month web-based BOT while using the JITAI to prevent dietary lapses. Each time the JITAI detects elevated lapse risk, the participant will be randomized to no intervention, a generic risk alert, or 1 of 4 theory-driven interventions (ie, enhanced education, building self-efficacy, fostering motivation, and improving self-regulation). The primary outcome will be the occurrence of lapse in the 2.5 hours following randomization. Contextual moderators of intervention efficacy will also be explored (eg, location and time of day). The data will inform an optimized JITAI that selects the theory-driven approach most likely to prevent lapses in a given moment.

Results: The recruitment for the microrandomized trial began on April 19, 2021, and is ongoing.

Conclusions: This study will optimize a JITAI for dietary lapses so that it empirically tailors the provision of evidence-based intervention to the individual and context. The finalized JITAI will be evaluated for efficacy in a future randomized controlled trial of distal health outcomes (eg, weight loss).

Trial Registration: ClinicalTrials.gov NCT04784585; http://clinicaltrials.gov/ct2/show/NCT04784585

International Registered Report Identifier (IRRID): DERR1-10.2196/33568

(JMIR Res Protoc 2021;10(12):e33568) doi:10.2196/33568

KEYWORDS

obesity; weight loss; dietary adherence; just-in-time adaptive intervention; microrandomized trial; mobile phone

Introduction

Background

Behavioral obesity treatment (BOT), a first-line intervention for overweight and obesity, typically produces a 5% to 10% reduction in initial body weight [1,2]. However, many individuals lose less weight than expected, thereby negating the potential health benefits of weight loss (eg, reduced cardiovascular disease [CVD] risk and severity) [3,4]. These suboptimal outcomes can be, in part, attributed to nonadherence to the prescribed calorie goal and recommended dietary guidelines to reduce energy intake [5]. Research has shown that dietary lapses (ie, specific instances of nonadherence to BOT dietary goals) occur 3-4 times per week in BOT and are associated with poorer weight losses on average [6,7]. Although the ability to cope with temptation and prevent lapse has been associated with BOT success [8-10], there is insufficient evidence on how to provide these necessary skills for individuals to reduce dietary lapses in BOT.

Extant strategies to improve adherence in BOT (eg, stimulus control) require vigilance for potential lapse triggers and the ability to implement an effective plan to avoid lapse. Alternatively, just-in-time adaptive interventions (JITAIs) can proactively monitor lapse risk and provide support to prevent lapses in an adaptive manner and in exact moments of need [11,12]. Our team developed a smartphone-based JITAI that uses ecological momentary assessment (EMA) [13] to monitor triggers for lapses via repeated surveys throughout the day [14]. The JITAI analyzes EMA responses in real time using a machine learning algorithm to calculate the ongoing level of risk for lapsing and then delivers preventive intervention as needed. This JITAI has demonstrated feasibility and acceptability in two 8- to 10-week pilot studies [15,16]. Using simple intervention messages (ie, 1-2 screens of text), the JITAI was associated with *average* reductions in dietary lapses. However, the JITAI has not been evaluated for efficacy directly in the moments of heightened lapse risk, and there is little evidence (or theory) available to guide *which* interventions should be delivered in these moments of vulnerability to achieve maximum clinical benefit.

Objectives

To develop a scientifically rigorous and maximally effective JITAI for dietary adherence, research must experimentally evaluate the proximal efficacy of theory-driven interventions for reducing lapses [17]. This paper describes the design of a microrandomized trial (MRT) to optimize a JITAI for dietary lapses by empirically determining which theory-driven interventions are effective in preventing lapses and contexts that could influence intervention effectiveness [18,19]. Each time a participant is determined to be at high risk for lapsing based on the JITAI's algorithm, they will be randomized to either no intervention, a generic alert to risk, or 1 of 4 theory-driven intervention options to provide education on dietary goals, increase self-efficacy, enhance motivation, or improve self-regulation. Each participant can be randomized over 100 times during the study (based on the rate of algorithm-determined lapse predictions), which will efficiently provide the critical information required to optimize the JITAI [17,18]. The results of this study will inform an improved JITAI for lapses that can be evaluated in a future randomized controlled trial (RCT) and contribute to the broader evidence base of developing JITAIs for problematic eating behaviors (ie, understanding the relative efficacy of theory-based approaches to modifying behavior and informing dynamic theoretical models of behavior).

Methods

Study Aims and Design

This study aims to optimize a smartphone-based JITAI for dietary lapses by evaluating the efficacy of 4 theory-driven interventions on the proximal, immediate outcome of lapse during BOT. This study uses an MRT design because it is the most efficient experimental design to determine *which* interventions are efficacious *at a given moment in time* [18]. The use of the MRT, with more than 100 randomizations and observations of the outcome per participant, allows for the evaluation of each intervention condition with full statistical power [17]. In stage 1, the JITAI and MRT study procedures (including the microrandomization algorithm) will be tested with a small number of participants for 3 months to ensure proper functioning before proceeding to stage 2. In stage 2, adults with overweight or obesity and ≥1 CVD risk factor (eg, diagnosis of hypertension, hypercholesterolemia, and type 2 diabetes) will participate in a well-established 3-month web-based BOT (BOT + JITAI) with 3 months of JITAI-only follow-up. During BOT and follow-up, participants will use the smartphone-based JITAI consisting of the following: (1) EMA to assess lapses and relevant behavioral, psychological, and environmental triggers; (2) a machine learning algorithm that uses information gathered via EMA to determine real-time lapse risk; and (3) randomized administration of intervention to counter lapse risk. When an individual is at risk for lapsing, they will be randomized to no intervention, a generic risk alert, or 1 of 4 theory-driven interventions with skills training. The primary proximal outcome of interest will be the occurrence (or lack thereof) of dietary lapse, as measured by EMA [7], in the 2.5 hours following randomization. The secondary proximal outcomes of interest will be the passive measurement of eating characteristics (ie, duration, rate of eating, and count of bites taken in the 2.5 hours following randomization) via wrist-based monitoring for the first 14 days of treatment and subsequent 14-day periods at 3 and 6 months [20]. Contextual moderators will be explored to determine the circumstances under which interventions are more or less effective (ie, location, time of day, whether in active BOT or follow-up, and type of lapse triggers endorsed). JITAI engagement, satisfaction, and weight will be measured at baseline, 3 months, and 6 months. When the MRT is complete, stage 3 will consist of using the data to inform an optimized JITAI that selects the theory-driven approach most likely to counter lapse risk in a given moment. This study has 4 aims:

- Aim 1: evaluate the effects of any intervention (ie, theory-driven or generic risk alert) versus no intervention

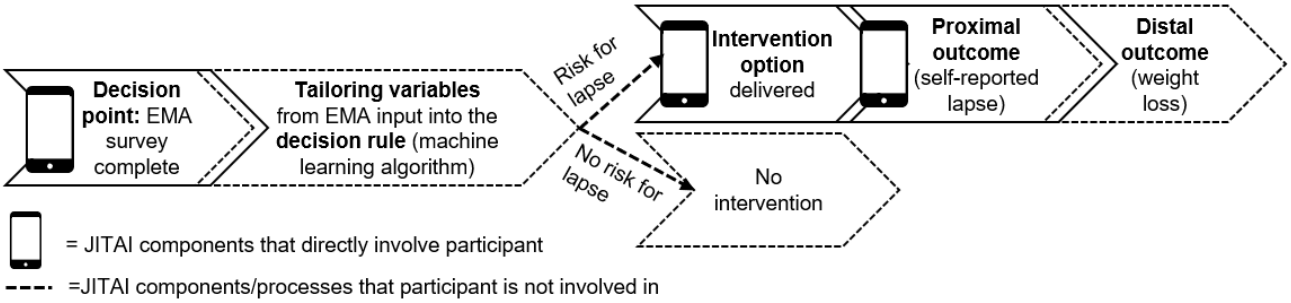
on the occurrence of dietary lapse in *each moment* when the lapse risk is predicted to be high.
- Aim 2: compare the effects of theory-driven interventions and generic risk alerts on the occurrence of dietary lapse.
- Aim 3: use the data from the MRT to optimize an algorithm for intervention delivery that will drive the JITAI in a future RCT examining the effects on overall weight change in an obesity treatment program.
- Exploratory aim: examine contextual moderators (eg, time, location, and active BOT or follow-up) of interventions.

JITAI for Dietary Lapses

Overview

The JITAI for dietary lapses to be optimized by the current trial was developed in line with the conceptual framework set forth by Nahum-Shani et al [21]. According to their established framework, JITAIs should include the following components: decision points (times at which an intervention decision is made), tailoring variables (information that is used at a decision point to decide when and how to intervene), decision rules (algorithms deciding which intervention option to offer and for whom and when), intervention options, proximal outcomes (behaviors directly targeted by the JITAI), and distal outcomes (health conditions that are expected to improve as a result of targeting proximal outcomes). A conceptual model of the JITAI components in the current trial and how they work together to provide real-time adaptive intervention to prevent dietary lapses is shown in Figure 1.

Figure 1. Conceptual model of just-in-time adaptive intervention components. EMA: ecological momentary assessment; JITAI: just-in-time adaptive intervention.



Decision Points

As shown in Figure 1, the decision points in this trial occur immediately following the completion of each EMA survey [21]. EMA is well suited to inform decision points because the measurements of tailoring variables can be repeated over time in the changing context of everyday life, thus informing multiple opportunities for assessment and intervention [22]. Consistent with previous studies, the JITAI for lapses will prompt participants via vibration and audible tone to complete 6 EMA surveys throughout the day (anchor times at 8:30 AM, 11:00 AM, 1:30 PM, 4:00 PM, 6:30 PM, and 9:00 PM) [7,15,16]. Participants are given 90 minutes to respond to an EMA survey before it expires. The 6 EMA surveys inform 6 decision points each day for which an intervention *could be provided*. Randomization to an intervention option will only be triggered at a subset of decision points in which an EMA survey is completed, *and* lapse risk is judged to be elevated, which previous work has shown occurs approximately once per day on average [15].

Tailoring Variables

A JITAI tailoring variable is participant information that is used to decide (1) when to intervene (ie, help define the decision point) and (2) how to intervene (ie, which type of intervention to administer) [21]. The tailoring variables used to determine *when* to intervene in the proposed JITAI will be measured via 17 EMA survey questions that assess behavioral, psychosocial, and environmental triggers for lapse. Pilot studies confirmed that these 17 variables are feasible to assess via EMA and are suitable for predicting lapse in the JITAI (see the *Measures* section for a complete list of tailoring variables) [7,15,23]. The exploratory aim of this research is to identify other tailoring variables (eg, contextual moderators) to refine the JITAI by explaining *how* to intervene under specific risk conditions.

Decision Rule

The decision rule uses tailoring variables to identify the current state of vulnerability and specifies when it is appropriate to offer intervention [21]. Owing to substantial individual variability in what tailoring variables and at which thresholds indicate a heightened state of lapse risk, a machine learning algorithm informs the decision rule in this JITAI for lapses [6,24-26]. In formative work to develop this JITAI, a supervised machine learning approach was used to train an algorithm using previously collected data on tailoring variables and dietary lapses. Preliminary research revealed that ensemble classifiers, a series of C.5 decision tree algorithms, predicted the likelihood of reporting a lapse in the next EMA survey (in approximately 2.5 hours) with 72% specificity and 70% sensitivity [7]. This study also showed that combining group- and participant-level data is the most efficient approach to lapse prediction; therefore, the decision rule algorithm allows the JITAI to start with a base algorithm comprised of data from previous trials and then continuously adapt itself to the individual via incoming information. When piloting this JITAI for lapses, the decision rule algorithm predicted lapses with 80% negative predictive value (n=43) [15] and 76.5% accuracy (n=116) [16], thus indicating that it is ready for use in the current trial. At each decision point, the tailoring variables from a participant's EMA survey will be uploaded to the JITAI platform (operating via PiLR Health, a product of MEI Research Ltd to execute EMA

studies), which will process the data using the above-described decision rule algorithm (Figure 1). On the basis of these data, the algorithm will then predict whether or not a participant is likely to lapse in the following 2.5 hours. If the prediction for lapse is *yes*, then the participant will be randomized to 1 of 6 intervention conditions (ie, 4 theory-driven interventions, generic risk alert, and no intervention). If the prediction for lapse is *no*, then nothing will be done at that time because the participant is not in a state of heightened lapse risk.

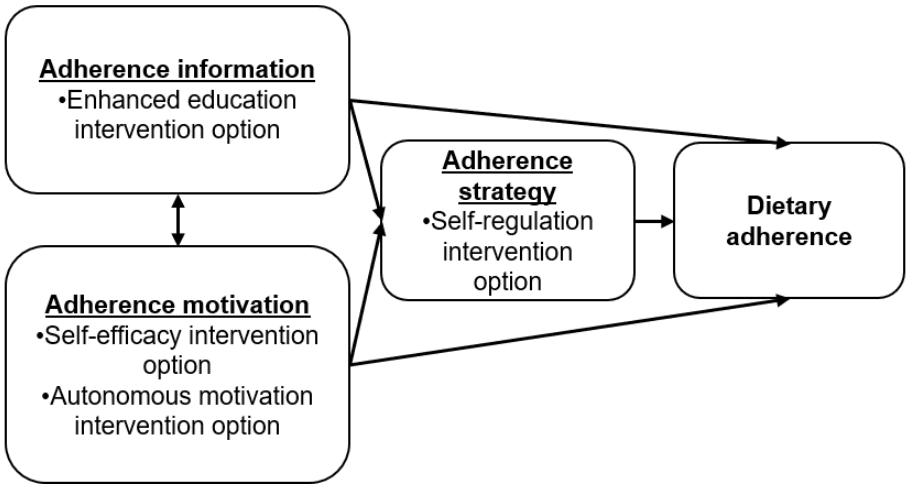
Intervention Options

Overview

The intervention options in a JITAI should be driven theoretically or empirically [21]. Previous pilot studies to develop this JITAI for lapses have used simple—interventions (ie, 1-2 screens of text) based on a multitude of behavior change taxonomies. This study will improve upon previous work by using an a priori selected conceptual model of adherence behavior to guide theory-driven intervention options that are designed to be interactive and engaging.

The theory-driven intervention options to be evaluated in this study were developed using the Information-Motivation-Strategy (IMS) model as a theoretical basis [27]. The IMS model extends and is grounded in several health behavior models (eg, Health Belief Model and Theory of Planned Behavior) and has been shown to be a valid approach to understanding adherence behaviors via meta-analytic reviews and large-scale trials [27,28]. The IMS model posits that there are 3 influences on adherence to health recommendations or guidelines: (1) information (ie, providing education on factors that influence adherence and treatment goals), (2) motivation (ie, motivating patients to carry out recommendations via self-efficacy and aligning to a person's values), and (3) strategy (ie, strategizing with participants to ensure capability and ability to adhere). In addition to being an empirically validated model for studying adherence behavior, generally, the IMS model can flexibly incorporate theory-driven interventions with empirical support for dietary adherence, specifically. The IMS model also encourages tailoring within the categories, making it consistent with the JITAI framework. Figure 2 illustrates how the IMS model informed the following theory-driven intervention options to be tested within this MRT, focusing on enhanced education, self-efficacy, autonomous motivation, and self-regulation.

Figure 2. The information-motivation-strategy model that informed the just-in-time adaptive intervention options.



The selected intervention options act as companions to the web-based BOT program. They are designed to remind participants to use skills that they have already been taught through the web-based BOT (ie, self-monitoring, setting dietary goals, basic self-regulation skills, and problem-solving) or provide easy-to-digest new strategies to facilitate engagement in behavioral skills. Each intervention option (as well as the active comparator and generic alerts to risk) comprises a library of brief intervention modules that can be administered in any order. The variation in intervention content is expected to facilitate long-term engagement via reduced repetition and encourage well-rounded skill development [29,30]. If a participant is randomized to a theory-driven intervention option or active comparator condition, a module will be randomly selected from the library of that condition. Each module is designed to have the highest impact while minimizing burden. The content of these modules, which is hosted in the PiLR Health platform, consists primarily of 3- to 5-minute instructional videos that are interactive where possible (eg, prompting participant responses and using branching logic to tailor content) [12]. A description of the modules included in each theory-driven intervention option as well as active and inactive comparators is presented in subsequent sections.

Enhanced Education Intervention Option

The IMS model highlights the importance of participant knowledge in determining adherence [27,31]. Providing education on the link between dietary recommendations and health has improved dietary adherence among participants with CVD risk [32,33]. In particular, asking participants to repeat key points has been shown to increase the understanding of disease and enhance adherence to dietary guidelines [34,35]. A library of 6 independent modules was created; all modules seek to promote the understanding of health behavior links, improve health literacy by using brief quizzes, and remind participants of important elements of the BOT dietary goals. When participants are randomized to the enhanced education intervention option, they will randomly receive one of the

following independent modules focused on (1) the role of dietary fat in health and strategies to reduce the consumption of saturated and trans fats, (2) the role of sodium in health and recommendations for sodium intake to reduce CVD risk, (3) the role of added sugars in health and strategies to reduce the consumption of foods with added sugar, (4) the role of small lapses in contributing to higher caloric intake for the day and strategies for reducing small lapses, (5) preventing lapse during a high-risk time by choosing foods that are low in calories and filling, *or* (6) the role of evening calorie consumption on health and weight loss (delivered in evenings only). This intervention option is expected to improve dietary adherence by reminding participants of important health goals and improving knowledge retention.

Self-efficacy Intervention Option

According to the IMS model, participants' confidence in their ability to change behavior (ie, self-efficacy) is essential for adherence [27]. Self-efficacy has been robustly associated with improved weight loss and adherence to dietary recommendations, which provides strong justification for targeting it in the JITAI for lapses [36,37]. A library of 4 independent modules was created based on self-efficacy–based BOT [38], a multi-component intervention that has been shown to improve self-efficacy for weight loss via goal-setting, problem-solving, self-reward, and coping with difficult thoughts. When participants are randomized to the self-efficacy intervention option, they will randomly receive *one* of the following modules developed to emulate self-efficacy–based BOT: (1) setting attainable goals related to dietary adherence; (2) barrier identification for adhering to dietary goals along with a brief problem-solving exercise; (3) devising a small, non–food-related self-reward for adhering to the day's dietary goal; *or* (4) a self-assessment of negative thoughts that could interfere with dietary adherence in the next several hours, along with suggested coping statements. This intervention option is expected to facilitate dietary adherence by improving self-efficacy in moments of heightened lapse risk, which will enhance motivation and the ability to engage in adherence strategies.

Autonomous Motivation Intervention Option

Another central tenant of the IMS model is that beliefs about the value of engaging in a behavior are critical to adherence [39-41]. A library of 4 independent modules was created based on principles from motivational interviewing (MI) and acceptance and commitment therapy (ACT) [42,43]. Both MI and ACT are widely used strategies for improving and maintaining motivation for health behavior change [44,45]. MI and ACT use a collaborative and nonjudgmental approach to identify valued directions and make mindful decisions about engaging in behaviors that are consistent with short- and long-term goals. When participants are randomized to the autonomous motivation intervention option, they will randomly receive *one* of the following modules: (1) guidance in identifying values related to healthy eating and weight control (eg, longevity and quality of life) and connecting those values to daily dietary goals, (2) exploring the short- and long-term consequences of choosing to lapse or stay the course (eg, "Take a moment to consider the effect on your longevity if you let your preferences for sweets determine your behavior"), (3) clarifying values and thinking about every behavior (including a lapse) as an *up* or *down* vote for their values, *or* (4) engaging participants in a brief self-assessment of motivation for dietary adherence. This intervention option is expected to facilitate dietary adherence by increasing the salience of participants' beliefs about the importance of their dietary goals.

Self-regulation Intervention Option

The IMS model indicates that participants must have *capacity* and *ability* in order for adherence to occur [27]. The *capacity* to adhere, in particular to self-regulate dietary intake and thus prevent lapse, largely depends on the ability to maintain awareness of eating behavior [46,47]. The self-regulation approach to BOT has been extensively tested and encourages the self-regulation of dietary intake via increased prompts to intensify self-monitoring of dietary intake [48-50]. A library of 5 independent modules was developed to prompt self-monitoring and improve self-awareness. When participants are randomized to the self-regulation intervention option, they will randomly receive *one* of the following modules: (1) a prompt to self-monitor any foods before they are consumed in the next 2 to 3 hours, (2) introduce the *traffic light* model to improve the awareness of intake using a quick rule-of-thumb system especially when the risk for lapse is high [51], (3) increase the awareness of portion sizes during heightened lapse risk (eg, reading labels, weighing and measuring, and portion size guide), (4) provide a tutorial on noticing hunger and satiety cues and slowing down the rate of eating, *or* (5) prompt an awareness of end-of-day grazing or mindless eating that may lead to lapses (delivered during evenings only). The self-regulation intervention option is expected to facilitate the necessary self-regulation strategies required for dietary adherence.

Generic Risk Alert (Active Comparator)

A generic risk alert intervention option is included as an active comparator to the theory-driven intervention options, as it controls for the potential influence of receiving any notification of risk. For example, the notification alone could be expected to influence lapse risk via heightened awareness of behavior. A library of 3 generic risk alert messages was created (eg, "We have detected that your risk of lapsing from your weight loss diet is higher than usual and may require attention"). When participants are randomized to the generic alert active comparator, they will randomly receive *one* of these simple text-based messages (containing no interactive components or video).

No Intervention (Inactive Comparator)

A *no intervention* option will be used as an inactive comparator to the theory-driven intervention options and the generic risk alert. Randomizing to *no intervention* will control for the potential impact of being notified of heightened lapse risk, which could activate any pre-existing strategies to prevent lapse. When participants are randomized to the no-intervention inactive comparator, they will *not* receive any notification that the lapse risk is elevated.

Web-Based BOT Used to Test the JITAI: Rx Weight Loss

Given that dietary lapses are specific instances of nonadherence to one or more BOT dietary goals, interventions examining and targeting lapses must be tested within the context of BOT so that participants have dietary goals to lapse from. Participants will be provided with a well-established web-based BOT called Rx Weight Loss (RxWL). The RxWL program was initially developed to facilitate weight loss in 154 primary care patients, whose mean weight loss was 5.8% (SD 4.4%) of the initial body weight at 3 months that was maintained for an additional 3 months [52]. Since then, RxWL has been refined and tested in multiple contexts (eg, worksites and community settings) and consistently produces similar weight losses [53-55].

The RxWL program begins with a 30-minute introductory session in which a member of the research team introduces the program eating and activity goals, teaches the participants how to use RxWL, and provides brief instructions on self-monitoring. Participants are given a goal of losing 1 to 2 pounds per week to achieve a total weight loss of approximately 5% to 10% of their initial body weight. In order to achieve weight loss, they are prescribed a calorie goal of 1200 to 1800 kilocalories per day tailored to their initial weight, given guidelines to follow a low-fat or Mediterranean diet [56-58] and asked to gradually increase their physical activity to 200 minutes per week of aerobic exercise [59]. Participants are asked to self-monitor their daily weight, daily dietary intake, and daily physical activity [60]. Following the introductory session, RxWL consists of 12 weekly 10- to 15-minute multimedia lessons for training in behavioral strategies for healthy eating and physical activity. Lessons are interactive to improve patient engagement; they incorporate video, animation, audio, quizzes, and exercises for goal-setting, planning, and problem-solving [61]. Topics are drawn from gold standard, empirically supported weight management programs such as Look AHEAD and Diabetes Prevention Program [62,63] and include meal planning, developing an exercise schedule, restaurant eating, changing the home environment, obtaining social support, and weight loss maintenance. Each week, participants submit daily values for tracked weight, caloric, and physical activity minutes to the RxWL platform (or this information can be automatically shared with RxWL if the participant chooses to use the Fitbit app for self-monitoring). Participants then receive automated feedback messages on their progress to date in the form of text appearing on the RxWL platform. Messages contain encouragement for meeting weight, diet, and activity goals, as well as strategies to improve weight loss if goals are not met. As dietary feedback is based on average weekly caloric intake, RxWL feedback is distinct from interventions provided within the JITAI for dietary lapses, which focus on lapses and triggers occurring at specific moments in time. To ensure adequate engagement with RxWL, email reminders will be sent to participants who have not visited the platform in a given week. Participants will use RxWL for 3 months and then be asked to continue to follow the dietary recommendations and self-monitoring during the 3-month follow-up period (during which time they will be receiving the JITAI with no access to RxWL).

Stage 1: Technical Preparation and Refinement

Although many of the components of the JITAI for dietary lapses have been extensively piloted, this will be the first time that it is being hosted on the PiLR Health platform, which ultimately supports improved scalability and delivery in future work. The first phase of this trial will therefore consist of a small refinement study to ensure proper functionality of the JITAI in PiLR Health and to identify any barriers to implementing the study protocol (eg, microrandomization and assessment procedures). Participants from the target population (n=15) will complete the trial protocol procedures as described below for 3 months. Participants will complete study assessments, which include questionnaires and wearing a wrist-based device to passively sense eating behavior at baseline and at 3 months. Semistructured interviews will be used to collect feedback at the 3-month assessment visit, during which time participants will be queried to identify initial problems and potential solutions related to using the JITAI in conjunction with the web-based BOT. Problems that arise during stage 1 will be resolved before commencing stage 2 (the fully powered MRT).

Stage 2: The Microrandomization Trial

Overview

Stage 2 will consist of an MRT to evaluate the effects of 4 theory-driven interventions, generic risk alerts, or no intervention on the immediate occurrence of dietary lapse during a 6-month web-based BOT. The participants (n=159) will receive 3 months of web-based BOT + JITAI, followed by 3 months of JITAI only. The follow-up period allows the JITAI to be evaluated during active BOT and JITAI-only follow-up (during which time participants may choose to pursue continued weight loss or weight loss maintenance). The MRT includes sequential randomization to intervention options each time the JITAI identifies heightened lapse risk. The participants will attend an in-person orientation session, followed by baseline, 3-month, and 6-month assessments. The primary proximal outcome is dietary lapse (assessed via EMA after the randomization of intervention options). The secondary proximal outcome is eating characteristics (measured via wristwatch device at assessments) following the randomization of intervention options. Contextual moderators, such as location, time of day, whether the participant is in active BOT or follow-up, and the type of lapse trigger will be collected to fulfill the exploratory aim of this project. Information regarding JITAI engagement and satisfaction, and weight change will be collected and used for descriptive purposes. To ensure the safety of participants and staff during the COVID-19 pandemic, procedures have been designed such that they can be conducted via remote means (eg, video calls for study appointments and wireless scales) and in person. Participants will be compensated for completing the study appointments, completing EMA surveys, and wearing the wristwatch device.

Participant Eligibility Criteria

The following eligibility criteria ensure a generalizable sample of individuals with CVD risk who are interested in and would benefit from weight loss. Inclusion criteria are as follows: BMI

between 25 and 50 kg/m^2; age between 18 and 70 years; physician-confirmed diagnosis of prediabetes, type 2 diabetes mellitus, hypercholesterolemia, or hypertension; able to walk 2 city blocks without stopping; and English language fluency and literacy at the 6th grade level. Exclusion criteria are as follows: currently participating in another weight loss program; currently taking weight loss medication; having lost >5% of body weight in the 6 months before enrollment; pregnant within the 6 months before enrollment; plans to become pregnant within 6 months of enrollment; endorses experiencing chest pain during periods of activity or rest, or loss of consciousness in the 12 months before enrollment; endorses any medical condition that would affect the safety of participating in unsupervised physical activity; history of bariatric surgery; and endorses any condition that would result in an inability to follow the study protocol, including terminal illness, substance abuse, eating disorder (not including binge eating disorder), and untreated major psychiatric illness.

Recruitment and Enrollment

Participants will be recruited via advertisements in local media (eg, newspapers and radio), targeted web-based advertising (including social media), flyers and advertisements posted in waiting rooms and examination rooms in primary care offices, referrals from physicians within the Lifespan health system and hospital network, informational materials made available as part of the health and wellness program for employees in the hospital network, and direct mailings. Recruitment of men and minorities will be maximized by tailoring the advertisement content and placement. Interested individuals will be given a brief study description and screened via a web-based survey or telephone to determine eligibility. Those who appear eligible will be invited to attend an orientation session, where the study will be described, informed consent will be obtained, and BMI will be confirmed via height and weight measurements. Before returning for the baseline visit in approximately 1 week, participants will be asked to have their physician sign a permission form that confirms their CVD diagnosis as well as safety to participate in the weight loss program, complete baseline questionnaires, adequately record dietary intake for 7 days (at least two meals or snacks per day), and complete 7 days of the JITAI EMA protocol (at least 70% of EMA surveys completed). These procedures ensure that only eligible participants who are capable and willing to adhere to study procedures move forward with the remainder of the study. At the baseline appointment, participants receive a 30-minute introductory session to the web-based BOT and training in using the JITAI for dietary lapses.

Microrandomization

Sequential randomization (or microrandomization) to intervention options will occur via an algorithm that was created by the research team and embedded within the PiLR Health system server. Microrandomization begins at the start of the third week after participants have completed 2 weeks of EMA without any interventions on their dietary lapses and relevant triggers. PiLR Health will then use the algorithm and accrued participant data to microrandomize the delivery of interventions at each decision point (ie, when a participant is determined to be at risk for lapse after completing an EMA survey). The randomization is independent of prior randomization and participants' responses to previously delivered interventions for lapse [18]. On the basis of pilot work, the predictive algorithm that guides the decision rule in this JITAI is expected to predict a heightened state of lapse risk approximately 1 to 2 times per day *on average* across participants [15]. This estimated average accounts for potential decreases in EMA adherence and the likelihood of lapse that may occur during the study. As such, each participant will likely be randomized to an intervention option approximately 180 times over the study period. In accordance with the primary aim to compare the immediate, proximal effect of any active intervention option as compared with no intervention, intervention options will be randomized based on the following probabilities: 0.4 of decision points will be randomized to no intervention (inactive control), 0.12 to generic risk alerts (active control), 0.12 to the enhanced education intervention option, 0.12 to the self-efficacy intervention option, 0.12 to the autonomous motivation intervention option, and 0.12 to the self-regulation intervention option. As such, a given participant is expected to receive no intervention at approximately 72 decision points over the study, and the remaining 108 decision points will be divided equally among the 5 remaining intervention options (approximately 21-22 each).

Measures

Participants will complete assessments with a research assistant who does not need to be blinded because of sequential randomization at baseline, 3 months, and 6 months to complete the measures. Outcomes collected via the JITAI EMA will occur 6 times per day over the 6-month study period.

Primary Proximal Outcome Measure

As in several previous trials conducted by the research team and others, dietary lapses will be assessed via EMA [6,7,64]. EMA typically captures naturalistic eating behavior better than lab-based tasks because near real-time reporting has the potential to reduce bias and improve validity [13,65,66]. Participants will be asked at each EMA survey to report whether they have experienced a dietary lapse since the last survey. A dietary lapse will be defined as any "eating or drinking likely to cause weight gain and/or put weight loss/maintenance at risk." Participants will be asked to record the time of the lapse and will be asked to describe the lapse using the following select all-that-apply options: "I ate a larger portion of a meal or snack than I intended," "I ate when I had not intended to eat," or "I ate a type of food that I intended to avoid." Participants will be trained to identify and report dietary lapses at the baseline visit and retraining will occur at 3- and 6-month visits.

Secondary Proximal Outcome Measures

Wrist-based accelerometry will be used to passively infer the frequency of eating, duration of eating episodes, rate of eating, and estimated count of bites during eating. The goal of including these objectively measured eating characteristics is to examine the potential effects of the JITAI intervention options on eating behaviors that are difficult to capture via self-report (eg, longer duration of eating [67], slower eating [68], more regular eating

patterns [69], and more bites per meal). Participants will wear the ActiGraph GT9X Link (ActiGraph, LLC) on their dominant wrist for 2 weeks at each assessment point (first 14 days of treatment, 3 months, and 6 months). Although the ActiGraph is typically used to measure physical activity and sleep, the inertial measurement unit, which contains an accelerometer and a gyroscope, allows for the detection of a characteristic wrist-roll motion that occurs when food is brought to the mouth. These data will be analyzed using eating detection and characterization algorithms that have been extensively developed and validated by the research team [20,70-73]. These studies have shown that wrist-roll patterns and velocity can be analyzed to infer the timing and duration of eating with approximately 81% accuracy and estimate the number of bites taken during a meal with 86% sensitivity [20,71]. Both metrics can then be used to calculate the rate of eating (seconds/bite) [20]. After inferring and characterizing eating episodes, the following variables will be calculated: number of eating episodes, the average duration of eating episodes, total duration of eating, average bites taken during each episode, total bites taken, and the average rate of eating. During the baseline assessment period, these variables will be calculated at the day level and used descriptively because microrandomization will not take place. During the 3- and 6-month assessment periods, these variables will be calculated at the level of microrandomization (eg, 2-3 hours between intervention access and the next EMA survey).

Tailoring Variables

Each JITAI EMA prompt will measure tailoring variables that have been previously validated for lapse prediction across several pilot studies [7,15,23]. The data will be used by the predictive decision rule algorithm to determine whether an individual is likely to be in a state of heightened lapse risk. The following tailoring variables will be assessed: hunger, cravings, missed meals or snacks, presence of tempting food, urges to eat, socializing (with and without food), watching television, affect, negative interpersonal interactions, seeing advertisements for food, hours of sleep, fatigue, confidence, planning meals and snacks, boredom, cognitive load (ie, amount of cognitive difficulty during everyday tasks), level of motivation for weight loss, alcohol consumption, and time of day (automatically recorded by PiLR Health). Each EMA question and the respective response options that will be used to measure the tailoring variables are featured in Table 1. As described in the analytic plan, tailoring variables will also be evaluated as exploratory contextual moderators (eg, if the presence of a particular trigger impacts the efficacy of intervention options).

Table 1. Just-in-time adaptive intervention tailoring variables that inform the determination of heightened states of risk for dietary lapse.

Tailoring variable	Ecological momentary assessment question	Response options
Missed meal or snack	"Have you eaten since the last survey?"	• Yes • No
Affect	"Please rate your current mood"	• I am in an especially good mood • I am in a good mood • I feel slightly stressed/upset • I feel very stressed or upset • I feel intensely stressed or upset
Fatigue	"Do you feel tired right now?"	• Yes • No
Hunger	"Are you hungry right now?"	• Yes • No
Boredom	"Are you bored right now?"	• Yes • No
Motivation for weight loss	"Compared with other things in your life, is weight control a high priority for you right now?"	• Yes • No
Cravings	"Are you experiencing a craving (an intense desire or urge to eat a specific food) right now?"	• Yes • No
Urges to eat	"Since the last survey, have you had a sudden urge to go off your eating plan for the day?"	• Yes • No
Cognitive load	"Since the last survey, please rate the difficulty of tasks that you have been working on in terms of the mental effort required (eg, work, planning, decision-making)."	• Requiring almost no mental effort • Requiring slight mental effort • Requiring moderate mental effort • Requiring most of my mental effort • Requiring almost all of my mental effort
Confidence	"How confident are you that you can meet your dietary goals for the rest of the day?"	• Not at all • A little bit • Somewhat • A lot • Very • Extremely
Socializing	"Since the last survey, have you engaged in socializing with coworkers, family, or friends?"	• None • Yes, and there was food present • Yes, and there was not food present
Watching television	"Since the last survey, have you watched TV?"	• Yes • No
Interpersonal interactions	"Since the last survey, have you had an unpleasant encounter with another person?"	• Yes • No
Presence of tempting foods	"In the past hour, would it have been easy to access delicious (but unhealthy) food/drink?"	• Yes • No
Food advertisements	"In the past hour, have you seen an advertisement for food?"	• Yes • No
Planning meals or snacks	"To what extend have you planned your eating in the next few hours?"	• Not at all • Slightly • Moderately • Very • Extremely

Tailoring variable	Ecological momentary assessment question	Response options
Alcohol consumption	"Since the last survey, have you consumed any alcohol?"	• Yes • No
Sleep	"How many hours of sleep did you have last night?"	(Numeric response)
Time of day	Automatically recorded by the PiLR app	Automatically recorded in PiLR

Contextual Moderators

Contextual moderators will be used to further optimize intervention delivery within the JITAI. In addition to informing the JITAI decision rule, the above-described tailoring variables will be evaluated as contextual moderators (eg, if the presence of a particular trigger impacts the efficacy of intervention options). In addition, analyses will explore potential moderators of location (self-reported via EMA as described in Table 1) and whether the participant is in active BOT or JITAI-only follow-up.

Measures for Descriptive Purposes

Engagement and Satisfaction

Engagement with the JITAI (ie, the degree to which surveys and interventions within the JITAI were completed) will be assessed via PiLR Health. The following information will be automatically timestamped by the server: EMA surveys delivered, EMA surveys completed, interventions delivered, interventions accessed, and any responses recorded in interactive content. From this information, the percentage of EMA surveys completed, percentage of interventions accessed, and percentage of interventions with recorded participant interaction will be calculated. Participants will be asked to indicate satisfaction with the intervention content using a 5-star rating system (1 star is least helpful and 5 is the most helpful) at the conclusion of each module [74].

Participant Characteristics

Demographic information, health, and weight history will be assessed at baseline. Weight will be measured to the nearest 0.1 kg using a digital scale at each assessment; height will be measured to the nearest millimeter with a stadiometer at baseline, using standard procedures. Measurements will be made in light indoor clothing without shoes. Height and weight are measured solely for descriptive purposes and are to be used in reporting.

Analytic Plan, Sample Size, and Power Estimates

Analytic Plan

Statistical analysis will follow good practices for the evaluation of RCTs as embodied in the Consolidated Standards of Reporting Trials statement [75]. Preliminary analyses will include descriptive statistics and exploratory graphing for all variables of interest that are measured at all assessment points. Initial exploratory data analysis will be used to identify outliers, such as measurement and recording errors, logical inconsistencies in data, and values extreme in the marginal distributions of the variables in question. Key baseline variables (eg, baseline BMI, age, and sex) will be considered for use as covariates in the proposed analyses. Missing data will be imputed using a multiple imputation approach and outcome models averaged across imputations to adhere to the intent-to-treat principle. A sensitivity analysis will explore the impact of various assumptions about missing data on study results, including assumptions that the outcome (lapses) is missing not at random, as participants may be more likely to skip surveys when they have lapsed.

Generalized multilevel models will be used to evaluate the study aims [76,77]. These types of models allow for increased statistical power, account for a hierarchical data structure (eg, observations nested within individuals within days), and include all participants regardless of whether there are missing data at particular time points [78]. First, a generalized multilevel model will be used to examine the effect of any intervention (4 theory-driven interventions and generic risk alert) compared with the *no intervention* condition on the occurrence of lapse (aim 1). Whether an intervention is provided at a decision point will be used to predict each participant's probability of reporting a lapse in the following EMA survey. Next, an interaction between the intervention indicator variable and the week in which the intervention occurred will be added to test time trends in intervention effects [79]. Different distributions and link functions will be evaluated by comparing and assessing model assumptions and goodness-of-fit measures. Restricted maximum likelihood will be used to estimate the model parameters and to test the significance of random effects. Statistical significance will be accepted when $P<.05$ (2-tailed) and the estimated coefficient for the predictor (without accounting for the time trend) will represent the overall (average across all decision points) effect of delivering any intervention versus providing no intervention on the probability of lapse.

Second, similar methods will be used to build generalized multilevel models that examine the efficacy of the 4 individual theory-driven intervention options, compared with the generic risk alert, on the immediate occurrence of lapse (aim 2). In total, 4 intervention indicator variables will be used separately to represent whether each of the 4 theory-driven interventions was provided at a decision point, which allows for the comparison of the average effects of the theory-driven intervention options versus the generic risk alert on the probability of reporting a lapse in the next EMA survey. A comparison among the intervention options will be informed by estimated effect sizes.

Aim 1 and aim 2 analyses will be repeated to evaluate the immediate effects of intervention options on objectively measured eating characteristics at 3 and 6 months. Generalized multilevel models will be used to examine the effects of intervention indicators on the number of eating episodes detected via ActiGraph between the decision point and the next EMA survey, and the duration, rate of eating, and number of bites taken per eating episode recorded during that period.

Intervention indicators will be allowed to interact with the day of assessment (eg, day 1 vs day 14 of wear time) and assessment period (eg, baseline vs 3 months) to account for potential time trends in intervention effects. In addition to other key demographic variables (eg, baseline BMI, age, and sex), ActiGraph wear time (hours per day that the device was worn) will be considered as a potential covariate.

Third, potential contextual moderators (ie, time of day, location, active treatment vs follow-up, and type of lapse trigger) will be added to the above-described generalized multilevel models to further inform JITAI optimization (exploratory aim). Moderators will be allowed to interact with the intervention indicators to determine whether these variables moderate the effect of the intervention on probability of reporting a lapse in the next EMA survey. Meaningful moderators will have interaction terms that are statistically significant at the $P<.05$ level. Statistically significant interactions will be interpreted by plotting simple regression lines for each level of categorical variables or for high and low values of continuous variables. Given the exploratory nature of this aim, analyses will not formally control for multiple comparisons, but claims about results will be made with appropriate caution.

All analyses will be conducted on the intent-to-treat sample (every instance of microrandomization and subsequent intervention delivery will be included in the final analysis), and several assumptions about the missing data mechanism will be evaluated. Sensitivity to these assumptions will be tested by collecting follow-up information on all participants (including dropouts), and loss-to-follow-up censoring will be employed. In total, 3 statistical approaches for handling missing data will be compared: a multiple imputation approach to impute missing outcomes, inverse probability weighting with propensity scores to produce unbiased estimates provided that data are missing at random, and pattern mixture models to allow for the possibility that data are not missing at random.

Sample Size and Power Estimates

The sample size requirements of this trial were based on analyses proposed to accomplish both aim 1 (ie, compare the effects of no intervention option and any intervention option) and aim 2 (ie, compare the effects of theory-driven intervention options and the active comparator to one another). Statistical power and sample size were calculated according to the established procedures for powering MRTs, as described by Liao et al [17], which enable robust treatment effect estimation using the centered and weighted least squares method [80]. On the basis of previous work, participants are expected to average 180 points of randomization during the trial with an assumed 100% availability (because a participant in an algorithm-determined heightened state of lapse risk will have just completed an EMA survey, indicating that they are near a smartphone and able to engage [15]).

The sample size calculation began with aim 2, given that the minimum clinically significant difference among active intervention options will likely be smaller than comparing no intervention with any intervention. Using available data from previous studies, a standardized effect size of 0.1 for aim 2 was calculated (which corresponds to a minimum clinically significant difference of reducing lapses by an average of 1 lapse per week, with an SE of 3.27). A reduction of 1 lapse per week is estimated to be associated with an *additional* 2.6% weight loss over 6 months for a single intervention option, which could substantially boost the overall proportion of participants achieving meaningful weight losses. The estimated number of decision points available in which any of the 2 single intervention options were delivered is 43 (180 total decision points × 0.24 probability of delivering either of 2 intervention options). Thus, the required sample size to detect any given contrast between intervention options in aim 2 at 80% power and 0.05 type 1 error rate is 106. Inflating this number by 50% to account for the binary nature of the proximal outcome brings the required sample size to 159. For aim 1, a larger standardized effect size of 0.153 was estimated that corresponds to reducing lapses by an average of 2 lapses per week with an SE of 3.27. With the projected sample size of 159, type 1 error rate of 0.05, 180 decision points at which either intervention or no intervention was provided, and 0.60 probability of providing any intervention option, there will be at least 90% power to detect the specified effect for aim 1.

Stage 3: Application of MRT Results for Optimization

Stage 3 of this trial will involve using the results of the MRT to inform additional algorithms that will ultimately optimize intervention delivery within the JITAI for dietary lapses. Results from aims 1 and 2 will contribute to an understanding of the most effective intervention for preventing the immediate, proximal occurrence of dietary lapse, whereas results from the exploratory aim will inform which interventions are effective in a particular context (eg, if the autonomous motivation intervention option is effective in the afternoon vs other times of day). Together, these findings will be used to optimize the current JITAI decision rule (ie, deliver an intervention whenever any participant is in a heightened state of lapse risk) by training the intervention delivery algorithm to also consider *contexts* in which *certain types* of intervention options should be delivered. The resulting new decision rule algorithm, ideally using models that are minimally computationally intensive and easy to interpret (eg, regressions and decision trees), will be dynamic and personalized by considering baseline variables (eg, sex, age, race, ethnicity, and baseline BMI), specific trigger types (eg, feelings of hunger vs feelings of boredom), and context (eg, location and time of day). The finalized JITAI will no longer randomize intervention but administer the intervention option likely to have the greatest effect under the current risk conditions. Stage 3 ensures the development of an optimal JITAI for dietary lapses that is ready to be tested in a future RCT to evaluate the effects on distal clinical outcomes such as weight and CVD risk.

Results

This study was funded by the National Heart Lung and Blood Institute (Multimedia Appendix 1). As of the date of submission of this manuscript, the trial is ongoing. Data collection for stage 1 began on April 19, 2021, and has been completed. Stage 2 recruitment is scheduled to begin by October 1, 2021. As this research involves no more than minimal risk, there will be no

interim analysis, and data and safety monitoring will occur in accordance with guidelines by the National Institutes of Health and the Institutional Review Board of record. Ethical approval was granted by the Miriam Hospital Institutional Review Board.

Discussion

Anticipated Findings

Overweight and obesity remain major public health concerns [81,82]. BOT is a recommended first-line treatment for weight loss and has the potential to reduce the severity of CVD risk factors [1-4]. However, nonadherence to the prescribed diet in BOT (ie, dietary lapse) has been shown to prevent many individuals from achieving expected weight loss outcomes [5,6]. Although gold standard BOT protocols typically provide behavioral strategies that are intended to promote dietary adherence (eg, stimulus control and meal planning), these interventions do not appropriately account for the complex, momentary, and dynamic nature of the numerous potential triggers of dietary lapses in everyday life [12]. Instead, a smartphone-based JITAI for dietary lapses that assesses potential triggers for lapse via EMA and provides intervention during heightened states of lapse risk, is a scalable approach that has shown promise for improving dietary adherence in BOT [15,16]. This clinical optimization trial represents a critical next step in developing this JITAI for dietary lapses, aiming to optimize the approach by empirically tailoring the provision of an evidence-based intervention to the individual and the context.

This study will use a JITAI to compare which theory-driven interventions (vs no intervention or a generic alert to lapse risk) have an immediate, proximal impact on dietary lapses and other characteristics of eating behavior (eg, rate of eating and bite count). The results will establish, for the first time, whether the provision of in-the-moment intervention during heightened states of lapse risk has a direct effect on preventing lapse. These data will inform the optimization and refinement of the JITAI by revealing which types of interventions and in what contexts have the greatest impact on lapse [18,79]. Using this formative work to optimize the JITAI now ensures that the intervention is maximally effective, efficient, and directly targets the proximal outcome of interest (ie, dietary lapses) before conducting a future RCT to evaluate the efficacy of the JITAI for improving weight loss and reducing CVD risk [18].

An MRT design will be used to examine immediate, proximal effects of intervention options on lapse and thus provide the necessary data to optimize the JITAI. Rather than randomizing an individual only once to a single treatment, as is typical in an RCT, the MRT uses sequential randomization to repeatedly randomize individuals to intervention at specific instances based on their current state or context (in the current trial and heightened lapse risk) [17,19]. As each participant will be randomized approximately 180 times over the course of the study, the design requires fewer participants to achieve sufficient power to detect the proximal main effect of an intervention option. In contrast, using a traditional RCT to optimize this JITAI would require numerous participants across 6 intervention conditions *and* would not be able to directly compare intervention options within subjects. The MRT is therefore a major strength of this research, as it accelerates the translation of research to practice by answering several research questions within one study using fewer participants than a traditional RCT [83,84].

This project will be the first known implementation of an MRT protocol to optimize a JITAI on the proximal outcome of eating behavior. Across the field of health behavior change, MRTs remain novel; there are several MRTs in the process of optimizing JITAIs in the areas of physical activity [85,86], smoking cessation [87,88], stress management [88], mood [86], medication adherence [89], and substance use [90,91]. A recently completed MRT to increase self-monitoring in a commercial wellness app for lifestyle behaviors found that sending prompts with tailored suggestions (vs tailored feedback) significantly increased the odds of self-monitoring and that the frequency of engagement with the app moderated this effect (eg, as frequency of self-monitoring increased and sending prompts with suggestions reduced the odds of engagement) [92]. The results of this trial demonstrate the way in which MRTs provide crucial information about how context impacts intervention efficacy. One of the most influential MRTs was the microrandomized optimization trial of HeartSteps, which has provided a guiding framework for harnessing the MRT design for JITAI optimization [18]. The trial evaluated the efficacy of different types of suggestions to increase physical activity via the HeartSteps mobile app [79]. The results revealed that providing a walking suggestion (vs no suggestion) increased step count by an average of 24% and that suggestions to reduce sedentary time did not affect step count. The study also found that the efficacy of suggestions in HeartSteps was initially stronger and diminished over the course of the study. The HeartSteps trial has informed several methodological and practical guidelines for executing MRTs [17,19,93,94] and provided a rich data source to optimize future versions of HeartSteps via innovative algorithms that personalize the content and timing of activity suggestions [95-97].

A major strength of the proposed JITAI for dietary lapses is the use of previously validated machine learning algorithms to determine the heightened states of lapse risk. Machine learning has enormous possibility for informing precision medicine tools; the ability to make sense of vast amounts of individual data through dynamic algorithms enables highly sophisticated and nearly automatic patient feedback [98-100]. One aim of the proposed MRT is to develop *additional* algorithms that can dovetail with the current decision rule infrastructure, resulting in an even more precise and potent JITAI for lapses. For example, data from this MRT can support simulation studies to develop reinforcement learning algorithms that continuously adapt the provision of support to changing contexts between and within individuals [96]. There is also potential for these data to be used in a *warm start* fashion, which would involve using participant data from this MRT to boost effective learning more quickly in future versions of the JITAI for lapses [97]. Both of these examples demonstrate how products resulting from this MRT can optimize future versions of this JITAI for lapses, but also lead to important methodological discoveries in using personal health data to inform precision medicine.

In addition, systematic evaluation of the efficacy of theory-driven interventions will allow the findings from this MRT to advance the science of dietary lapse etiology and prevention specifically and nonadherence more generally. As dietary lapses are relatively understudied, it is not known which theory-driven approaches to behavior change will be most effective for preventing lapses during heightened lapse risk [101,102]. The MRT will provide important data about the role of each theory-driven intervention in preventing lapse and how these roles may change over time and across different contexts [18]. For example, if the motivation intervention option is effective in reducing dietary lapse and this effect is moderated by whether a participant is in active treatment or follow-up, this might indicate that motivation is an important momentary factor contributing to adherence, *especially during JITAI-only follow-up*. The results of this MRT will therefore contribute to the development of more dynamic theories of adherence or nonadherence behavior by directly comparing the immediate effects of multiple behavior change theories repeatedly over the course of a behavioral intervention [11].

Limitations

This study also has several notable limitations. First, the JITAI for dietary lapse is currently solely reliant on EMA, which improves the rigor of self-report but also incurs a high level of participant burden. Although, previous work indicates that participants are willing to respond to EMA prompts 6 times per day, there is a high priority for this research to transition to passively sensed dietary lapses or relevant triggers [64,103]. Second, the selected theory-driven intervention options to be evaluated in this MRT are based on the best available, but nonetheless static, model of adherence behavior. Without a dynamic model of behavior to guide the selection of intervention options, there is a risk that the interventions within this JITAI do not fully appreciate the known complexity of dietary adherence behaviors [101]. This MRT is designed such that the results are expected to inform dynamic models of behavior for future studies. Third, the analytic plan does not adjust for multiple comparisons with regard to the exploratory analyses that will be used for JITAI optimization. The results of these analyses will be interpreted with caution, and a distinction will be made between findings from the stated primary aims and exploratory analyses to develop and refine future iterations of the JITAI. Finally, study procedures have been modified such that they can be delivered in-person *and* remotely in response to the COVID-19 pandemic. The assessment of primary and secondary study outcomes, involving EMA and wrist-based eating detection and characterization, will remain unaffected by these changes, but other descriptive measures (eg, height and weight) may be affected.

Conclusions

This project targets dietary lapses, which are a major cause of poor outcomes during BOT. An MRT will be used to test 4 possible theory-driven intervention options within a JITAI that monitors risk and intervenes on lapses as needed. The primary proximal outcome is the occurrence of dietary lapse, as measured via EMA, between when the intervention was delivered and the next EMA prompt. Secondary proximal outcomes of interest are objectively assessed eating characteristics via wrist-worn device. Contextual moderators of intervention efficacy, such as location and time of day, will be explored. Data from the MRT will inform additional algorithms to personalize the timing of intervention delivery, thus optimizing the JITAI such that it has the greatest potential to show clear clinical impact in future RCTs and pragmatic trials.

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Conflicts of Interest

JGT participated in a scientific advisory board and served as a paid consultant for Lumme Health.

Multimedia Appendix 1
National Institutes of Health study section reviews.
[PDF File (Adobe PDF File), 222 KB - resprot_v10i12e33568_app1.pdf]

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Abbreviations

BOT: behavioral obesity treatment
CVD: cardiovascular disease
EMA: ecological momentary assessment
IMS: Information-Motivation-Strategy
JITAI: just-in-time adaptive intervention
MI: motivational interviewing
MRT: microrandomized trial
RCT: randomized controlled trial
RxWL: Rx weight loss

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Protocol

An eHealth Intervention for Promoting COVID-19 Knowledge and Protective Behaviors and Reducing Pandemic Distress Among Sexual and Gender Minorities: Protocol for a Randomized Controlled Trial (#SafeHandsSafeHearts)

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Abstract

Background: Existing data on COVID-19 disparities among vulnerable populations portend excess risk for lesbian, gay, bisexual, transgender (LGBT) and other persons outside of heteronormative and cisgender identities (ie, LGBT+). Owing to adverse social determinants of health, including pervasive HIV and sexual stigma, harassment, violence, barriers in access to health care, and existing health and mental health disparities, sexual and gender minorities in India and Thailand are at disproportionate risk for SARS-CoV-2 infection and severe disease. Despite global health disparities among LGBT+ populations, there is a lack of coordinated, community-engaged interventions to address the expected excess burden of COVID-19 and public health–recommended protective measures.

Objective: We will implement a randomized controlled trial (RCT) to evaluate the effectiveness of a brief, peer-delivered eHealth intervention to increase COVID-19 knowledge and public health–recommended protective behaviors, and reduce psychological distress among LGBT+ people residing in Bangkok, Thailand, and Mumbai, India. Subsequent to the RCT, we will conduct exit interviews with purposively sampled subgroups, including those with no intervention effect.

Methods: SafeHandsSafeHearts is a 2-site, parallel waitlist-controlled RCT to test the efficacy of a 3-session, peer counselor–delivered eHealth intervention based on motivational interviewing and psychoeducation. The study methods, online infrastructure, and content were pilot-tested with LGBT+ individuals in Toronto, Canada, before adaptation and rollout in the other contexts. The primary outcomes are COVID-19 knowledge (index based on US Centers for Disease Control and Prevention [CDC] items), protective behaviors (index based on World Health Organization and US CDC guidelines), depression (Patient Health Questionnaire-2), and anxiety (Generalized Anxiety Disorder-2). Secondary outcomes include loneliness, COVID-19 stress, and intended care-seeking. We will enroll 310 participants in each city aged 18 years and older. One-third of the participants will be cisgender gay, bisexual, and other men who have sex with men; one-third will be cisgender lesbian, bisexual, and other women who have sex with women; and one-third will be transfeminine, transmasculine, and gender nonbinary people. Participants will be equally stratified in the immediate intervention and waitlist control groups. Participants are mainly recruited from online social media accounts of community-based partner organizations. They can access the intervention on a computer, tablet, or

mobile phone. SafeHandsSafeHearts involves 3 sessions delivered weekly over 3 successive weeks. Exit interviews will be conducted online with 3 subgroups (n=12 per group, n=36 in each city) of purposively selected participants to be informed by RCT outcomes and focal populations of concern.

Results: The RCT was funded in 2020. The trials started recruitment as of August 1, 2021, and all RCT data collection will likely be completed by January 31, 2022.

Conclusions: The SafeHandsSafeHearts RCT will provide evidence about the effectiveness of a brief, peer-delivered eHealth intervention developed for LGBT+ populations amid the COVID-19 pandemic. If the intervention proves effective, it will provide a basis for future scale-up in India and Thailand, and other low- and middle-income countries.

Trial Registration: ClinicalTrials.gov NCT04870723; https://clinicaltrials.gov/ct2/show/NCT04870723

International Registered Report Identifier (IRRID): DERR1-10.2196/34381

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KEYWORDS

COVID-19; eHealth; RCT; protective behaviors; psychological distress; LGBT+; India; Thailand

Introduction

Background

As of September 30, 2021, India reported 33,739,980 COVID-19 cases and 448,062 deaths [1], and Thailand [2] reported 1,603,475 cases and 16,727 deaths [3,4]. In India, the vast informal workforce, poverty, food insecurity, and an underfunded health care system make projections difficult [5]. Thailand faces similar socioeconomic challenges but on a lesser scale. World Bank [6,7] data reveal that India (0.9/1000) and Thailand (0.8/1000) have nearly 3-fold lower ratios of physicians per capita compared with those of the United States and Canada (both 2.6/1000), with a 5-fold lower ratio of hospital beds in India (0.5/1000) compared with those of the United States (2.9/1000), Canada (2.5/1000), and Thailand (2.1/1000). These data indicate serious health care system challenges amid unknown third and fourth waves of infections and emerging variants of concern [8].

Sexual and gender minorities in India and Thailand, as in many contexts, face pervasive HIV and sexual stigma, harassment, violence, and barriers in access to health care [9-15]. In India, national HIV prevalence among men who have sex with men (MSM) and transgender people is 20-fold higher than that of the general population [16-18]. Depression and alcohol dependence incidence is 5-fold higher among lesbian, gay, bisexual, and transgender (LGBT) people than that among the general population [19-21]. Thailand has a 10-fold higher HIV prevalence among MSM versus the general population [22]. Limited research indicates that depression among LGBT adults is ~10-fold higher than that of the general population [23,24]. High rates of suicidal ideation and substance use have been documented among transgender people [25,26], lesbian women [27,28], MSM [29,30], and LGBT youth [31].

The ongoing pandemic along with various forms of lockdowns and stay-at-home orders in India and Thailand amid new waves of COVID-19 pose particular threats to LGBT and other persons outside of heteronormative and cisgender identities (LGBT+) populations [5,32]. Existing data on COVID-19 disparities among vulnerable populations [33,34] portend an excess risk for LGBT+ people. Mental health challenges due to public health–recommended protective measures (eg, masking, physical distancing) [35], stay-at-home orders, and community-based organization (CBO) closures threaten excess risks for LGBT+ people compounded by stigma and related stress [36,37]. Social and structural vulnerabilities among LGBT+ people that are associated with existing mental health disparities are likely to be exacerbated due to the trauma and social isolation of the pandemic [38], including increases in depression, anxiety, and loneliness [35,39-42].

Adverse social determinants of health [43] (SDOH), including unstable housing, marginal employment, and discrimination in health care, impact the ability to enact physical distancing, work from home, and access testing [33,35]. LGBT+ people, who are more vulnerable owing to adverse SDOH [38,44-48], are among the populations at excess risk, along with people living with HIV [49], ethnic and racial minorities [31], and immigrants and refugees [31,50]. The gendered impacts of the pandemic, including women's disproportionate responsibilities for informal care within families and employment on the frontlines of health care [51], also intersect with these other vulnerabilities [52]. Populations in low- and middle-income countries (LMICs), including LGBT+ people in particular, face risks exacerbated by structural challenges and lack of human rights protections [5,53].

Despite pervasive global health disparities among LGBT+ populations, adverse SDOH [54-56], and lack of human rights protections [32,57], there is a lack of coordinated, community-engaged responses to address the expected excess burden of COVID-19 and public health–recommended protective measures. Public health responses and communications for LGBT+ communities are impeded by lack of LGBT+ community engagement, along with lack of data on health disparities and community needs in the pandemic. Lessons learned from Ebola, H1N1 influenza, and SARS [58,59] indicate that engaging vulnerable communities and building trust are crucial to public health communication and responses [58-61]. With pandemic planning typically framed around the traditional nuclear family and stereotypical gender role assumptions [58], public health–recommended measures often overlook LGBT+ people with different living configurations than those of heterosexual, cisgender people: living with same-gender partners/spouses, friends, hostile families, or alone.

This compounds vulnerabilities due to social isolation, and lack of social support and safety [58,62]. Undifferentiated public health responses can exacerbate mistrust among vulnerable communities due to existing disparities, fueling loss of confidence in public health communications [58,59] in a broader context of rampant COVID-19 misinformation [63].

Some restrictions on rights are justified in response to a public health emergency. Nevertheless, as reported by Human Rights Watch [64], UNAIDS (Joint United Nations Programme on HIV/AIDS) [65], the Office of the United Nations High Commissioner for Human Rights [66], and the media [67,68], government emergency powers in response to COVID-19 have led to abuses against LGBT+ people worldwide. These include housing discrimination, evictions, and police brutality against transgender people in India [67]; disproportionate job loss and lack of access to government subsidies for LGBT+ people in Thailand and India, many of whom are marginalized from the mainstream workforce [42]; and exacerbation of sexual and HIV stigma [65,66].

In sum, heightened vulnerability among LGBT+ populations in the COVID-19 pandemic may result from existing health disparities amid ongoing adverse SDOH, compounded by human rights violations and social-structural constraints on enacting public health–recommended protective measures. Yet, public health responses largely do not address LGBT+ vulnerabilities. Extensive evidence supports the acceptability [36,69] and effectiveness of eHealth interventions with LGBT+ and other vulnerable populations in increasing health knowledge and preventive behaviors, and reducing psychological distress [70,71]. Our World Health Organization (WHO)-recommended approach based on community engagement [72] in intervention development, capacitation of CBOs, and cogovernance by trusted CBO partners supports the feasibility, acceptability, and scalability of the intervention [60,73]. The proposed #SafeHandsSafeHearts intervention aims to support LGBT+ individuals amid the pandemic and to advance the broader pandemic response for LGBT+ populations.

Research Questions

This study addresses the following research questions: What are the needs and challenges faced by diverse LGBT+ people in India and Thailand in the COVID-19 pandemic? What is the level of COVID-19 knowledge, public health–recommended protective behaviors, and psychological distress? Will a brief, tailored, peer-led eHealth intervention increase COVID-19 knowledge and protective behaviors, and reduce psychological distress among LGBT+ people?

Specific Objectives

The specific objectives of the study are to (1) increase knowledge about COVID-19 transmission, risk, and public health–recommended protective behaviors among diverse LGBT+ persons in India and Thailand; (2) increase public health–recommended protective behaviors, including handwashing, physical distancing, and wearing masks; and (3) reduce pandemic-related psychological distress (anxiety, depression, social isolation/loneliness).

Methods

Ethics Approval and Consent to Participate

Ethics approvals have been received from the University of Toronto Research Ethics Board (RIS Protocol: 39769); the Humsafar Trust Institutional Review Board (Protocol: HST-IRB-51-06/2021); and the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (Protocol: 272/64).

Study Design

We use a sequential quantitative-qualitative mixed methods design [74]. We will implement a 2-site, parallel waitlist-controlled randomized controlled trial (RCT) to test the efficacy of a 3-session, peer counselor–delivered eHealth intervention to increase COVID-19 knowledge and protective behaviors, and decrease pandemic-related psychological distress. The immediate versus waitlist allocation ratio is 1:1. We conducted a formative intervention development phase with LGBT+ individuals in Toronto to pilot test and refine the online study infrastructure (participant eligibility screening, randomization, survey programming and administration, databases, and dashboard interface for tracking and monitoring) and peer counselor training before rollout in the other 2 sites. All study materials were culturally and contextually adapted through consultation with experts in each site, pilot-tested among individuals from locally eligible study populations, and then revised before implementation.

The immediate intervention group to be enrolled over a 2-month period will complete the 3-session biweekly intervention from August to October 2021. The randomized waitlist control group will crossover to receive the intervention from October to December 2021, after the immediate group finishes. Waitlist control groups, often used in psychosocial interventions [75], avert ethical problems with no-treatment controls, particularly with groups that experience health disparities, moreover amid a pandemic, and also avoid alienating the community.

Sample Size Calculations

The sample size was calculated based on power to detect significant differences in 3 primary outcomes: proportion of participants with: (1) accurate COVID-19 knowledge, (2) consistent public health–recommended handwashing behaviors, and (3) pandemic-related psychological distress. Given baseline differences in the two countries, we first describe the detailed power analysis for India, where (1) COVID-19 knowledge ranges from 18.2% (fever a major symptom) to 43.0% (highly contagious) [76], and (2) a national survey [77] estimated that 35.8% of the population wash their hands with soap and water. Our baseline estimates are 40% for knowledge and 36% for handwashing (proxy for 3 protective behaviors). A 30% increase postintervention attains clinical/public health significance [78] and a substantial effect size. For (3) psychological distress (depression, anxiety, social isolation), we use a baseline depression rate of 50% (based on a systematic review [19]) as a proxy, with an expected 30% reduction [79]. Using Stata-16, the required sample size to detect significant differences between the waitlist control and immediate-intervention groups, with

power of 80%, α of .05 for the 95% CI, and a two-tailed test, ranged from 78 to 86. Assuming 20% attrition, the final sample size was increased to 103 per group (cisgender men, cisgender women, transgender and gender nonbinary people) with power to detect significant differences in each of the 3 groups, for a total sample of 309 in Mumbai.

Using published prevalence of primary outcomes and estimated effect sizes based on similar in-country interventions, we estimated a sample size of 309 for Bangkok [23,28,80-82]. Thus, the trial is powered to detect overall (and by city) sex and gender differences in the primary outcomes (COVID-19 knowledge, protective behaviors, and psychological distress) and the efficacy of the intervention [83].

Procedures

Inclusion Criteria

Participants are eligible for enrollment if they are (1) aged 18 years and older; (2) self-identify as LGBT+ using local, culturally appropriate self-identifications [10,57,79]; (3) reside in one of the two cities (Bangkok and Mumbai); (4) able to understand and willing to provide informed consent; and (5) able to understand primary language(s) at the site (Thai, Hindi/Marathi, or English). We do not use exclusion criteria based on mental health. The Patient Health Questionnaire-2 (PHQ-2) will be administered in the baseline survey; those with scores indicative of clinical depression (≥3 on the depression scale) will be referred by peer counselors to in-house mental health professionals on call at the site.

Recruitment

Participants will be recruited online with electronic flyers and social media messages developed with CBO partners, through CBO social media accounts in WhatsApp groups, e-groups, virtual LGBT+ groups, Facebook, and a study website linked to all CBOs to reach potentially eligible participants.

Randomization

Participants will be randomized to the immediate intervention group or waitlist control group (12-week waitlist) at a 1:1 ratio, stratified by sex and gender [83] (cisgender men, cisgender women, transgender and gender nonbinary people), with a computer-generated sequence. Participants and researchers will not be blinded; in the informed consent process, potential participants will be told about the waitlist control.

Informed Consent

Immediately upon screening into the study, potential participants will be shown an informed consent form online and given time to read through it. Potential participants will be instructed to contact the study coordinator and provided with an email address if they wish to ask any questions or request clarifications before providing consent.

Intervention

Overview

As there is no manualized intervention for COVID-19 prevention, we adapted efficacious eHealth interventions for HIV, the largest pandemic of the last century, by members of our research team [79,84]. The 3 primary outcomes—increasing COVID-19 knowledge, protective behaviors, and reducing psychological distress—are central to public health approaches to halt SARS-CoV-2 transmission [85,86].

Motivational Interviewing and Psychoeducation

The intervention builds on evidence-based eHealth interventions using motivational interviewing (MI) [87,88] and psychoeducation [89] approaches to increase health knowledge, behaviors, and reduce psychological distress [90-94]. Several MI-based studies have been conducted with LGBT+ people [95-97], including in India [79,84] and Thailand [98]. MI is a client-centered counseling approach that elicits and strengthens intrinsic motivation for change [87,99,100]. MI is based on Stages of Change theory, which enables tailoring to individual readiness for change with an emphasis on supporting client autonomy and volition [101,102]. Psychoeducation integrates education and counseling to promote mental health [89]. Consonant with MI, it is a strengths-based approach in which clients are considered partners in treatment [89]. Psychoeducational techniques are used to mitigate barriers to comprehending complex and emotionally laden information, with a focus on developing strategies to use the information proactively, such as in anticipating actions if one were to experience distress or loneliness [88].

Peer Counselor Training

Peer counselors will receive an initial 3-day online training along with a 2-day booster training immediately preceding the intervention. Training will be conducted by study coordinators and agency staff in each site, covering COVID-19, public health–recommended protective behaviors, pandemic stress (ie, anxiety, depression, social isolation), MI-based counseling, psychoeducation, and research ethics [78,103]. Training will include online small-group discussions, role-playing, and mock sessions, with peer counselor feedback also used to fine-tune the intervention.

Intervention Group

We use a 3-session peer-delivered MI-based brief counseling (45 minutes to 1 hour) format with weekly individual sessions, which has previously demonstrated effectiveness in interventions for alcohol, tobacco, and marijuana use, and HIV prevention [79,104-107]. Peer counselors will complete session-specific checklists (activities conducted, issues encountered, self-evaluated quality of engagement) following each session. To assess fidelity, supervisors will review a random selection of peer counselors' initial sessions, which will be digitally recorded, and provide feedback using a structured checklist. Supervisors will conduct biweekly online group discussions to provide feedback, emotional support, and discuss and troubleshoot challenges to protocol implementation. In each online session, participants will complete a 4-item survey to evaluate content, satisfaction with the session and its duration, and any exposure to other interventions. Peer counselors write up brief counseling notes after each session, along with the brief self-evaluation. We use process evaluation to assess dose and implementation fidelity [107].

Waitlist Control Group

Governments and public health ministries in India and Thailand provide almost daily briefings about COVID-19 via multiple sources: TV, newspapers, Facebook, WhatsApp, LineChat, Instagram, and SMS text messages. Online messenger platforms (eg, WhatsApp, Line) provide LGBT-targeted information, with additional government mobile apps developed for general populations. The waitlist control group will receive brief reminders by mobile phone to support retention.

Assessments

Each participant will complete a baseline survey, a postintervention survey 2 weeks after their final eHealth session, and a follow-up survey 2 months after the postintervention survey. Waitlist controls will complete a second baseline survey immediately before beginning the eHealth intervention.

Measures

Overview

Demographic data, including age, sex, gender identity, sexual orientation, city of residence, country of birth, education, and employment, will be obtained to determine the baseline equivalence of groups.

Primary Measures

Knowledge

COVID-19 knowledge [108,109] will be assessed using an index developed by the research team and based on published research [110,111].

Preventive Behaviors

Public health–recommended preventive behaviors [108,109] will be assessed using an index developed by the research team based on WHO and US Centers for Disease Control and Prevention guidelines.

Mental Health Measures

Depression and anxiety symptoms in the past 2 weeks will be measured using the PHQ-2 [112] and the Generalized Anxiety Disorder 2-item scale [113].

Secondary Measures

The indices assessed as secondary measures are listed in Textbox 1.

Textbox 1. Secondary measures.

- UCLA Loneliness Scale [114]
- COVID Stress Scales (COVID danger, COVID traumatic stress) [115]
- Intended care-seeking [116]
- Unmet health care needs and perceived quality of care [117]
- COVID-19–related risk perception and testing (developed for this study)
- COVID-19 vaccines (developed for this study)
- Discrimination in Medical Settings Scale (DMS Scale) [118]
- Conspiracy beliefs [116,119-121]
- Attitudes toward government handling of COVID-19 [110]
- Support for government action regarding the pandemic [122]
- Alcohol Use Disorders Identification Test (AUDIT-C) [123]
- Sexual and reproductive health changes [124]
- Intimate partner violence changes [125]
- General and HIV-specific COVID-19 impacts [47,126]
- Household Water InSecurity Experiences (HWISE Scale) [127]
- Response to Stressful Experiences Scale (RSES-4) [128]
- Outness indicator [129]
- Technology ownership (developed for this study)

Statistical Analysis Plan

Intervention efficacy will be assessed by comparing data from the second preintervention baseline survey from the waitlist control with postintervention data from the immediate intervention group. The χ^2 test for unadjusted analyses and logistic generalized estimating equations (GEEs) for adjusted analyses [130] will be used to assess dichotomous primary outcomes (COVID-19 knowledge, protective behaviors, psychological distress). Sensitivity analyses will use composite scores of primary outcomes with independent-samples *t* tests for unadjusted analyses and GEEs (Gaussian or Poisson) for adjusted analyses. To assess if intervention efficacy is sustained, waitlist control data from the second preintervention survey will be compared with intervention group follow-up data. We will use intention-to-treat analyses and also report per-protocol analyses [131]. In addition to analyses of efficacy for LGBT+ people as a whole, the sample size is powered for a priori

subgroup analysis (cisgender gay/bisexual men, cisgender lesbian/bisexual women, transgender and gender nonbinary people). We will assess if intervention effects on protective behaviors are mediated by increases in knowledge, self-efficacy, perceived vulnerability, and decreases in conspiracy theories and psychological distress, and if the effects on psychological distress are mediated by resilience.

Process Evaluation and Qualitative Analysis

Participant satisfaction and supervisor counseling session observation scores will be used to assess intervention satisfaction and fidelity, respectively. Dose will be determined by intervention session attendance. Post-RCT qualitative exit interviews will be conducted with purposive random samples [132,133] of select populations in each site, with selection criteria to be informed by survey data and focal populations of concern. These may include transgender and gender nonbinary persons, people living with HIV, and those with no intervention effect on reducing psychological distress (n=12 per group). In-depth interviews will be conducted online in accordance with methodological recommendations and ethical considerations amid a pandemic [134]. A semistructured interview guide will be used to explore experiences in the pandemic, focal challenges and strengths, identified supports, and thoughts about the intervention. Interviews will be audio-recorded, transcribed, translated into English, and examined using techniques from framework analysis [135] and thematic analysis [136] to explore pandemic-related challenges and resiliencies, population-specific and cross-group themes, perceived usefulness of the intervention, and intervention mechanisms.

Results

This study was funded by the International Development Research Centre, Canada, from 2020 through 2021. Some of the development costs were funded by the Social Sciences and Humanities Research Council of Canada. The enrollment of participants began in August 2021. Baseline assessments, allocation, and intervention are currently underway. The first results are expected to be submitted for publication in 2022.

Discussion

Principal Findings

This protocol outlines the design of an RCT to evaluate the effectiveness of an eHealth peer intervention for increasing COVID-19 knowledge and preventive behaviors, and reducing psychological distress among sexual and gender minority people. To our knowledge, the proposed intervention is the first peer-delivered prevention program delivered via Internet of Things (IoT) devices (eg, PC, laptop, tablet, mobile phone) for LGBT+ people in LMICs amid the COVID-19 pandemic. If effective, it has the potential for widespread implementation at a relatively low cost, as it relies on peers and uses a delivery method that is both acceptable and accessible for LGBT+ people, including in an LMIC, during the pandemic.

Strengths and Limitations

The key strengths of the proposed effectiveness study are the intervention's focus on marshaling peer support among LGBT+ adults (aged 18 years or over) during the pandemic using digital technology. Mobile delivery using IoT devices means that the intervention is accessible during continuing stay-at-home orders, lockdowns, and waves of the pandemic, particularly in LMICs in which vaccines are not broadly available. The intervention is also adaptable for future pandemics and emergency situations. Engaging with others over online messenger platforms and apps is also comfortable and culturally appropriate for LGBT+ people, including those who may opt not to self-disclose their sexual orientation or gender identity in public forums to protect their privacy and safety in adverse familial and social environments. The intervention also addresses what may be population-specific concerns among LGBT+ people, who are often not included or considered in pandemic response planning or interventions designed for the general public. Further, the intervention can be accessed from home in relatively private spaces not requiring public attendance at LGBT-identified CBOs or services. The latter presents barriers due to stay-at-home orders, as well as more general obstacles for some LGBT+ people who are not "out" and for whom the risk of disclosure may present unacceptable "costs," including loss of family support, job loss, harassment, and violence.

Another benefit of the intervention is its links to a broad spectrum of CBOs, both LGBT+-identified and non-LGBT+–identified. This means that CBOs could act as delivery partners to roll out the intervention if found to be effective. Relatedly, the intervention training and clinical supervision provided to peer counselors and counseling interns can act as a supportive mechanism during the pandemic for individuals from a vulnerable population, including CBO staff, as well as building capacity to address future emergency situations. Finally, the intervention was collaboratively designed by an international team with extensive experience in conducting research and providing health services to sexual and gender minorities in each country.

One limitation of the study is the reliance on participant self-report to collect data for the primary outcomes of this trial. Although this was chosen for feasibility and ethical considerations, and is a standard practice for psychosocial interventions, it is possible that measures of protective behaviors and mental health could be subject to underreporting or overreporting. To mitigate response bias and socially desirable responses, participants are reminded of the confidentiality of their responses at each survey occasion, are not asked for their names or home addresses, and are encouraged to be as honest as possible. Furthermore, the MI approach that guides the intervention is anchored in respect, lack of judgment, and acceptance of each participant's current behaviors and perspectives; this milieu contributes to participants' openness and honesty, and mitigation of socially desirable responses.

Due to time and budget constraints, the study was unable to provide tablets or smartphones to participants who did not own or have access to them. This may pose barriers to participation by individuals who do not have access to IoT devices or

broadband internet. However, we used cross-platform programming with a responsive web design to ensure that the online content and eHealth sessions function and display correctly on a variety of devices, platforms, and screen sizes, including tablets and smartphones. Thailand [137] and India [138,139] have high rates of mobile phone penetration, both being among the top 20 countries in smartphone users in the world [140]. Further investigation will be needed to examine feasibility and efficacy among LGBT+ adults in rural areas, who may face more protracted challenges in a pandemic [141], as well as the potential impact of the gender gap in smartphone ownership, with women in LMICs being 20% less likely than men to own a smartphone or access the internet via a mobile device [142].

We mitigate threats to internal validity due to differential attrition by implementing a brief, 3-session, weekly intervention with 2-week immediate follow-up, which reduces the waitlist time for the control group. There is a reduced risk of contamination as an eHealth intervention for which participants will be individually recruited online and participate online. This threat is also mitigated due to stay-at-home orders and physical distancing guidelines that deter or prevent attendance at CBO sites, although guidelines may change during the course of the intervention.

Finally, the unpredictable course of the pandemic, and regional and local variation in severity and public health responses, has delayed onset of the study and created intermittent barriers and interruptions in implementation. Nevertheless, the development and testing of the intervention during a pandemic may increase its feasibility and external validity. Once developed, implemented, and tested, the intervention may be more readily usable for LGBT+ and other marginalized populations in future pandemics and other emergency situations.

Conclusions

The development of a novel eHealth intervention designed for sexual and gender minority individuals to promote COVID-19 knowledge and protective behaviors, and reduce psychological distress represents an innovative approach to pandemic preparedness and response in real-world settings, including LMIC settings most severely impacted by the pandemic. The intervention protocol and materials will be linked and shared with existing CBOs and clinics serving sexual and gender minority populations, and if effective will be made publicly available, with the potential for broad implementation and a significant impact globally.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Four peer-review reports from the granting agency.
[PDF File (Adobe PDF File), 64 KB - resprot_v10i12e34381_app1.pdf]

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Abbreviations

CBO: community-based organization
GEE: generalized estimating equations
IoT: Internet of Things
LGBT: lesbian, gay, bisexual, and transgender
LGBT+: LGBT and other persons outside of heteronormative and cisgender identities
LMIC: low- and middle-income country
MI: motivational interviewing
MSM: men who have sex with men
PHQ-2: Patient Health Questionnaire-2
RCT: randomized controlled trial
SDOH: social determinants of health
UNAIDS: Joint United Nations Programme on HIV/AIDS
WHO: World Health Organization

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Protocol

Getting "Back on Track" After a Cardiac Event: Protocol for a Randomized Controlled Trial of a Web-Based Self-management Program

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Abstract

Background: After a cardiac event, a large majority of patients with cardiac conditions do not achieve recommended behavior change targets for secondary prevention. Mental health issues can also impact the ability to engage in health behavior change. There is a need for innovative, flexible, and theory-driven eHealth programs, which include evidence-based strategies to assist patients with cardiac conditions with their recovery, especially in behavioral and emotional self-management.

Objective: The aim of this study is to determine the short- and longer-term behavioral and emotional well-being outcomes of the *Back on Track* web-based self-management program. In addition, this study will test whether there is enhanced benefit of providing one-on-one telephone support from a trained lifestyle counselor, over and above benefit obtained through completing the web-based program alone.

Methods: People who have experienced a cardiac event in the previous 12 months and have access to the internet will be eligible for this study (N=120). Participants will be randomly assigned to one of the two study conditions: either "self-directed" completion of the *Back on Track* program (without assistance) or "supported" completion of the *Back on Track* program (additional 2 telephone sessions with a lifestyle counselor). All participants will have access to the web-based *Back on Track* program for 2 months. Telephone sessions with the supported arm participants will occur at approximately 2 and 6 weeks post enrollment. Measures will be assessed at baseline, and then 2 and 6 months later. Outcome measures assessed at all 3 timepoints include dietary intake, physical activity and sitting time, smoking status, anxiety and depression, stage of change, and self-efficacy in relation to behavioral and emotional self-management, quality of life, and self-rated health and well-being. A demographic questionnaire will be included at baseline only and program acceptability at 2 months only.

Results: Recruitment began in May 2020 and concluded in August 2021. Data collection for the 6-month follow-up will be completed by February 2022, and data analysis and publication of results will be completed by June 2022. A total of 122 participants were enrolled in this study.

Conclusions: The *Back on Track* trial will enable us to quantify the behavioral and emotional improvements obtained and maintained for patients with cardiac conditions and, in particular, to compare two modes of delivery: (1) fully self-directed delivery and (2) supported by a lifestyle counselor. We anticipate that the web-based *Back on Track* program will assist patients in their recovery and self-management after an acute event, and represents an effective, flexible, and easily accessible adjunct to center-based rehabilitation programs.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620000102976; http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378920&isReview=true

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KEYWORDS

coronary heart disease; heart disease; coronary; cardiovascular; prevention; RCT; randomized control trial; secondary prevention; self-management; online; randomised controlled trial; health behaviours; health behaviour; health behavior; depression; cognitive behaviour therapy; motivational interviewing

Introduction

Background

Cardiovascular disease is the primary cause of death and disability, both globally [1] and in Australia [2]. With improvements in medical care, increasing numbers of people survive their first cardiac event; however, those who survive are at increased risk of a subsequent event and premature death [3]. The major focus of preventive cardiology is the recovery and rehabilitation of these survivors, with a view to reducing re-events and premature mortality [4].

Secondary prevention, including behavior modification and mood management, is essential for people who have experienced a cardiac event [5]. Up to 90% of the overall risk of acute myocardial infarction (AMI) is attributed to modifiable factors including, physical inactivity, poor diet, cigarette smoking, and medication nonadherence [6]. The survival benefits of increased physical activity, dietary change, and smoking cessation in patients with cardiac conditions have been demonstrated in numerous studies [7,8]. In addition, emotional well-being is essential for the overall health of those with cardiac conditions. Those who experience postevent mental health problems such as anxiety or depression have a poorer recovery than their nondistressed counterparts, with higher rates of hospital readmission [9], more re-events [10], and earlier mortality in the years following [11,12].

Unfortunately, despite the known benefits of behavior change, a large majority of cardiac event survivors do not achieve recommended targets for secondary prevention, with high rates of unhealthy diets, physical inactivity, and resumption of smoking in the postevent year [4,13,14]. Even among those who attend cardiac rehabilitation (CR) programs, initial lifestyle changes are rarely sustained [15]. Mental health problems, such as depressed mood [16] and cognitive barriers, such as negative thoughts [17], also decrease cardiac patients' ability to undertake health-enhancing behavior change.

While CR is recommended for all cardiac event survivors after an acute event [18] and has been shown to improve health outcomes [19,20], center-based programs are underutilized with evident low participation rates [21,22]. In Australia, research has demonstrated that only approximately 30% of eligible people attend CR programs within 10 weeks of discharge [23]. Nonattendance is partly attributable to access difficulties, with travel time and distance from the venue, and limited car access being key barriers [24]. Regional and rural-based patients with cardiac conditions, as well as those who are younger and have returned to work, are particularly disadvantaged in terms of access to center-based support [25].

Up to 50% of cardiac event survivors have expressed the desire for flexible alternatives to center-based programs, many preferring home-based options, including eHealth [26]. Systematic reviews of telehealth interventions for people with coronary heart disease (CHD), including both telephone- and internet-based interventions, indicate that these programs provide effective risk factor reduction and secondary prevention [27,28]. Research on the effectiveness of web-based support for people with CHD has demonstrated improvements in behavioral and physiological indicators [29-31]. Emerging evidence suggests that outcomes can be enhanced by the addition of concurrent one-on-one telephone support from a health professional [32]. Current estimates suggest that almost 90% of Australian adults are active internet users [33] and that approximately 50% of users, including those of older ages, access health-related information [34], highlighting the potential for the use of web-based health programs with this population.

To our knowledge, there are no programs that aim to equip people with CHD with cognitive and behavioral skills to maintain psychosocial and behavioral health in the long term. People need evidence-based strategies and tools to develop skills to self-manage their health in the longer term [15]. Research has consistently highlighted the importance of theory-driven programs in assisting people with behavior change [35]. For example, self-regulation theory, defined as a goal guidance process aimed at the attainment and maintenance of personal goals [36], underpins several behavioral interventions to support change, such as self-monitoring, feedback, reward, and goal-setting [37,38]. Likewise, cognitive-behavioral therapy (CBT) has been used successfully to assist people with CHD in self-management of both behavioral [39] and psychosocial [40] risk factors. Motivational interviewing (MI) has also been shown to improve engagement and to decrease resistance [41], and it can enhance CR outcomes [42]. For cardiac patients, self-efficacy of behavior change has been shown to be associated with short- and longer-term maintenance of exercise and smoking cessation [43,44]. Evidence suggests that outcomes are optimal when these theories, interventions, and strategies are integrated [45,46].

With the aim of addressing gaps in secondary preventive care for people with CHD, the Australian Centre for Heart Health (ACHH) developed a face-to-face, group-based self-management program, *Beating Heart Problems*, which was underpinned by a framework of self-regulation theory and patient-centered care.

Based on the principles and strategies of CBT and MI, the program was designed to provide cardiac event survivors with the cognitive and behavioral skills to self-manage their mood and health behaviors in the long term. A randomized controlled trial (RCT) of the *Beating Heart Problems* program, involving 275 cardiac event survivors, demonstrated that the intervention group showed a superior reduction in 2-year risk of a recurrent event, greater improvements in functional capacity and behavioral health, and greater reductions in depression incidence and severity, compared to the control group [47,48]. To overcome issues of access, accessibility, and inequities, the face-to-face program was translated for web-based delivery. The web-based program, titled *Back on Track*, is underpinned by the same frameworks and theories as the face-to-face program and includes modules that focus on both behavioral and emotional aspects of recovery. In a pilot study, the web-based *Back on Track* program was shown to be acceptable and useful in terms of self-management support following a cardiac event [49].

Objectives

The aim of this study is to assess the benefits, in terms of behavioral and emotional well-being, of the web-based *Back on Track* self-management program, and to test whether participants obtain enhanced benefit through the provision of one-on-one telephone support from a trained lifestyle counselor (supported arm), over and above benefit obtained through completing the web-based program alone (self-directed arm). By including 2 follow-up assessments, one on postprogram completion (2 months) and one at 4 months post program (6 months postenrollment), we aim to assess both immediate and sustained benefits.

We hypothesize that participants randomly allocated to each arm of the trial will show significant improvement in their behavioral and emotional well-being, self-efficacy, and self-rated health from the preprogram to postprogram assessments, with benefits sustained 4 months after program completion. We also hypothesize that participants allocated to the supported program will demonstrate superior improvements in behavioral and emotional well-being, self-efficacy, and self-rated health compared to those allocated to the self-directed arm, at both the postprogram and follow-up assessments.

Ethical approval was granted by the Deakin University Human Research Ethics Committee (2019-438). This project has been funded by the HCF Research Foundation. This study will be conducted and reported in accordance with the CONSORT-EHEALTH guidelines [50].

Methods

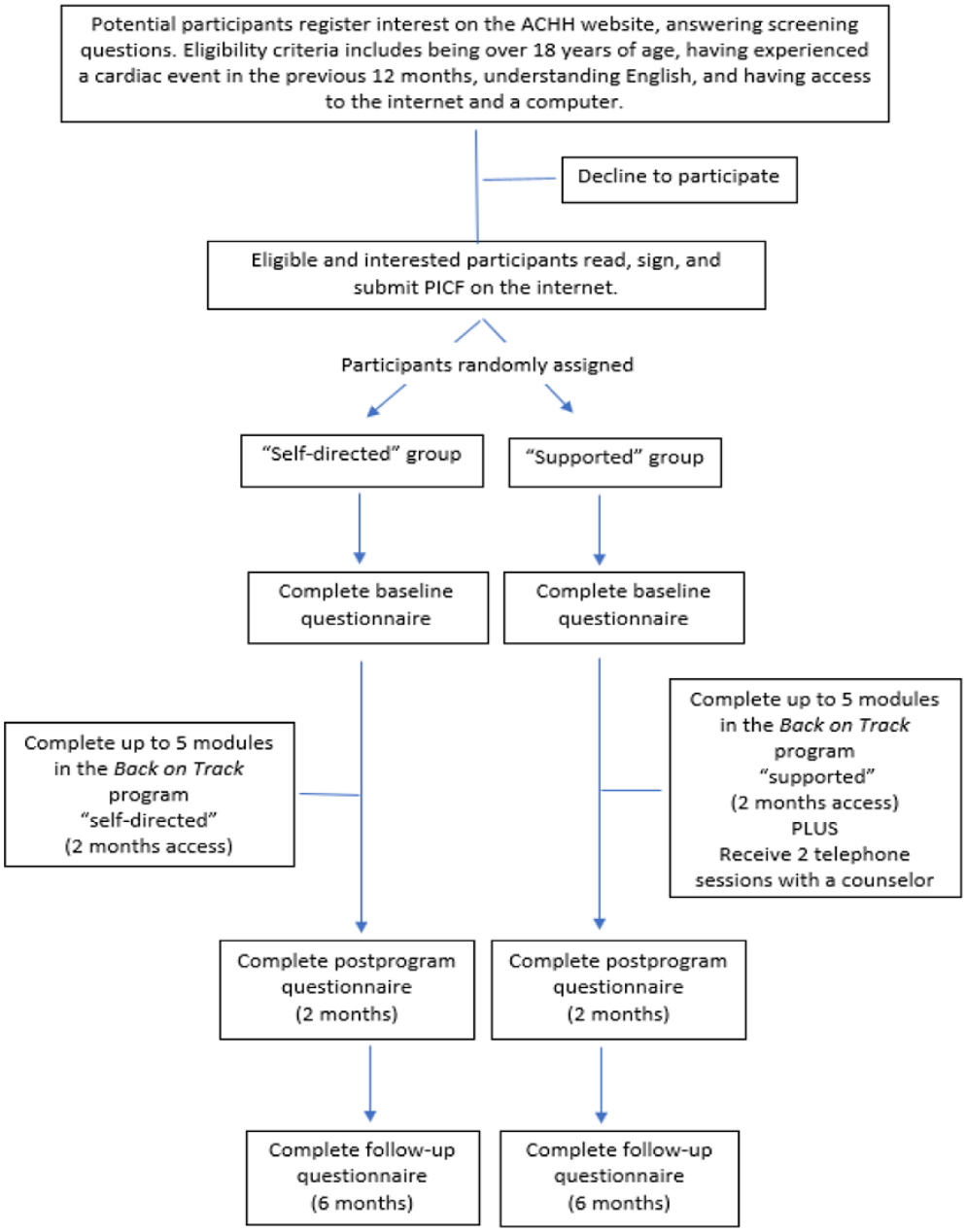
Study Design

This project uses a 2-armed RCT design, with participants who register to be involved in the trial being randomly allocated to one of two arms: either “self-directed” completion of the *Back on Track* program or “supported” completion of the *Back on Track* program. The self-directed arm involves participants completing the web-based *Back on Track* program at their own pace without assistance. The supported arm involves the addition of 2 telephone sessions with a trained lifestyle counselor. The telephone sessions are protocol driven, with a written manual developed by a health psychologist.

Measures are assessed at three timepoints across the study: a baseline questionnaire is completed prior to participants receiving access to the web-based program, a postprogram questionnaire at the conclusion of the web-based program access (2 months after baseline), and a follow-up questionnaire 4 months later (6 months after baseline). Figure 1 shows a flowchart of the study design and the participant numbers.

An RCT design was chosen for this trial to accurately compare outcomes for the 2 modes of delivery of the web-based *Back on Track* program, either self-directed or supported. By comparing outcomes for participants in the 2 groups, we will be able to determine whether the supported approach provides benefits over and above the self-directed use of the web-based *Back on Track* program. The result will then inform the optimal form of delivery of the *Back on Track* program for future rollout to people with CHD across Australia.

Figure 1. Trial design based on CONSORT (Consolidated Standards of Reporting Trials) requirements. ACHH: Australian Centre for Heart Health; PICF: participant information consent form.



Recruitment and Participants

A total of 120 participants will be recruited into the trial, with 60 randomly allocated to each of the 2 arms of the trial. Participants will be adults (over 18 years of age) who have had an acute cardiac event, such as AMI, coronary artery bypass graft surgery (CABGS), or percutaneous coronary intervention (PCI), in the past 12 months. Participants are required to be fluent in English to comprehend the *Back on Track* program, which is currently available in English only. Participants are also required to have access to the internet and a computer or tablet.

Participants are being recruited using both direct engagement via a nationwide social media recruitment drive, and indirect engagement via cardiac health professionals and community-based cardiac support organizations, namely HeartBeat Victoria and Heart Support Australia. A promotional flyer is used for all promotion and recruitment. The nationwide social media recruitment drive involves announcements about the trial on internet-based social media platforms such as Facebook, Twitter, and LinkedIn. HeartBeat Victoria and Heart Support Australia also promote the study to their members, who are all people living with heart disease. Details of eligibility criteria are provided on the relevant websites and organization promotional material. Likewise, the trial is being promoted among cardiac health professionals, based on a list of health professionals who are involved in cardiac rehabilitation services across Australia or have attended past ACCH training programs.

In all cases of recruitment, both direct and indirect, potential participants are directed to the ACHH website for detailed information about the study and for instructions on how to register on the internet. Screening for eligibility is undertaken at the time of participant registration via the ACHH website using a set of brief screening questions; specifically, participants are asked to provide their name and contact details, type, and date of cardiac event and to confirm that they are able to read and understand English and that they have access to the internet and a computer or tablet device. All participants are asked to read, sign, and return the participant information and consent form (PICF) after registration and prior to randomization and being given program access. The PICF is emailed to participants via the secure web-based data management and survey program, Research Electronic Data Capture (REDCap), which they sign and return electronically to ACHH.

Once registered, participants are randomly allocated to either the self-directed or the supported arm of the trial using an independent and automatic random allocation numbering system. The person undertaking the random allocation is blind to group and participant details. All participants are then asked to complete the web-based baseline questionnaire, also disseminated using REDCap. The link to questionnaires is emailed to participants at each timepoint. Access to the *Back on Track* program is granted to participants for a 2-month period after they complete the baseline questionnaire.

Participants are asked to recomplete the main outcome measures again post program (2 months after initial access to the program) and at 4-month follow-up (6 months after program access). Again, the REDCap survey link is emailed to participants.

Sample Size and Power

Our sample size is based on a systematic review of telehealth-based cardiac rehabilitation [28] on lifestyle behaviors, health outcomes, and quality of life, where the effect sizes on promoting healthy lifestyle ranged from 0.42 to 1.29. Taking a conservative approach, we expect a medium effect size of 0.55. Allowing for 80% power and a significance threshold of .05, the estimated sample size is 120 (60 per arm), which takes into consideration an expected attrition rate of 12% based on prior studies with similar posttest time points of 2-4 months [31,51].

Intervention

Back on Track Program

The *Back on Track* program begins with a goal-setting module, followed by 4 self-selected modules relating to (1) healthy eating, (2) physical activity and reduced sitting, (3) smoking cessation, and (4) cardiac blues and depression. Participants in both the self-directed and supported arms are asked to complete modules relevant to them, in their own time and in any order over the course of 2 months. Within each module, participants undertake exercises that enable them to review situations in their lives, and using concepts from CBT, to identify, challenge, and change the unhelpful thoughts and beliefs associated with risk factors and negative emotions. Participants are prompted to develop action plans and coping plans for implementing practical health behaviors, including goal-setting, and identifying motivators for change, resources, barriers, rewards, and relapse prevention strategies. Other activities include using strategies to increase self-efficacy, including stories of role models, and exploring ratings of importance of and confidence to undertake behavior change.

The behavioral recommendations included in the modules (eg, healthy eating, physical activity, and smoking cessation) are all based on the current National Heart Foundation of Australia (NHFA) guidelines [52]. Although not being the central focus of the *Back on Track* program, it is important to present, up-to-date, relevant information on these guidelines and recommendations. This can help participants with aspects of their self-management, including goal-setting. Figures 2 and 3 show screenshots of various aspects of the web-based *Back on Track* modules.

Figure 2. Examples of informative slides in the *Back on Track* program.

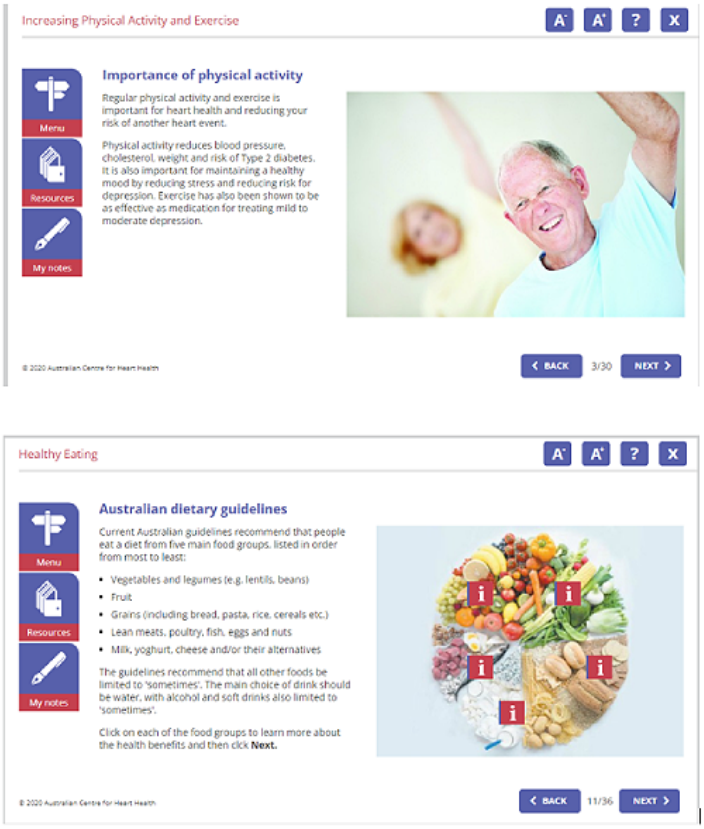
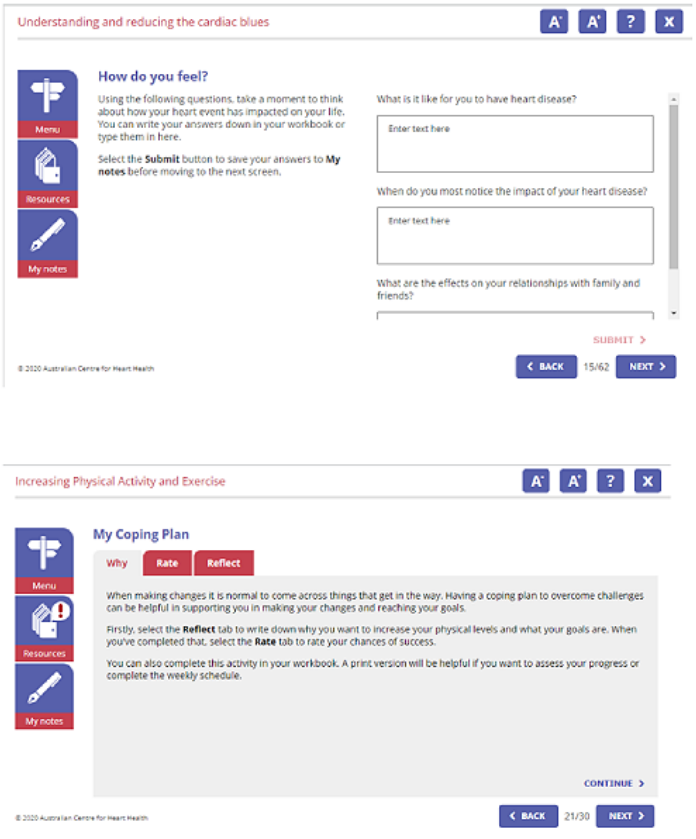


Figure 3. Examples of interactive slides in the *Back on Track* program.



Additional Telephone Sessions for the Supported Group

Supported group participants are offered 2 telephone sessions with a trained lifestyle counselor to assist them in goal-setting and overall self-management while undertaking program modules. The session duration is 45-60 minutes for session 1 and up to 30 minutes for session 2. The first session occurs around 1-2 weeks postenrollment. The counselor begins the session with rapport development, then screens for anxiety and depression using the Patient Health Questionnaire-4 (PHQ-4) [53]. Self-efficacy for managing changes associated with health behaviors and emotional well-being is also assessed. Decisional balance and ambivalence are explored.

Motivational interviewing strategies are used to support participants to articulate clear and achievable goals and to identify areas they wish to address in behavioral and emotional self-management. Action and coping planning interventions are used to support translation of goals into actions. At completion of the first session, the second telephone session is scheduled for a mutually agreed time (approximately 4 weeks after the first session). The second telephone session includes a reflection on anxiety or depression symptoms, self-efficacy, coping and action plans, relapse prevention, and maintenance of behaviors. In addition, if the counselor considers that the individual requires more intensive mental health support, referral options for counseling are discussed.

An SMS reminder is sent 24 hours prior to each telephone session appointment to facilitate engagement. To ensure consistency and quality of program delivery, lifestyle counselors receive fortnightly supervision with an experienced registered health psychologist.

Measures

Sociodemographic information is collected at baseline only. All participants complete the outcome measures of dietary intake, physical activity and sitting time, smoking status, anxiety and depression, stage of change, and self-efficacy in relation to behavioral and emotional self-management, quality of life, self-rated health, and well-being at baseline, post program (2 months after initial access to the program), and at 4-month follow-up (6 months after program access). Program acceptability is assessed post program only using a 6-item scale developed specifically for this study.

Primary Outcome Measures

Depression

Depression is assessed using the PHQ-9 [54]. The PHQ-9 is a brief 9-item depression screening tool based on the symptoms that comprise a diagnosis of major depressive disorder. Scores range from 0-27, with scores between 0-4 indicating minimal depression, 5-9, mild depression; 10-14, moderate depression; 15-19, moderately severe; and ≥20, severe depression. In patients with cardiac conditions, research has demonstrated an optimal PHQ-9 threshold of ≥6 [55,56], which combined improved sensitivity and retained specificity (sensitivity=83% and specificity=76% [56]) as compared to a threshold of ≥10, for detecting major depressive disorder based on a structured clinical interview. The PHQ-9 has been endorsed by the NHFA as the recommended tool for depression screening [57].

Physical Activity and Sitting Time

Physical activity and sitting time are measured using the Active Australia Survey (AAS) [58] with sitting questions from the International Physical Activity Questionnaire (IPAQ) (long form) [59]. The 8-item AAS measures frequency of walking, moderate activity, and vigorous activity in the last 2 weeks. The AAS has acceptable reliability and validity in the Australian community [60] and CR populations [61]. Participants are classified, according to the NHFA, as achieving the recommended target for adequate physical activity for secondary prevention [52] if they have been engaged in ≥150 minutes of physical activity per week combined across the 3 domains assessed. Sitting time is measured using the relevant questions from the IPAQ long form which asks participants about their total time spent sitting on a typical weekday and weekend day [59].

Dietary Intake

Diet quality is assessed using the Diet Quality Tool (DQT) [62], a 13-item questionnaire where all questions relate to nutrients of concern in the prevention of CVD (eg, fruit and vegetable, saturated fat, total fat, ω-3 fatty acids, fiber, and salt intake). Each item is scored from 0 to 10, where 10 indicates that the participant is meeting the NHFA's secondary prevention nutrition guidelines [52]. Participants are classified as achieving a healthy diet for CHD secondary prevention if they receive a total DQT score >60%. This cut-off was originally identified by a panel of four accredited practicing dieticians with clinical, CR, and dietary research methodology experience, and validated against a 4-day food diary in Australian patients with cardiac conditions attending CR [62]. The DQT was found to be a valid and useful dietary assessment tool in a secondary CVD prevention setting [62].

Secondary Outcome Measures

Smoking Status

Smoking is assessed on the basis of self-reports by asking participants "Do you smoke?" Current smokers are asked how many cigarettes they smoke per day. Former smokers are asked when they quit smoking.

Anxiety

Anxiety is assessed using the 7-item Generalized Anxiety Disorder instrument (GAD-7) [63]. The GAD-7 was developed to provide a brief self-report measure to identify generalized anxiety in primary care, and asks participants, using 7-items, to indicate how often they have been bothered by certain problems over the past 2 weeks. The GAD-7 has good reliability and validity for detecting generalized anxiety [64]. The GAD-7 has been validated within a large sample of people in a primary care setting [63] and in cardiac populations [65].

Well-being

Well-being is assessed using the World Health Organization–Five Well-Being Index (WHO-5) [66]. This is a short, self-reported measure of current subjective mental well-being. The WHO-5 has adequate validity as an outcome

measure in clinical trials and has been applied successfully as a generic scale for well-being across a wide range of study fields [67]. It has also been successfully used as a predictive tool for patients with cardiac conditions [68].

Quality of Life and Self-rated Health

Quality of life is measured using the Short Form Health Survey (SF-12) [69]. The SF-12 is a 12-item measure often used to compare health status between 2 groups of people, to identify predictors of health status and to determine health status in a specific disease population [70]. The SF-12 also includes one item that assesses self-rated health, which has been shown to predict survival [71]. The instrument is regarded as a reliable and valid generic measure of health-related quality of life in cardiac populations [72,73].

Self-efficacy

Self-efficacy is assessed using an 8-item scale, which has been designed specifically for this study. Participants indicate on a 5-point Likert scale how confident they are that they can make or sustain relevant behavioral and emotional changes.

Readiness to Change (Stages of Change)

Participants are asked to indicate their readiness to change relevant behaviors on a 5-point Likert scale from not thinking about making changes to have maintained changes for more than 6 months. This scale has been developed specifically for this study using wording from the Stages of Change model.

Additional Measures

Basic sociodemographic (namely age, sex, country of birth, marital status, living arrangement, employment status, educational level, and financial strain), medical (other physical and mental health conditions), and event-related information (event type, date of event, and attendance at cardiac rehabilitation) is collected via a self-report questionnaire, using standard questions used in previous ACHH studies [74].

Data Analysis

In evaluating outcomes, there will be two groups of participants based on the mode of delivery: "self-directed" and "supported." All statistical analyses will be performed on an intention-to-treat (ITT) basis with $P<.05$. In the case that ITT produces a null finding, it is possible that this is due to participants in the supported group not participating in the additional telephone sessions (that is, not receiving the intended treatment). To test that hypothesis, we will then undertake treatment-received analysis (also called Per Protocol) whereby only those who received the treatment in accordance with the protocol are included. This will enable us to determine whether any differences were obtained between those who received the self-directed treatment and those who received the supported treatment. *P* values less than .05 will be considered significant for the primary outcome and those less than .01 will be considered significant for secondary outcomes. The effect of the intervention on the primary and secondary outcomes at 6 months will be assessed using analysis of covariance (ANCOVA) models that include the baseline value of the outcome as a covariate and the group assignment (self-directed versus supported) as a categorical variable. The treatment effect, its effect size (Hedge g), and 95% CIs for the treatment effect and within-group changes from baseline to 6 months will be calculated from the ANCOVA models. The sensitivity of the results to missing data will be evaluated using a data-based multiple imputation procedure.

Primary Outcome Measures: Depression, Physical Activity, and Dietary Intake

As the main outcomes, we will examine differences between the 2 groups in the proportion of participants who are:

1. classified as *nondepressed* at baseline, post program, and follow-up (based on a PHQ-9 score of <6) [55,56],
2. achieving physical activity guidelines of ≥150 minutes of physical activity per week [52] at baseline, post program, and follow-up, or
3. achieving healthy dietary guidelines of DQT scores >60% [62] at baseline, post program, and follow-up.

Secondary Outcome Measures

Smoking Rates

Among smokers, the proportion of people who have quit smoking will be compared for the 2 groups.

Change Over Time in Other Psychosocial and Attitudinal Measures

Change over time in scores on the GAD-7, WHO-5, and SF-12 and in self-efficacy and readiness to change behaviors and emotions will be compared between the self-directed and supported groups using repeated-measures analysis of variance. Multiple regression analysis, with groups entered as potential predictors, will be used to predict participants with greatest improvements in GAD-7, WHO-5, SF-12, and self-efficacy scores, and readiness to change behaviors and emotions.

Assessing the Back on Track Program Acceptability

Proportions will be calculated for all items on the program acceptability scale.

Results

Recruitment began in May 2020 and concluded in August 2021. A total of 122 participants were enrolled in this study. Data collection, including 2- and 6-month follow-up is expected to be completed by February 2022, and data analysis and publication of results will be completed by June 2022.

Discussion

With cardiac event survivors at a heightened risk of a recurrent events and premature death, and with suboptimal attendance at center-based rehabilitation and secondary prevention programs, there is a need for innovative eHealth programs to support people in their behavioral and emotional self-management after an acute cardiac event. We anticipate that the *Back on Track* program will assist people in their recovery after an acute event and will represent a flexible, easily accessible, user-friendly, and effective adjunct to center-based programs. Our findings will enable us to quantify the behavioral and emotional improvements obtained and sustained for people with CHD

who participate in the *Back on Track* program, while also comparing two methods of delivery: one fully self-directed and the other supported by a lifestyle counselor.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

AAS: Active Australia Survey
ACHH: Australian Centre for Heart Health
AMI: acute myocardial infarction
ANCOVA: analysis of covariance
CABGS: coronary artery bypass graft surgery
CBT: cognitive-behavioral therapy
CHD: coronary heart disease
CR: cardiac rehabilitation
DQT: Diet Quality Tool
GAD-7: 7-item Generalized Anxiety Disorder instrument
IPAQ: International Physical Activity Questionnaire
ITT: intention to treat
MI: motivational interviewing
NHFA: National Heart Foundation of Australia
PCI: percutaneous coronary intervention
PHQ: Patient Health Questionnaire
PICF: participant information consent form
RCT: randomized controlled trial

REDCap: Research Electronic Data Capture
SF-12: Short Form Health Survey
WHO-5: World Health Organization–Five Well-Being Index

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Protocol

Combined Clinical Audits and Low-Dose, High-frequency, In-service Training of Health Care Providers and Community Health Workers to Improve Maternal and Newborn Health in Mali: Protocol for a Pragmatic Cluster Randomized Trial

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Abstract

Background: Although most births in Mali occur in health facilities, a substantial number of newborns still die during delivery and within the first 7 days of life, mainly because of existing training deficiencies and the challenges of maintaining intrapartum and postpartum care skills.

Objective: This trial aims to assess the effectiveness and cost-effectiveness of an intervention combining clinical audits and low-dose, high-frequency (LDHF) in-service training of health care providers and community health workers to reduce perinatal mortality.

Methods: The study is a three-arm cluster randomized controlled trial in the Koulikoro region in Mali. The units of randomization are each of 84 primary care facilities. Each trial arm will include 28 facilities. The facilities in the first intervention arm will receive support in implementing mortality and morbidity audits, followed by one-day LDHF training biweekly, for 6 months. The health workers in the second intervention arm (28 facilities) will receive a refresher course in maternal neonatal and child health (MNCH) for 10 days in a classroom setting, in addition to mortality and morbidity audits and LDHF hands-on training for 6 months. The control arm, also with 28 facilities, will consist solely of the standard MNCH refresher training delivered in a classroom setting. The main outcomes are perinatal deaths in the intervention arms compared with those in the control arm. A final sample of approximately 600 deliveries per cluster was expected for a total of 30,000 newborns over 14 months. Data sources included both routine health records and follow-up household surveys of all women who recently gave birth in the study facility 7 days postdelivery. Data collection tools will capture perinatal deaths, complications, and adverse events, as well as the status of the newborn during the perinatal period. A full economic evaluation will be conducted to determine the incremental cost-effectiveness of each of the case-based focused LDHF hands-on training strategies in comparison to MNCH refresher training in a classroom setting.

Results: The trial is complete. The recruitment began on July 15, 2019, and data collection began on July 23, 2019, and was completed in November 2020. Data cleaning or analyses began at the time of submission of the protocol.

Conclusions: The results will provide policy makers and practitioners with crucial information on the impact of different health care provider training modalities on maternal and newborn health outcomes and how to successfully implement these strategies in resource-limited settings.

Trial Registration: ClinicalTrials.gov NCT03656237; https://clinicaltrials.gov/ct2/show/NCT03656237

International Registered Report Identifier (IRRID): DERR1-10.2196/28644

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KEYWORDS

perinatal mortality; low dose high frequency training; maternal and newborn health outcomes; Mali

Introduction

Background

Mothers and their babies are at the highest risk of death during delivery and during the first week postpartum [1]. Even though 59% of births in sub-Saharan African countries now occur in health facilities [2], in 2018, approximately 2.476 million babies died during the first 28 days of life, with approximately 1 million dying during the first day of life and almost another 1 million within the first week [3,4]. In Mali, an estimated 67 stillbirths [5] and an additional 75 newborn deaths [6] occur on average every day; the predominant causes are birth asphyxia, prematurity, and sepsis [7]. The maternal mortality ratio in Mali is 562 per 100,000 live births [3], almost 2.7-fold the global rate [3]. Most of these deaths are because of factors related to the place of delivery and quality of care [4,8]. In particular, the lack of appropriately trained staff in facilities, delays in referrals, and inadequate supplies and equipment are evident in many resource-poor settings [9]. This suggests that high-quality care, especially during late pregnancy, childbirth, and the early newborn period, are essential [10], and simple evidence-based interventions are likely to meaningfully reduce the number of maternal deaths, stillbirths, and early neonatal deaths [11,12].

Traditional capacity-building models for training health care providers, delivered through off-site classroom-style lectures or directed reading, are still the norm in low- and middle-income countries [8,13,14]. However, to disrupt the delivery of services, these approaches have been found to have limited (if any) impact on learning outcomes, and any knowledge and skills gained are neither transferred to other coworkers at the facility nor translated into improved provider practice and performance [13,15]. Moreover, there is no evidence that these methods contribute to knowledge retention after training, and limited conclusions can be drawn about their long-term impact on measures of performance in terms of service quality and maternal and newborn outcomes. A review of intervention studies aimed at improving the performance of health workers in low- and middle-income countries has suggested that problem-based learning and competence-based learning [15], including supervision and audits with feedback [13,14], along with brief team learning sessions within the workplace (health facility), using simulation, followed by simulation-based practice and feedback, can improve learning outcomes and provider performance compared with training approaches that do not include subsequent practice [13,16].

Over the last few years, an increasing number of African countries have implemented competency-based training of health care providers with the goal of improving maternal and child health outcomes and reducing perinatal mortality [17-19]. Low-dose, high-frequency (LDHF) training is a type of competency-based training that promotes maximal retention of clinical knowledge, skills, and attitudes through short, targeted, simulation-based learning activities, delivered during several in-service sessions and reinforced with structured practice sessions [20].

In that vein, in response to a World Health Organization report on health systems and policy indicators documenting that Mali did not have a policy on maternal, perinatal, and neonatal death audit (World Health Organization 2014), Mali's Ministry of Public Health and Hygiene made it mandatory to report maternal, perinatal, and neonatal deaths and adverse events within 48 hours of their occurrence, through the Integrated Disease Surveillance and Response Network, and to convene an audit of the events within 15 days of the notification.

Mali's national directive to implement facility-based maternal and perinatal morbidity and mortality audits offers an opportunity to leverage it and target training on skills and competency gaps identified during audits. However, to the best of our knowledge, the potential of using facility-based maternal and perinatal morbidity and mortality audits to identify areas that require attention for subsequent LDHF hands-on training has not yet been exploited. Moreover, even though LDHF hands-on training has demonstrated a significant positive impact on maternal and early neonatal outcomes, including reduced rates of fresh stillbirth and first-day mortality [17,21], retained placenta, and postpartum hemorrhage [19]. Limited conclusions can be drawn about the impact of LDHF hands-on training on maternal and neonatal care practices during intrapartum and postpartum periods and other perinatal outcomes, especially 7-day mortality and morbidity. There is very little known about the cost-effectiveness and the processes of implementation of LDHF training [22,23].

Objective

This study proposes a strategy to leverage maternal and perinatal morbidity and mortality audits being implemented in Mali, as a basis for identifying gap areas that can be addressed by a case-based focused LDHF on-site training strategy within primary health care–level facilities (Centre de Santé Communautaire [CSCOM]). These trainings will also target community-based causes of mortality and morbidity in health facilities. The trial will assess the effectiveness of LDHF

hands-on training informed by maternal and neonatal mortality audits in reducing perinatal mortality and in increasing adoption of key maternal and newborn care practices during the delivery and the postpartum period. Secondary objectives include assessment of the implementation process and the cost-effectiveness of the intervention.

Methods

Study Setting

The study will be conducted in 4 districts in the Koulikoro region, Mali. The study area was selected as it is part of a larger project implemented by the Canadian Red Cross in collaboration with the Malian Red Cross (Croix-Rouge Malienne). This project is an integrated 4-year (2016-2020) maternal neonatal and child health (MNCH) intervention that targets 6 districts across the Koulikoro and Sikasso regions and is funded by the Government of Canada. The project supports the primary and secondary health facilities (CSCOMs and Centre de Santé de Référence [CSREF]—referral health centers) to improve the quality of their MNCH services and strengthen the health management information system. At the community level, the Malian Red Cross has a strong presence because of the training and support of local community health workers and volunteers for MNCH-related activities at remote integrated management of childhood illness sites.

The Koulikoro region is the second-most-western region of Mali. It covers an area of 90,120 square kilometers. With an estimated population in 2017 of 3.1 million and a density of 26.8 people per square kilometer. The Koulikoro region is separated into 7 districts: Kati, Kangaba, Koulikoro, Kolokani, Nara, Banamba, and Dioïla. The Canadian Red Cross and Malian Red Cross program encompasses the latter five. Of these, 4 districts (Koulikoro, Kolokani, Banamba, and Dioïla) will be included in this study.

Trial Design

This pragmatic (effectiveness) cluster randomized controlled trial will be implemented in 84 community health facilities (CSCOM) in the Koulikoro region, Mali. Facilities will be randomly allocated into either of two intervention arms or the control arm.

- Intervention arm 1: audit and feedback with LDHF hands-on training and 6 months follow-up.
- Intervention arm 2: MNCH refresher training and audit, and feedback with LDHF hands-on training and 6 months follow-up.
- Control arm: allocated to receive MNCH refresher training and follow-up.

Cluster Size and Selection

Community health facilities, including community health workers serving the catchment area, are the units of randomization (clusters). Although there are some differences in the services provided at these facilities according to the baseline facility assessment conducted in December 2016, only those health facilities providing basic obstetric care with at least one health care provider trained in the active management of the third stage of labor (AMTSL), essential newborn care (ENC), perinatal care (PNC), and those who had not yet started implementing the audits are considered for inclusion in the study. All facility deliveries (both mother and newborn) within study clusters and live home births referred to a facility within the perinatal period are included in the trial, subject to informed consent. In that respect, a master list of 84 facilities meeting the inclusion criteria within the 4 districts will be generated.

Randomization

Health facilities were randomly allocated into one of the three study arms, resulting in 28 facilities per study arm. The randomization of clusters was performed by an independent epidemiologist not directly involved in the research project using a pseudorandom number sequence generated using Excel (Microsoft). Owing to the nature of the intervention, blinding of study participants and data collectors is not possible; however, outcome data will be collected by independent data collectors not involved in the intervention delivery. The study setting (Figure 1), recruitment strategies, random allocation sequence, intervention implementation, and data collection points (Figure 2) are summarized below.

Figure 1. Geographical location of health districts and health facilities under study. LDHF: low-dose, high-frequency; MNCH: maternal neonatal and child health.

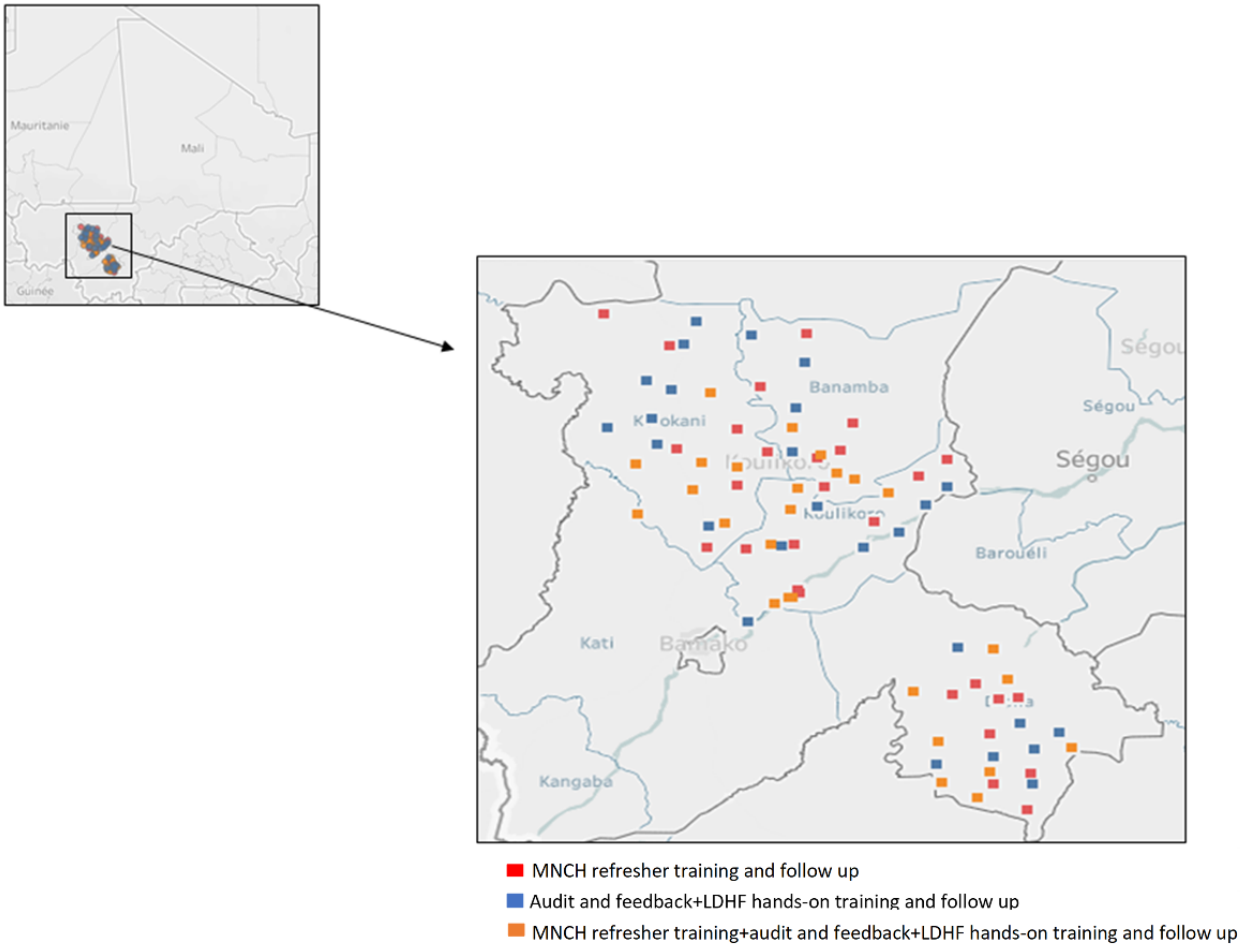
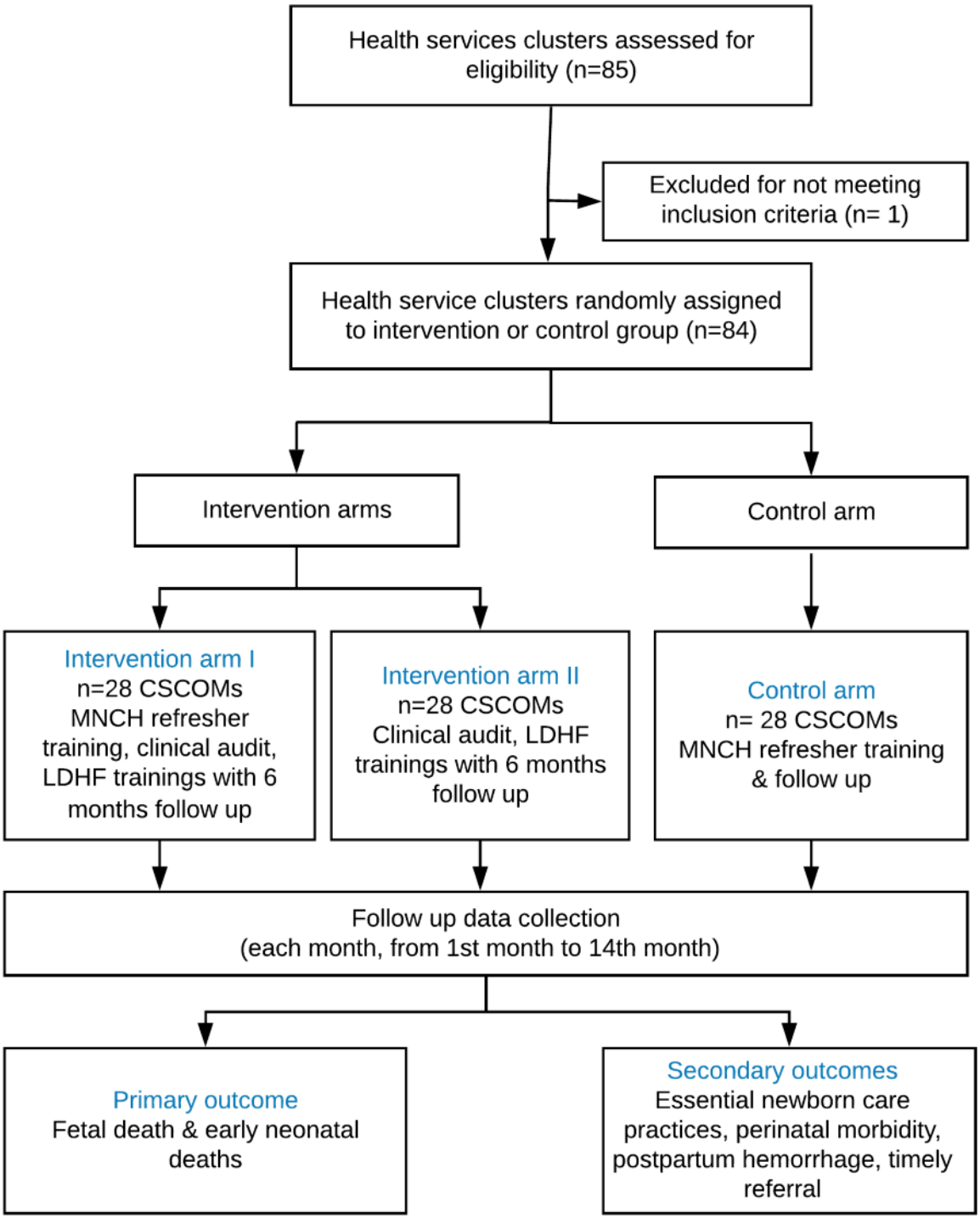


Figure 2. Flow chart of community health services clusters recruitment and follow-up. CSCOM: Centre de Santé Communautaire; LDHF: low-dose, high-frequency; MNCH: maternal neonatal and child health.



Trial Participants and Units of Randomization (Clusters)

The group of facility-based health workers and community health workers within the 4 health districts of the Koulikoro region within each facility (unity of randomization) are eligible to enter the trial. Eligible facilities are those that provide basic obstetric care and have at least one facility-based health care provider trained in AMTSL, ENC, and PNC. The eligibility assessment of facilities was made possible through the data collected during the baseline facility assessment conducted in December 2016.

Facilities within the 4 health districts of the Koulikoro region that did not provide basic obstetric care or those who did not have any health workers who received training in maternal and neonatal health care providers in AMTSL, ENC, and PNC have

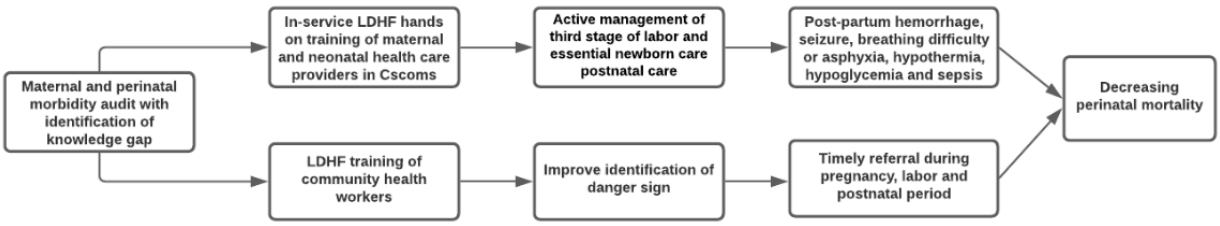
been excluded. Rural maternities were not eligible, as they are not included in the national audit policy.

Intervention Strategy

The intervention uses a problem-based learning approach that uses the information emerging from the implementation of maternal and newborn audits to improve health worker skills training. This training is delivered by a study-trained facilitator, employed by Mali's Ministry of Public Health and Hygiene, that attends and provides feedback during the audit meeting, followed by an immediate (next day) one-day in-service case-based focused training [8,13,14]. Specifically, each training cycle starts with the implementation of a maternal and neonatal morbidity and mortality audit, during which the trainer identifies gaps in knowledge and skills. This is followed by on-site LDHF hands-on training of maternal and neonatal health care providers on the skills and competency gaps highlighted by the audits. The training sessions also include direct observation of care, supervision, and use of simulations. In addition, community health workers are also trained when issues identified during the audit are related to their practice, such as in the identification of danger signs in the community or timely referral to the facility.

We hypothesize that the provision of on-site case-based LDHF hands-on training of maternal and neonatal health care providers, focused on gaps identified through clinical audits, will improve quality of care, thus decreasing adverse events during labor and the immediate postpartum and perinatal period in facility births, in comparison to traditional off-site generic training. The training of community health workers will improve community management via identification of danger signs and timely referral during pregnancy, labor, and the postnatal period (Figure 3). Ultimately, the aim of the intervention is to address key barriers to improving maternal and perinatal health by focusing on increasing the capacity of maternal and neonatal health care providers along with improving the recognition of danger signs and referral during the natal and postnatal period by community health workers.

Figure 3. The intervention model. LDHF: low-dose, high-frequency.



Study Arms

Overview

This study is a three-arm cluster randomized controlled trial including one control and two intervention arms with a gradual increase in the intervention components.

- MNCH refresher training and follow-up: the control arm will consist of standard MNCH refresher training delivered in the classroom using multi-method classroom training delivered as part of the larger Canadian Red Cross and Malian Red Cross project. For these training sessions, two maternal and neonatal health care providers from each facility randomized to the control study arm received 10-day classroom training on AMTSL, ENC, PNC, and integrated community case management of childhood illnesses.
- Audit and feedback with LDHF hands-on training and 6 months follow-up: the first intervention arm will include 28 facilities in which mortality and morbidity audits will be implemented by the study team, followed by one day of case-based focused LDHF hands-on training biweekly for 6 months.
- MNCH refresher training followed by audit and feedback combined with LDHF hands-on training and 6-month follow-up: the second intervention arm will include 28 facilities that will benefit from MNCH refresher training, in addition to mortality and morbidity audits implemented by the study team, followed by one day of case-based focused LDHF hands-on training biweekly for 6 months.

Consent to Participate

Written consent will be obtained from mothers or fathers of newborns at the follow-up household visit and for verbal autopsy. If the mother is not able to give consent, her husband or other adult family member will be requested to give consent to participate in the study. If the respondent cannot read, the consent statement will be read to them, and a thumb impression by the respondent in place of a signature will signify consent. The data collector will explain the risks and benefits to potential enrollees before conducting the verbal autopsy and administering the household questionnaire in the intervention and control clusters. Participants will be informed that they have the right to withdraw from the study at any time and that there are no penalties from doing this, and this will not in any way affect their ability to receive any health care services.

Ethical Approval and Protocol Registration

Ethical approval was obtained from the Sickkids Research Ethics Committee (Research Ethics Board number 1000060635) and from the University of Bamako's Faculty of Medicine Ethics Committee. The project was registered at ClinicalTrials.gov (NCT03656237).

Process of the Intervention Implementation

Audit and Feedback

An audit committee comprising a health facility manager, basic obstetric and neonatal care providers, and district or regional health department representatives will be formed in each facility, following the guidelines developed by Mali's Ministry of Public Health and Hygiene. The health facility representative designated by the audit committee will be responsible for audit support, including providing medical records and supporting documentation to the audit committee, assisting in the development of the process, procedural walkthroughs, and responding to various inquiries to assist the committee with the development and documentation of the audits.

Low-Dose, High-frequency Training

Mali's Ministry of Public Health and Hygiene's 10 senior physicians, with gynecological or obstetrical background, will be trained on the implementation of the intervention and will support implementation of the audits, facilitate the process and discussions, and during the audit meeting, identify key knowledge gap areas for the subsequent on-site case-based focused LDHF hands-on training, mentoring, and supervision of MNCH care providers. In this regard, the intervention trainers will stay at the health facility for one consecutive day to implement case-based focused LDHF hands-on training to the facility staff involved in basic obstetric and neonatal care and to community health workers linked to each facility when appropriate, as described above. The training modules will be based on recommendations from the clinical audit and focus on strengthening the core competencies identified by the audit committee as the cause of death or complications in the patient. The trainers will also observe health care providers during service delivery and postnatal care and will use direct observation skills checklist to record identified gaps in clinical skills and knowledge and will assist the health care provider in implementing national service delivery standards and guidelines. The audits will be implemented following the Ministry of Public Health and Hygiene guidelines and will serve as a platform for the identification of cases for case-based, focused LDHF hands-on training. Data from the partographs and facility birth registers will be used to identify the case to be audited. Once identified, audit cases will be anonymized and summarized by the health facility representative. The case summaries will be discussed in detail, identifying causes of death or near miss, perinatal or maternal complications, and assessing the quality of care provided. The findings will be evaluated against existing service delivery standards and protocols. In addition, external factors that adversely affect patient outcomes, such as delayed recognition of danger signs during pregnancy or labor, delayed referrals, and delayed recognition of danger signs during the perinatal period, will be identified during the audit for community health worker training at the corresponding facility. Audit information is the basis for identifying knowledge or case management gaps among health care providers, knowledge-to-action gaps, and training requirements. The summary of each audited case will have a structured section in which the trainer will document action points for training and managerial support, and these will also be recorded in the minutes of the audit committee meeting.

Research Questions

This cluster randomized trial aims to assess whether LDHF hands-on training, informed by maternal and neonatal mortality audits in routine clinical settings, reduces perinatal mortality. Secondary objectives include estimating the effectiveness of the intervention in improving maternal and neonatal care practices among health workers and the comparative cost-effectiveness of the case-based focused LDHF hands-on training, compared with traditional training.

Primary Outcome

The perinatal mortality rate per 1000 live births occurring in each facility and the corresponding catchment area for the births that had taken place in the facility will be used to assess the effectiveness of the intervention. It is defined as the sum of *fetal deaths* (stillbirth), defined as the death of a fetus weighing 500 g or more, or of 22 weeks of gestation or more, occurring in health facilities, and *early neonatal death*, namely, the death of a live born within the first 7 days of life occurring in the facility or in the community. As health facility studies are not an appropriate source of data for calculating perinatal mortality incidence [24] unless all babies are born and stayed in a health facility for 7 days, the data on perinatal mortality will be extracted from both facility-level data and household survey questionnaires.

Secondary Outcomes

The secondary outcomes are as follows:

1. Proportion of newborns stimulated or with airways cleared using a suction bulb, catheter or a bag and mask to resuscitate per 1000 facility live births.
2. Proportion of children breastfed within an hour of birth per 1000 facility live births.
3. Proportion of newborns that were given breast milk and no other food or drink for the first 7 days of life, per 1000 facility live births.
4. Proportion of newborns dried and wrapped immediately after birth, per 1000 facility live births.
5. Proportion of newborns immediately placed on the chest of the mother—skin to skin after birth per 1000 facility live births.
6. Proportion of newborns who were not bathed within the first 24 hours of life, per 1000 facility live births.
7. Proportion of all newborns who received all four elements of ENC: immediate and thorough drying, immediate skin-to-skin contact, delayed cord clamping, and initiation of breastfeeding in the first hour.
8. Proportion of neonatal hypothermia, per 1000 facility live births.
9. Proportion of newborns referred from CSCOM to a higher-level facility because of obstructed labor, low birth weight, hypothermia, or severe infection.
10. Proportion of newborn mothers who experienced postpartum hemorrhage in the facilities.

11. Proportion of deliveries referred to the higher-level facility from a primary facility because of postpartum hemorrhage, per 1000 deliveries.

Sample Size

A sample size of 600 births per cluster was calculated to have 80% power to detect a reduction in the perinatal mortality rate from 30% to 27% live births, which corresponds to a 10% reduction in the perinatal mortality rate between intervention and control arms (α=5%, intracluster correlation of 0.003, and coefficient of variation of cluster size 0.9 and a 0.96 correlation of baseline measures with outcome). The number of clusters available per arm was 28. The expected average number of deliveries per month in each cluster was approximately 38, resulting in 16 months of follow-up. Two additional months of data collection are planned to account for losses and refusals and allow for adjustments in the analysis, resulting in a final average cluster size of approximately 675 births over 18 months.

Data Collection Methods

Health Facility Data

All the facilities in the intervention and control clusters will be visited once a month to retrospectively and systematically collect detailed data from partographs and registries for all facility births and any newborn that was not delivered in the facility but was referred to the facility for PNC within the first 7 days following birth.

Household-Level Interviews

The data collectors will also conduct a follow-up home visit (during the monthly health facility data collection visit, described above) to all women who recently gave birth in facilities since their last visit to administer a short questionnaire after at least 7 days postpartum to capture any perinatal death, complications, or adverse events, the status of the newborn during the perinatal period, and the mother's satisfaction with the health care during the facility delivery.

Verbal Autopsy in the Household

In the case of perinatal death in the household recorded during their monthly visits, the data collector will pay a visit after the 40-day bereavement period to conduct a verbal autopsy. Two local independent physicians will review each completed verbal autopsy and assign the cause of death using International Classification of Diseases 10th Revision. If the two physicians do not assign the same diagnosis, a third physician (adjudicator) will review the two causes of death and assign a final cause of death.

Process Data From Audits and Training

The intervention trainers will collect data on the implementation of audits and training, the training modules provided, and the data on the health providers' skills, using a structured checklist to examine providers' skills related to AMTSL, ENC, and PNC. To ensure the quality of the data and training, supervisors will work full-time to monitor the data collection and training process and to check the reliability and accuracy of data compared with facility registries. Given the length of the project and action of multiple nongovernmental organizations in the study area, we will prospectively collect data on the concurrent implementation of MNCH interventions and health care worker training in the study facilities that may affect the study outcomes.

All data will be collected on tablets using ODK Collect and then uploaded to the server in real time. We will use a monitoring tool to oversee, in real time, the process of intervention implementation for evaluation. The study monitoring data included the number of health providers in the health facility trained, the number of community health workers trained, and the number of on-site case-based focused LDHF sessions conducted.

Data Management and Analysis

Blinding

Owing to the nature of the intervention, facility staff cannot be blinded to the study allocation. Independent data collectors not involved in the intervention delivery will collect data to minimize bias in data collection. The primary outcome data analysis will be blinded to the intervention status of the facilities.

Data Safety Monitoring

To assess the progress and help ensure the validity and credibility of the trial results, a data and safety monitoring board will be convened with 3 individuals, respectively an epidemiologist from the Hospital for Sick Children, an obstetrician gynecologist, and a pediatrician from the University of Science and Technology of Bamako. Interim analyses will be conducted during the course of the trial, based on accumulating data on efficacy, to help the data and safety monitoring board determine whether there is sufficient evidence to recommend whether to continue, emend, or terminate the trial or if there is already clear evidence that (1) the intervention is beneficial, (2) the intervention is either harmful or has little or no effect, or (3) the trial will likely be unable to detect the effect of the intervention, for example, because the incidence of perinatal mortality and morbidity is too low or because of the low follow-up rate of the mothers during the perinatal period.

Process Evaluation

As this study is a complex intervention delivered in the context of an operational research, we will undertake a mixed methods process analysis to provide policy makers and practitioners information about how and why the intervention was effective and how it might be replicated [25,26]. First, the process evaluation will explore whether the intervention is delivered as intended [27], both at the facility level (training) and the individual level (provider delivery). Second, process evaluation will allow exploring the mechanisms through which interventions affect perinatal mortality and morbidity. As the intervention may have different effects in different facilities even if implementation was identical [28], we will assess the variability in the implementation to provide an understanding of how contextual and factors related to health facility features could act synergistically to influence the intervention implementation and perinatal mortality and to identify the contextual factors most likely to lead to successful implementation in other settings.

The process evaluation will be conducted in both intervention arms using the study monitoring data, semistructured interviews with stakeholders (n=12) and focus groups with facility providers and community health workers. Health care providers will be asked about their experiences and satisfaction with the intervention and suggestions to improve care for the AMTSL, ENC, and PNC. Health care providers will be asked about their perception of how to strengthen and sustain this intervention and other efforts to improve care for the AMTSL, ENC, and PNC in Mali. These steps will also help identify barriers to and facilitators of intervention implementation. Details on the protocol of our mixed methods process evaluation will be published in a separate paper.

Economic Evaluation

We will undertake an economic evaluation to determine the incremental cost-effectiveness of each of the case-based focused LDHF hands-on training strategies in comparison to MNCH refresher training in a classroom setting. This assessment will be conducted from the perspective of the health system. The resources used to deliver the intervention, including staff, training, implementation, and monitoring costs, will be used to derive the costs. The efficacy measurement will be based on the primary outcome variable of this study, namely perinatal mortality with a one-year time horizon and expressed in terms of the number of healthy years of life lost because of premature mortality [29]. The cost-effectiveness of the intervention will be measured in dollars per disability-adjusted life-year (DALY) saved, and we will estimate the incremental cost-effectiveness ratios of each training strategy compared with traditional training methodology by dividing the difference in mean costs between groups by the difference in mean effects between groups measured by DALYs. We will compare the LDHF hands-on training group with the traditional training in terms of (1) costs incurred over the 12-month period and (2) DALYs. All costs will be adjusted for inflation using the Malian Consumer Price Index and presented in international dollars.

Interim Analyses and Stopping Rules

No interim analysis was performed. However, in the event of disruptive events such as conflict, natural disaster, implementation of similar interventions in the study area, or the deteriorating health and humanitarian situation, we will assess the implications of the study design, stop the study if necessary, and assess the implications on the feasibility of the design to produce evidence on the implementation and effectiveness of the intervention.

Results

The trial is completed. The recruitment began on July 15, 2019, and data collection began on July 23, 2019, and was completed in November 2020. Data cleaning or analyses began at the time of submission of the protocol. As the randomization is performed at the health facility level, we will undertake aggregate cluster-level analysis comparing the proportion between treatment arms [30]. We will compare differences in the proportion of perinatal mortality between intervention and control groups using a chi-square statistic adjusted for the effect of clustering within health facilities [31] using a formula that incorporates the intraclass correlation coefficient as a measure of the extent of clustering [32].

The analysis and report of the intervention effect will be carried out in accordance with CONSORT (Consolidated Standards of Reporting Trials) principles and its extension for pragmatic trials [33].

We will perform all analyses using Stata version 16.1 software (Stata Corp).

Discussion

Study Dissemination Strategy

This operational research study aims to improve the practical knowledge of health workers to improve the quality of management of childbirth and PNC to reduce perinatal mortality. It is part of Mali's ongoing efforts to achieve target 3 of the Sustainable Development Goals and whose results would be useful for potential replication or scale-up. We will valorize the findings by adopting strategies for dissemination and knowledge transfer. For this purpose, the results will be disseminated to the Ministry of Health and Health Care providers. We will also hold a deliberative workshop with project users and stakeholders to discuss the results and lessons learned from the implementation and effects of the intervention to provide guidance from the perspective of replication or scaling-up. In addition, we will disseminate the results among the scientific and political communities through publications in scientific journals and presentations at international conferences.

Strengths of the Study

The distinctive feature of this intervention compared with the other LDHF interventions is that it adopts problem-based learning, including supervision and audits with feedback [14]. Thus, the audit component will identify knowledge gaps related to the maternal and neonatal care provided in the facilities and then identify the appropriate training modalities to correct deficiencies in the management of maternal and neonatal care around the delivery and in the postpartum period.

The analytical approaches will provide evidence about the benefits and costs of this pragmatic intervention to improve the quality of maternal and newborn care in Mali with the aim of reducing perinatal mortality. The results will provide policy makers and practitioners with crucial information to facilitate the translation of best practices in capacity strengthening for health care providers in the routine practice of maternal and child care services. Indeed, although LDHF hands-on training has been implemented and evaluated in some resource-limited settings with the aim of reducing maternal and perinatal mortality, previous studies have analyzed only a few outcomes [17,21].

Another distinctive feature of this trial is that it adopts a pragmatic and holistic approach, and the analysis will contain both qualitative and quantitative data collected over a period of 14 months. The trial will provide a better understanding of how LDHF hands-on training of health care providers and community health workers could complement routine care to improve maternal and child health outcomes in resource-limited settings.

In addition, this trial occurs during routine health service delivery and will demonstrate the potential of routinely collecting health management information system data to analyze the effectiveness of a major public health intervention.

Limitations of the Study

Despite these strengths, some limitations of this study need to be considered. The facility-level data collection instrument was developed based on existing consultation and delivery registries, as well as partograph forms. As data are not being collected by direct observation of health care providers but rather from the partographs and registries they fill out, we are also concerned with the completeness, reliability, and accuracy of data to be collected. To overcome this important limitation, refresher training on the use of partographs will be held in all health facilities that are part of the trial. This will strengthen the health care providers' capacity to use the partograph and aim to improve data completeness and quality for this study.

Some data will be lost to follow-up if the newborn's mothers are referred to higher-level health facilities. However, we estimate that this will be a minimal disruption to the trial, and we will report the number of these cases in our analyses. In addition, underreporting of infant deaths is usually greater for deaths that occur very early in infancy in low-income countries [24]. As the Ministry of Health is a stakeholder in this project, a strategy will be developed in cooperation with the study team to motivate health workers to improve data completeness, reliability, and accuracy. We will also triangulate mortality data collected in the health facility with the mortality data collected in the household surveys to assess the level of completeness and accuracy and to reduce the likelihood of underreporting of perinatal and maternal deaths in the facility. The data collector will also conduct a follow-up home visit, aided by community relays and volunteers, for all facility births to minimize losses to follow-up.

Finally, completeness and accuracy of recall, including age at death, may deteriorate with time and is also related to the skill and cultural sensitivity of the person carrying out the interview [24]. However, as the recall period was relatively short in this trial (<21 days), the risk of recall bias will be reduced.

Acknowledgments

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The authors thank the in-country project implementation partner and team composed of the study supervisor and coordinator with the help of four field-monitoring officers, trainers, and data collectors. They also thank the Canadian Red Cross, the regional director of health of Koulikoro, and health district authorities in Kolokani, Banamba, Koulikoro, and Dioïla, as well as the health workers for their collaboration in this study.

Authors' Contributions

DGB, ZAB, and SS were the principal investigators of the study. DGB designed the study and led the protocol development with FZ, JLK, KM, and DZ. MD contributed in designing the questionnaires, planned the data collection, and superviseed the implementation of the intervention and data collection. SD coordinated the implementation of the intervention and data collection. FH supervised the implementation of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by SickKids - The Hospital for Sick Children (Toronto, Canada).
[PDF File (Adobe PDF File), 270 KB - resprot_v10i12e28644_app1.pdf]

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Abbreviations

AMTSL: active management of the third stage of labor
CONSORT: Consolidated Standards of Reporting Trials
CSCOM: Centre de Santé Communautaire
CSREF: Centre de Santé de Référence
DALY: disability-adjusted life-year
ENC: essential newborn care
LDHF: low-dose, high-frequency
MNCH: maternal neonatal and child health
PNC: perinatal care

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Protocol

Evaluation of the Efficacy of a Smoking Cessation Intervention for Cervical Cancer Survivors and Women With High-Grade Cervical Dysplasia: Protocol for a Randomized Controlled Trial

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Abstract

Background: The prevalence of smoking among cervical cancer survivors is strikingly high, yet no smoking cessation interventions to date have specifically targeted this population. This paper describes the study design, methods, and data analysis plans for a randomized clinical trial designed to evaluate the efficacy of a theoretically and empirically based Motivation And Problem Solving (MAPS) approach for promoting and facilitating smoking cessation among cervical cancer survivors. MAPS is a comprehensive, dynamic, and holistic intervention that incorporates empirically supported cognitive behavioral and social cognitive theory–based treatment strategies within an overarching motivational framework. MAPS is designed to be appropriate for all smokers regardless of their motivation to change and views motivation as dynamically fluctuating from moment to moment throughout the behavior change process.

Objective: This 2-group randomized controlled trial compares the efficacy of standard treatment to MAPS in facilitating smoking cessation among women with a history of high-grade cervical dysplasia or cervical cancer.

Methods: Participants (N=202) are current smokers with a history of high-grade cervical dysplasia or cervical cancer recruited nationally and randomly assigned to one of two treatment conditions: (1) standard treatment (ST) or (2) MAPS. ST consists of repeated letters referring participants to their state's tobacco cessation quitline, standard self-help materials, and free nicotine replacement therapy when ready to quit. MAPS has all ST components along with 6 proactive telephone counseling sessions delivered over 12 months. The primary outcome is abstinence from tobacco at 18 months. Secondary outcomes include abstinence

over time across all assessment points, abstinence at other individual assessment time points, quit attempts, cigarettes per day, and use of state quitlines. Hypothesized treatment mechanisms and cost-effectiveness will also be evaluated.

Results: This study was approved by the institutional review boards at the University of Texas MD Anderson Cancer Center, the University of Oklahoma Health Sciences Center, and Moffitt Cancer Center. Participant enrollment concluded at Moffitt Cancer Center in January 2020, and follow-up data collection was completed in July 2021. Data analysis is ongoing.

Conclusions: This study will yield crucial information regarding the efficacy and cost-effectiveness of a MAPS approach for smoking cessation tailored to the specific needs of women with a history of high-grade cervical dysplasia or cervical cancer. Findings indicating that MAPS has substantially greater efficacy than existing evidence-based tobacco cessation treatments would have tremendous public health significance.

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International Registered Report Identifier (IRRID): DERR1-10.2196/34502

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KEYWORDS

smoking cessation; cervical cancer; cancer survivor; motivation; tobacco treatment; cancer; smoking; RCT; randomized controlled trial; cognitive behavior; intervention

Introduction

The incidence of cervical cancer in the United States declined by more than half between 1975 (14.8 per 100,000 population) and 2018 (6.7 per 100,000 population) [1] owing to the widespread uptake of screening, primarily with the Pap test. Owing to early detection, mortality has also declined substantially. Despite these declines, 14,480 new cases of cervical cancer are expected to be diagnosed and 4290 women are estimated to die from the disease in 2021 [2]. As of January 2019, there were estimated to be approximately 288,710 cervical cancer survivors in the United States [3,4]. Furthermore, there are profound racial/ethnic and sociodemographic disparities in the incidence and mortality of cervical cancer [4-9].

Smoking is a well-established risk factor for cervical intraepithelial neoplasia (CIN), also known as high-grade cervical dysplasia [10], which is the immediate precursor to cervical cancer. Women with a history of CIN have a considerably higher risk of developing cervical cancer [11]. Furthermore, nationwide data indicate that cervical cancer survivors have among the highest rates of continued smoking post diagnosis—between 30% and 48% [12-14]. Continued smoking is associated with several adverse outcomes including increased cancer recurrence, increased risk of a secondary malignancy, poor treatment outcomes, and decreased quality of life [15-20]. Hence, it has been recommended that cervical cancer survivors receive a survivorship care plan that addresses the dangers of continued tobacco use and the risk of subsequent malignancy that persists throughout the survivor's lifetime. A crucial part of this survivorship plan should involve the delivery of smoking cessation treatment designed to address the specific needs of these women [21].

No known smoking cessation interventions have specifically targeted cervical cancer survivors. This study is, to our knowledge, the first to evaluate the efficacy and cost-effectiveness of an intervention designed to address the specific needs of this population. Motivation And Problem Solving (MAPS) is a holistic, dynamic approach to facilitating and maintaining behavior change that utilizes a combined motivational enhancement and social cognitive approach based on motivational interviewing (MI) [22,23] and social cognitive theory [24,25]. Because the MAPS approach is built around a wellness program that addresses numerous barriers and concerns prevalent among cervical cancer survivors (eg, anxiety, depression, stress, and fear of cancer recurrence), we believe it is appropriate for treating this population. In addition, previous research has supported the efficacy of MAPS in diverse populations of smokers for motivating quit attempts, increasing cessation, and preventing relapse [26-28].

This paper describes the research design, methods, and data analysis plans for an ongoing randomized controlled trial (RCT) designed to evaluate the efficacy of MAPS in facilitating smoking cessation among high-grade cervical dysplasia and cervical cancer survivors. The primary aim is to compare the efficacy of MAPS in facilitating smoking cessation with standard treatment (ST) among women with a history of high-grade cervical dysplasia or cervical cancer. Secondary aims include (1) evaluating the effects of MAPS on hypothesized treatment mechanisms (motivation, agency, and stress/negative affect) and the role of those mechanisms in mediating MAPS effects on abstinence, and (2) assessing the cost-effectiveness of MAPS compared with ST (Multimedia Appendix 1).

Methods

Study Design

This RCT comprises 2 treatment arms. The ST group receives a mailed packet with a letter referring participants to their state's tobacco cessation quitline, standard self-help materials, and free nicotine replacement therapy (NRT) when ready to quit. These treatment components are delivered at three timepoints: baseline, 6 months, and 12 months. MAPS has all ST components plus 6 proactive telephone counseling sessions delivered over 12 months. The timing of the telephone counseling sessions is flexible and determined jointly by the participant and the counselor. Assessments are conducted via telephone at baseline, 3, 6, 12, and 18 months. The primary outcome is 7-day point prevalence abstinence from tobacco at 18 months. Secondary outcomes are abstinence from tobacco at all other assessment

points (3, 6, and 12 months), quit attempts, cigarettes per day, use of the state quitline, and cost-effectiveness.

We hypothesized that MAPS participants will have higher rates of smoking abstinence at 18 months than ST participants. Similarly, for secondary outcomes, we hypothesized that MAPS participants will have higher rates of smoking abstinence across all assessment points, more quit attempts, fewer cigarettes per day (when smoking), and greater use of the state quitline. Secondary hypotheses were that MAPS will (1) lead to higher abstinence rates through influencing the treatment mechanisms of motivation, agency, and stress/negative affect; and (2) be more cost-effective.

Participants

Participants (target sample size, n=300) are women with a history of high-grade cervical dysplasia or cervical cancer, recruited via the following: (1) a gynecologic oncology clinic within a National Cancer Institute–designated cancer center in the South Central United States, (2) a university-based women's health clinic, (3) a university-based tobacco treatment program, and (4) nationally via Facebook and paid Google search advertisements. Inclusion criteria are (1) being aged 18 years or older; (2) self-reporting smoking within the last 30 days and having a history of at least 100 lifetime cigarettes; (3) having a history of high-grade cervical dysplasia or cervical cancer; (4) having a working cell phone; (5) having a valid home address; and (6) being able to speak English, Spanish, or both languages. Exclusion criteria are (1) current use of NRT or other smoking cessation medications (eg, varenicline or bupropion), (2) being pregnant or breastfeeding, (3) having another household member enrolled in the study, or (4) having a contraindication of nicotine patch use.

Procedures

This study was reviewed and approved by the University of Texas MD Anderson Cancer Center institutional review board (IRB), the University of Oklahoma Health Sciences Center IRB, and Advarra (H. Lee Moffitt Cancer Center IRB), and is registered on ClinicalTrials.gov (NCT02157610).

Potentially eligible women recruited in clinic were identified through electronic health record reviews and approached by research staff in person during medical visits or contacted via telephone. Participants referred by the tobacco treatment program were screened by research staff via telephone. Participants recruited via Facebook and Google paid search ads were initially directed to a Research Electronic Data Capture (REDCap) screener and asked to complete a brief set of screening questions. REDCap is a secure, web-based application designed to support data capture and utilizes a computer-administered self-interview format. This system is designed to comply with all Health Insurance Portability and Accountability Act (HIPAA) regulations. Those who passed the initial screening criteria were asked to provide their contact information so that they could be contacted by a research coordinator for further screening. All eligible women were invited to participate. A detailed description of the study was provided, and those who agreed to enroll completed an informed consent process either in person or over the telephone. Women who declined or were ineligible were offered self-help materials and a referral to other cessation programs.

Individuals who meet eligibility criteria and provide informed consent complete the baseline assessment over the telephone with a research coordinator or via a secure electronic REDCap link sent via email or text message. Participants are then randomized to ST or MAPS using a form of adaptive randomization called minimization [29,30]. Compared with techniques such as stratification, minimization results in better group balance with respect to participant characteristics. Minimization also provides balanced treatment groups throughout the randomization process. Thus, the treatment groups remain balanced with respect to participant characteristics that may be related to time of accrual. Variables for the minimization were race/ethnicity (nonminority or minority), age (≤35 or >35 years), education (<high school/general education development or ≥ high school/general education development), cigarettes per day (≤19 or ≥20), diagnosis at study enrollment (high-grade cervical dysplasia, stage 1 or 2, stage 3, or stage 4), treatment status (in active treatment or completed treatment), and time since diagnosis (≤1 year or >1 year). Following randomization, participants are mailed the appropriate intervention materials. Twelve weeks of combination NRT (patch + lozenge) are sent via mail when ready to quit.

Follow-up assessments occur at 3, 6, 12, and 18 months. Participants are provided the option to complete the assessment over the telephone with a research coordinator or on the internet via a secure REDCap link. Participants receive US $30 of compensation for completing the baseline assessment and US $30 for each completed follow-up assessment. In addition, participants receive US $30 at the baseline and all follow-up assessments to compensate for use of their personal cell phones for study participation. Participants may also be compensated US $30 at the 3-, 6-, 12-, and 18-month assessments for returning saliva cotinine tests to biochemically confirm smoking status.

Intervention Conditions

Standard Treatment

ST consists of a mailed packet of materials including a letter referring smokers to their state's tobacco cessation quitline, NRT when ready to quit, and standard self-help materials (1-800-QUIT-NOW booklet, 211 flyer). ST is mailed at 3 timepoints including baseline and following completion of the 6- and 12-month follow-up assessments.

MAPS

MAPS has all ST components along with 6 proactive telephone counseling sessions delivered over 12 months. The timing of the telephone counseling sessions is flexible and determined jointly by the participant and the counselor. Each call lasts approximately 30 minutes. Calls are scheduled based on participants' needs in negotiation with the MAPS counselor. For example, a participant who is not yet ready to quit might schedule a second call to occur many months later or to occur sooner if there are specific barriers that the individual wishes to address (eg, stress, social support, and family problems).

Similarly, participants struggling with maintaining abstinence may request several calls in a shorter period of time to get through the problematic period, whereas others prefer a less compressed counseling schedule and may need less frequent help.

The MAPS counselor for this study has completed 20 hours of MAPS training and is able to deliver MAPS in both English and Spanish. To monitor deviation or drift from the MAPS treatment manual, the calls are digitally recorded and encrypted. A random sample of 10% are reviewed and coded using a modified version of the Motivational Interviewing Treatment Integrity (MITI) manual to ensure adequate competence and adherence to the motivational interviewing components of MAPS. The MITI manual [31] has empirically validated reliability and validity and is used to code sessions and ensure treatment fidelity. The protocol stipulates that if a counselor's performance falls below the stipulated performance criteria, there will be additional training. MITI results are reviewed regularly throughout the study during supervision, and the instrument works well to ensure that counselors are utilizing the general motivational interviewing spirit. In addition, the MITI has been modified slightly for the current project to include coding of discussions around social cognitive/problem solving strategies and transitions between motivational enhancement and problem solving. To monitor implementation, weekly monitoring reports are reviewed to track call completion and follow-up rates.

Nicotine Replacement Therapy

All participants in both treatment groups are provided a 12-week supply of nicotine patches and lozenges when ready to quit. Included with the NRT, all participants receive educational materials describing potential side effects, proper use of the patch, and an illustration demonstrating the proper placement of the patch on the body. The nicotine patch and lozenge regimens are based on each participant's self-reported smoking rate. Participants who smoke >10 cigarettes/day receive 8 weeks of 21-mg patches, 2 weeks of 14-mg patches, 2 weeks of 7-mg patches, and 12 weeks of 2-mg lozenges. Those who smoke <10 cigarettes/day receive 8 weeks of 14-mg patches, 4 weeks of 7-mg patches, and 12 weeks of 2-mg lozenges.

Measures

Baseline Assessment

Individuals who met eligibility criteria and provided informed consent completed the baseline assessment either over the phone with a research coordinator or via a secure electronic link sent via email or SMS text message. REDCap was used to administer all questionnaires over the telephone, in person, and via a weblink. REDCap is a secure, web-based application designed to support data capture and utilizes a computer-administered self-interview format. This system is designed to comply with all HIPAA regulations. The baseline assessment included questionnaires assessing sociodemographics, smoking history, and nicotine dependence [32], cancer status (ie, cervical cancer vs high-grade cervical dysplasia diagnosis, cancer stage at diagnosis, time since diagnosis, current cancer stage, and treatment status), fear of cancer recurrence [33], health literacy [34], subjective numeracy [35], subjective social status [36], financial strain [37], motivation to quit smoking [38], reasons for quitting [39], sense of control [40], self-efficacy [41], coping inventory [42], loneliness [43], perceived stress [44], positive and negative affect [45], psychological distress [46], smoking dependence motives [47,48], smoking withdrawal symptoms [49], quality of life [50], and health utilities/health-related quality of life [51,52].

Follow-up Assessments

Participants are asked to complete follow-up assessments by telephone or a secure emailed weblink at 3, 6, 12, and 18 months post baseline. All baseline measures are included in the follow-ups with the exception of sociodemographics and nicotine dependence. In addition, smoking status is assessed on the basis of recommendations from the Society for Research on Nicotine and Tobacco (SRNT), including both prolonged and point-prevalence abstinence [53]. Prolonged abstinence refers to abstinence beginning with the initiation of treatment and including a grace period. The prolonged abstinence measure utilizes the SRNT recommendation for determining relapse (ie, 7 consecutive days of smoking or smoking in each of 2 consecutive weeks). In addition, 2 point-prevalence abstinence measures are evaluated: (1) no smoking during the previous 7 days and (2) no smoking during the previous 30 days. The primary outcome is 7-day point prevalence abstinence from smoking at 18 months.

Participants who self-report 7-day point prevalence abstinence at any follow-up assessment are mailed a prepaid envelope with instructions for providing the saliva sample and a saliva collection kit. Research staff contact participants by phone to ensure the arrival of the packet, review the contents of the packet, and answer any questions participants may have about collecting a saliva specimen. Although cotinine cannot comprehensively validate the various abstinence definitions and timeframes, the most comprehensive review on biochemical validation concluded that misreporting is typically very low (~2%), and adjustment for misreporting almost never influences analyses regarding relative treatment efficacy [54]. As such, our biochemical validation procedures are well justified both scientifically and practically.

Data Analysis Plan

Analysis Overview

The primary aim is to compare the efficacy of MAPS in facilitating smoking cessation with ST among women with a history of high-grade cervical dysplasia or cervical cancer. The primary outcome is 7-day point prevalence abstinence from smoking at the 18-month assessment. Logistic regression will be used with treatment (ST vs MAPS) as the predictor. The model will include as covariates those variables used in the minimization procedures (race/ethnicity, age, education, cigarettes per day, diagnosis at study enrollment, cervical cancer stage, treatment status, and time since diagnosis).

Secondary outcomes include 7-day point prevalence abstinence over time across the 3-, 6-, 12-, and 18-month assessments as well as 7-day point prevalence abstinence at 3, 6, and 12 months. Abstinence over time will be examined using generalized linear

mixed model regression (GLMM) [55,56] with a logit link, and binomial variance function will be used to analyze the effects of MAPS. Treatment, month of assessment, and their interaction are the primary predictors with adjustment for relevant covariates. Similarly, analyses will be conducted to assess the aggregate effect of MAPS on the secondary outcomes of quit attempt and use of the quitline (both binary). For the continuous secondary outcomes of cigarettes per day and the purported mechanisms, linear mixed model analysis will be performed to evaluate treatment differences using the same predictors and covariates.

To manage missing data, multiple imputation under the Missing at Random assumption will be applied using a Markov Chain Monte Carlo method [57] via PROC MI in SAS (version 9.4, The SAS Institute) given the expected large numbers of nonmonotonic missing data patterns and auxiliary variables (eg, baseline measures that predict smoking status or missingness). In total, 20 data sets will be created. For smoking status, a post hoc adjustment [58] will be applied to implement an influence of Missing Not at Random (MNAR) (ie, *missing* is due to smoking). In recent publications [59], we have applied a small to medium effect size (Cohen *d*=0.35). This approach provides better parameter estimates and tests of hypotheses than does imputing missing equals smoking.

Sample Size Estimation

Our power analysis is based primarily on the comparison of 18-month abstinence rates between MAPS and ST using the full sample without attrition (N=300; n=150 per group). All power analyses assume a significance level of .05 and a 2-sided test. Based on the Treating Tobacco Use and Dependence Clinical Practice Guideline [60], we estimated that abstinence for ST would be approximately 10%. Using a chi-square test to examine the effect of treatment on abstinence at 18 months, a sample size of 300 (n=150 per group) will provide 80% power to detect an overall treatment effect that corresponds to an abstinence rate of 21.9% in MAPS. Analyses conducted using GLMM will have greater power to detect the same average differences over time.

Cost-effectiveness Analysis

The cost-effectiveness of MAPS will be carefully evaluated using state-of-the art methodologies. It should be noted that interventions targeted at expanding the population or increasing the intensity or duration of treatment often lead to an increase in health care utilization (and consequently costs); hence, an intervention may not be cost saving but still cost effective. Because health outcomes, costs, and efficient allocation of limited resources are paramount concerns, this study will yield crucial information necessary in determining whether MAPS should be widely implemented following the study.

Cost-effectiveness analyses (CEA) will compare the two interventions: ST and MAPS. The conventional CEA summarizes study findings in terms of the incremental cost-effectiveness ratio (ICER) [61,62]. The ICER, calculated as the difference in mean costs between the new and standard treatment divided by the difference in mean effectiveness between the new and standard treatment, estimates the additional resource consumption needed to achieve an increase in an additional unit of effectiveness. The ICER is then compared with a commonly cited or published threshold value associated with an intervention already found to be cost-effective to determine whether a new intervention is cost-effective. The net benefit approach, introduced more recently [63,64], transforms the ICER into the net benefit, defined as $NB(\lambda) = \lambda \bullet \Delta E - \Delta C$, where λ represents a societal willingness-to-pay, ΔC represents the incremental costs, and ΔE represents the incremental effectiveness. We report the CEA results for both the conventional ICER and the cost-effectiveness acceptability curve [63,65]. The net benefit approach has been incorporated into a regression framework to allow for covariate adjustments and the examination of interaction effects in CEA [66]. This regression-based approach is relevant to our study because there may be moderating factors such as individual characteristics that affect the cost-effectiveness of interventions.

To facilitate comparing ICER estimated from our CEA with that from other published studies, we will include three effectiveness measures: number of quitters, years of life saved (YOLS), and quality-adjusted life year (QALY). The number of quitters in each treatment arm will be retrieved from the primary abstinence endpoint at month 18. We will extrapolate from abstinence to YOLS using a published algorithm that models YOLS per quitter for persons in various age-specific subgroups [67]. We will calculate QALY from the health utilities obtained from the EQ-5D [68].

We will compare the cost-effectiveness of the interventions in three time frames: short-term, mid-term, and long-term. The short-term and mid-term CEA will use “number of quitters” as the effectiveness measure and assess cost-effectiveness on the basis of information collected at months 3 and 6 (short-term), month 12 (mid-term), and month 18 (long-term), respectively. The long-term analysis will extrapolate the intervention effect to lifetime and use YOLS and QALY as the effectiveness measure. A 3% discount rate will be applied to costs and outcomes accrued in the second year and thereafter.

We will perform deterministic CEA on the basis of ICER and will apply the Bayesian approach to construct the cost-effectiveness acceptability curve and conduct probabilistic sensitivity analysis [69,70]. We will perform the Bayesian analysis using WinBUGS, with costs modeled as a gamma or lognormal distribution and abstinence from tobacco as a binomial distribution.

Finally, we will apply the regression-based CEA. Individual-level net benefit will be regressed on covariates, plus a binary variable indicating the ST versus MAPS arm. Using the ST arm as the reference group, the regression coefficient associated with the treatment binary variable will provide information on the cost-effectiveness of the MAPS intervention compared with ST.

Results

This study was funded by the National Cancer Institute in 2015 and approved by the IRBs at the University of Texas MD Anderson Cancer Center, the University of Oklahoma Health

Sciences Center, and Moffitt Cancer Center. Participant enrollment concluded at Moffitt Cancer Center in January 2020 (n=202), and follow-up data collection was completed in July 2021. Data analysis is ongoing.

Discussion

There is a crucial need to provide cervical cancer survivors with evidence-based smoking cessation treatment designed to facilitate long-term cessation while addressing related survivorship issues. This need is enhanced by nationwide data, indicating that there are profound racial/ethnic and sociodemographic disparities in the incidence and mortality of cervical cancer [4-9]. For example, cervical cancer and cervical dysplasia survivors with lower socioeconomic status and limited social support are at an even greater risk for poor health outcomes. There is also widespread evidence suggesting that women who are members of racial/ethnic minority groups and with low socioeconomic status are known to disproportionately be faced with the health consequences of smoking [5,71,72]. Existing evidence suggests that these individuals may have greater difficulty quitting smoking [5,73-75]. Furthermore, disparities in tobacco use by socioeconomic status have increased over the last several decades despite widespread availability of free, effective cessation treatment. As such, women who are current smokers and who have a history of cervical cancer or high-grade cervical dysplasia represent a particularly vulnerable subgroup at substantially elevated risk.

This study represents the first large-scale smoking cessation treatment study designed to address the specific needs of high-grade cervical dysplasia and cervical cancer survivors using the MAPS approach. MAPS utilizes an innovative combination of motivational enhancement and cognitive-behavioral treatment techniques; is built around a structure derived from effective approaches to chronic care management and patient navigation; is designed for all individuals regardless of their readiness to change; and specifically targets cardinal mechanisms underlying tobacco use including motivation, agency/self-efficacy, and stress/negative affect. Furthermore, the creation of a wellness program for each individual makes MAPS particularly well suited for addressing the broader context of stressors and concerns faced by this vulnerable and underserved population [76].

Although previous research has supported the efficacy of MAPS for motivating quit attempts, increasing cessation, and preventing relapse [26-28], and motivationally based interventions have demonstrated efficacy for problematic alcohol use among individuals not ready to change [77,78], there are no empirically validated treatments that increase cessation among smokers who may not be ready to quit. It was anticipated that a fair proportion of women will not be ready to quit at the time of study enrollment [60], and, as such, the wellness program component of MAPS will enable these individuals to focus on other life issues (eg, stress, family issues, finances, adjustment to a cancer diagnosis, and fear of cancer recurrence). Thus, MAPS is designed to treat all individuals regardless of their readiness to change, thereby addressing this lack of evidence-based treatment.

In addition to being appropriate for individuals with different levels of motivation to change, MAPS has been designed to handle heterogeneity regarding time since cervical cancer diagnosis and treatment. For example, it is anticipated that women with more recent diagnosis and treatment experiences may be interested in discussing issues related to treatment side effects or fear of cancer recurrence, whereas women with more distal diagnoses and treatment experiences may prefer not to address such issues.

Prior to initiating the RCT, we conducted a series of in-depth interviews with cervical cancer survivors who currently smoked to gather feedback about how to best adapt MAPS for this specific population. Our results indicate that most participants attributed their diagnosis solely to human papillomavirus and did not believe that smoking had played a role in causing their cervical cancer. Participants suggested that the intervention include education about smoking and cancer and the benefits of quitting, help with planning for quitting, strategies for coping with cravings/withdrawal, social support, real-time support, a nonjudgmental and understanding counselor, tailoring, and follow-up. They recommended that negativity or judgment not be a part of the intervention. In-depth interview participants also indicated that it would be important to address stress, issues specific to cervical cancer survivorship, and lifestyle factors such as physical activity and healthy eating. Finally, they emphasized the importance of including NRT as part of the intervention [79].

This study has several unique strengths. First, this is the only RCT to target the specific needs of high-grade cervical dysplasia and cervical cancer survivors using the MAPS approach. Second, there are no empirically validated treatments that increase cessation among smokers who may not be ready to quit. Third, the delivery of MAPS via telephone offers a less resource-intensive modality while also minimizing participant burden.

In summary, this study will yield crucial information regarding the efficacy and cost-effectiveness of a MAPS approach for smoking cessation tailored to the specific needs of women with a history of high-grade cervical dysplasia or cervical cancer. Findings indicating that MAPS has substantially greater efficacy than existing evidence-based tobacco cessation treatments would have tremendous public health significance.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports from the Psychosocial Risk and Disease Prevention Study Section - Center for Scientific Review (National Institutes of Health).
[PDF File (Adobe PDF File), 144 KB - resprot_v10i12e34502_app1.pdf]

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Abbreviations

CEA: cost-effectiveness analysis
CIN: cervical intraepithelial neoplasia
GLMM: generalized linear mixed model regression
ICER: incremental cost-effectiveness ratio
IRB: institutional review board
MAPS: Motivation And Problem Solving
MI: motivational interviewing
MITI: Motivational Interviewing Treatment Integrity
MNAR: missing not at random
NRT: nicotine replacement therapy
QALY: quality-adjusted life years
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SRNT: Society for Research on Nicotine and Tobacco
ST: standard treatment
YOLS: years of life saved

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Original Paper

Accuracy of Physical Assessment in Nursing for Cervical Spine Joint Pain and Stiffness: Pilot Study Protocol

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Abstract

Background: Cervical spine dysfunction is a condition with high personal, social, and economic impact worldwide. Although its etiology is described as multifactorial, there is a need for further clarification. The literature has demonstrated the anatomical, physiological, and pathophysiological relationship among the cervical spine, temporomandibular joint, and visceral system. To guide and contribute to the accuracy of the physical assessment performed by nurses, we will study the influence of the stomatognathic system and viscerosomatic reflexes on pain and joint stiffness of the cervical spine.

Objective: The aim of this study is to describe a pilot study protocol to investigate the influence of the stomatognathic system and viscerosomatic reflexes on cervical structures.

Methods: A pilot study with a quasi-experimental design was conducted with 50 volunteers from the university population of the Universidade Católica Portuguesa-Porto. We studied the influence of changes in the usual intercuspation, the occlusal deprogramming, and the pressure stimulus of the reflex skin region of the ilium/colon in the cervical spine. This study was divided into 2 phases. In the first phase, we performed the kinematic and pain analysis during the passive mobilization of the upper cervical spine using the Motion Capture System at the Motion Capture Laboratory at UCP-Porto and the Visual Analog Scale. In the second phase, we evaluated the pain threshold on palpation of the erector neck muscles and the structures of the stomatognathic system using algometry. The influence of viscerosomatic reflexes on the structures of the stomatognathic system was also analyzed.

Results: Selection and preparation of the data collection site, acquisition of materials, constitution of the sample group and data collection were completed. The analysis of the results is being carried out.

Conclusions: The data from this study will allow for the detection of the possible influence of the stomatognathic system and viscerosomatic reflexes on pain and range of motion of the upper cervical spine, providing data for future randomized studies. We have also identified potential limitations of this study.

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KEYWORDS

nursing process; nursing assessment; pain; referred pain; range of motion; neck pain; stomatognathic system; viscerosomatic reflexes; cervical spine dysfunction

Introduction

Cervical spine dysfunction (CSD) is a pathological condition of the spine with high prevalence worldwide that is expected to increase in the future. It dramatically impacts individuals, families, and society. This condition is characterized by pain phenomena, functional disability, decreased quality of life, social activity and mental health impacts, and increased mortality; CSD therefore has both individual and societal costs [1-4].

According to estimates from the Global Burden of Disease Study 2017 [1], both the prevalence and burden of CSD are high worldwide, with a global prevalence of 288.7 million cases, an incidence of 65.3 million cases, and 25.6 million years lived with disability.

Although pain and joint stiffness are associated with CSD, imaging studies in a population with this condition have not identified any specific lesion, leaving the etiology of this condition unknown, resulting in inaccurate diagnoses [5-8]. This may be the reason why therapeutic interventions tend to have insufficient results [1,2,9].

The cervical dysfunction etiology is thus described as multifactorial, mediated by central neuronal commands resulting from complex biological interactions of the local or distant structures of the cervical segment; this creates great variability in the course and clinical severity of the condition [1,3-5,10].

It is therefore important to integrate these components when evaluating the person with CSD to identify the mechanisms underlying their health condition and apply interventions adjusted to their physical condition. In this way, nurses should use strategies consistent with scientific methodology when conducting physical assessments of CSD patients, providing reliability to their approach and aiding their decision-making [11,12].

The assessment of the person with CSD is assumed to be objective, using a set of measurement methodologies consisting of physical assessment, specific pain analysis, and complementary means of diagnosis [5,13,14].

From the multifactorial perspective of CSD, the function and dysfunctions of the stomatognathic system, due to reciprocal synergistic action, alter the neck's correct functioning [15-18].

This coactivation coordination between the stomatognathic system and the cervical spine appears to be related to the neuronal network centers that regulate the muscles of these body segments and are mediated by the cervical motor sensory system and the trigeminal nerve [17,19].

On the other hand, nociceptive hyperexcitability can promote the development or maintenance of chronic pain, such as by triggering painful reflex disorders [20].

Other neurological phenomena that seem to influence this relationship are the viscerosomatic reflexes. These are the result of harmful afferent signals of visceral origin that converge in somatic structures by common innervation or by induction of neuronal plasticity of the central, peripheral, and autonomic nervous system, involving multiple organs and body structures [21-25]. Regarding the interdependence of the cervical spine and the stomatognathic system, visceral sensory convergence through the vagus nerve at the trigeminal and spinothalamic tract of the C1-C2 level has an important role in the functioning of the upper cervical segments through the integration of the converging entrances of somatic and visceral organs [26].

Given these connections between different body systems, this study aims to analyze the influence of the stomatognathic system and viscerosomatic reflexes on pain and joint stiffness of the UCS. Two research questions were defined in this study: (1) What is the influence of the stomatognathic system and viscerosomatic reflexes on pain and joint stiffness in UCS? (2) What is the influence of viscerosomatic reflexes on the stomatognathic system?

The main objective of this study is to contribute to the clarification of the pain and joint stiffness etiology of the cervical spine to increase the accuracy of physical assessment performed by nurses.

To achieve the aforementioned major objective, the following objectives were defined: (1) to identify the influence of the stomatognathic system on pain and cervical mobility, (2) to identify the influence of viscerosomatic reflexes on pain and cervical mobility, and (3) to identify the influence of viscerosomatic reflexes on the stomatognathic system.

Methods

To our best knowledge and based on the literature review conducted, no prior studies investigated the same variables with similar methodologies. Therefore, this study presents a preclinical/pilot study profile.

In this investigation, we adopted the methodology of a quasi-experimental study with an interrupted time series design.

Data Collection Phases

The study will consist of 2 data collection phases:

- Phase I: Kinematic analysis. Assessment of the rotational range of motion of the UCS and pain during passive mobilization
- Phase II: Palpation of neck and oral muscles. Assessment of pain threshold on palpation (algometry)

The Population Under Study and Constitution of the Sample

The study population consisted of university students at the Academic Federation of Porto as this population is made up of adults of different age groups who tend to be healthy and exhibit similar behaviors, habits, and lifestyles. From this population, a nonprobabilistic sample by voluntary response was drawn, composed of 50 volunteers. The volunteers included students, professors, and nonacademic staff.

The study was publicized by placing posters on the Universidade Católica Portuguesa-Porto (UCP-Porto) premises, and a call for volunteers was made on the UCP-Porto Facebook page. Volunteers registered by sending an email indicating their name,

including their contact details, and declaring their interest in participating in the study.

Afterwards, researchers contacted participants to confirm their interest in participating, apply the inclusion and exclusion criteria, and schedule the data collection if they were accepted for the sample group, guaranteeing ethical principles and confidentiality.

The criteria for inclusion in the sample were:

1. Being 18 years of age or older.
2. Agreeing to participate in the study.

The exclusion criteria for the formulation of the study sample were:

1. Receiving pharmacological therapy (analgesics, anti-inflammatory drugs, and/or muscle relaxants).
2. The existence of neuromuscular pathology, congenital alteration, pathological condition in the acute phase, or functional disturbances of the cervical spine and/or mandibular that make the application of variables or passive mobilization of the cervical spine unfeasible.
3. A history of bone fractures; surgery to the cervical spine, skull, and/or mandibular; or cancer.
4. Undergoing a physical rehabilitation program.

Operationalization of Variables

The variables will be operationalized as follows:

- Range of motion of the UCS: variable operationalized using the Motion Capture System, which allows for the measurement of the range of motion from 0° to 90°.
- Pain during mobilization of the UCS: variable operationalized through an open-ended question corresponding to a numerical value between 0 and 10, as recommended by the Visual Analog Scale (VAS).
- Pain threshold on palpation of the erector neck muscles: variable operationalized in two dimensions, pain and pressure force. Pain will be operationalized through an open-ended question, corresponding to a numerical value between 0 and 10, as recommended by the VAS. The pressure force will be operationalized through algometry corresponding to a numerical value between 0 and 4315 kPa.

Interventions

Occlusal Deprogramming

Neuromuscular occlusal deprogramming aims to reduce the action of masticatory muscles on the mandible, promoting its centric position within the temporomandibular joint. We chose to use cotton balls for this study in a simple and economical methodology with an immediate neuromuscular result, allowing the necessary time for the evaluations to be performed [27]. This intervention strategy consists of placing a pair of cotton balls bilaterally at the height of the premolars and asking the participant to vigorously compress them for approximately 3 to 5 minutes, as shown in Figure 1.

To understand if the change in the usual intercuspation altered the pain and joint stiffness of the UCS, before promoting the occlusal deprogramming, when placing the cotton rolls at the premolar level, a kinematic evaluation of the UCS was conducted (Figure 2).

Figure 1. Neuromuscular occlusal deprogramming. The moment of compression of the cotton balls by the participant.

Figure 2. The change in the usual intercuspation with placement of cotton balls bilaterally at the level of the premolars.

Pressure Stimulus of the Reflex Cutaneous Region of the Ilium/Colon

No physical assessment methodologies capable of promoting the assessment of the viscerosomatic reflexes influence on musculoskeletal structures were found in a literature review. In this sense, a pressure stimulus was performed on the abdominal cutaneous region described by Arendt-Nielsen et al [28], corresponding to the ilium/colon reflex, as depicted in Figure 3.

The application of a pressure of 196 kPa in this anatomical region was determined to stimulate the superficial tissues using an algometer (Force Dial FDK/FDN 40, Wagner Instruments). We did this to ensure accuracy and standardization of the stimulus in Test 3 (Figure 4).

Figure 3. Reflex cutaneous region of the ilium/colon.

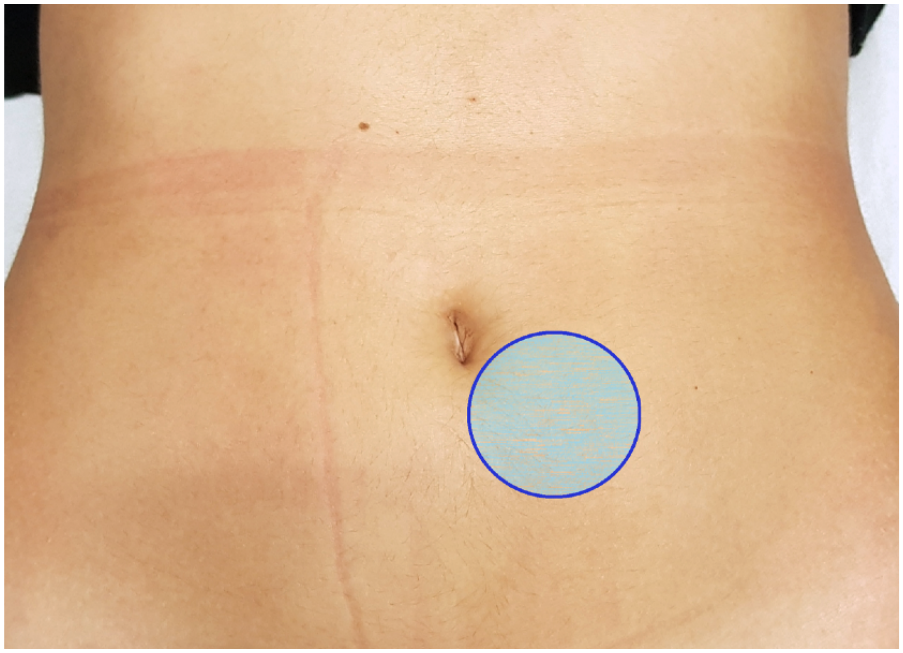
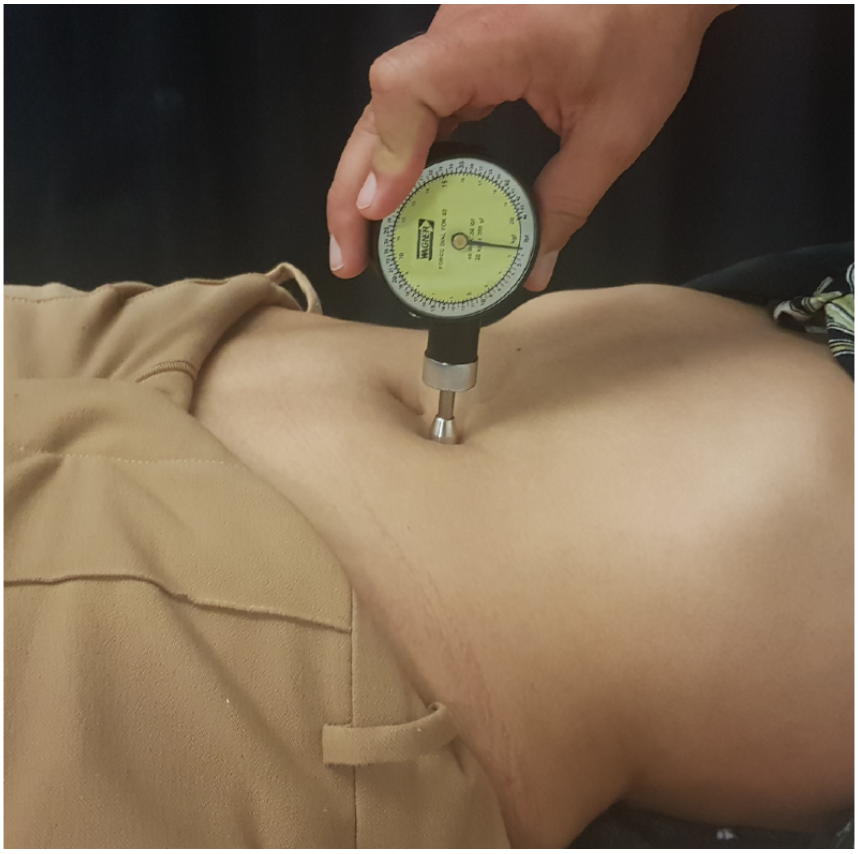


Figure 4. Tactile stimulation of the reflex skin region of the ilium/colon.



Data Collection Instruments

Motion Capture System

The Motion Capture System at the Motion Capture Laboratory at UCP-Porto allows for the capture of 3D motion and has been used for the kinematic analysis of the human body in clinical evaluations and in the study of biomechanics (Figure 5). Data collection is performed in a computerized room with data collection cameras around the room. The cameras are connected to a computer in a control system that allows for the visualization of the collected data and its registration. The collected data come from sensors that are placed on the body of the study participants. Participants must wear a fabric suit that allows for different sensor allocations and the standardization of their placement between participants (Figure 6). The data provided by this assessment methodology are enhanced as they are in 3D, while data collected by goniometry are in 2D; this methodology also does not require the intervention of the researcher to collect the data, allowing them greater freedom to promote interventions [29,30].

This assessment methodology allows for less evaluator interference but maintains the same reliability as goniometry [30,31], the gold standard in range of motion assessment [13,32].

As this is a 3D system, it allows for the collection of movement in the x-axis, y-axis, and z-axis. For this study, only data from the z-axis were counted because the analysis took place on the longitudinal axis of the cervical spine. Data collection was conducted at the Motion Capture Laboratory at UCP-Porto, a laboratory financed by the Foundation for Science and Technology, where the Motion Capture System is located (Figures 7 and 8).

Figure 5. A 3D image reproduced from the Motion Capture System sensor data collection.

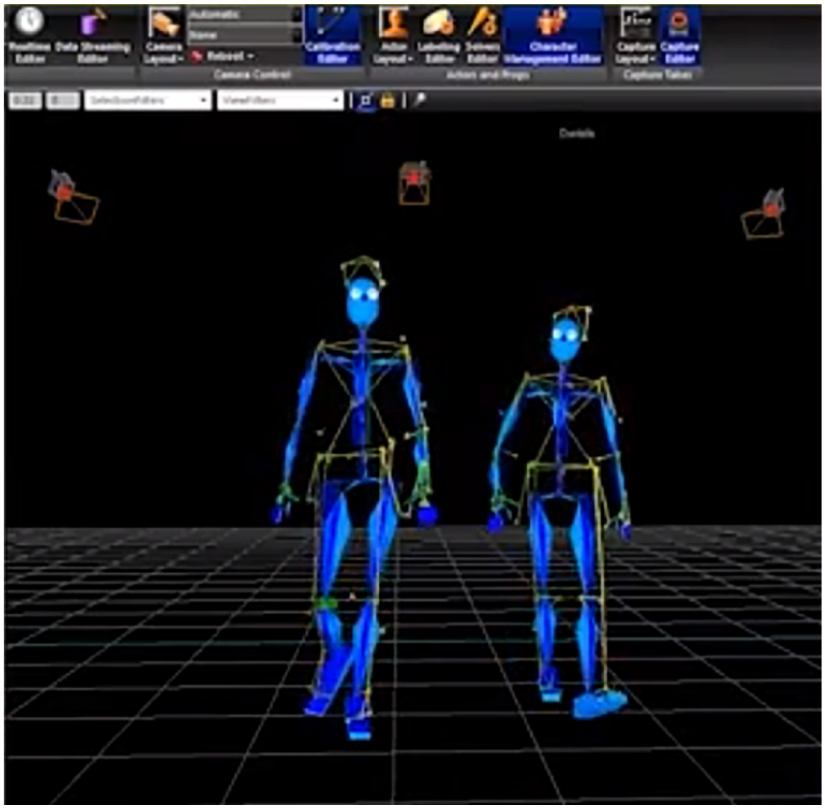


Figure 6. Fabric suits worn by participants on which Motion Capture System sensors were placed.

Figure 7. Motion Capture Central Processing Unit (CPU) Room at UCP-Porto.

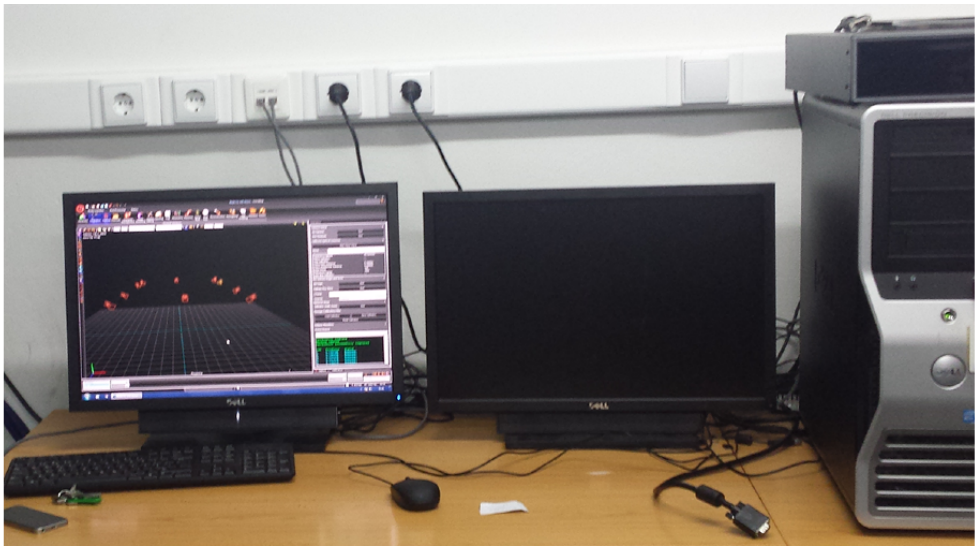
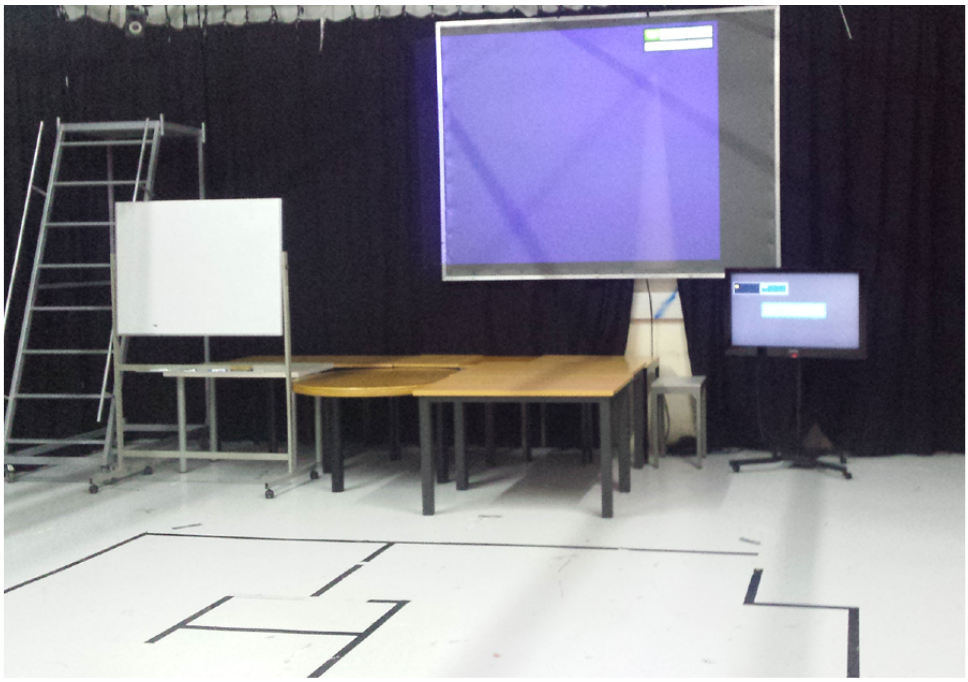


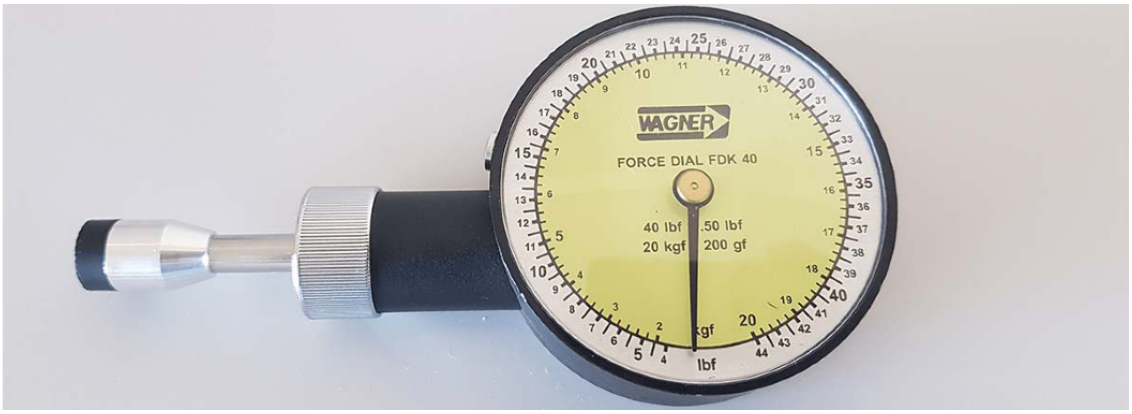
Figure 8. UCP-Porto Motion Capture Room.



Algometer

The palpation of body structures is one of the methodologies used in the physical assessment, allowing for the examination and perception of the condition and characteristics of the evaluated structures, the existence of hypersensitivity or hyposensitivity, the presence or absence of injury, as well as the detailed evaluation of each body structure. In applying this methodology, one should start with the minimum pressure and increase the intensity of its application according to the characteristics of the structures and the tolerance of the participant or patient [13,14]. Algometry allows for the measurement of the force produced and is considered a reliable methodology [33]. In this study, the Force Dial FDK/FDN 40 algometer was used, allowing for the measurement of the applied force in kg/cm^2 (Figure 9).

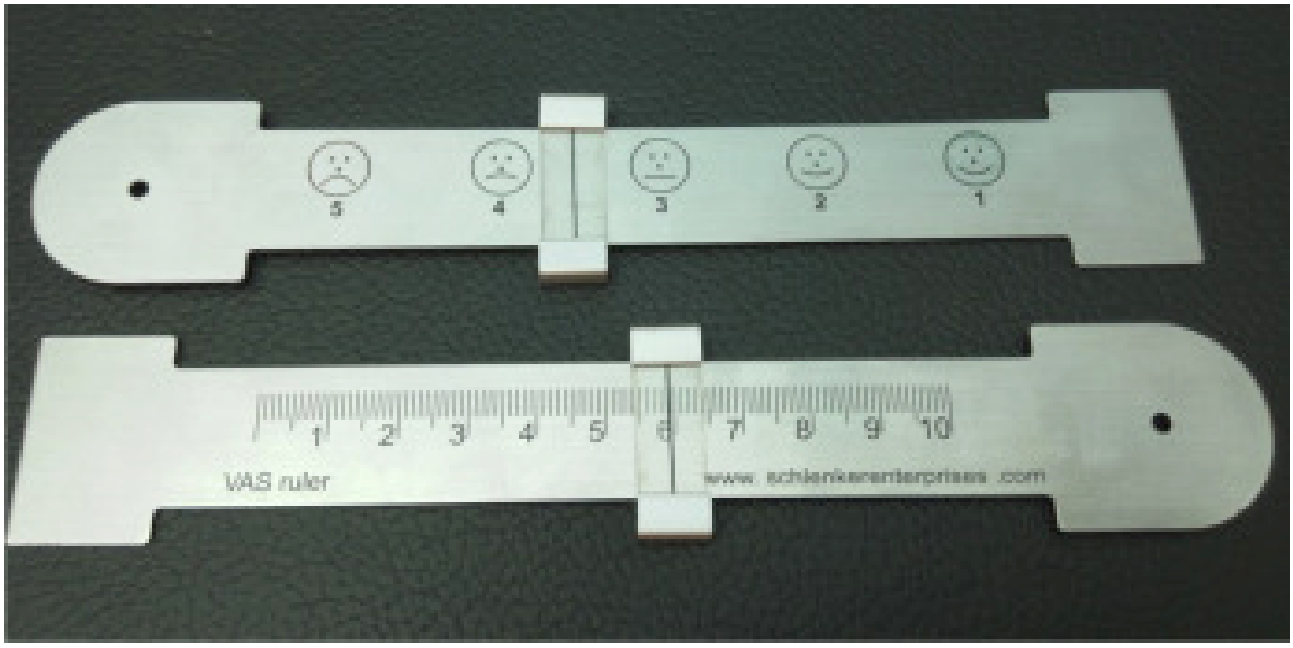
Figure 9. The algometer used in the study (Force Dial FDK/FDN 40, Wagner Instruments).



Visual Analog Scale (VAS)

For the self-assessment of the pain intensity experienced at different phases by the participants, we used the VAS, shown in Figure 10 [34].

Figure 10. Visual Analog Scale for pain measurement [34].



Performance and Data Collection Protocols

To ensure maximum reliability in data collection, we ensured that the researcher had more than 10 years of experience in manual therapy and assessment of spinal mobility, following literature guidelines [35,36]. To gain familiarity with the data collection methodology, handling of materials, and standardization of the assessment, the researcher performed pretests on more than 30 volunteers.

Data were collected between June and July 2019. There was a gap of 1 week between phase I and phase II.

Environmental Conditions

Data collection took place in two separate rooms. In both rooms, the environmental conditions were stabilized using (1) artificial lighting, allowing for the stabilization of light intensity, and (2) a heater, allowing for the stabilization of the room temperature between 20 °C and 22 °C.

Phase I Procedures: Kinematic Analysis

In phase I, kinematic and pain evaluation during mobilization of the first (C1) and second (C2) cervical vertebrae was performed. We used the Motion Capture System to measure the range of motion.

Upon arrival of the participant at the Motion Capture Laboratory, we proceeded to collect or confirm the following data:

- Name
- Eligibility for participation based on the inclusion and exclusion criteria
- Informed consent

We then:

- Explained all study procedures.
- Presented data collection materials.
- Answered remaining questions.
- Signed and delivered the informed consent forms to the participant and the researcher.
- Completed the sociodemographic characterization survey. If the participant met the conditions for participation and accepted of their own free will, the procedures for the operationalization of the study would start.

During the preparation for data collection, a cloth helmet with three sensors was applied to each participant's head (Figure 11). Subsequently, the participant was placed in the supine position on a gurney as this position allows for maximum relaxation of the cervical spine structures (Figure 12).

Data collection involving C1 and C2 passive joint mobilization (Figure 13) occurred in five phases: (1) Initial Assessment, (2) Test 1, (3) Test 2, (4) Initial Assessment 2, and (5) Test 3 (Table 1). Between Test 2 and Initial Assessment 2, an interval of 15 to 20 minutes took place, to promote washout, with the objective of having the participant in their usual condition to assess the influence of Test 3.

Figure 11. Fabric helmet with sensors for data collection.

Figure 12. Data collection position, allowing for maximum relaxation of the cervical spine structures.

Figure 13. Passive mobilization of the upper cervical spine (UCS), applying a rotational movement to the right and to the left.

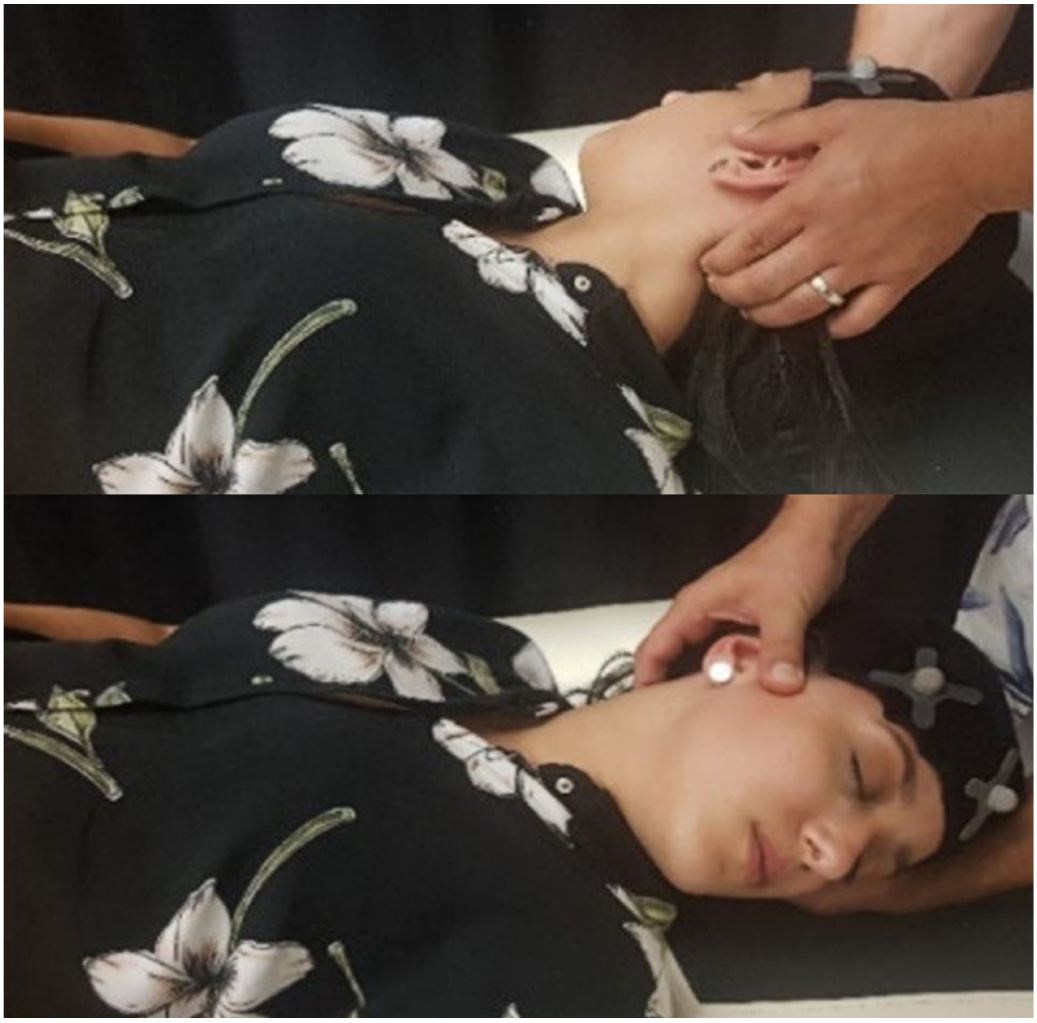


Table 1. Description of the 5 phases in which data collection occurred during C1 and C2 passive joint mobilization.

Phase	Description
Initial Assessment	Assessment during maximum body relaxation, with the teeth in intercuspation without load
Test 1	Change of usual intercuspation with cotton balls
Test 2	Occlusal deprogramming
Initial Assessment 2	Assessment during maximum body relaxation, with the teeth in intercuspation without load
Test 3	Application of a pressure stimulus to the reflex cutaneous region of the ilium/colon

Phase I Protocol

The steps of the phase I protocol are as follows:

1. Initial Assessment: Passive mobilization of the cervical spine was performed to assess the rotational range of motion and pain perceived at the time of assessment, at C1 and C2 levels, with the teeth in intercuspation without load (antagonistic teeth touching without a load exerting force). A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.
2. Test 1: The researcher performed cervical passive mobilization to assess the rotational range of motion and pain, at C1 and C2 levels, promoting the alteration of the usual intercuspation with placement of cotton balls between the dental arches. A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.
3. Test 2: The researcher performed cervical passive mobilization to assess the rotational range of motion and pain, at C1 and C2 levels, after performing the procedures for occlusal deprogramming. These procedures include placement of cotton balls between the dental arches, vigorous compression of cotton balls for 3 to 5 minutes, removal of cotton balls, and placement of the patient in a position of maximum relaxation with intercuspation without load. A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.

4. Pause: a pause of 15 to 20 minutes was taken to promote washout.
5. Initial Reassessment 2: The researcher performed cervical passive mobilization to assess the rotational range of motion and pain perceived at the time of assessment, at C1 and C2 levels, with intercuspation without load (antagonistic teeth touching without exerting force). A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.
6. Test 3: The researcher performed cervical passive mobilization to assess the rotational range of motion and pain, at C1 and C2 levels, with the application of a pressure stimulus of less than 196 kPa in the reflex cutaneous region of the ilium/colon continuously throughout the evaluation. A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.

This evaluation phase lasted 30 minutes per participant.

Phase II Procedures: Palpation of Neck and Orofacial Muscles

Data collection took place at least 1 week after phase I to rule out any type of influence from previously applied interventions.

Upon arriving, the participant was reminded of the procedures to be performed and the algometer and the VAS were presented again, enabling participants to characterize any type of pain they might experience during data collection. After confirming their willingness to continue the study, each participant was placed in the supine position on a gurney.

The tests and procedures used were the same as in phase I, with the exception of Test 1. The exclusion of this test is because the presence of an object that prevents habitual occlusion can stimulate the muscle contraction of the stomatognathic system and UCS, altering their “normal” condition and consequently altering their painful sensitivity to palpation.

The following erector muscles of the neck and stomatognathic system were evaluated in phase II (Figure 14):

- Trapezius
- Suboccipital musculature
- Sternocleidomastoid
- Temporal (anterior, middle, and posterior portions)
- Masseter (Upper to origin, body, and insertion)
- Ear-jaw articulation
- Medial pterygoid site

Due to its anatomical location, it is not possible to use the algometer to assess the medial pterygoid site; therefore, it was only evaluated by direct palpation with the finger (Figure 15).

Figure 14. Pain threshold assessment on palpation.

Figure 15. Palpation of the medial pterygoid site.

Phase II Protocol

The steps of the phase II protocol are as follows:

1. Initial Assessment: The researcher performed palpation of the erector neck muscles and of the stomatognathic system structures with intercuspation without load, using the AVS to characterize the resulting pain. Algometry was used to measure the pressure applied to the evaluated muscles A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.
2. Test 2: The researcher performed palpation of the erector neck muscles and of the stomatognathic system structures after occlusal deprogramming, using the VAS to characterize the resulting pain. Algometry was used to measure the pressure applied to the evaluated muscles. A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.
3. Pause: A pause of 15 to 20 minutes was taken to promote washout.
4. Initial Reassessment 2: The researcher performed palpation of the erector neck muscles and of stomatognathic system structures with intercuspation with load, using the AVS to characterize the resulting pain. Algometry was used to measure the pressure performed on the evaluated muscles. A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.
5. Test 3: The researcher performed palpation of the erector neck muscles and of the stomatognathic system structures using the VAS to characterize the resulting pain during tactile compression of the reflex region of the ilium/colon (pressure less than 196 kPa). This was controlled with algometry. A total of 3 measurements were taken and were later averaged. Between each measurement was a pause of 20 seconds.

This evaluation phase lasted 45 minutes per participant.

Ethical Procedure

This study was reviewed and approved by the Ethics Committee of the Regional Center of Porto, from the Catholic University of Portugal (CE.219.[11].2018).

To guarantee the safety of the participants and the confidentiality of the data and information from the study, an informed consent form containing the purpose of the study and interventions to which participants would be subjected was delivered for reading and signing. The signed document was delivered to the researcher.

Data Procedures

After collecting data from our sample, they will be entered into Excel (Microsoft Corporation) and then transferred to R (R Foundation for Statistical Computing), a free software for statistical analysis and graph construction, which is considered a variant of the S language. This program was developed by the R Foundation for Statistical Computing, with the aim of creating a tool for free use.

Descriptive statistics will be used to analyze the data relating to the characterization of the sample. This includes analysis of frequency distributions (for qualitative and discrete quantitative variables) and descriptive measures (minimum, maximum, mean, median, quartiles, standard deviation, coefficient of variation and Fisher asymmetry coefficient for discrete or continuous quantitative variables). This data will also be presented in graphical format using histograms and boxplots for better visualization of the results.

For the inferential statistics of the variables (range of motion, pain associated with passive mobilization, pressure exerted in the assessment of the pain threshold, and pain experienced by the pressure stimulus), the following procedures will be used:

- To perform result comparisons at the time of evaluation, it will be necessary to first check that the data have a normal distribution using the Shapiro-Wilk normality test (P<.001).
- The results will be compared using the Friedman test (P<.001), also known as analysis of variance in Friedman orders, because the data come from related samples (the same participants in the various evaluation phases).
- Due to the completion of the Friedman test, it will be necessary to proceed with multiple comparisons. As the samples are paired (since they are the same participants in both evaluation phases), the Wilcoxon test (P<.001) will be used, allowing for the identification of the differences between the evaluation phases.
- To analyze the relationship between the variables at different phases of evaluation, we will use the Spearman order correlation coefficient (P<.001).

Results

The selection and preparation of the data collection site, the acquisition of materials, the constitution of the sample group, and data collection have been completed. The results are being analyzed.

Discussion

The data from this study will allow for the observation of the possible influence of the stomatognathic system and viscerosomatic reflexes on pain and range of motion of the UCS, providing data for future randomized studies.

Limitations

As this is a pilot study, the objective is not to generalize the results, but to describe the behavior of the variables and contribute data for the development of future randomized studies.

No clinical diagnoses were made regarding the cervical spine, stomatognathic, or visceral system condition, allowing for the stratification of the participants.

Tactile stimulation of the reflex cutaneous region of the ilium/colon was a methodology designed for the study because the local physiology of this skin region was correlated with viscerosomatic reflexes. The physiological phenomena of this stimulus must be studied to better understand its mechanism of action.

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Authors' Contributions

BS, RF, PF, and PA designed the study, participated in the data collection, and wrote the paper.

Conflicts of Interest

None declared.

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Abbreviations

CSD: cervical spine dysfunction
UCP-Porto: Universidade Católica Portuguesa-Porto
UCS: upper cervical spine
VAS: Visual Analog Scale

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Protocol

Health Impacts and Characteristics of Deprescribing Interventions in Older Adults: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Deprescribing, a relatively recent concept, has been proposed as a promising solution to the growing issues of polypharmacy and use of medications of questionable benefit among older adults. However, little is known about the health outcomes of deprescribing interventions.

Objective: This paper presents the protocol of a study that aims to contribute to the knowledge on deprescribing by addressing two specific objectives: (1) describe the impact of deprescribing in adults ≥60 years on health outcomes or quality of life; and (2) determine the characteristics of effective interventions in deprescribing.

Methods: Primary studies targeting three concepts (older adults, deprescribing, and health or quality of life outcomes) will be included in the review. The search will be performed using key international databases (MEDLINE, EMBASE, CINAHL, Ageline, PsycInfo), and a special effort will be made to identify gray literature. Two reviewers will independently screen the articles, extract the information, and evaluate the quality of the selected studies. If methodologically feasible, meta-analyses will be performed for groups of intervention studies reporting on deprescribing interventions for similar medications, used for similar or identical indications, and reporting on similar outcomes (eg, benzodiazepines used against insomnia and studies reporting on quality of sleep or quality of life). Alternatively, the results will be presented in bottom-line statements (objective 1) and a matrix outlining effective interventions (objective 2).

Results: The knowledge synthesis may be limited by the availability of high-quality clinical trials on deprescribing and their outcomes in older adults. Additionally, analyses will likely be affected by studies on the deprescribing of different types of molecules within the same indication (eg, different pharmacological classes and medications to treat hypertension) and different measures of health and quality of life outcomes for the same indication. Nevertheless, we expect the review to identify which deprescribing interventions lead to improved health outcomes among seniors and which of their characteristics contribute to these outcomes.

Conclusions: This systematic review will contribute to a better understanding of the health outcomes of deprescribing interventions among seniors.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42015020866; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42015020866

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KEYWORDS

deprescribing; older adult; aging; medication use; inappropriate prescribing; potentially inappropriate medication; polypharmacy; comorbidity; multimorbidity; systematic review

Introduction

Polypharmacy and Older Adults

The use of multiple medications in older adults is on the rise [1], and the well-known risk of adverse medication events, defined as the undesired effects or toxicities caused by a medication, increases with the number of medications prescribed [2]. Polypharmacy (ie, >5 concurrent medications) among older adults is a worldwide problem with prevalence estimates varying between 39% for the United States in 2010 [3] to 74% in Sweden in 2018 [4]. Associated with aging is the onset of chronic conditions, often coexisting in a phenomenon termed multimorbidity [2]. Polypharmacy may be deemed necessary, or rational, for patients suffering from multimorbidity; this is because, in many cases, at least 1 medication is needed to treat each condition [5]. Polypharmacy is, however, associated with many adverse outcomes, including undesired medication reactions, increased time of hospital stay, as well as the risk of readmission to hospital soon after discharge, falls, and mortality [2]. The risk of an adverse medication event has been estimated at 13% with 2 medications, increasing to 58% and 82% with 5 and 7 or more medications, respectively [6], underlining the need to limit medication use and to prescribe wisely among older and particularly more vulnerable adults.

Inappropriate Prescribing

Pharmacotherapy is deemed inappropriate when the risks associated with the used medications exceed their benefits [5]. This risk-benefit ratio should therefore be considered by health professionals before prescribing a medication, and it often differs for seniors as they encounter a physiological decline in all aspects of pharmacodynamics and pharmacokinetics [7]. Indeed, potentially inappropriate medication (PIM) can be dangerous for older patients [8]. Several lists of PIMs have been elaborated in an attempt to limit inappropriate prescribing. Explicit criteria, such as the Beers criteria from the United States [9], or the STOPP/START criteria from Europe [10], are widely known and have been adapted to the clinical context of specific countries [11-13]. Health professionals may also use implicit criteria, such as the Medication Appropriateness Index [14]. Given the great number of PIMs and their consequences, medication reviews should be conducted on a regular basis, especially for older adults [5]; however, health care providers still struggle with this process [15].

Interventions to Improve Inappropriate Prescribing and Polypharmacy

In recent years, interventions to decrease inappropriate prescribing and polypharmacy have increasingly been developed. A Cochrane review [16] and its updates [15,17] studied such interventions: the results from randomized controlled trials (RCTs) on interventions (educational programs for prescribers, medication reviews by pharmacists, and tools to aid in clinical decision-making) showed effectiveness in decreasing inappropriate prescribing, but their clinical effects remained unclear [17].

Deprescribing

The deprescribing process is defined as the reduction, tapering, or discontinuation of medication deemed inappropriate for a specific patient, with the aim of minimizing polypharmacy and improving patient outcomes [18]. Presently, there is a lack of knowledge regarding the association of specific, effective elements of deprescribing for certain medication classes and the resulting health outcomes. Indeed, knowledge users participating in the development of this study (ie, the National Stakeholder Council on Safe Medication Management for Older Men and Women of the Canadian Institutes of Health research [19], physicians, pharmacists, and patients) have expressed the need for evidence on health outcomes and quality of life regarding deprescribing.

The findings from some RCTs are encouraging: deprescribing of antipsychotics was found to have no detrimental effects [20,21] and to reduce the risk of falls [22]. Deprescribing of benzodiazepines showed subtle cognitive advantages [23], while the discontinuation or dose-reduction of statins in patients with reduced life expectancy had no negative impact [24]. As for the deprescribing of chronic diuretics, 1 study reported preserved health outcomes after deprescribing [25], but 2 others failed to do so [26,27]. A 2016 review by Page et al [28] aimed to determine if deprescribing is a safe, effective, and feasible intervention to reduce mortality in older adults. Their systematic review, reporting on nonrandomized deprescribing interventions, showed a significant decrease in mortality: it found that generalized education programs had no impact on mortality, but patient-specific interventions decreased mortality. Other systematic reviews on the effects of deprescribing of specific medication classes have been performed in the past years (eg, for proton pump inhibitors, benzodiazepines, and antipsychotics [29-31]) in order to develop algorithms to guide deprescribing in clinical practice. Moreover, systematic reviews of the effects of deprescribing among special populations of older adults have been performed, such as a 2018 review by Thillainadasan et al

[32] on hospitalized older adults, on older residents in nursing homes by Kua et al [33], in 2019, on older patients with life-limiting illness, by Shrestha et al [34], in 2020, and on older people living with frailty by Ibrahim et al [35], in 2021. Generally, these reviews found deprescribing interventions to be safe and feasible, but they concluded that better evidence on their effects on clinical outcomes was needed; a medication review directed at deprescribing in nursing home residents showed that deprescribing significantly reduced mortality by 26% and the number of fallers by 24%, in a subgroup meta-analysis [35]. Similarly, Hansen et al [36] conducted a systematic review on behavior change techniques in deprescribing and found a combination of such techniques involving a range of interventions to be successful. A 2019 review by Ulley et al [37] found insufficient evidence to confirm that deprescribing improves medication adherence. Bloomfield et al [38] performed a review of the effects of deprescribing interventions on all-cause mortality, hospitalizations, health-related quality of life, and falls among community dwelling older adults in 2020; they concluded that comprehensive medication review may have reduced all-cause mortality, but the certainty of evidence was low, while the effect on hospitalizations, health-related quality of life, and falls was found to be small or absent. Finally, Monteiro et al [39], in a 2019 review, found that computerized decision support tools consistently reduced the number of potentially inappropriate prescriptions started, as well as reducing the mean number of potentially inappropriate prescriptions per patient.

Nevertheless, challenges remain regarding evidence on the health effects of deprescribing interventions across various medication classes and among older adults in particular. To inform about the health outcomes of such deprescribing interventions in older adults, this systematic review will include all recently published intervention studies and report on the characteristics of interventions that are successful at reducing medication and improving or maintaining older adults' health or quality of life. Ultimately, this systematic review aims to contribute to the development of an interdisciplinary consensus on effective interventions in deprescribing, which may lead to the development of guidance for health professionals and patients, as detailed in the Methods section of the development of public health guidance of the National Institute for Health and Care Excellence [40].

Objectives

The review will describe the impact of deprescribing on health and quality of life in patients aged 60 years and older, as well as the characteristics of effective deprescribing interventions. To meet these objectives, the study aims to answer the following research questions:

1. What are the impacts of deprescribing interventions in older adults on health outcomes or quality of life?
2. What are the characteristics of deprescribing interventions, or elements thereof, that achieve positive or at least neutral effects on the health or quality of life of older adults?

Methods

Literature Review

The review method will be based on the Cochrane Handbook for Systematic Reviews of Interventions [41]. The following keywords and terms will be combined to identify deprescribing intervention studies: (1) polypharmacy, deprescribing, Beers's criteria, potentially inappropriate; (2) withdraw*, withhold, withheld, stop*, cease*, discontinu*, reduc*; and (3) aged, geriatri*, frai*.

Knowledge users in the study team suggested the collection of relevant key papers that would inform the development of search strategies, which was carried out by 2 scientific librarians in consultation with the review authors. These strategies will be adapted for each database. References will be searched using key international databases such as MEDLINE, EMBASE, CINAHL, Ageline, and PsycInfo, without date limitation. When available, limits will be set to restrict the search to humans aged 60 years and over and publications. Moreover, the search languages will be set to English, French, or German, as the members of the research team are fluent in those languages. The search strategy is featured in Multimedia Appendix 1.

The reference lists of relevant review articles and of included studies will be checked manually for additional relevant articles. We made a special effort to identify relevant gray literature, as can be seen in Multimedia Appendix 2.

Study Selection

Study selection will be performed by 2 independent reviewers according to the following inclusion and exclusion criteria:

- Population studied: study groups with participants aged 60 years and older will be considered for this review. Study groups with a mean age of ≥60 years, for which at least 80% of participants were ≥60 years old, will be included; we also consider the possibility of extracting data related to a subgroup of participants aged ≥60 years. In addition, the participants will have at least 1 medication prescribed for a chronic condition.
- Interventions: deprescribing interventions, regardless of the intervention target (patients, caregivers, or health professionals) in any intervention setting (hospital, nursing home, etc) will be selected.
- Comparison: only the comparison of deprescribing interventions with usual care or between different types of deprescribing interventions will be considered for this review.
- Outcome: for interventions having affected the participants' medication regimen, all health outcomes will be considered, including withdrawal symptoms, adverse medication reactions, clinical outcomes, cognition, behavior, falls, use of health services, quality of life, mortality, or survival.
- Study design: all robust study designs will be included (RCT, non-RCT; controlled before-after studies; interrupted time-series studies; and repeated measures).

All included studies will be primary studies; therefore, reviews, editorials, letters to the editor, commentaries, and other similar publications will be excluded.

All identified references will be combined into an EndNote library, and multiple copies will be eliminated. The systematic review software DistillerSR (Evidence Partners) will be used for the subsequent steps. Two reviewers will independently determine the eligibility of the retrieved studies by comparing their titles and abstracts to the inclusion criteria. Subsequently, the full texts of the retained articles will be screened to confirm their relevance. The process will be similar for all types of literature sources. The study selection form can be found in Multimedia Appendix 3.

Data Extraction

The extraction of data will be completed using DistillerSR (Evidence Partners) and pre-established forms regarding the following:

- Study characteristics (design, date, and location)
- Population selection and participants' characteristics (age, sex, and residency)
- Intervention description (providers, targets, duration, and follow-up)
- Outcomes (medication regimen, health, and quality of life)

An example of a data extraction form is featured in Multimedia Appendix 4.

The Cochrane Collaboration's GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach will be used for grading the quality of the body of evidence for each analyzed intervention outcome [42]. The GRADE score, varying from high to moderate, low, or very low quality, will indicate the level of confidence we have in the effect of the intervention, as reported in any study. The risk of bias of the individual, eligible studies will be assessed using the SIGN (Scottish International Guideline Network) tool for observational studies [43] and the Cochrane risk of bias tool for RCT studies [42]. The process will be carried out by 1 reviewer and reviewed by a second one.

Data Synthesis

A meeting after the first selection process between researchers and knowledge users (ie, patient experts and clinicians) allowed us to prioritize analyzing the deprescribing of specific medication classes with particular indications (eg, bisphosphonates against osteoporosis) over analyzing the deprescribing effect on one more general health outcome (eg, mortality reduction, as in the review by Page et al [28]). If methodologically feasible, meta-analyses will be performed for intervention studies reporting on deprescribing interventions for similar medications or a specific medication class, used for similar or identical indications, and reporting on similar outcomes (eg, benzodiazepines against insomnia, reporting on sleep quality). If meta-analyses are not possible, the study results will be summarized in a transparent and reproducible narrative synthesis, based on the methods published by Rodgers et al [44,45] (objective 1). Descriptive numerical summary tables will also be completed, including but not limited to the following patient characteristics: (1) author, year, country; (2) study design and setting; (3) number of participants, mean (SD) age, male proportion (%); (4) intervention or control; (5) outcome measures; (6) follow-up duration; and (7) study results (effect of intervention on discontinuation; and health outcomes, quality of life outcomes). In order to answer objective 2, we will identify the most effective interventions or the associated intervention components.

Comparative qualitative analysis will be used to analyze the causal contribution of different intervention components toward health outcomes [46]. The sets of characteristics associated with the specific outcome will be charted. Afterward, they will be subjected to a minimization procedure to identify a simpler set of conditions accounting for observed health outcomes. This will result in a matrix of intervention characteristics and related outcomes.

Meta-analyses

If outcomes or medications are sufficiently similar, the results of deprescribing interventions will be subjected to meta-analyses using RevMan 5.3.5 (The Nordic Cochrane Centre). Comparisons between interventions will be performed for one outcome at a time. A risk ratio will be estimated for the studies comparing an intervention group with a usual care or control group, using a random effects model, assuming that the risk of publication bias will be low. For studies with more than one intervention group, the usual care or a control group will be appropriately split for each intervention, and a sensitivity analysis will evaluate the impact of this split [47,48]. Any heterogeneity indicated by the χ^2 test of heterogeneity and the I^2 statistic with its 95% CI [49] will be investigated through subgroup analyses. Though care will be taken to reduce the risk of publication bias, this assumption will be investigated by a funnel plot analysis [50]. If the follow-ups of interventions have different durations, the effect of the intervention has to be comparable at different times of follow-up. In such a case, a meta-regression model may be used to investigate the potential effect of follow-up duration on the results [51].

Integrated Knowledge Exchange

The participation of patients and clinical experts in the fields of deprescribing and geriatrics is crucial in order to make the review useful for patients and health professionals, as well as making it applicable to the local setting. Hence, researchers and knowledge users met after the selection of eligible studies and will meet again before the submission of the publication of the results. Each of these meetings will follow a rigorous and transparent methodology and will be documented in detail. The knowledge user team will discuss the prioritization of medication classes for individual review chapters and will also participate in the final interpretation of results before publication, giving their own perspective as clinicians, patients, and decision-makers. All data generated or analyzed during this study will be included in published articles.

Results

To respond to the first research question, bottom-line statements based on the evidence gathered or the results from meta-analyses will be formulated. For the second research question, a matrix will summarize the effective deprescribing interventions or their components. The results will then be interpreted by the knowledge user team in order to determine their merits and the

need for additional research to validate the identified deprescribing interventions. They will also assist the team in determining which results can be generalized for certain medication groups and which require further specific research. The review results will then be modified and finalized through email exchanges.

The review results will be published in peer-reviewed, open-access journals and disseminated to all stakeholders in different forms (eg, as web-based guidance) as part of continuous education material or as documentation for health professionals. They will be integrated into health professionals' academic training and presented at appropriate annual meetings and websites. The study results (ie, evidence for successful interventions and recommendations to adapt or develop interventions) will be communicated to patients, caregivers, the scientific community, stakeholders, health professionals, and the general community. An integrated knowledge transfer strategy targets this aim (Table 1).

This study is expected to conclude in the winter of 2022.

Table 1. End of project knowledge transfer strategy.

Medium	Target
Journal publication	• Peer-reviewed, open-access journal (undefined yet)

Communication	• Annual meeting of:
	  • Canadian Geriatrics Society
	  • Canadian Association of Population Therapeutics
	  • Family Medicine Forum
	  • Le Fonds de recherche du Québec – Santé (FRQS), the Quebec Network for Research on Aging
	  • Canadian Pharmacists' Association (CPhA)

Website publications	• Publishing the results on the following websites:
	  • Canadian Geriatrics Society
	  • Canadian Association of Population Therapeutics
	  • Family Medicine Forum
	  • FRQS

Web-based guidance and documents	• Present successful characteristics of deprescribing intervention on the CPhA website via the initiative "the Translator" • The Quebec "Institute National d'Excellence en Santé et en Services Sociaux" will participate in knowledge exchange via the development of guidance documents
Education and training	• Offer a continuous education activity for health professionals, led by the Centre d'excellence sur le vieillissement de Québec, which has a strong record of continuous education for clinicians in all settings • Integrate into health professionals' academic training

Continuous collaborations	• Pursue our collaboration with several institutions:
	  • Seniors Health Research Transfer Network and OPEN (Ontario Pharmacy Evidence Network)
	  • Institute for Health Services and Policy Research at the Canadian Institutes of Health Research
	  • Canadian Dementia Knowledge Translation Network

Discussion

Expected Challenges

Several challenges may be encountered during the review. Preliminary searches have identified some high-quality deprescribing interventions [20-23,26,52], but there may still be a lack of studies describing health outcomes, as noted by Page et al [28]. Their literature search was completed in February 2015, so more study results can be expected, given the increased acceptance of deprescribing and the expressed need for more high-quality deprescribing RCTs [53]. Gray literature was found to be scarce on deprescribing interventions, but trial registers will also be checked to assure complete coverage.

Deprescribing interventions may be available for some medication groups only. We may thus not be able to generalize the evidence on these intervention elements to other medication classes. Given the great variety of studies, it may be difficult to retrieve studies that will be sufficiently homogenous to allow for meta-analyses. Finally, the studies may report various health outcomes, and their relevance could be difficult to compare. To solve this problem, the knowledge user experts will evaluate the importance of such limitations, disregarding certain evidence if deemed not relevant for the clinical context.

Deprescribing interventions for different medication classes, such as psychotropics or statins, may yield nonhomogeneous results, which will be challenging. However, there may exist common characteristics among deprescribing interventions for different medication classes, such as careful patient selection or continuous patient surveillance, leading to positive health

outcomes in deprescribing for different medication classes. Finally, different health outcomes may be reported for interventions on similar medications (eg, blood pressure or incidence of cardiovascular disease for the deprescribing of antihypertensives), and it may be challenging to prioritize their relevance.

Risk of Bias

Some biases, possibly inherent to the review process itself, will be addressed by the review methodology to minimize their effect on the review's results.

Selection and Information Bias

Deprescribing was termed in 2003 [54] and only became a Medical Subject Heading term in 2016. Therefore larger, more scoping terms, such as "discontinuation," will be used for database searches regarding earlier studies on medication discontinuation. We expect this to lead to a large number of retrieved references. Having 2 independent reviewers screen all references is meant to limit selection bias. The team will carefully verify gray literature (Multimedia Appendix 2) to gain the most complete review possible.

Confounding Bias

Retrieved studies may lack homogeneity, making planned meta-analyses more difficult. Moreover, some health outcomes may not be comparable. We will perform narrative syntheses for medication classes where meta-analyses will be impossible. Furthermore, confounding factors may have not been considered in some studies, affecting the quality grades of these studies and of the resulting evidence. The results of this systematic review will help to identify deprescribing interventions leading to desired health or quality of life outcomes and therefore contribute to a better understanding of how deprescribing may improve seniors' health and well-being.

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Authors' Contributions

All authors discussed core ideas, participated in the interpretation of data, and contributed to the writing of the paper. All authors read and approved the final manuscript. EK is the corresponding author; she will provide full access to all aspects of the research and writing process upon request, and takes final responsibility for the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Final search strategy.
[XLSX File (Microsoft Excel File), 38 KB - resprot_v10i12e25200_app1.xlsx]

Multimedia Appendix 2
Complete list of consulted databases and websites.
[DOCX File , 25 KB - resprot_v10i12e25200_app2.docx]

Multimedia Appendix 3
DistillerSR Deprescription selection questions.
[DOCX File , 29 KB - resprot_v10i12e25200_app3.docx]

Multimedia Appendix 4
Data extraction grid.
[DOCX File , 23 KB - resprot_v10i12e25200_app4.docx]

Multimedia Appendix 5
Peer reviewer report from the Canadian Institutes of Health Research.
[PDF File (Adobe PDF File), 479 KB - resprot_v10i12e25200_app5.pdf]

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Abbreviations

PIM: potentially inappropriate medication
RCT: randomized controlled trial

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Protocol

The Relationship Between Paternal Preconception Obesity and Health Behaviors and Childhood Obesity: Protocol for a Systematic Review

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Abstract

Background: Childhood obesity is a global public health concern and is a priority for researchers and policy makers. To overcome the epidemic of obesity, influencing factors throughout the life span need to be addressed, including those in the preconception period. A better understanding of the association between paternal preconception factors and childhood obesity is important for public health interventions.

Objective: This systematic review will examine the relationship between paternal preconception obesity and health behaviors and their offspring's overweight or obesity.

Methods: Peer-reviewed quantitative studies and grey literature that report associations between paternal preconception obesity and health behaviors—such as smoking, exercise, and eating habits—and childhood overweight and obesity will be identified through a computerized literature search in 7 databases. The quality of each study will be assessed using the Quality Assessment Tool for Quantitative Studies. Characteristics of the included studies will be reported, and relevant findings from each paternal preconception exposure will be narratively synthesized. This review will follow the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines.

Results: This systematic review is anticipated to begin in December 2021 and be completed by the end of August 2022.

Conclusions: This systematic review will contribute to a better understanding of the relationship between preconception paternal exposures and their offspring's overweight or obesity. Findings will help support health professionals working with prospective parents to educate fathers on the benefits of improving their weight and health behaviors during the preconception period.

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KEYWORDS

childhood obesity; preconception; paternal obesity; health behaviours; obesity; public health; children; adolescents; body weight; parenting; health behaviors

Introduction

Childhood obesity is a widely acknowledged health concern whose prevalence is increasing rapidly at the international level. According to the World Health Organization, childhood obesity is defined as an abnormal or excessive accumulation of body fat that can be harmful to health [1]. In 2016, the global prevalence of childhood obesity was assessed at 18% [2]. At that time, it was estimated that approximately 340 million children and adolescents between 5 and 19 years of age were obese or overweight, which represents a considerable increase over the last 30 years [2].

The high prevalence of childhood obesity not only poses a considerable challenge to the health care system in the future, but it can also affect children's short- and long-term health and well-being. For example, children who are obese have an increased risk of cardiovascular disease [3], including coronary heart disease and atherosclerosis, gastrointestinal disease [4], diabetes, and even some cancers in adulthood [5]. In addition to these long-term serious physical health conditions, obesity can also lead to various psychological, social, and educational consequences in childhood [6-9]. Therefore, global calls for action have been made to halt the rise in childhood obesity [1].

Various risk factors are associated with childhood obesity, making this public health issue a complex one to solve. Research has recognized that risk factors can be behavioral, biological, environmental, and societal [10-13]. According to the Commission on Ending Childhood Obesity [1], risk factors throughout childhood need to be addressed, beginning with preconception. In fact, there is growing evidence that an individual's genetic makeup is important in determining the risk of obesity [8]. Thus, it is recommended that health professionals address modifiable risk factors of both parents before conception [14-16]. For example, according to Barker et al [17], children's growth, development, and long-term health can be shaped by parental nutritional status before conception.

Studies examining preconception risk factors of childhood obesity have mainly focused on mothers. This focus on women has also contributed to gender bias, suggesting that women bear the sole responsibility for their child's health outcomes [18,19]. Nevertheless, growing evidence from human and animal studies suggests that preconception paternal risk factors could also play an important role in the health and development of their offspring [13,14,16,18-21]. For example, Braun et al [22] found that various paternal behavioral risk factors before conception, such as stress and diet, were associated with some diseases and obesity in children. Similarly, Mejia-Lancheros et al's [23] prospective cohort study found a positive association between paternal smoking during preconception or the early gestational period and childhood obesity at 5 years of age. Comparably, a longitudinal study by Northstone et al [24] found a positive association between fathers who started smoking before the age of 11 years and their son's BMI in adolescence. Transgenerational effects of smoking on adolescents' body composition have also been studied. Dougan et al [25] found that grandpaternal smoking was positively associated with their granddaughter's obesity or overweight at 12 years of age but not with their grandson's weight.

In addition to behavioral risk factors, paternal preconception weight has also been linked to obesity or overweight in children [26-28]. For example, Rath et al [28] found that 14-year-old adolescents were three times more likely to be obese if their father was overweight before conception compared to those who had fathers who had a healthy weight before conception. Furthermore, the risk of obesity at 14 and 22 years old quadrupled for children whose father was obese before conception [28]. Similar to Dougan et al's [25] study, Jääskeläinen et al [27] found that paternal overweight or obesity preconception was a stronger predictor of overweight or obesity among daughters than sons.

The link between paternal preconception weight and behaviors and childhood obesity may be partially explained by epigenetics. Specifically, epigenetics involves the transmission or modification of gene expression, which is inherently responsible for health and disease pathogenesis [18,19,29-31]. It has been reported that gene expression could be influenced by adiposity [32] and various health behaviors, such as tobacco use, physical activity, and unhealthy eating [33]. Since children inherit a complete set of genes from each parent, paternal weight and health behaviors may modify fathers' gene expression, which can be passed down to their offspring and future generations. Although some researchers claim that genetics plays only a small role in childhood obesity [8,34], others argue that parents' health at the time of conception is critical in shaping the health of their future child and therefore deserves particular consideration [20,35].

While most systematic reviews have reported on the impact of paternal BMI on child health outcomes [36], paternal risk factors and offspring cardiometabolic disease [16], and paternal BMI and childhood obesity [37], none have looked at preconception paternal obesity and health behaviors, such as diet, exercise, and smoking, and their association with childhood obesity. A better understanding of this relationship would help support the implementation of interventions before conception and help address the epidemic of childhood obesity. This evidence is also needed to support public health action throughout the preconception period.

This systematic review will summarize peer-reviewed studies and grey literature publications that have examined how paternal preconception obesity and health behaviors are associated with childhood obesity. Specifically, this review will examine how fathers' obesity and health-related behaviors such as smoking, exercise, and eating habits before conception are associated with their offspring's weight status. The main objective of this review will be to identify the potential importance of preconception health and behaviors of fathers on their offspring's health and suggest avenues for future research.

Methods

Design

This systematic review will follow the updated guidelines from the PRISMA (Preferred Reporting Items for Systematic reviews

and Meta-Analyses) 2020 statement [38]. The 27-item checklist from the PRISMA 2020 statement will be used to ensure full transparency and completeness of the reporting, particularly related to the methods used to identify, select, appraise, and synthesize the included studies [39].

Eligibility Criteria

Studies will be included in this systematic review if they meet the following criteria: (1) they assess the unique contribution of paternal preconception obesity or health behaviors to children's weight status, (2) they focus on one or more paternal health behaviors (ie, smoking, exercise, and eating habits) or overweight/obesity before conception, (3) they focus solely on the weight status of children <18 years of age, and (4) they are published in either English or French. Studies that include secondary analyses that meet the above criteria will also be included. Studies that focus on paternal prenatal (after conception) health or behaviors, or those that include fathers with complex health conditions (eg, diabetes, cardiovascular disease), will be excluded from this review.

Types of Studies

Peer-reviewed, quantitative studies will be included in this systematic review. Due to the nature of this systematic review's objectives, prospective and retrospective cohort studies will be included to assess the relationship between paternal preconception obesity and health behaviors and childhood overweight/obesity. Although unlikely, experimental study designs (randomized controlled trials, clinical control trials, pre-post designs) will also be considered if they meet the inclusion criteria. To ensure all relevant literature is identified, reference lists of any previous systematic, scoping, or narrative reviews will also be checked. Grey literature (eg, dissertations, theses, reports) will also be included in this review, considering the novelty of this topic and the potentially limited number of relevant publications. Qualitative and animal studies will be excluded from this review.

Population and Exposure of Interest

This review will focus on males who may or may not have been actively trying to conceive. Objectively and subjectively measured paternal preconception overweight/obesity and health behaviors will be the primary exposures included in this review. Health behaviors will include smoking (ie, cigarettes, tobacco, vaping), exercise (ie, physical activity, sedentary behavior), and eating habits (ie, dieting, dietary intake, food intake, behaviors), as these have been shown to influence gene expression in human or animal studies.

Outcome of Interest

Objectively or subjectively measured childhood obesity will be the primary outcome of this systematic review. Childhood will encompass any child <18 years of age. Childhood obesity will be defined as any child reported to have overweight or obesity, based on the method of measurement's guidelines (eg, World Health Organization, Centers for Disease Control and Prevention, BMI). All body composition or adiposity measurements will be included, such as BMI, waist circumference, waist to height ratio, skin folds, bioelectrical impedance analysis, and dual-energy X-ray absorptiometry (DXA).

Search Methods

The search strategy used for this review will be developed in collaboration with an experienced research librarian. Relevant studies will be identified through a computerized search in the following databases: Cochrane, PubMed, EBSCO Host (CINAHL, APA PsycINFO), ProQuest, Scopus (Science Direct), and Google Scholar. A specific search strategy will be formulated in PubMed and adapted for each of the above databases (Table 1). Reference lists of retained studies will also be searched to ensure that all relevant studies have been identified. All articles that will have emerged from the computerized search will be exported to Mendeley, and any duplicates will be removed.

Table 1. Strategy search sample for PubMed.

Concepts	Mesh and keywords
Paternal	("Fathers"[Mesh] OR "Paternal Inheritance"[Mesh] OR "Paternal Behavior"[Mesh] OR "Paternal Exposure"[Mesh] OR "Paternal Age"[Mesh] OR "Father-Child Relations"[Mesh] OR father*[Title/Abstract] OR paternal[Title/Abstract])
Preconception	("Preconception Care"[Mesh] OR "Fertilization"[Mesh] OR "Posthumous Conception"[Mesh] OR "Prenatal Care"[Mesh] OR "Prenatal Exposure Delayed Effects"[Mesh] OR preconception[Title/Abstract] OR pre-conception[Title/Abstract] OR fertiliz*[Title/Abstract])
Health habits and obesity	("Obesity"[Mesh] OR "Overweight"[Mesh] OR "Body Composition"[Mesh] OR "Body Weight"[Mesh] OR "Intra-Abdominal Fat"[Mesh] OR "Body Fat Distribution"[Mesh] OR "Adipose Tissue"[Mesh] OR "Life Style"[Mesh] OR "Healthy Lifestyle"[Mesh] OR "Smoking"[Mesh] OR "Tobacco Products"[Mesh] OR "Smokers"[Mesh] OR "E-Cigarette Vapor"[Mesh] OR "Vaping"[Mesh] OR "Cigarette Smoking"[Mesh] OR "Nutritional Status"[Mesh] OR "Diet Therapy"[Mesh] OR "diet therapy" [Subheading] OR "Eating"[Mesh] OR "Exercise"[Mesh] OR "Sedentary Behavior"[Mesh] OR "Sports"[Mesh] OR "Physical Exertion"[Mesh] OR "Risk Factors"[Mesh] OR "Health Risk Behaviors"[Mesh] OR obese[Title/Abstract] OR obesity[Title/Abstract] OR "body composition" [Title/Abstract] OR "body weight"[Title/Abstract] OR "body fat"[Title/Abstract] OR "Intra-abdominal fat"[Title/Abstract] OR "adipose tissue"[Title/Abstract] OR "life style"[Title/Abstract] OR smoking[Title/Abstract] OR tobacco[Title/Abstract] OR smoker*[Title/Abstract] OR "e-cigarette" [Title/Abstract] OR vaping[Title/Abstract] OR "nutritional status"[Title/Abstract] OR diet[Title/Abstract] OR exercise[Title/Abstract] OR sedentary[Title/Abstract] OR "physical activity"[Title/Abstract])
Childhood obesity	("Pediatric Obesity"[Mesh] OR ("Child"[Mesh] AND "Obesity"[Mesh]) OR "pediatric obesity" [Title/Abstract] OR "child obesity"[Title/Abstract] OR ("Child"[Mesh] AND "body composition"[Title/Abstract]) OR ("Child"[Mesh] AND "Adiposity*"[Mesh]) OR ("Child"[Mesh] AND "Body Mass Index"[Mesh]) OR ("Child"[Mesh] AND "Waist Circumference"[Mesh]) OR ("Child"[Mesh] AND "Waist-Height Ratio"[Mesh]) OR ("Child"[Mesh] AND "DXA" [Title/Abstract]) OR ("Child"[Mesh] AND "skin fold" [Title/Abstract]))

Selection of Studies

All titles and abstracts that will emerge from the computerized search will be independently assessed for relevancy by at least two investigators. Half of the titles and abstracts will be assessed by MEL and LAL, and the other half will be assessed by SW and FM. If there is a disagreement between the two investigators, the full text will be verified by a third investigator. The full text of all remaining articles will be read by at least two investigators, who will independently assess them against the eligibility criteria (MEL and LAL will assess half of the articles and SW and FM will assess the other half). In the case of a disagreement, the full text will be read by a third investigator. All studies that do not meet eligibility criteria will be excluded. In cases where the full text of an article cannot be accessed, efforts will be made to contact the corresponding author of that article. As per the PRISMA 2020 guidelines, a flow diagram depicting how articles were identified, screened, and included in the systematic review will be constructed. The full text of all remaining relevant studies will be kept in a folder shared between the investigators in Mendeley.

Data Extraction and Management

Two independent investigators will enter data from each relevant study into a spreadsheet software such as Excel (MEL and LAL will enter data from half of the studies, and SW and FM will enter data from the remaining half). Extraction issues and missing data problems will be resolved through discussion among the four investigators. The following variables will be extracted from each article: (1) characteristics of the study (ie, author names and publication date, title of the study, country/location of origin), (2) the study's goals or objectives, (3) type of study (ie, design, length of follow up), (4) characteristics of the population (ie, child and paternal age, sample size, time of preconception, ethnicity), (5) exposure variables (ie, paternal weight and health behaviors) of interest, (6) methods of assessment or tools for both paternal and childhood obesity variables, (7) methods of analysis, and (8) main results and study limitations.

Quality Assessment

All included studies will be assessed for quality using the Quality Assessment Tool for Quantitative Studies. This validated tool was developed to improve the quality of systematic review reporting, particularly in public health contexts [38]. This tool involves giving a strong, moderate, or weak rating for 8 indicators, including selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis. These ratings are then used to provide an overall methodological rating for the article in question. Compared to other tools that were mainly developed to assess the quality of experimental studies, the Quality Assessment Tool for Quantitative Studies can evaluate the quality of observational studies. For this study, two investigators will independently assess the quality of each of the studies included in the systematic review (MEL and LAL will assess half of the included studies, and SW and FM will assess the remaining half). In the case of a disagreement, a third investigator will evaluate the quality of the study.

Data Analysis and Reporting

Since it is anticipated that there will be considerable heterogeneity in study exposure, methods, and measurement tools, data will be narratively synthesized. A descriptive summary of the studies' characteristics will first be presented. This summary will be supported by a table presenting all extracted data from the included studies, including their methodological quality assessment. The outcomes of this review will be presented and discussed in line with each paternal preconception exposure. If possible, results will also be stratified by the offspring's age—that is, infants and toddlers (birth to 2 years), preschoolers (3-5 years), school-age children (6-10

years), and preadolescents and adolescents (11-17 years). The overall strength of evidence will be determined by the strength of the methodological assessment of each study, the number of studies included, and the homogeneity of the findings across the studies. Implications for childhood obesity prevention and recommendations for future research avenues will be discussed.

Results

This systematic review is anticipated to begin in December 2021. Study selection and data extraction will begin in February of 2022, and quality assessment and data synthesis will begin in April of 2022. The review is expected to be completed by the end of August 2022.

Discussion

Overview

Over the past decades, childhood obesity rates have increased dramatically across the globe. Although obesity is a multifaceted disease that is influenced by environmental, behavioral, biological, and genetic factors, it is well recognized that early intervention is necessary to prevent the onset of childhood obesity and its short- and long-term health consequences. Emerging research in epigenetics has suggested that the preconception period may be critical for obesity prevention. Some animal and human studies have supported this notion by reporting strong associations between maternal preconception risk factors and their offspring's obesity. However, evidence on how paternal preconception risk factors are associated with childhood obesity has never been synthesized.

Given the urgency of addressing childhood obesity and the possible role of epigenetics in the onset of this chronic condition, identifying potential parental preconception risk factors may be one strategy to intervene at the earliest possible time. Although mothers have been the target of previous preconception public health interventions, fathers have been relatively dismissed. Therefore, this systematic review will provide valuable information on whether paternal preconception obesity and health behaviors are linked to their offspring's obesity and body weight. Findings from this review may be used as a tool by health care professionals working with prospective parents to educate fathers on the benefits of improving their weight status and health behaviors alongside their partner during the preconception period.

Strengths and Limitations of the Review

This systematic review will be the first to synthesize evidence related to the association between paternal preconception obesity and health behaviors and their offspring's obesity. One of the main strengths of this systematic review is the breadth of health behaviors that will be assessed, allowing for a more comprehensive overview of the topic. Other strengths of this review include using a comprehensive search strategy in 7 different databases, using a validated tool to assess observational-type studies, including studies published in either English or French, and not limiting the publication period.

Since epigenetics is a relatively new field of research, it is possible that only a small number of studies will be included in this review. This limitation must be acknowledged, as it could limit the strength of the overall conclusions.

Dissemination

Any changes made to this protocol will be reported, with justification, in the final review. Findings from this systematic review will be disseminated through traditional approaches, including scientific peer-reviewed publications and conferences. Nontraditional methods of dissemination will also be used, including fact sheets for primary care providers (eg, family physicians, nurses, fertility specialists), public health nurses and dietitians, patients, and the general public.

Conflicts of Interest

None declared.

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Abbreviations

DXA: dual-energy X-ray absorptiometry
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

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Protocol

Patient-Facing Mobile Apps to Support Physiotherapy Care: Protocol for a Systematic Review of Apps Within App Stores

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Abstract

Background: Care delivered by physiotherapists aims to facilitate engagement in positive health behaviors by patients (eg, adherence to exercise). However, research suggests that behavioral interventions are frequently omitted from care. Hence, better understanding of strategies that can be used by physiotherapists to support patients to engage in positive behaviors is important and likely to optimize outcomes. Digital health interventions delivered via mobile apps are garnering attention for their ability to support behavior change. They have potential to incorporate numerous behavior change techniques (BCTs) to support goals of physiotherapy care, including but not limited to self-monitoring, goal setting, and prompts/alerts. Despite their potential to support physiotherapy care, much is still unknown about what apps are available to consumers, the BCTs they use, their quality, and their potential to change behaviors.

Objective: The primary aim of this study is to systematically review the mobile apps available in app stores that are intended for use by patients to support physiotherapy care, including the BCTs within these apps. The secondary aims are to evaluate the quality and behavior change potential of these apps.

Methods: A systematic review of mobile apps in app stores will be undertaken. This will be guided by recommendations for systematic reviews in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement but adapted to suit our app store search, consistent with similar systematic reviews of apps published in the *Journal of Medical Internet Research*. Apple Store and Google Play will be searched with a two-step search strategy, using terms relevant to physiotherapy, physiotherapists, and common physiotherapy care. Key eligibility criteria will include apps that are intended for use by patients and are self-contained or stand-alone without the need of additional wearable devices or other add-ons. Included apps will be coded for BCTs and rated for quality using the Mobile Application Rating Scale (MARS) and for potential to change behavior using the App Behavior Change Scale (ABACUS).

Results: App store search and screening are expected to be completed in 2021. Data extraction and quality appraisal are expected to commence by November 2021. The study results are expected to be published in a subsequent paper in 2022.

Conclusions: Knowledge gained from this review will support clinical practice and inform research by providing a greater understanding of the quality of currently available mobile apps and their potential to support patient behavior change goals of physiotherapy care.

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KEYWORDS

physiotherapy; physical therapy; digital health intervention; mobile app; eHealth; behavior change technique; behavior change; exercise; digital health; mHealth

Introduction

Care delivered by physiotherapists involves a complex mix of biopsychosocial components that aim to facilitate engagement in positive health behaviors by patients, such as adherence to prescribed exercise programs or greater participation in physical activity [1-5]. Facilitating positive behavior change is particularly important as care moves to the home or community, where patients typically spend increasing time without physiotherapist supervision [2]. To promote this, various strategies that support patient engagement in desired behaviors may be used by the physiotherapist, such as education, provision of a home exercise program as a component of self-management, demonstration of these exercises, and instructional information about how to perform the behavior [1,3]. Despite this, research suggests that positive patient behaviors are suboptimal and that behavioral interventions are frequently omitted from physiotherapy care [3]. Thus, strategies that support patients to achieve and maintain positive behavior change over the long-term, particularly where supervision from the physiotherapist has ceased, are important and likely to optimize treatment benefits [1,3].

Digital health interventions are gaining increasing attention in various physiotherapy contexts [6-13]. They are defined as "...interventions delivered via digital technologies...to provide effective, cost-effective, safe, and scalable interventions to improve health and healthcare" [14]. These technologies include but are not limited to the internet, smartphones, wearables, and other connected devices. Mobile apps are a form of digital health interventions that are receiving increasing attention for supporting care and driving behavior change [15], including patient behaviors such as self-management activities (eg, exercise participation) [7,16-20]. A key strength of mobile apps is their potential to support patients' ongoing behavioral performance during and between consultations, or when formal treatment has ceased. They are widely available, inexpensive, and scalable [21]. Apps have the capacity to deliver numerous behavior change techniques (BCTs) conducive to physiotherapy care. BCTs are defined as "an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behavior" [22]. These techniques refer to the "active ingredients" of the intervention, which facilitate the intended behaviors one wishes to change [2,23]. BCTs can be further unpacked using a clustering taxonomy, the Behavior Change Technique Taxonomy version 1 (BCTTv1), which was developed to create a more robust system for reporting about behavior change interventions [22]. In this digital context, these interventions may include but are not limited to self-monitoring, goal setting, prompts/alerts, social support, feedback, action planning, rewards, scheduling, instructional information, and social support [7,10,15,18]. The research landscape surrounding mobile apps and health behavior change is still maturing, and to date, there is no agreement on how to facilitate behavior change. Research still seeks to understand which components of apps may best facilitate behavior change in the user. Further, there is a dearth of evidence regarding the features of apps that are most conducive to delivering evidence-based BCTs, as well as how to evaluate and categorize these features [15]. It was for this reason that the authors McKay, Slykerman, and Dunn [15] developed the App Behavior Change Scale (ABACUS) with the aim to support the assessment of the behavior change potential of mobile apps through quantification of BCTs.

Specifically for physiotherapy, little is currently known about the range of apps available on the market to support physiotherapy care, the quality of these apps, and their potential to change behavior. Hence, the objectives of this review are to catalogue the apps (intended for use by patients) that are available in app stores, the BCTs they contain, their quality, and their potential to change behavior. Our specific research question is "What is the quality of mobile apps designed for patients to support physiotherapy care, and what BCTs do they contain?"

Methods

Study Design

The proposed study is a systematic review of mobile apps available in app stores that are intended for use by patients to support physiotherapy care. This review will be guided by principles for systematic reviews in line with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement [24] but will be adapted to suit a search of app stores, which differs from searches of published or grey literature for most systematic reviews. This approach is well-grounded in published literature in this journal, in which systematic reviews were conducted examining mobile apps within app stores [7,25]. The search will be developed in line with the 2015 PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist for developing a systematic review protocol [26].

Study Objectives

Our study objectives are as follows.

Primary

The primary objective of the study is to describe mobile apps intended for use by patients to support physiotherapy care, including a description of any BCTs contained within them (coded against the BCTTv1 taxonomy) [22].

Secondary

The secondary objectives of the study are (1) to evaluate app quality, using the Mobile Application Rating Scale (MARS) [27], and (2) to evaluate apps for their potential to change behavior, using the App Behavior Change Scale (ABACUS) [15].

Ethics

This study design does not require ethical approval.

Eligibility

The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Mobile app inclusion and exclusion criteria.

Inclusion criteria

- Apps are intended for use by patients to support physiotherapy care they are receiving or have received. Note that it must be clear in either the description/title/screenshots on the app store or within the app itself that the intended use of the app is to support physiotherapy or physical therapy care (eg, alongside standard physiotherapy care, prescribed by the physiotherapist, or monitored by their physiotherapist).
- Apps are designed for self-contained/stand-alone use without the need of additional wearable devices or other add-ons (eg, wearable sensors).
- Apps are available on either the Apple App Store or Google Play platform.
- Apps are available in the English language.
- Apps will be considered irrespective of whether they are free or paid; where both exist (eg, a "lite" and full paid version), both versions will be evaluated.
- Apps will be considered irrespective of time passed since the app launch or last update, providing they are compatible with current mobile devices at the time of searching.

Exclusion criteria

- Apps are designed for exclusive use by health care professionals (and not by patients).
- White-labelled apps are designed for exclusive use by a specific clinic or health care service and are not available for use by the general public (eg, those requiring a unique login for that organization).
- Apps cost more than Aus $10 (US $7.33) (this is in line with other study protocols evaluating mobile health apps, as research indicates that consumers are unlikely to purchase health apps that cost more than this) [26,28].

Sources

Because Apple (iOS) and Android devices combined accounted for 99.4% of mobile operating systems worldwide as recently as November 2020 [29], we will search their respective app platforms, the Apple App Store (Apple) and Google Play (Android). Any unique apps eligible for screening and inclusion identified through this additional search will be added.

Search Strategy

A two-step strategy will be used to search app store platforms, consistent with the most comprehensive search strategy and study design used across other systematic reviews of health-based apps in app stores published in the *Journal of Medical Internet Research* [7]. A review of health-based apps using this two-step strategy identified 6579 apps [25], while reviews using a single-step search have typically resulted in <1000 identified apps [7,28,30]. Thus, the two-step search strategy is most appropriate and is expected to result in a greater number of identified apps, owing to differing platform search algorithms. The Apple App Store search algorithm is optimized by using a single keyword, while the Google Play store search algorithm is optimized by using string keywords [25]. For the full list of key terms searched, and both steps of the search strategy, see Textbox 2. The search will be rerun at the time of final manuscript preparation to ensure up-to-date coverage.

Textbox 2. Search strategy.

Step one:

"physiotherapy", "physio", "physical therapy", "physiotherapist", "physical therapist"

Step two:

"physiotherapy", "physio", "physical therapy", "physiotherapist", "physical therapist"

and

"assessment", "diagnosis", "digital", "eHealth", "evaluation", "examination", "exercise", "health promotion", "intervention", "physical activity", "plan", "care", "prevention", "rehabilitation", "screening", "pain", "self-management", "treatment", "support", "adherence"

In the first step, app store platforms will be searched using a predefined list of relevant key terms. This includes terms used commonly to describe physiotherapy or physiotherapists [31]. This step was based on previous reviews, which used keywords recommended by reputable sources [30]. The predefined terms used in this review have been obtained from the glossary provided by World Physiotherapy (formerly the World Confederation of Physical Therapy), the peak body for

physiotherapists globally (representing >650,000 physiotherapists worldwide with 122 member organizations). This glossary was developed to support policies, guidelines, and other resources, and to aid in consistency of terminology internationally.

For the second step, app store platforms will be searched again using string keywords. This search will be performed by combining terms from step one and terms used to describe common physiotherapy care, such as “physio” and “exercise”. The terms used in step two to describe physiotherapy care are also obtained from the glossary provided by World Physiotherapy. Terms synonymous with physiotherapy care were extracted based on title and descriptions provided. The authors agreed to include additional terms (“self-management”, “pain”, “treatment”, “support”, and “adherence”), given their obvious association with physiotherapy care.

To ensure feasibility, each key term search will be limited to the first 100 apps identified, as platforms continuously refresh the end of each search list to retrieve additional apps of less relevance [25].

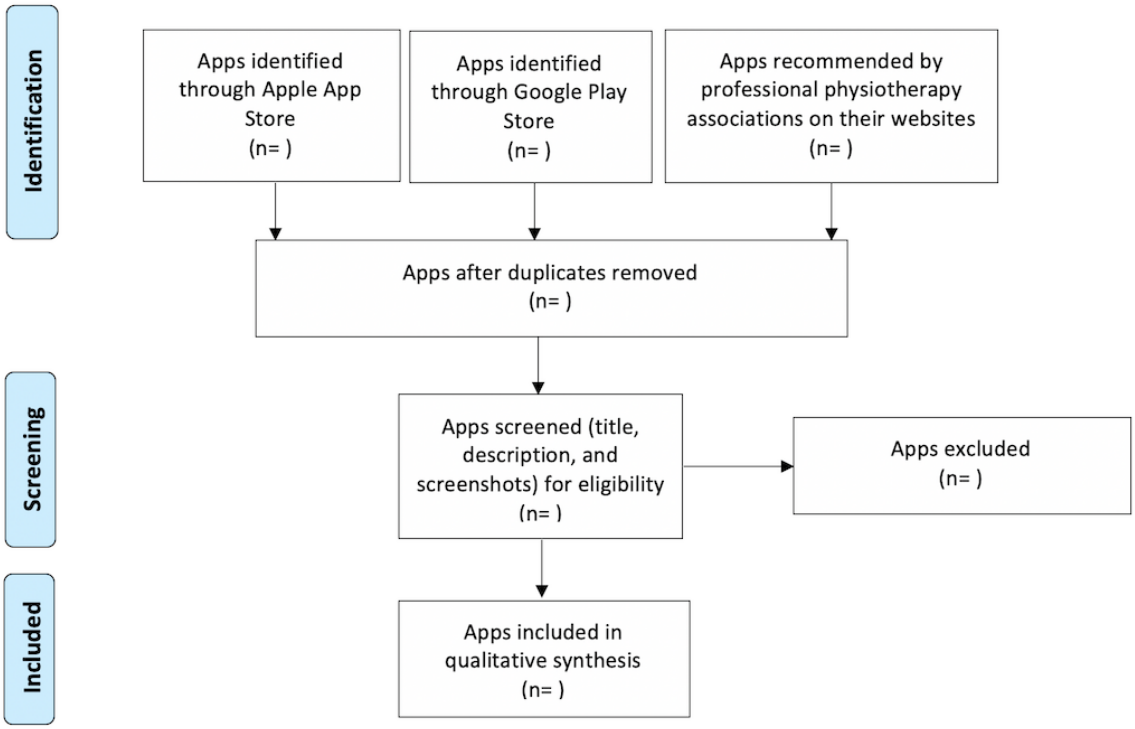
Additionally, websites of professional physiotherapy associations will be searched for the presence of specific pages or sections dedicated to any mobile apps that may be recommended for use by patients to support physiotherapy care. Multimedia Appendix 1 details the list of associations that will be searched, including their websites. These associations include the top 10 member organizations of World Physiotherapy based on number of members, with websites that are in English and do not require a paid membership or login to access.

App Records

Selection Process

The review flow is shown in Figure 1. The source search, as described above, will be performed by two reviewers (MM and PV). Duplicates will be removed, and the same two reviewers will perform the screening independently across 4 devices (2 Apple; 2 Android). This search will be based on the app title, its description, and screenshots included in the app store description [32]. Any disagreements will be resolved by discussion, and where consensus is not achieved, a third reviewer (PM) will decide. The resultant apps will be downloaded to the 4 mobile devices for use by the reviewers (MM and PV) [25].

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Extraction of Data Items

Two reviewers (MM and PV) will extract descriptive data from within the app store or within the app itself, based on information provided about the app, or within it, from its developers (ie, from the description and title of the app, “about this app” section, or any accompanying marketing or tutorial screenshots and videos). Where additional information is required (eg, whether a health care professional was involved in development), further information will be sought from the app’s source website if this is supplied in the app store description or within the app. Data will be added to an electronic spreadsheet (Excel, Microsoft Corporation) (Multimedia Appendix 2). The descriptive data to be extracted are detailed in Textbox 3.

Textbox 3. Descriptive characteristics that will be extracted from the included apps.

- App name
- App developer
- Size of app (MB)
- Focus of app (specific condition/bodily region or more general, eg, low back pain; specialty, eg, neurological physiotherapy)
- Targeted behaviors if described, such as exercise (stretching, strengthening, etc), monitoring of pain (data entry), physical activity (walking, cycling, etc)
- Country of origin
- Developer qualifications (ie, health care professional or other)
- Consultation/involvement of health care professional in development
- App date of creation
- App date of update (most recent) and current version (eg, version 1, version 2)
- Cost: payment method (one-off or subscription, in-app purchases), amount (Aus $)
- Platform (Apple App Store or Google Play)
- Consumer reviews (number, ratings from 0 to 5) and times downloaded (where available)
- Any mention in the title or description of app use in published peer-reviewed literature
- Data privacy policy provided in or via the app store

Additionally, both reviewers will interact with all functions of the included apps for a minimum of 10 minutes to become familiar with the apps. The purpose of engaging with the apps and their functionalities will be to code and score the following aspects.

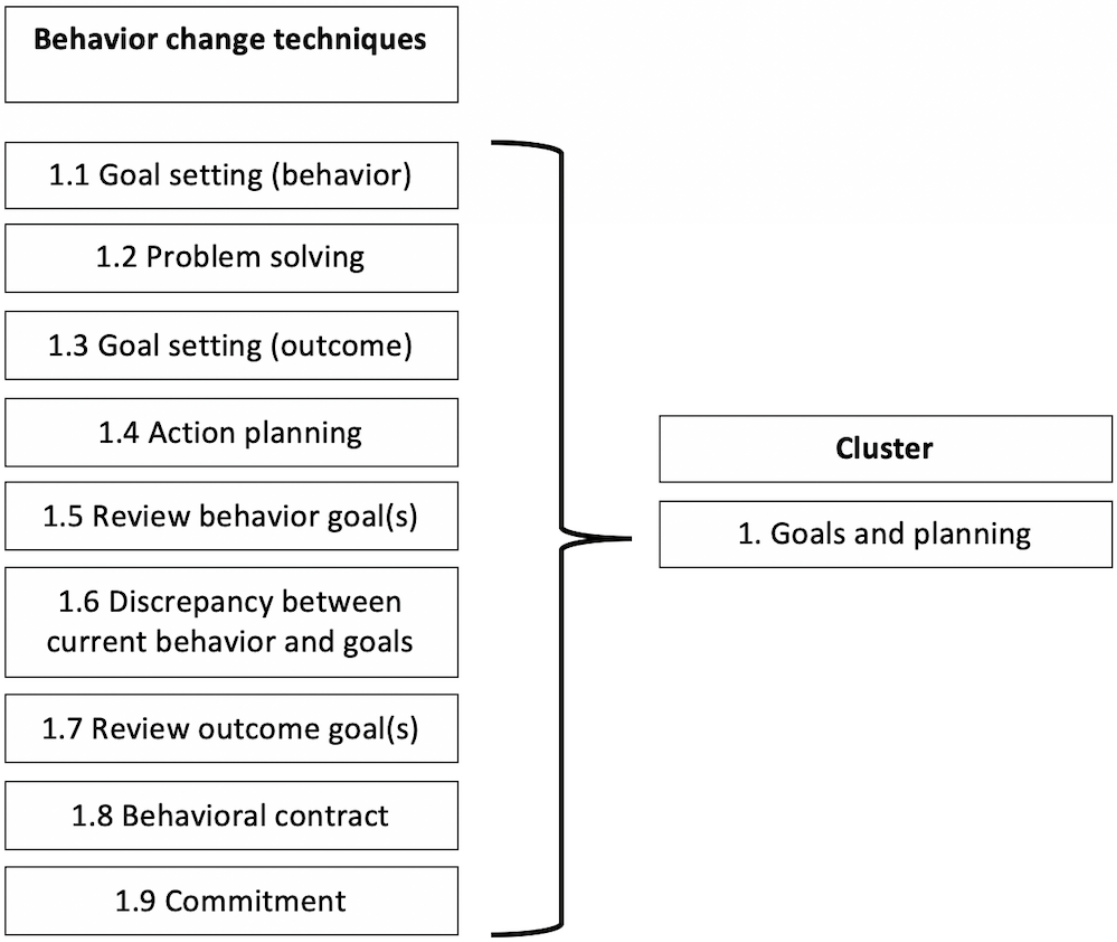
BCT Identification

Reviewers will identify and code included BCTs within the apps. Coding will be conducted by two reviewers (MM and PV) who have completed web-based training to receive certification for recognizing and coding BCTs [33]. This web-based training is based on a tutorial session model that improved coder agreement with expert consensus, confidence to assess BCTs, and coding competence [34]. A third experienced behavior change expert reviewer (JF), who was one of the original creators of the BCTTv1 and hence an expert in BCTs, will be involved to resolve any disagreements between the reviewers (MM and PV) via discussion.

Based on identified target behaviors within included apps, the reviewers will independently identify BCTs and categorize them into corresponding clusters in line with the BCTTv1 (Multimedia Appendix 3) [22]. The BCTTv1 is a framework of 93 clustered BCTs that was developed to ensure methodological rigor for the reporting on behavior change interventions. Using the BCTTv1, BCTs can be characterized, reported, or integrated into interventions more specifically and accurately [22]. Including the clusters that the identified BCTs belong to at this stage will support a more efficient process of clustering BCTs for further examination against the ABACUS scale [15]. The BCTTv1 was developed to provide a standardized terminology when classifying active intervention components as BCTs. In total, the BCTTv1 identifies 93 BCTs that are distinct, nonredundant and precise, and these are further organized into 16 clusters, with the BCTs in each cluster proposed to influence behavior through a similar causal pathway (Figure 2) [22]. Figure 2 provides an example of how the BCT taxonomy [22] will be used to code BCTs within a given app and organize them into their corresponding clusters.

Reviewers will also pilot BCTTv1 coding before use on the included mobile apps to ensure that an acceptable level of interrater agreement is achieved prior to this review (>0.80) [35]. This process will be completed on two apps that are not included in this review. If required, a “codebook” will be developed to clarify coding decision rules in relation to specific features of the apps.

Figure 2. Example of behavior change techniques organized into their corresponding cluster [22].



Mobile App Quality

The MARS will be used to appraise the quality of each app included in the review (Multimedia Appendix 4). The MARS measures four objective domains: engagement, functionality, aesthetics, and information. It also measures a subjective rating of quality. It contains a further subjective rating for app-specific perceived impact on targeted health behaviors (although this is not included in the total score). The total score and the four objective domains have high internal consistency, suggesting that the total score provides a reliable mHealth quality rating. This also suggests that the individual domains provide reliable measures of the quality of their targeted app components (eg, engagement) [27].

Two reviewers (MM and PV) will independently apply the 23-item MARS to the included mobile apps [27]. The MARS is a reliable, simple, highly cited, and widely applicable tool designed to assess the quality of mHealth interventions [27]. It was developed and piloted in a systematic manner by an expert multidisciplinary team that included both health professionals and mHealth developers. Both reviewers will complete MARS outcome training, in line with the recommendations of Stoyanov and colleagues [27]. Reviewers will also pilot the MARS before use on the included mobile apps to ensure that an acceptable level of interrater agreement is achieved prior to this review (>0.80) [35]. This process will be completed on 2 apps.

Disagreements will be resolved by discussion, and where consensus is not possible, a third reviewer will decide (PM). Interrater reliability will be calculated for the MARS total score and for all four individual objective domains between the reviewers using an identical method to the BCT coding reliability analysis.

Behavior Change Potential

The ABACUS will be used to evaluate the behavior change potential of the included apps (Multimedia Appendix 5) [15]. The ABACUS assesses four BCT clusters: knowledge and information, goals and planning, feedback and monitoring, and actions [15]. As this scale provides a validated framework for the identification and quantification of the behavior change potential of mobile apps, it provides an excellent measure and fit to suit our research objectives [15]. Based on the BCTs identified in apps in earlier steps of this review, two reviewers (MM and PV) will independently score the behavior change potential. BCTs identified in apps that are not covered by the ABACUS will also be recorded to capture those not already covered as part of the ABACUS outcome.

In line with the protocols for application of the BCT coding and MARS instrument scoring, the reviewers will pilot the ABACUS before use on the included mobile apps to ensure that an acceptable level of interrater agreement is achieved prior to this

review (>0.80) [35]. This process will be completed on two apps.

Disagreements will be resolved by discussion, and where consensus is not possible, a third reviewer will decide (JF).

Data Synthesis

As outlined in Textbox 3, app characteristics will be organized as proportion (percentage) for categorical data. This will include BCTs (and the behaviors they are targeting) and their corresponding clusters identified in the included apps; involvement of a health care professional in development (yes/no; role); the cost category (free, app purchase or in-app purchases); the platform (Apple App Store, Google Play, or both); the top apps for MARS total score as well as for the individual objective MARS domain scores; the top-scoring apps according to the ABACUS; and app focus (specific condition/painful region, or more general; specialty).

A matrix will be used to visualize the BCTs used to target different behaviors. Continuous data will be presented both as individual scores for each included app and also as mean (standard deviation), such as cost amount and consumer review ratings.

Results

The app store search and screening are expected to be completed in 2021. Data extraction and quality appraisal are expected to commence by November 2021. The study results are expected to be published in a subsequent paper in 2022.

Discussion

Expected Findings and Interpretations

Despite the potential of apps to support the delivery of physiotherapy care, there is little information about the range, content, and quality of mobile apps available for consumers in app stores. Understanding about (1) what apps are available, (2) the BCTs they use, (3) their quality, and (4) their potential to change behavior is still in its infancy. Our systematic review of apps in app stores will lay the groundwork to address these gaps, helping to identify limitations of currently available apps and providing guidance for researchers and app developers about how to improve or expand mobile apps intended for use by patients to better support physiotherapy care.

This review will also allow for comparison of the behaviors targeted by apps with the behaviors that physiotherapists routinely aim to target when delivering care [1]. Ultimately, the findings of this review will determine the likely utility of such apps for supporting physiotherapy care in patient users. At present, it should be noted that there is no agreed-upon validated overall MARS or ABACUS score that infers validity of these apps [15,27,36]. A recent study was conducted to validate the MARS scale [37]. This study combined mobile app quality data from several international MARS reviews, suggesting that overall MARS quality was moderate across a range of mobile health apps (mean score 3.74/5). The study further presents variable data for average quality scores across all domains of the MARS. This finding is echoed by the creators of the ABACUS [15]. The ABACUS does not presently propose to suggest a correlation between score and outcomes [15]. In a validation study of the ABACUS, the authors present an average score of 7.8 out of 21 for mobile health apps, suggesting a low to moderate number of BCTs in these apps. They suggest that the implications of the relative scores of apps remain to be ascertained. This is required to understand and infer the relative importance of these ratings. Although no final agreed scoring cutoffs are recommended, research may benefit from comparison against these mean scores [15,37].

Future research may involve a systematic literature review to evaluate the evidence for the efficacy of the apps that we identify. This research may seek to analyze the multiple features of mobile apps and their relationship to BCTs and clinical outcomes, to guide recommendations for their use. We further envision that using the findings from our review, physiotherapy researchers may be able to consider the mean quality and behavior change potential scores derived as a benchmark for apps in the physiotherapy care arena. The knowledge gained from this review will also support further clinical research, including formal randomized evaluations that use mobile app–based interventions, or potential enhancement of existing apps. It may also inform decision-making about whether to integrate apps into patient care in clinical practice. Importantly, this review will also identify market gaps that can stimulate future research in the development and evaluation of evidence-based and BCT-informed mobile apps.

Limitations

Although this study protocol is grounded in well-established and evidenced methods for searching, extracting, and evaluating information from within mobile apps in app stores, it is not without limitation. The proposed search strategy is designed to capture the most commonly searched and downloaded apps, while retaining feasibility by limiting the number of apps retrieved with each search to the first 100 [25]. Considering that in total, 210 searches will be performed (10 in step one and 200 in step two), as many as 21,000 apps could foreseeably be retrieved despite the limit. Furthermore, in developing the search strategy, we deliberately sought to include only apps that pertain to physiotherapy or physical therapy to further enhance the feasibility and specificity of the retrieval. Without this targeting, it is likely that the search will yield thousands of apps that are not relevant to physiotherapy care. However, we acknowledge that it is possible that our targeted selection criteria (that exclude apps that do not specifically mention physiotherapy) may miss some apps that physiotherapists recommend to patients. This review also follows other similar published systematic review research into health-based apps within app stores published in this journal, which identified 6579 apps [25]. It is possible that this cap limits other apps that would have been included without a search limit. However, based on this published approach [25] that included 18 apps for full analysis, we anticipate we will identify a similar number using our pre-selected terms. Additionally, to enhance coverage and to ensure that the retrieved apps are relevant to the outcomes of this study are not missed, we plan to search the websites of professional physiotherapy associations for any mobile apps that may be recommended for use by patients to support physiotherapy care.

As this systematic review of apps in app stores is not a systematic review of published literature, we will not be able to draw conclusions about the efficacy of the apps for changing patient behaviors or for improving outcomes of physiotherapy care. This may be an area to target for future research.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
List of World Physiotherapy member organizations to be searched for recommended mobile apps.
[DOCX File , 17 KB - resprot_v10i12e29047_app1.docx]

Multimedia Appendix 2
Descriptive data extraction spreadsheet.
[PDF File (Adobe PDF File), 103 KB - resprot_v10i12e29047_app2.pdf]

Multimedia Appendix 3
Behavior change technique coding spreadsheet.
[PDF File (Adobe PDF File), 329 KB - resprot_v10i12e29047_app3.pdf]

Multimedia Appendix 4
Mobile Application Rating Scale data extraction spreadsheet.
[PDF File (Adobe PDF File), 72 KB - resprot_v10i12e29047_app4.pdf]

Multimedia Appendix 5
App Behaviour Change Scale data extraction spreadsheet.
[PDF File (Adobe PDF File), 76 KB - resprot_v10i12e29047_app5.pdf]

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Abbreviations

ABACUS: App Behavior Change Scale
BCT: behavior change technique
BCTTv1: Behavior Change Technique Taxonomy version 1
MARS: Mobile Application Rating Scale
mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Developing an mHealth Application to Coordinate Nurse-Provided Respite Care Services for Families Coping With Palliative-Stage Cancer: Protocol for a User-Centered Design Study

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Abstract

Background: Patients living with palliative-stage cancer frequently require intensive care from their family caregivers. Without adequate community support services, patients are at risk of receiving inadequate care, and family caregivers are at risk for depression and poor health. For such families, in-home respite care can be invaluable, particularly when the services are flexible and staffed by trusted care providers, such as nurses. Other industries are using mobile apps to make services more flexible. However, few apps have been developed to coordinate nurse-provided respite care services, and to our knowledge, none have been designed in conjunction with families affected by cancer.

Objective: The aim of this study is to develop a mobile health (mHealth) app prototype for coordinating flexible and trusted in-home respite care services provided by nurses to families coping with palliative-stage cancer in Québec, Canada.

Methods: This user-centered design research comprises the core component of the *iRespite Services iRépit* research program. For this study, we are recruiting 20 nurses, 15 adults with palliative-stage cancer, and 20 of their family caregivers, from two palliative oncology hospital departments and one palliative home-care community partner. Overseen by an Expert Council, remote data collection will occur over three research phases guided by the iterative Information Systems Research Framework: Phase 1, brainstorming potential app solutions to challenging respite care scenarios, for better supporting the respite needs of both family caregivers and care recipients; Phase 2, evaluating low-fidelity proofs of concept for potential app designs; and Phase 3, usability testing of a high-fidelity interactive proof of concept that will then be programmed into an app prototype. Qualitative and quantitative data will be descriptively analyzed within each phase and triangulated to refine the app features.

Results: We anticipate that preliminary results will be available by Spring 2022.

Conclusions: An app prototype will be developed that has sufficient complimentary evidence to support future pilot testing in the community. Such an app could improve the delivery of community respite care services provided to families with palliative-stage cancer in Québec, supporting death at home, which is where most patients and their families wish to be.

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KEYWORDS

respite care; caregivers; cancer; neoplasms; user-centered design; mobile applications; palliative care; home care services; information systems research framework; hospice and palliative care nursing

Introduction

Background

Cancer is the leading cause of death in both Canada and Québec, with nearly 50% of Canadians developing the disease at some point in their lives [1,2]. Cancer symptoms often result in patients relying heavily on the skilled assistance of their family caregivers to continue living in the community, where most palliative care patients want to be [3-5]. However, without adequate support services, patients are at higher risk of receiving inadequate care and for costly hospital readmissions if their care becomes impossible to manage at home [6,7]. Simultaneously, family caregivers encounter a high risk of negative role consequences, including sleep deprivation, depression, reduced immunity, and early-onset mortality [6,8,9]. These risks are heightened during the palliative stage of cancer, when management of complex symptoms is prioritized over curative treatments [6,9].

As the number of cancer cases in Québec continues to rise [2], in-home respite care can be a crucial support service for families [7,10]. Respite care services offer opportunities for caregivers and care recipients to experience short breaks from each other and their caregiving/care-receiving family roles, while another person provides care [11,12]. Yet, based on our preliminary research, including literature reviews and discussions with directors of palliative and respite care organizations, the current landscape of these services in Québec is fragmented, with services often being difficult to access [5]. Most families accessing respite care services pay out-of-pocket, creating a potential affordability barrier [13,14]. Furthermore, respite care services often have inflexible hours, and they are typically staffed by home care providers who lack clinical expertise [10,15-17]. As a result of these barriers, respite care services are often underused, especially by families managing complex medical cases such as palliative-stage cancer [12,15].

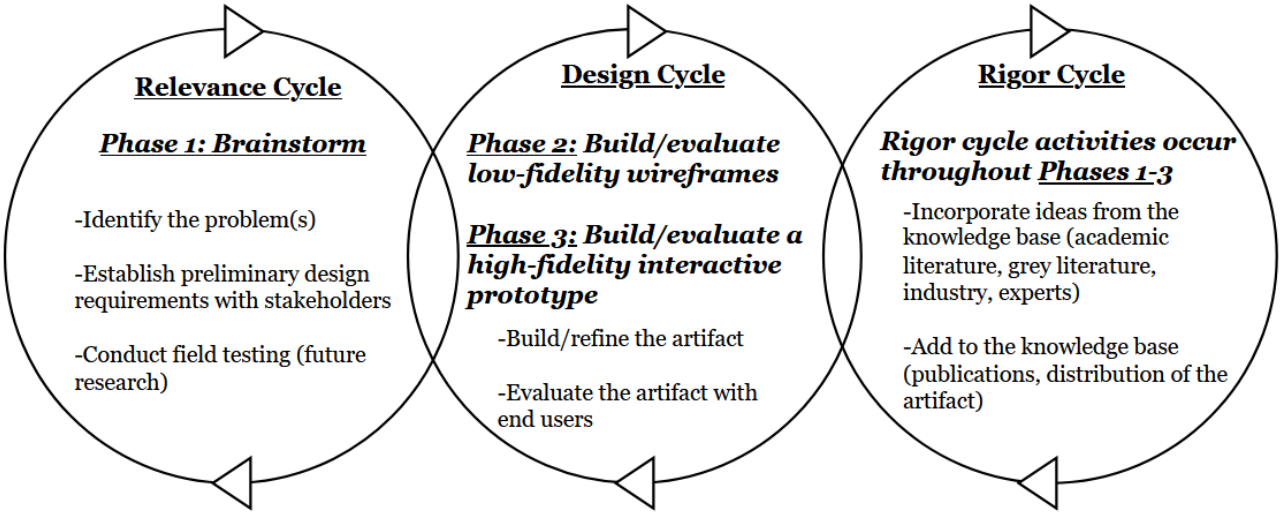
Families coping with palliative-stage cancer require easily scheduled respite care services staffed by trusted providers [15,16,18]. Nursing is consistently ranked as the most respected and trusted profession by the public [19]. With their extensive clinical and theoretical training, nurses may be best positioned to provide trusted respite care services to families coping with complex care conditions [16,18]. Furthermore, these nursing services could be flexibly scheduled with opportunities to personalize the services received, by mobilizing the capabilities of mobile health (mHealth) apps [20,21].

This context warrants the creation of a new mHealth app to optimize the flexible coordination of respite care services in Québec, beginning with nurse-provided services for palliative-stage cancer. Other service providers, such as Airbnb and DoorDash, are using apps to improve service coordination by facilitating communication and scheduling. However, we have not identified any apps in academia or industry that focus on providing respite care services to families coping with cancer. Moreover, we have only identified one app in the research literature for specifically coordinating nurse-provided respite care services for families affected by age-related chronic conditions [21]. Therefore, the aim of this study is to develop an mHealth app prototype for coordinating flexible and trusted in-home respite care services, provided by nurses to families coping with palliative-stage cancer in Québec. This study has been awarded a Rossy Cancer Network Care, Quality, and Innovation research fund grant (2020) to support the work described (Multimedia Appendix 1).

Study Design and Framework

Following ethical approval, a user-centered design study will be conducted over three phases to develop a rigorous and relevant app prototype [22-25]. An Expert Council composed of the research team and five key informants will oversee the study. Phase 1 will consist of brainstorming how an app might be used to address families' needs, given various respite care scenarios. Phase 2 will involve wireframing of several low-fidelity proof-of-concept app designs and prioritizing key features. Phase 3 will consist of designing and testing the usability of a high-fidelity interactive proof of concept (ie, the online design will be "clickable"), which will then be programmed into a functional app prototype. The cyclical Information Systems Research Framework [26] has been adapted to inform each study phase (Figure 1). The iterative and integrative cycles of this framework consist of the (1) relevance cycle**,** composed of research activities supporting end-user app refinement; (2) rigor cycle, where external knowledge and research is synthesized to inform the app design; and (3) design cycle**,** where the app is built into a functional prototype.

Figure 1. An adaptation of the Information Systems Research Framework [26], with its three methodological cycles, which will guide the proposed study.



Objectives

The objectives are as follows: (1) to explore participants' perspectives on the relevance of mHealth for the provision of nurse-provided respite care services, and (2) to design a rigorous and relevant proof of concept of a mHealth app for coordinating trusted and flexible respite care services, provided by nurses, to families coping with palliative-stage cancer, and (3) to conduct usability testing on the interactive proof of concept to support the development of a functional app prototype.

Description of the Potential App

The development of this app comprises the core component of the *iRespite Services iRépit* research program led by the manuscript authors. Depending on participants' needs identified throughout the study, the resulting app prototype could facilitate advanced and flexible scheduling for respite care with the same nurse-providers, or perhaps even offer on-demand scheduling. We predict that the final prototype will include features to support separate but integrated processes (ie, dashboards) focused on the needs of the two primary end users of the app: family caregivers and nurses. The dashboard for family caregivers will likely allow caregivers to sign up and directly schedule nurse-provided respite care services, with opportunities to request a nurse with specific skills (eg, experience caring for patients with a specific type of cancer) or payment option (eg, nurses whose services may be reimbursed through insurance). The dashboard for nurses will likely allow the nurses to sign up, describe their skills and certifications, and indicate their availabilities to provide respite care. However, since this study will incorporate ongoing end-user participation, we anticipate that our current predictions of the prototype features will differ significantly from the final prototype design.

Methods

Sampling Methods

Target Sampling Networks

The targeted web-based sampling networks will comprise the patient, family, and nursing networks of two palliative oncology hospital departments and one palliative home-care community partner in Montreal, Québec.

Participant Eligibility

The recruited sample will be composed of (1) family caregivers of adults living with palliative-stage cancer ("family caregivers"), (2) adults living with palliative-stage cancer ("care recipients"), (3) registered nurses ("nurses"), and (4) key informants.

Inclusion criteria for all participants will consist of adults (aged 18 years or older) who live in Québec. *Family caregivers* must self-identify as a family caregiver providing in-person care to a person diagnosed with cancer who is receiving palliative care services or is known to the palliative care teams of the target sampling networks. Family caregivers may also be up to 6 months post bereavement for a person diagnosed with cancer who had received palliative care services via the target sampling networks. *Care recipients* will be cancer patients who have a family caregiver providing them with regular in-person care. Care recipients will be either receiving palliative care services or known to the palliative care teams of the target sampling networks. *Registered nurses* will consist of nurses who are licensed in Québec and who have experience in providing home care, palliative care, respite care, and/or oncology care. *Key informants* will be identified by the research team as having relevant knowledge and expertise related to the management and deployment of the overall project.

Exclusion criteria for all participants will be that they (1) are not comfortable speaking and reading in English or French, (2) are unable to provide consent, or (3) do not have access to an internet-connected device capable of videoconferencing.

Sample Size

Sample Sizes for Phases 1 and 2 Focus Groups and Interviews

The participant numbers and research activities for each research phase are displayed in Multimedia Appendix 2.

A total of 30 participants (10 nurses, 10 family caregivers, and 10 care recipients) will be needed for the Phase 1 focus groups

and individual interviews. These same participants will be invited to participate in Phase 2 focus groups and interviews. Focus groups for formative user-centered design research should be large enough to encourage brainstorming among diverse, representative target end-users, but these groups should be no larger than 12 participants [23,27]. Therefore, a total of 10 participants for each major type of focus group (nurse, family caregiver, and care recipient), further divided into English or French focus groups, should offer appropriate focus group sizes for the proposed research.

Sample Sizes for Phase 3 Usability Testing

Phase 1 and 2 nurses and family caregivers will be invited to participate in Phase 3. An additional 5 nurses and 5 family caregivers will be recruited for individual usability testing to provide new perspectives on the interactive proof of concept [23,25], for a total of 15 nurses and 15 family caregivers participating in this phase. A sample size of 15 in each sample subgroup is estimated to identify at least 90% of usability problems in artifact design [28,29].

Expected Recruitment for This Study, Accounting for Attrition Rates

Attrition rates for palliative care studies that are conducted over the course of several months to over 1 year can range from 24% [30] to 63% [31]. Flexible research strategies, videoconferencing, and in-home data collection can increase enrolment and reduce attrition in the palliative care population [32-34]. Our research will be implementing these strategies of virtual and in-home data collection, which should improve participant enrolment and retention in our study.

We anticipate that family caregivers will have similar retention rates to those of care recipients, given how intertwined family caregiver and care recipient roles are [32]. Assuming a 50% attrition rate for each group of participants over the course of the study, we expect to recruit 15 care recipients, 20 family caregivers, and 20 nurses in total, to achieve the above sample sizes for each phase. With 5 key informants recruited for the Expert Council, the total sample size will be 60 participants recruited remotely across the study sites.

Recruitment

In the current context of COVID-19, this study has been adapted to recruit and collect data solely on the web. Purposive sampling will be used to recruit potential participants via the targeted nursing-, respite-, and cancer-related networks [23,35]. Collaborators within these target networks will be requested to share the bilingual study brief with nurse employees in the networks, as well as with families receiving palliative care services, via the associated social networks and institutional apps of the target networks (ie, the organizational social media accounts; email listservs; workplace communications; intranets; institutional apps; and on-site television screens). The study brief will contain bilingual links to the study Qualtrics contact forms for interested family caregivers, care recipients, and nurses to follow up with the team. Key informants will be directly recruited via email by the doctoral candidate on this study.

Eligible recruits who follow up using the Qualtrics contact form, as well as key informants who indicate interest, will be contacted by a member of the research team to set up a videoconferencing appointment to further explain the study. Once they have received information about the study purpose and scope, informed consent will be sought by all participants through a Qualtrics e-consent form.

Participants will be purposively chosen based on a few demographic questions that will be included in the consent forms. Family caregivers and care recipients will be chosen to achieve sample diversity according to age [36], cancer typology [37], and gender [36,38]. These factors are known to affect individuals' cancer caregiving and care receiving experiences [36-38], as well as their perspectives on mHealth supports [39,40]. Nurses will be purposively recruited to ensure a diversity of relevant perspectives on palliative care, oncology nursing, respite care, and home care services [41,42].

Purposively chosen participants will be contacted by email, a mutually agreed upon focus group or individual interview date will be arranged, and a videoconferencing invitation will be sent. Once the target size and diversity of the sample have been achieved, any additional eligible recruits will be placed on a waitlist for future inclusion, should participant attrition of the original 30 participants from Phase 1 occur.

Each participant will be offered a CAD $25 (US $19.55) gift card for either Visa or Mastercard following each interview or focus group that they choose to participate in [43]. A CAD $500 (US $391) stipend will be offered to each key informant at the end of the study, following their participation in the fourth Expert Council meeting and their ongoing advisement on the study. Key informants will be asked to provide a maximum of 15 hours of work over the course of the study [43].

Data Collection

Setting

Participant data will be collected remotely using videoconferencing software. All Expert Council meetings, focus groups, individual interviews, and usability test sessions will be video-recorded using Microsoft Teams or Zoom built-in recording functionalities, to record participant interactions with the different app designs. Although we will encourage key informants and participants to keep their video cameras on, they will be allowed to turn off their video cameras if they choose to do so. All meetings will also be audio-recorded for backup using a voice recorder. Focus groups, individual interviews, and usability testing sessions of the proof of concept should last between 60 to 90 minutes. The interviewer (Phases 1 and 2) or test session guide (Phase 3) will be PhD candidate ARC and/or a member of the research team. Another member of the research team will record field notes during data collection, recording observations about what participants see, say, and do [23,44].

Phases 1 to 3: Rigor Cycle 1 (Ongoing)

Literature and app store reviews are presently ongoing and will continue throughout the three phases with the support of a librarian scientist. Google Scholar and Google Search Engine alerts have been set up to receive notifications of new, relevant

data sources to further inform the design of the proofs of concept and the development of the functional app prototype.

Phase 1: Brainstorm mHealth Solutions to Respite Care Scenarios

Relevance Cycle 1: Determine Respite Care Problem Scenarios and Brainstorm Together

During the first Expert Council meeting, the key informants will review the study materials prior to the recruitment of other participants. The review of the study materials by the key informants will help ensure that the proposed study is designed to meet the needs of end users and other stakeholders. In this first meeting, the Expert Council will also determine 2 to 3 brief respite care video scenarios to be created using animation software, such as Doodly [45]. These videos will be discussed during the upcoming Phase 1 focus groups and interviews with nurses, family caregivers, and care recipients. Summary notes will be taken during all Expert Council meetings.

Next, 3 to 6 focus groups will be conducted in English and French with nurses (1 to 2 groups), family caregivers (1 to 2 groups), and care recipients (1 to 2 groups). Each participant will complete a web-based Qualtrics demographic survey prior to the meetings. Using semistructured interview guides, the interviewer will ask participants about their experiences and interests in respite care, their thoughts on mHealth apps to potentially support palliative-stage family caregiving, and any service coordination apps they currently like or dislike and why. Examples of the key questions and instructions for participants in each phase are listed in Multimedia Appendix 3. The whiteboard, chat, and other key features of the videoconferencing software will be used to help illustrate key points arising from the discussion and promote online engagement. Following these initial discussions, the interviewer will share various potential respite care scenarios that palliative-stage oncology families may find themselves in. Participants will discuss if and how mHealth apps might be used to support the families in those situations.

Finally, follow-up semistructured individual interviews will be conducted with a total of any 8 to 10 participants who agree to be individually interviewed, to gain a more in-depth understanding of participants' perspectives on mHealth, apps, and respite care [46]. These individual interview participants will be recruited from among participants who participated in the focus groups, or selected from eligible recruits who preferred to only participate in individual interviews.

Phase 2: Build and Evaluate Several Low-Fidelity Wireframes

Design Cycle 1a: Build Several Wireframes

The Expert Council will review the potential design features identified through the data collected and analyzed in Phase 1. This second Expert Council meeting will focus on achieving consensus as to which design features should be prioritized for the app design. A list of design feature requirements derived from the ongoing data collection, and the creation of a value versus feasibility matrix, will help guide these discussions [47]. Potential design features will be categorized by Expert Council members as being perceived to be (1) of high or low value to the end users and (2) of high or low feasibility to implement in practice. Features that are deemed completely unfeasible to implement and are perceived to be of very low value to end users will be excluded at this stage. All other features will be included, if these features do not prevent the inclusion of the highest priority features (ie, high value, high feasibility).

Using Figma rapid prototyping software [48], the research team will construct several wireframes (ie, low-fidelity/nonclickable proofs of concept) of potential app designs. These wireframes will be based on the Phase 1 rigor and relevance cycle data collected, as well as the Expert Council discussions prioritizing different design features. Creating different wireframes will help prevent premature anchoring of the final design, allowing for more diverse ideas to emerge in subsequent focus groups and interviews [23].

At this time, a member of the research team will begin programming the back-end software needed to make the proofs of concept into a functional app prototype. This software programming will be updated to incorporate new design features identified throughout data collection.

Design Cycle 1b: Evaluate Several Wireframes

Next, 3 to 6 semistructured focus groups will be conducted using interview guides designed for Phase 2. At each focus group, the interviewer will screenshare the low-fidelity Figma wireframes of each dashboard. All focus groups will review the wireframes of the family caregiver dashboard. The nurse focus groups will also review the wireframes of the nurse dashboards. Participants will be asked to share detailed feedback on the different proof-of-concept wireframe design features and their perceptions of the potential usefulness of the wireframes. Participants will be asked which of the low-fidelity wireframe features should be prioritized for a future app prototype.

Semistructured individual interviews will also be conducted with any 8 to 10 participants who agree to participate, to gain a deeper understanding of their perceptions of the wireframes. These individual interview participants will be recruited from among participants who participated in the focus groups or from eligible recruits who preferred to only participate in individual interviews.

Phase 3: Build and Evaluate an Interactive Proof of Concept of the App and Develop a Functional App Prototype

Design Cycle 2a: Build an Interactive Proof of Concept for Usability Testing

The Expert Council will have a third meeting to discuss the ongoing data analyses and the preferred prototype features of the Phase 2 participants. Figma will be used to construct a high-fidelity interactive ("clickable") proof of concept [48] based on the prioritized design features from the Expert Council meeting. The interactive proof of concept will be combined with Maze usability testing software [49] to create a URL to be shared with participants for online usability testing.

Design Cycle 2b: Evaluate the Usability of the Proof of Concept and Program the Final Prototype

Design cycle 2b will be used to quantitatively assess the usability of the high-fidelity, interactive proof of concept in individual test sessions using the Maze usability testing link with the two primary end-user groups: family caregivers and nurses. All new participants will be asked to fill out the Qualtrics demographic survey in advance prior to the meeting, after providing e-consent. Participants will be asked to share their screens, so their assessments of the proof of concept will be video-recorded by the videoconferencing software. Family caregiver participants will be asked to assess the family caregiver dashboard, and nurse participants will be asked to assess both dashboards.

The Maze software will collect usability metrics for effectiveness and efficiency of the proof of concept. Effectiveness will be assessed based on (1) success rate (ie, the proportion of participants who successfully click through the proof-of-concept tasks); (2) the type of errors made by participants while navigating the different features of the proof of concept; and (3) the number of errors made by participants while navigating the proof of concept [49,50]. Efficiency will be measured based on (1) the time spent on specific steps while using the proof-of-concept dashboards and (2) the total time taken for participants to use the proof of concept [49,50].

These data will be analyzed to further refine the interactive proof of concept using Figma software. *Refinement #1* will occur after 7 nurse test sessions and 7 family caregiver test sessions have been conducted. *Refinement #2* will occur after the final 8 nurse test sessions and 8 family caregiver test sessions have been conducted. The new recruits for Phase 3 will be purposively distributed to participate either before Refinement #1 or before Refinement #2, to achieve a roughly equal mix of new perspectives (ie, new recruits for Phase 3) and old perspectives (ie, participants from Phases 1 and/or 2) during Phase 3 data collection. Participants will also be distributed to achieve a roughly equal mix of perspectives from participants with varying levels of comfort with technology based on participants' demographic questionnaire responses.

The fourth Expert Council meeting will (1) review the findings from Phase 3 and (2) determine the final design features to prioritize for building into the functional app prototype being programmed in parallel, based on general consensus within the Expert Council.

During *Refinement #3*, the interactive proof-of-concept design will be refined based on the Expert Council meeting decisions, and these features will be programmed into the functional app prototype.

Data Analyses

Data collection and analyses will occur simultaneously, with ongoing discussion with members of the research team. Qualitative data sources will include focus group and individual interview transcriptions; observations and field notes taken during all Expert Council meetings and participant interviews and focus groups; rigor cycle literature review findings; and screenshots of the proof of concept. These data sources will be copied into Excel (Microsoft Corporation) for qualitative content analysis to determine key design features for the app prototype [23,51]. Quantitative demographic survey data will be analyzed using descriptive statistics and displayed in a demographic data table to offer a rich presentation of the characteristics of the participants who informed the app design. Descriptive statistics will also be used to analyze the Maze usability data for the interactive proof of concept. These data will help the Expert Council decide if more data need to be collected to improve the proof of concept prior to the final programming of the functional app prototype.

Ethical Considerations

The ethical review of this study is pending (McGill University Health Centre, MP-37-2022-7986). There is minimal personal risk involved in participating in this study. In the event that family caregivers or care recipients become distressed, the note-taking member of the research team will ask the participant via a private chat box message if they would like to take a break from the meeting [34]. This research team member will also suggest that the participant follow up with their primary treating clinician at the study site [34]. We will have a list of available resources on-hand for cancer support recommended by the study sites.

Results

The estimated milestones include (1) 4 months for study setup (eg, ethical approval, hiring and training of personnel, and establishing of the Expert Council key informants); (2) 3 months for Phase 1 recruitment, data collection and analysis; (3) 3 months for Phase 2 recruitment, data collection, and analysis; (4) 3 months for Phase 3 recruitment, data collection, and analysis; and (5) 2 months for final programming of a functional app prototype and knowledge translation. We anticipate that preliminary results will be available by Spring 2022.

Discussion

We are proposing a new solution to eventually address a significant gap in access to care, namely, access to trusted and flexible respite care services, to ameliorate the current fragmented services rendered to families coping with palliative-stage cancer. To our knowledge, this is the first app being designed to coordinate nurse-provided respite care services to families coping with palliative-stage cancer. A few scholars [21] and industry leaders [52,53] are designing apps for coordinating other forms of respite care services, such as services staffed by nonclinician providers for families coping with age-related chronic health conditions. However, based on our ongoing literature and app store searches, an app for coordinating nurse-provided respite care services, designed with and for palliative oncology families, has not been developed to date.

The proposed research is clinically important because palliative-oncology families require uniquely intensive and skilled respite care services to allow their dying loved ones to remain at home [7,15,41]. Respite care providers without nursing or palliative care training likely do not have these skills, limiting

their ability to meet the respite care needs of families coping with palliative-stage cancer [7,16]. Without trusted, flexible, and accessible respite care services, achieving death at home can become an impossible endeavor [5,15]. However, an app for improving the coordination of respite care could have features that would make this endeavor possible. Such features could include flexible scheduling options and choosing among diverse skill sets by the trusted nurse providers of care. These mHealth capabilities could improve the support services rendered to families wishing to support death at home, thus improving the quality of life of patients and their families.

The proposed research is also methodologically important because our rigorous user-centered design study will help to ensure the sustainability of the proposed app-based respite care service by focusing on the needs of end users [22-25]. This app will be collaboratively developed with our transdisciplinary research team of nurse scholars, computer scientists, institutional and community partners, and key informants. With a functional app prototype designed with end users, additional grant applications will be submitted to support future pilot testing and to assess further relevance of the prototype in the field [26]. Although the initial findings will be contextualized to Québec, this innovative methodological approach may be transferable to other populations and settings. Future research could explore the potential of this respite care app to support families with other complex health conditions in other provinces, leading to improved coordination of respite care services across Canada—services that are centered on families' individualized respite care needs.

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Authors' Contributions

ARC conceived the project for her doctoral studies. AT and AA provided significant input for the preliminary study design, with all coauthors contributing critical refinements to the protocol. ARC and AT drafted the grant and this manuscript, with all coauthors contributing feedback for improvement.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Documents confirming the grant support and peer review process by the Rossy Cancer Network Cancer Care Quality and Innovation Research Fund (2020).
[PDF File (Adobe PDF File), 7159 KB - resprot_v10i12e34652_app1.pdf]

Multimedia Appendix 2
Research activities and participant numbers for each phase, displayed in tabular form.
[PDF File (Adobe PDF File), 719 KB - resprot_v10i12e34652_app2.pdf]

Multimedia Appendix 3
Key questions and instructions for participants during each research phase.
[PDF File (Adobe PDF File), 209 KB - resprot_v10i12e34652_app3.pdf]

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Abbreviations

ARCC: Canadian Centre for Applied Research in Cancer Control
mHealth: mobile health

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Proposal

Conjugation of Silver Nanoparticles With De Novo–Engineered Cationic Antimicrobial Peptides: Exploratory Proposal

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Abstract

Background: Cationic antimicrobial peptides have broad antimicrobial activity and provide a novel way of targeting multidrug-resistant bacteria in the era of increasing antimicrobial resistance. Current developments show positive prospects for antimicrobial peptides and silver nanoparticles (AgNPs) individually.

Objective: The primary objective is to propose another method for enhancing antimicrobial activity by conjugating AgNPs with cationic antimicrobial peptides, with a subsequent preliminary assessment of the minimum inhibitory concentration of multidrug-resistant bacteria. The secondary objective is to evaluate the safety of the conjugated compound and assess its viability for in vivo use.

Methods: The proposal involves 3 stages. First, WLBU2C, a modified version of the antimicrobial peptide WLBU2 with an added cysteine group, needs to be synthesized using a standard Fmoc procedure. It can then be stably conjugated with AgNPs ideally through photochemical means. Second, the WLBU2C-AgNP conjugate should be tested for antimicrobial activity according to the Clinical & Laboratory Standards Institute manual on standard minimum inhibitory concentration testing. Third, the cytotoxicity of the conjugate should be tested using cell lysis assays if the above stages are completed.

Results: I-TASSER (iterative threading assembly refinement) simulation revealed that the modified peptide WLBU2C has a secondary structure similar to that of the original WLBU2 peptide. No other results have been obtained at this time.

Conclusions: The addition of AgNPs to already developed de novo–engineered antimicrobial peptides provides an opportunity for the development of potent antimicrobials. Future prospects include emergency last-line therapy and treatment for current difficult-to-eradicate bacterial colonization, such as in cystic fibrosis, implantable medical devices, cancer, and immunotherapy. As I do not anticipate funding at this time, I hope this proposal provides inspiration to other researchers.

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KEYWORDS

antimicrobial peptides; silver nanoparticles; ESKAPE pathogens; research proposal

Introduction

There is no longer doubt that present day bacteria are developing increasing resistance to our currently available group of antimicrobial agents [1]. Extensive research has already been performed in the hopes of creating more strategies to counter the increasing resistance of bacteria [1-4]. One such line of study is on cationic antimicrobial peptides (CAPs). CAPs are ubiquitous in nature, being present in all living species [5]. In antimicrobial studies, CAPs are of interest due to their broad antimicrobial spectrum and cellular selectivity [6]. Their novel mechanisms of action, including both membrane and cellular interactions, provide good prospects for drug development against resistant bacteria in a variety of applications [6,7]. WLBU2 is a de novo CAP engineered thematically from the study of naturally occurring CAPs and virally derived peptides called lentivirus lytic peptides from human immunodeficiency

virus type 1 [8,9]. It was demonstrated that WLBU2 exerts great antimicrobial activity with the ability to inhibit the growth of multidrug-resistant bacteria, while being safe for mammalian cells [8]. In tandem, the element silver has also been found to have antimicrobial properties. It has practical applications in many health care technologies globally at present, and it is being increasingly studied for its potent antimicrobial and antibiofilm activity [10]. Silver affects bacterial cells by way of membrane disruption and disruption of internal cell processes, similar to CAPs (multiple sources as cited in the report by Franci et al [10]). Given that there are many similarities between WLBU2 and silver nanoparticles (AgNPs), including activity against biofilms and multidrug-resistant bacteria, I propose the conjugation of WLBU2 and AgNP via an additional cysteine amino acid group [1,11,12]. It has been shown that conjugation of AgNPs with proteins has the possibility to negate the negative side effects of both components while retaining the beneficial effects [8,13,14]. This proposal hopes to evaluate the synergistic benefit of AgNPs and WLBU2, and provide points of thought and consideration for future researchers who may find this article useful.

Methods

Synthesis of WLBU2C

This study proposes the synthesis of the conjugate WLBU2-AgNP starting with a modified version of WLBU2 (hereafter called WLBU2C) (wheel: CRRWVRRVRRWVRRVVRVVRRWVRR). The development of this peptide is theoretically proposed by assessing the structure of WLBU2C through I-TASSER (iterative threading assembly refinement) simulation and an alpha helical diagram (Figure 1 and Figure 2) to retain amphipathicity and secondary structure [15-17]. Synthesis should be performed with the standard Fmoc procedure, after which the product should be purified with reversed-phase high-performance liquid chromatography using a C18 Vydac column as the stationary phase and be confirmed with mass spectrometry. The secondary structure can be evaluated with circular dichroism (CD) in the presence of phosphate buffer with saline (PBS) for an aqueous environment or 30% trifluoroethanol for a membrane mimetic environment [8]. The addition of cysteine as the conjugation point between the proposed antimicrobial peptide and AgNP has been theorized through review of prior studies in which cysteine group conjugation provided enhanced binding and stability with increased activity against *Klebsiella pneumoniae* [18,19].

Figure 1. Three-dimensional model from I-TASSER (iterative threading assembly refinement) simulation of the secondary structure of the WLBU2C peptide.

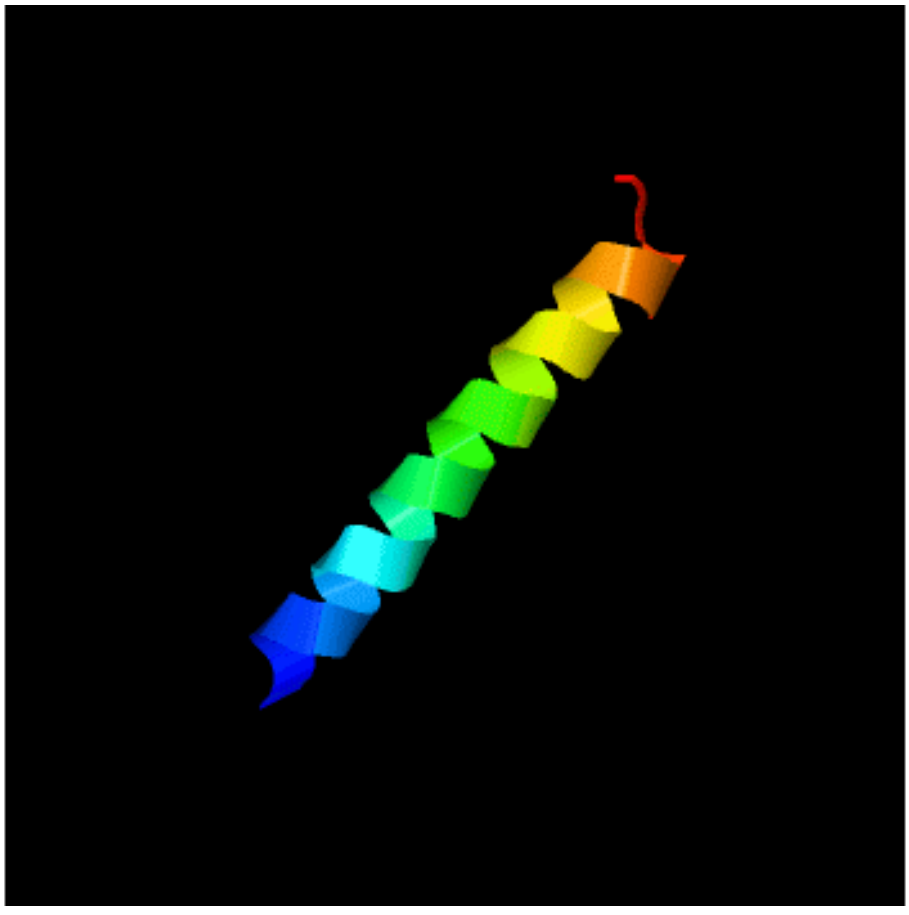
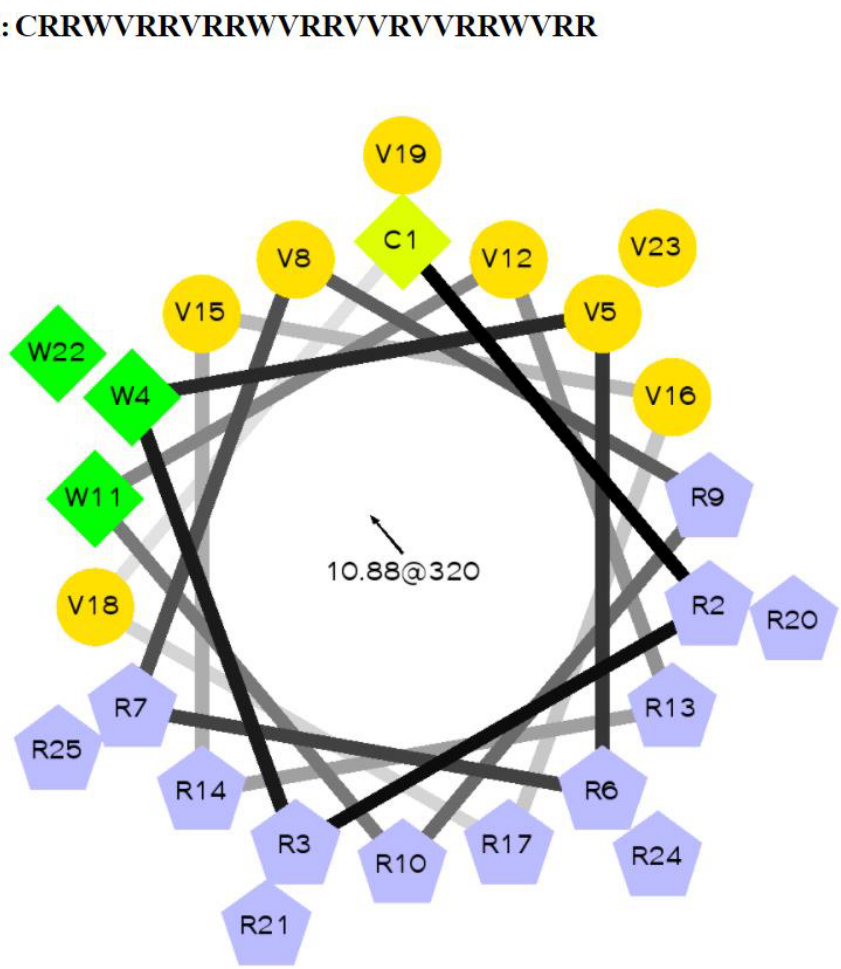


Figure 2. Alpha helical diagram of the proposed WLBU2C peptide shows retained amphipathicity.



Synthesis of WLBU2C-AgNP

This study proposes the synthesis of WLBU2C conjugated to AgNP (hereafter called WLBU2C-AgNP) by means of a photochemical method, as similarly described for LL37@AgNP by Vignoni et al [14]. The method specifically adapted for this research involves the use of deoxygenated silver nitrate ($AgNO_3$), Igracure 2959 as a photo initiator, and WLBU2C in sliding scale concentrations from 0 to 100 µM to test for the optimal concentration [20]. UVA lamps equivalent to Luzchem CCPV4 photoreactors should be used at 25°C, and the reaction can be monitored with UV-visible absorption spectroscopy. Based on the literature, the surface plasmon band is expected to be centered at around a wavelength of 395 to 425 nm [14]. According to a review of the above studies, it is expected that the absorption will increase in the UV-visible spectrum until all the Ag^+ molecules are reduced.

After synthesis and purification with a dialyzer of appropriate size, transmission electron microscopy and dynamic light scattering (DLS) should confirm the presence of a larger DLS particle size due to the binding of the proteins around the nanoparticles. The secondary structure can be evaluated by CD, unless the nanoparticles interfere with CD resolution.

Antibacterial Activity Evaluation

Testing of antibacterial activity is suggested against ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species). Bacterial killing can be evaluated in the setting of potassium phosphate buffer and PBS by the dilutional assay method, in which WLBU2C-AgNP (0-100 µM) is mixed with bacteria (diluted to 1×10^6 colony forming units/mL) at 37°C for 60 minutes, and the mixture is then plated and incubated (appropriate conditions and time) [8]. Subsequent analysis may be performed with spectrophotometry at 600 nm [21]. Further information regarding the tests for the minimum inhibitory concentration and minimum bactericidal concentration can be obtained from the Clinical & Laboratory Standards Institute manual for antibacterial susceptibility testing.

Cytotoxicity Evaluation

Once antimicrobial activity has been assessed, cytotoxicity can be evaluated against human red blood cells and normal cells, such as keratinocytes and fibroblasts, to explore practicality. The cytotoxicity protocol can be derived from the procedures performed by Deslouches et al [22]. Briefly, a red blood cell hemolytic assay can be performed in PBS by changing the WLBU2C-AgNP concentration. Further cytotoxicity can be assessed by culturing keratinocytes and fibroblasts in Dulbecco

Eagle's medium and performing tests with a range of WLBU2C-AgNP concentrations, as well as an MTT assay for metabolic activity.

Results

This proposal is currently theoretical and does not have reportable results other than structure simulations as listed above, where it was found that the modified WLBU2C peptide has a secondary structure similar to that of the original WLBU2 peptide. I do not anticipate proactively obtaining funding in the future due to insufficient resources.

Discussion

Limitations

Anticipated limitations of this study include the short half-life of CAPs and associated cytotoxicity in higher concentrations, which may be counteracted with immobilization of the peptide onto solid surfaces [23]. Silver might be toxic to mammalian cells and the environment [10]. As all proposed approaches are theoretical, there is no guarantee to achieve the expected outcome.

Conclusions

Recently, more research has been reported regarding the combination of antimicrobial peptides with AgNPs, with positive results [18,24]. This proposal provides another idea to efforts for counteracting antimicrobial resistance. It has been hypothesized that the conjugation of a de novo–engineered antimicrobial peptide and AgNP may increase the antibiofilm effect against multidrug-resistant bacteria while retaining selectivity and safety. The present method involving cysteine group modification on the antimicrobial peptide for conjugation with AgNP has to my knowledge not yet been published for de novo–engineered CAPs. De novo–engineered antimicrobial peptides are still undergoing active research to increase their potency while balancing cytotoxicity. The conjugation of improved peptides with AgNPs would provide a second degree of freedom to their functions, hopefully unlocking opportunities to develop more potent antimicrobials. If further studies on this topic are successful, future long-term prospects may include emergency last-line antibiotic therapy and treatment for difficult-to-eradicate bacterial colonization, such as in cystic fibrosis, implantable medical devices, cancer, and immunotherapy [25]. I encourage further studies on this topic to better understand the proposed theories. As I do not anticipate proactively obtaining funding for this idea in the future, I hope this proposal provides inspiration to other researchers.

Conflicts of Interest

None declared.

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Abbreviations

AgNP: silver nanoparticle
CAP: cationic antimicrobial peptide
CD: circular dichroism
DLS: dynamic light scattering
PBS: phosphate buffer with saline

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Proposal

Assessing Patient Engagement in Health Care: Proposal for a Modeling and Simulation Framework for Behavioral Analysis

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Abstract

Human behavior plays a vital role in health care effectiveness and system performance. Therefore, it is necessary to look carefully at the interactions within a system and how a system is affected by the behavioral responses and activities of its various components, particularly human components and actions. Modeling patients' engagement behaviors can be valuable in many ways; for example, models can evaluate the effects of therapeutic interventions on health improvement, health care effectiveness, and desired outcomes of changing health lifestyles. Modeling and simulation (M&S) help us to understand the interactions within a whole system under defined conditions. M&S in patient behavior analysis involve models that attempt to identify certain human behaviors that most likely have an impact on health care operations and services. Our study's overall aims are (1) to investigate the impacts of patients' engagement and various human behavior patterns on health care effectiveness and the achievement of desired outcomes and (2) to construct and validate a framework for modeling patient engagement and implementing and supporting patient management best practices, health policy-making processes, and innovative interventions in health care. We intend to extract routinely collected data of different parameters from general patients diagnosed with chronic diseases, such as diabetes. Our plan is to design data sets and extract health data from a pool of >4 million patient records from different general practices in England. We will focus on the primary electronic medical records of patients with at least 1 chronic disease (>200,000 records). Simulation techniques will be used to study patient engagement and its impact on health care effectiveness and outcome measures. The study will integrate available approaches to develop a framework for modeling how patients' behaviors affect health care activities and outcomes and to underline the characteristics and salient factors that operational management needs to be aware of when developing a behavioral model for assessing patient engagement. The M&S framework, which is under development, will consider patient behavior in context and the underlying factors of human behavior with the help of simulation techniques. The proposed framework will be validated and evaluated through a health care case study. We expect to identify leading factors that influence and affect patient engagement and associated behavioral activities and to illustrate the challenges and complexities of developing simulation models for conducting behavioral analyses within health care settings. Additionally, we will assess patients' engagement behaviors in terms of achieving health care effectiveness and desired outcomes, and we will specifically evaluate the impacts of patient engagement activities on health care services, patient management styles, and the effectiveness of health interventions in terms of achieving the intended outcomes—improved health and patient satisfaction.

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KEYWORDS

modeling and simulation; behavioral analysis; patient engagement; behavioral factors, health care; human factors; outcomes; patient health; health policy; chronic diseases; behavioral model

Introduction

Background

Behavioral analytics is the study of behavioral aspects through operational research methods for modeling, problem solving, and decision-making support [1]. Behavioral patterns can influence problem solving and policy making and enable modelers to mimic and study real-world situations.

Human behavior can alter the performance of any system with multi-stakeholder processes. An overall analysis of human behavior entails models of an entity, social interactions, and connections within a system [2]. It is therefore essential to incorporate human behavioral factors into the modeling of complex systems, such as health care.

Modeling and simulation (M&S) have been shown to be suitable methods for mimicking real-world scenarios and assisting researchers and practitioners in the manufacturing field and various other sectors [3,4]. M&S techniques lend themselves to the conceptual representation of the system at hand and its implementation via a computer model. By applying suitable methods in studies, M&S methods are used to represent different settings and real-world situations and determine the results of a specific state.

M&S have been shown to be useful methods for addressing health care—a complex and uncertain system involving a range of emergent behaviors that occur daily. Health care systems involve various actors and stakeholders and include diverse policy makers and practitioners, such as health sector regulators, patients, nurses, and physicians [5]. The features of M&S can be applied to health care systems to assess interventions and outcomes by incorporating human behaviors and human factors.

A wide range of M&S applications for enhancing ongoing developments in policy making and services continue to emerge. For instance, the use of the hybrid modeling approach has been shown to support short-term decision-making in emergency health care by helping emergency service facilities avoid overcrowding [6]. In the case of stroke care and within the context of precision medicine for stroke, a hybrid modeling approach has been shown to be the most beneficial [7]. The application of hybrid modeling has also been observed in the field of cardiovascular diseases; hybrid modeling approaches have been used to assess integrated care for challenging and complex diseases to offer comprehensive tools for decision-making [8].

A combination approach of using simulation and machine learning techniques, for example, has also been found to aid policy makers in designing care pathways and developing effective health care policies. The purpose of this approach is to use machine learning to provide valuable support in the development of simulation models [9]. Moreover, machine learning–based extractions, along with digital health tools and electronic health records, can improve health care providers' communications in the provision of precision care and services.

M&S aim at providing modelers with tools for assessing system performance under different conditions via a top-down approach and can be helpful in predicting behaviors and possible outcomes. Furthermore, M&S can offer modelers the ability to mimic real-world problems, for which the derivation of causal relationships is vital [10]. M&S have been shown to have the potential to improve health care services in several health care areas, such as health risk assessment and cost-benefit analysis and policy evaluation [11]. Moreover, combining analytical methods and simulation techniques can be useful in studying the effects of lifestyle risk factors, assessing the quality of services, and predicting lifestyle risk behaviors linked to prevalent chronic diseases [12,13].

The M&S of such health data are conducted to identify associations among risk factors and promote selective targeting and the use of behavioral interventions among health care providers. However, the interpretation of such models might not be easy if too many variables are involved, and modelers may choose to simplify their approach in the early stages of model development to gain a full understanding of the problem under study.

Different simulation approaches have been incorporated to study the effect of population changes on the demand for health care services [14]. Thus, simulation models for behavioral analytics can be used in the analysis of patient behavior to enhance decision-making and improve health care effectiveness (ie, with the help of hybrid approaches).

Modeling human behavior involves considering different activities within the system under study, primarily activities related to cognitive processes and systems' dynamic evolution (ie, mental activities resulting from the time-dependent interactions of humans and related activities) [4]. When modeling a system, such dynamic interaction needs careful assessment to ensure that human factors are weighted with external factors.

Brailsford and Schmidt [15] carried out research on incorporating human behavior in models of health care systems by using an M&S approach. They illustrated how simulation had been used to paint a picture of all of the parameters that contributed to the prevalence of disease by monitoring patients' behaviors, including individuals' characteristics. Furthermore, in their field study, which analyzed infectious diseases and infection control, Talib et al [16] noted that the spread of infections and diseases, such as HIV infection and AIDS, does not solely rely on physiological factors but also relies on behavioral aspects. This explains why it is essential to not ignore human behavior when developing models and applying M&S methods. Subsequently, if behavioral factors are overlooked, simulation results may not do much to help researchers and practitioners understand real-world situations.

When applying behavioral analysis approaches to model development, representations of various components of the system under study can provide insights for understanding how the system's various factors are interconnected and how it responds to changes over time. M&S methods have been typically used to account for social, economic, and environmental changes, as modeling provides insights into system behaviors and possible outcomes.

In general, M&S methods comprise evidence-based techniques and tools that can provide important insights toward gathering the evidence required to improve overall performance and aid policy settings, including sectors like health care [17]. M&S have been used to assess risk factors, including human factors, and to conduct behavioral analyses for establishing the interdependencies that exist among various components of complex systems via a process that focuses on interconnectivity and changes that occur over time [1,18-20].

In the health care sector, M&S have been effectively used to study crucial public health issues [21-23]. It has become evident that using M&S for behavioral analytics can be key in enabling modelers to recommend service improvements, of which the results can be directly reflected by patients' satisfaction and well-being. Our research focuses on the application of M&S to the analysis of patient behaviors within health care systems and aims to demonstrate how this method can help with the evaluation of health care effectiveness for suggesting service improvements.

Objectives

Patient engagement pertains to patients being active in decisions and actions related to their own health and preferences toward enhancing their satisfaction with the health care system and improving health care outcomes. In health care decision-making, patient engagement is described as the approach whereby health care staff members engage with patients as equal partners to make healthy choices based on the best health care evidence available and patients' informed preferences and care expectations [24]. The experience of engagement is a key qualifier of the exchanges between patients and their health care providers [25].

The overall goal of our study is to identify the leading factors underpinning patient engagement activities to achieve a proper understanding of the relationship between patient engagement experiences and health care effectiveness in terms of achieving the desired outcomes of health interventions and healthy lifestyles. Gauging the behavioral aspects of patients' engagement or disengagement activities can contribute to showing how patients respond to care plans and the delivery of health care interventions and can therefore help with optimizing health care outcomes. Hence, the main objectives of our study are as follows:

- To study the impact of patients' engagement behaviors on health care effectiveness and desired health outcomes
- To identify factors that drive and influence engagement and disengagement in patients with chronic diseases (ie, with a focus on diabetes)
- To develop a generic M&S framework for patient behavior analysis

As one of the most prevalent chronic diseases, diabetes can have long-term effects and induce profound changes to patients' lifestyles and behaviors. Patients with chronic diseases tend to exhibit various engagement behaviors and practice different lifestyles. Thus, they may or may not be willing to follow and be involved in all necessary actions within their care management plans. Therefore, our study sets out to use the M&S framework for behavioral analysis and incorporate human behavior in modeling to further demonstrate how patients' engagement behaviors may influence health care effectiveness and desired health care outcomes.

Methods

Study Type

The provided data will be analyzed to identify the leading behavioral factors of patient engagement and determine how engagement behaviors can affect health care effectiveness and the desired outcomes of following health care plans for chronic disease management and treatment, such as diabetes care plan outcomes. The following aims will be put forward: (1) to identify the causal influences and interdependencies in relationships between patients' behaviors and health care effectiveness and between patients' behaviors and the desired outcomes of following required healthy activities and (2) to evaluate the association between patients' engagement patterns and the achievement of effective patient care management and patient satisfaction. A hybrid M&S approach will be used to study patient behavior in the highly complex health care system and inform health care practitioners and stakeholders.

Appropriate and widely used M&S methods will be used to explore interdependencies among system parameters. M&S models have so far been used in health care systems to primarily analyze specific long-term diseases [26], virus spread and transmission [27,28], patient flow in accident and emergency (A&E) departments [29,30], and various policy evaluations [31,32], and little attention has been paid to behavioral factors and their influence. We intend to conduct M&S to potentially identify leading factors that influence and affect patient behavior and engagement.

The proposed hybrid M&S approach will involve the combination of qualitative system dynamics (QSD) with M&S techniques and be used to develop a generic hybrid M&S framework for behavioral analysis in health care. The hybrid M&S approach will be used in M&S framework development to help provide a deeper understanding of how human behavior affects health care outcomes in models. QSD can represent specific system dynamics and mediate the qualitative expression of system dynamics mechanisms and any possible quantitative representations.

System dynamics modeling will be used as a simulation technique to explore interdependencies among parameters. System dynamics modeling is a simulation method that applies to dynamic problems that arise in complex systems. It is one of the main techniques for analyzing complex systems and problems, as it allows modelers to understand the interfaces between system components and information feedback that show dynamic behaviors within a system [33,34].

A systems approach will be implemented to study the behavioral analysis of complex systems and inform health care policies and strategies. The simulation technique assumes that challenging behaviors within a system result from accumulations of people, information, and psychological states, and the technique is meant for reinforcing feedback mechanisms [35].

It incorporates the feedback processes that unfold over time to determine the dynamics of a system.

System dynamics models have been used in health care systems to analyze specific chronic diseases, the transmission of diseases, patient flow in A&E departments, and policy evaluation and decision support systems. System dynamics explores behaviors within the social systems of an organization, and systems dynamics modeling can be conducted to model the flow of each agent rather than individual agents' behaviors. Compared to other simulation methods, system dynamics modeling works at a more collective level to prove how organizational, human, and social structures and interactions influence the behavior of systems.

System dynamics has been applied in various behavioral analytics studies related to health care. It can help health care decision makers gain a deeper understanding of public health issues, such as the spread of an infectious disease [36,37]. It has also been used to analyze patient behaviors and unhealthy lifestyles that tend to contribute to major public health problems at the societal level [38,39]. Principally, system dynamics has been useful for incorporating behavioral factors as part of the feedback that affects decision-making in health care settings [40].

We intend to use a hybrid M&S approach, and the M&S framework for behavior analysis will use system dynamics modeling as one of the simulation techniques to focus on viewing patients as aggregates with common characteristics and to potentially identify the leading factors that influence and affect patient behavior and engagement. The study intends to integrate the hybrid M&S approach to construct a model for studying behavioral changes. Stock-and-flow diagrams based on defined conceptual models will be created for illustrative purposes, and inputs from available data sources will be integrated into the model.

Agent-based simulation (ABS) can also be valuable in analyzing individual behaviors from large health care data sets. After evaluating the developed M&S framework as an instrument of guidance that modelers can use for incorporating human behavior, more work and future studies will be carried out to use other simulation techniques, such as ABS and discrete-event simulation (ie, when the initial evaluation of the framework is done and large data sets become available). This will encourage modelers and practitioners to incorporate behavioral characteristics per the framework guidance.

Study Design

Our exploratory study will use M&S methods to investigate factors that influence patient engagement in chronic disease care, specifically engagement in diabetes care. We will examine various aspects of behavioral engagement activities, such as outpatient attendance, patients' adherence to medication, compliance in terms of follow-up visit adherence, A&E department attendance, and bed occupancy. The study will focus on engagement behaviors during diagnosis and treatment and factors that can result in better patient engagement to ensure the effectiveness of health care.

Patient engagement is characterized by various closely connected aspects related to cognitive, behavioral, emotional, and mental factors. The study will assess the behavioral aspects of engagement that may not be totally separated from other aspects in an attempt to shed light on how to link such aspects with operational and clinical factors within health care settings.

Textbox 1 provides a list of tentative variables that may be associated with patients and health data set records. Simulations based on a hybrid approach and a combination of QSD and system dynamics modeling will be conducted to evaluate different engagement patterns and strategies based on desired outcomes and health care effectiveness.

Textbox 1. List of possible patients' various variables to be extracted from the data sets.

Demographic variables

- Age, ethnicity, gender, education, occupation, income range, employment, and postcode

Mental health variables

- Psychotropic medications, antidepressant prescriptions, antidepressant scripts, issued sick notes, and sick certificates

Chronic disease variables

- Height, weight, systolic and diastolic blood pressure, temperature, and diabetes

Behavioral and operational variables

- Number of appointments, wait time, arrival time, length of stay, immunization and vaccination status, screening, counseling, medication adherence, antidepressant adherence, antidepressant scripts, refill prescriptions, access to treatment, treatment adherence, session adherence, therapy attendance, health care visit adherence, self-management behavior, care seeking, number of disease episodes, the course of therapy completed, number of admissions, inpatient admission (number of occupied bed days), accident and emergency department attendance, outpatient attendance, bed occupancy, number of bed days, test results, hospitalization rates, and recovery rates

Sample Size and Power Calculation

It is estimated that the sample of patient records (ie, those of patients with at least 1 specific chronic disease, such as diabetes) will consist of >200,000 of the >4 million available records of general patients. With this sample size, a high statistical confidence in the results is expected.

Study Population

It is anticipated that the study population will pertain to >4 million records of general patients aged ≥16 years, and >200,000 records are expected to pertain to patients with at least 1 specific chronic disease, such as diabetes.

Exposures

There is no treatment to be offered in the study. However, data related to general treatment and medication adherence will be analyzed as part of the study.

Outcomes

The study will identify the leading factors that influence and affect patient engagement and the interdependencies between patient engagement and the effectiveness of health care management plans. We will report on the following outcomes:

- The identification of the leading factors of patients' engagement behaviors
- A demonstration of how the incorporation of human behavior and actions in modeling would help modelers achieve a better representation of complex issues in health care and reflect on the desired outcomes of health care interventions
- Suggestions for improving health care management plans

Use of Any Linked Data and Plans to Link Data

We plan to use the data sets described by de Lusignan et al [41]. Their source is the Research and Surveillance Centre of the Royal College of General Practitioners—a collection and network of general practitioners that cover the UK population. We plan to use the primary care electronic medical records of patients with chronic diseases, such as diabetes.

The primary care data collected from several general practices will be linked by using the Secure and Private Record Linkage (SAPREL) method. The SAPREL method allows for the linking of patients' records without the need to know patients' identities [41] and therefore allows for the collection of general patients' variables, including various physical and mental variables. For example, in a study by de Lusignan et al [41], the authors calculated the number of issued prescriptions as a proxy measure of medication adherence, as collecting only a single script without conducting further follow-ups would be a big problem. Furthermore, the authors suggested that more careful studies would be needed to gauge patient engagement and its relationship with clinical, operational, and mental variables, such as bed occupancy and outpatient attendance [41].

At this stage, there are no plans for involving patients or user groups. However, at a later stage and on the basis of study outcomes, we may be required to consider this for further research.

Data and Statistical Analysis Plan

We will make use of an M&S behavioral analysis approach and use real health care data sets of patients with a chronic disease diagnosis to conduct a real-world case study that uses the developed M&S framework for behavioral analysis. The patients will be classified based on their patterns of engaging or not engaging with the required actions in the health care management plans provided to them. Hypotheses of causal influences will be formulated to compare behavioral patterns and gain insights into the impacts of different behaviors on health care operations. The model will compare different simulated behavior patterns over time in relation to the health data variables of patients.

Results

We anticipate that we will finish the extraction of data and the analysis of results by March 2022. After completing the M&S study, the dissemination of results will occur in due course. The model will be used for the evaluation and validation of the M&S framework under development. The findings will be published in conference proceedings and peer-reviewed journals related to M&S applications in health care management and primary health care informatics.

We also anticipate some limitations to our study. In relation to data sources, possible limitations are foreseen to pertain to the availability of well-defined behavior parameters and the nature of data related to patients' adaptability, engagement, and communication skills, which vary among patients. Other limitations could be related to the very nature of models and simulations in the health care sector, as health issues may arise from the interactions of a relatively large number of parameters. Therefore, a health system is not constrained to patients' personal and unique characteristics and is highly complex [42].

To study how behavioral analysis can be linked to health care effectiveness and service enhancements in health care management, general patients' variables, including demographic, physical, mental, and behavioral aspects, will be collected. Chronic diseases are embedded in the complex connections and interactions among the multiple and diverse variables that add to health care–related challenges [43]. Some data are expected to be missing or incomplete for some patients (eg, some variables related to follow-up visits may not exist).

Discussion

Our study aims to analyze and model the leading factors of patients' engagement behavior patterns in health care settings and the impacts of patients' engagement behaviors and to understand how patients' engagement behaviors can be linked to health care effectiveness in terms of achieving desired outcomes.

It has been argued that behavioral analysis, which is the study of human behavior and its impacts on systems and processes, can result in the increased effectiveness of health care interventions and policy making improvement [44]. Most traditional health care models rarely detail the precise impacts of behavioral reactions and interactions or the dynamics of these reactions and interactions. This indicates the need to construct models that more explicitly incorporate behavioral aspects to modulate the dynamics of health care systems. Such an aim can be achieved by applying a generic M&S framework with proper M&S techniques to the incorporation of human factors to understand the impacts of various patient engagement activities

on health care effectiveness in terms of achieving desired health outcomes.

Our framework seeks to provide specific guidelines for incorporating human behavior in hybrid M&S studies that take into consideration underlying factors and their influence and can possibly benefit from a mix of M&S methods [45,46]. The choice of using a simulation technique combined with operations research methods might help with examining and understanding the effect of incorporating human behavior and how to benefit from modeling to mimic real-world situations. Although the focus of our study is on evaluating the hybrid system dynamics–QSD framework, which uses a system dynamics technique to view patients as aggregates, the first step of this evaluation should be assessing the framework's understanding of the possible effects of human behaviors and actions. For future research, the applications of ABS QSD or discrete-event simulation QSD in behavioral analytics will also be investigated.

As previously stated, our main focus will be on the behavioral analysis of patients diagnosed with at least 1 chronic disease, such as diabetes. The data sets described by de Lusignan et al [41] will be used in our study to gain insights into patients' behavioral patterns. The study intends to identify patients' engagement behavior variables and intends to use and evaluate the M&S framework for behavioral analysis via simulation models.

Our goal is to guide modelers in developing approaches to tackling complex problems that will help shape processes, interventions, and policies for improving health care effectiveness and operations and, possibly, behavior change strategies. This is one of the necessary steps for incorporating behavioral analysis in the tackling of problems involving human actions, particularly those within health care settings. Once the framework has been evaluated and behavioral analysis has been incorporated into simplified health care environments, modelers will acquire the know-how for incorporating behavioral analysis into the assessment of human activities and the tackling of severe, worldwide health problems, such as the COVID-19 pandemic.

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Conflicts of Interest

None declared.

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Abbreviations

A&E: accident and emergency
ABS: agent-based simulation
M&S: modeling and simulation
QSD: qualitative system dynamics
RCGP: Royal College of General Practitioners
RSC: Research and Surveillance Centre
SAPREL: Secure and Private Record Linkage

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Early Report

Ecological Momentary Assessment of Weight-Related Behaviors in the Home Environment of Children From Low-Income and Racially and Ethnically Diverse Households: Development and Usability Study

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Abstract

Background: Ecological momentary assessment (EMA) is an innovative tool for capturing in-the-moment health behaviors as people go about their daily lives. EMA is an ideal tool to measure weight-related behaviors, such as parental feeding practices, stress, and dietary intake, as these occur on a daily basis and vary across time and context. A recent systematic review recommended standardized reporting of EMA design for studies that address weight-related behaviors.

Objective: To answer the call for reporting study designs using EMA, this paper describes in detail the EMA design of the *Family Matters* study and how it was adapted over time to improve functionality and meet the needs of a racially, ethnically, and socioeconomically diverse sample.

Methods: *Family Matters* is an incremental, 2-phased, mixed methods study, conducted with a racially and ethnically diverse, immigrant and refugee sample from largely low-income households, designed to examine risk and protective factors for child weight and weight-related behaviors in the home environment. The *Family Matters* study intentionally recruited White, Black, Hmong, Latino, Native American, and Somali parents with young children. Parents in phase 1 of the study completed 8 days of EMA on their smartphones, which included signal-contingent surveys (eg, asking about the parent's stress at the time of the survey), event-contingent surveys (eg, descriptions of the meal the child ate), and end-of-day surveys (eg, overall assessment of the child's day).

Results: A detailed description of EMA strategies, protocols, and methods used in phase 1 of the *Family Matters* study is provided. Compliance with EMA surveys and participants' time spent completing EMA surveys are presented and stratified by race and ethnicity. In addition, lessons learned while conducting phase 1 EMA are shared to document how EMA methods were improved and expanded upon for phase 2 of the *Family Matters* study.

Conclusions: The results from this study provided an important next step in identifying best practices for EMA use in assessing weight-related behaviors in the home environment.

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KEYWORDS

methods; ecological momentary assessment; weight-related behaviors; racially and ethnically diverse; children; mobile phone

Introduction

Background

Ecological momentary assessment (EMA) is an innovative method used to capture real-time information about people's health behaviors (eg, eating, physical activity, parental feeding practices, and stress and mood), which is becoming more commonly used by researchers who study weight-related behaviors. Although EMA is new to the field of weight-related health, it has been used for decades in other related fields such as smoking cessation, eating disorders, chronic pain, and sleep [1] as it is both dynamic and highly adaptable to the research questions and hypotheses being tested. EMA collects data from participants as they go about their regular lives (ecological) and involves repeated in-the-moment assessments of behaviors (momentary) [2]. In addition, EMA allows for capturing fluctuations in behaviors across time and context to identify behaviors that are more trait-like or state-like, which can be helpful in designing interventions to address weight and weight-related behaviors [3,4].

EMA was developed as a dynamic tool in response to the static nature of other self-report tools, such as retrospective surveys, which are subject to both random error and systematic bias [5]. The use of EMA across studies has varied in the frequency of assessment (eg, assessing participants hourly vs daily) and the length of the assessment (eg, days vs year-long assessment period) [2,6,7]. Furthermore, the technology used varies among studies, from paper diaries to smartphone-based apps (eg, mobile health [mHealth] technology). Studies also vary in their sampling design, whether it is time-based, event-based, or a combination [2]. EMA allows for sophisticated statistical analysis of data, such as cross-lagged models exploring how earlier events and behaviors (eg, stress) are associated with subsequent events and behaviors later on the same day or days later (eg, parent feeding practices) [3,4] and within-subject models examining how variations in the characteristics of events within a household are associated with each other (eg, preparing meals differently is associated with the types of foods served [8]).

Within the field of weight-related health behavior research, EMA is being used in the assessment of behaviors such as dietary intake and physical activity [9-16]. EMA is a valuable tool for assessing dietary intake; while eating is not a unique occurrence, the behaviors and contextual factors surrounding dietary intake (eg, parent feeding practices and family meal characteristics) fluctuate over time and are influenced by many factors, including stress, the home environment, and social interactions. EMA is well-suited for capturing fluctuations in behaviors and contextual factors and their associations with dietary intake. Similarly, EMA is being used in the field to assess behaviors and emotional states that fluctuate across time, such as mood, stress, and parental feeding practices (eg, restriction and pressure to eat) that have high potential to influence weight and weight-related behaviors. These behaviors and emotions are ideal to measure via EMA as they occur regularly on a day-to-day basis, may vary across time and context, and have a high potential to influence weight-related behaviors of children and other family members within the home environment.

A systematic review that evaluated the use of EMA to assess weight-related behaviors in youth and their families recommended standardizing the reporting of EMA measures across studies as details about EMA design are often absent and can lead to misinterpretation of study results [11]. As there is variation in the design and implementation of EMA across studies, it is important for researchers to describe their EMA protocols and processes in-depth to allow the field to develop EMA best practices going forward and to have standardization across studies to allow for the comparison of study results. In addition, as the use of EMA continues to increase in the field of weight-related health, it is important to understand how low-income, racially and ethnically diverse participants interact with data collection methods using EMA. This is especially important as children from low-income and minority households are at the highest risk for negative health outcomes (eg, obesity and cardiovascular disease) [17,18], and their households may be under higher levels of stress due to adverse environments and systemic structures that place undue burden on these populations [19]. Although several past EMA studies have included multiple races and ethnicities or targeted specific races and ethnicities, such as Latino [20] and Black or African American [21,22] participants, most EMA studies have included a predominantly White sample [12]. In addition, there appears to be a scarcity of EMA studies that specifically include immigrant populations [23].

Concerns have also been raised regarding the use of EMA with participants from low-income or low-educational attainment households and in populations who may be less technologically savvy [2]. Such populations may have jobs that make it particularly difficult to respond to EMA prompts during their work hours (eg, retail shift workers) [24]. Similarly, low-income and minority populations generally experience high levels of stress resulting from adverse environmental stimuli [25], which may make responding to EMA prompts more taxing. Therefore, understanding the application of EMA within low-income, racially and ethnically diverse, immigrant and refugee populations is the next necessary step for mHealth research.

Objective

Given the increased use of EMA in the field of weight-related health research and its high potential for measuring important weight-related behaviors in the home environment, this study seeks to provide a detailed description of the EMA strategies, protocols, and methods used in the *Family Matters* study to investigate weight-related behaviors among participants from low-income, racially and ethnically diverse, immigrant households in order to inform other studies that aim to assess weight-related behaviors within the home environment using EMA. Lessons learned from the EMA assessment of weight-related behaviors will be shared to document how EMA methods were improved and expanded across study phases to better capture momentary behaviors and accommodate the needs of the low-income, racially and ethnically diverse, immigrant sample. The results from this study provide an important next

step in identifying best practices for EMA use in assessing weight-related behaviors in the home environment.

Methods

Study Design and Population

Family Matters is an incremental, 2-phased, mixed methods study conducted with a racially and ethnically diverse, immigrant and refugee sample from largely low-income households. *Family Matters* examined risk and protective factors for child weight and weight-related behaviors in the home environment [4,16]. Phase 1 was an in-home observation of 150 families—25 each of African American, Native American, Somali, Latino, Hmong, and White families—with a child aged 5-7 years (ie, study), conducted between 2015 and 2016. Phase 2 is an ongoing longitudinal, epidemiological cohort study of racially and ethnically diverse, primarily low-income parent and child dyads (N=1307, approximately 200 families each per racial and ethnic group), with a subsample of 627 parent and child dyads who also completed the EMA. Phase 1 was intended to be both an in-depth observation of home environment risk and protective factors associated with weight and weight-related behaviors of diverse children and their families and a pilot study for our EMA protocols and analyses to inform phase 2 of our study. As phase 1 EMA informed phase 2 EMA development, we will first describe phase 1 EMA design, procedures, and protocols in detail and then discuss how it was adapted for phase 2, based on learnings from phase 1. Table 1 presents demographic characteristics of the phase 1 and phase 2 samples.

Participants from phase 1 of *Family Matters* were recruited from primary care clinics in the twin cities metro area. Families of children between the ages of 5 and 7 years (ie, the child in the study) who had a recent well-child visit were sent a recruitment letter from their primary care provider. Families were eligible if (1) the study child lived full-time with the parent or primary guardian and the child was away from home during the day (eg, school and summer camp)—to ensure all dietary and EMA measures occurred across similar contexts; (2) the child had no medical problem precluding study participation (eg, disease altering diet or physical activity, serious mental illness); (3) the child had a sibling living in the home between the ages of 2 and 12 years—as the study aims included understanding how family dynamics and structure were connected to child weight and weight-related behaviors; and (4) the family had at least 3 family meals per week. The primary study aim was to examine associations between family meal characteristics and child weight and weight-related behaviors. In addition, parents needed to be able to read and speak in English, Spanish, Hmong, or Somali.

In phase 1, mixed methods data were collected from family participants during an 8-10–day period, which included 2 home visits (parents or primary guardians were registered for EMA on an iPad mini [Apple Inc], at the first home visit, with more information to follow), and an 8-day observation period between home visits where EMA was collected. Detailed information about other measures from phase 1 collected besides EMA (eg, 24-hour dietary recalls, home food inventory, accelerometry, video-recorded task, and qualitative interviews) during in-home visits has been published elsewhere [16].

All study materials, including EMA survey questions, were translated from English into Spanish, Hmong, and Somali. The following process was used in the translation of materials: (1) a bilingual and bicultural team member translated materials into Spanish, Hmong, or Somali; (2) two additional bilingual and bicultural team members reviewed the translated materials; and (3) the 3 translators met to resolve any differences in translation, focusing on capturing the intent of the English question. The Institutional Review Board Human Subjects Committee of the University of Minnesota approved all protocols used in both phases of the *Family Matters* study.

Table 1. *Family Matters* phase 1 and 2 survey sample demographic characteristics (N=1457).

Participant characteristics	Primary caregiver	
	Phase 1 (n=150)	Phase 2 (n=1307)
Female, n (%)	137 (91)	1171 (90)
Age (years), mean (SD)	34.5 (7.1)	35.7 (7.9)
Born in the United States, n (%)	87 (58)	859 (66)
Immigrant time living in the United States (years), n (%)		
≤1	1 (2)	8 (2)
1 to ≤5	5 (8)	52 (12)
5-10	8 (13)	51 (11)
≥10	48 (76)	336 (75)
Not reported	1 (1)	—[a]
Household race and ethnicity, n (%)		
Native American	25 (17)	211 (16)
Hmong	25 (17)	226 (17)
Black	25 (17)	280 (21)
White	25 (17)	239 (18)
Somali or Ethiopian	25 (17)	136 (10)
Hispanic	25 (17)	215 (16)
Survey language (selected by participant), n (%)		
English	107 (71)	1148 (88)
Spanish	16 (11)	134 (10)
Hmong	7 (5)	8 (1)
Somali	20 (13)	17 (1)
Educational attainment, n (%)		
Some high school	32 (21)	183 (14)
High school or associates	88 (59)	521 (40)
Some college or bachelors	11 (7)	409 (31)
Graduate degree	18 (12)	194 (15)
Not reported	1 (1)	—
Household income (US $), n (%)		
≤20,000	50 (33)	393 (30)
20,000-34,999	55 (37)	323 (25)
35,000-49,999	16 (11)	203 (16)
50,000-74,999	12 (8)	143 (11)
75,000-99,999	7 (5)	75 (6)
≥100,000	9 (6)	159 (12)
Not reported	1 (1)	11 (1)

[a]No data were missing from phase 2.

EMA Design and Procedures

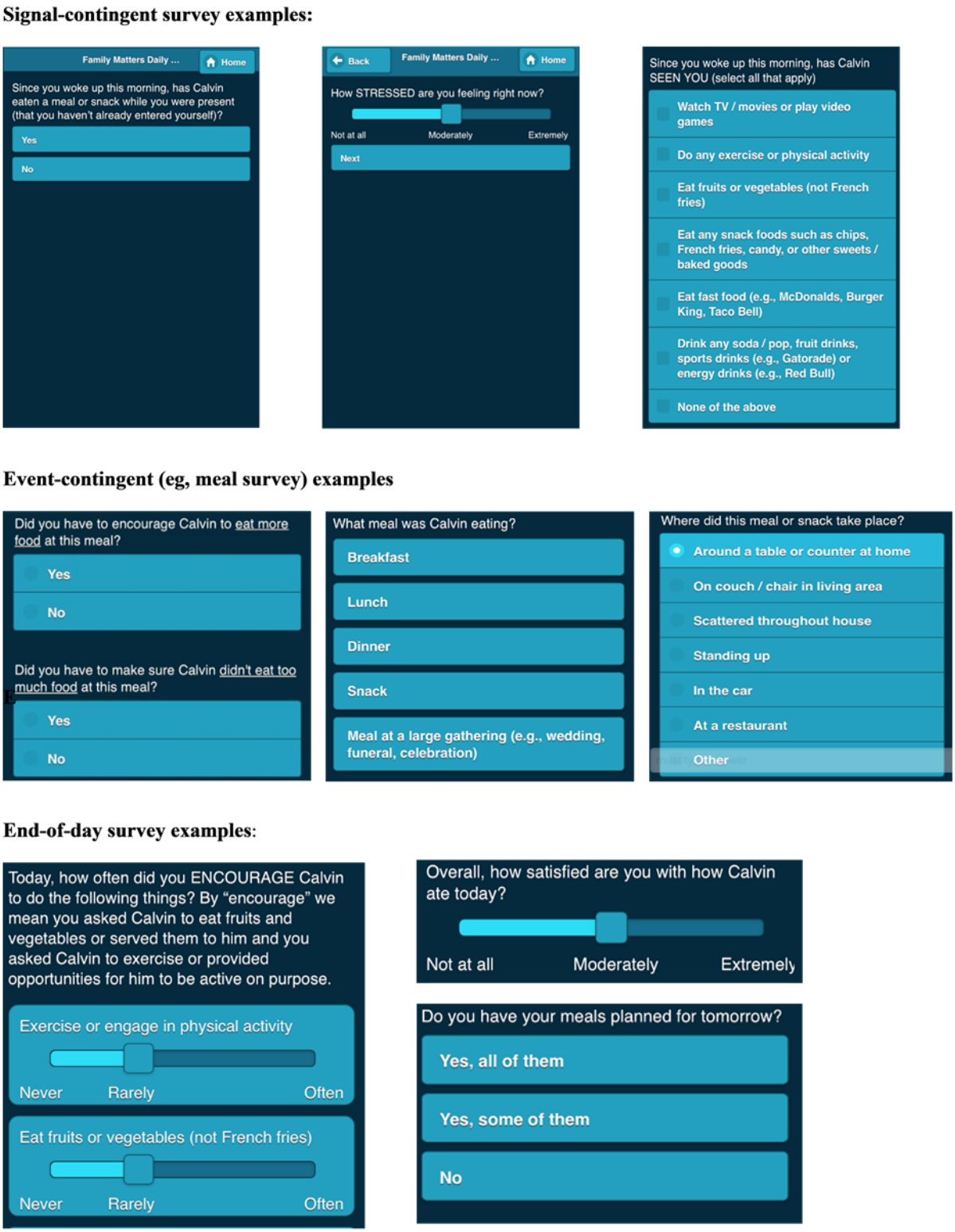
Overview

For the *Family Matters* study, we used the current EMA best practice design with the following 3 types of EMA messaging [2]:

1. event-based or event-contingent messaging, where parents completed a survey after every meal occurrence they shared with the study child aged 5-7 years;
2. time-based or signal-contingent, which assessed momentary constructs (eg, stress and coping) at random intervals throughout the day;
3. end-of-day, where parents provided an overall summary of their day. All surveys were designed to be experienced by the participant as calm, soothing via a blue color scheme.

Figure 1 shows examples of the color scheme used [26].

Figure 1. Screenshots of ecological momentary assessment survey questions answered by *Family Matters* study participants in phase 1.



Registration

At the end of the first home visit, parents worked with research staff on reviewing EMA instructions and protocols and registering for EMA on a study-provided iPad mini. During the visit, research members logged into a web-based EMA registration portal developed by the *Family Matters* team and asked parents to complete the registration sections (Multimedia Appendix 1 [27-45]). Once the participant was registered, a unique survey link was created using the EMA software program. This link was then added as an icon to the iPad mini home screen. Parents clicked on this icon to complete any of their EMA surveys. The iPad mini was restricted so that participants could access the home screen icon, but other capabilities, such as purchasing apps or browsing the internet, were blocked.

A research team member reviewed a binder of EMA instructions with the parent, which was then left at home. This binder included (1) descriptions of the surveys to be completed, as well as the number of daily surveys necessary to complete; (2) screenshots reminding participants how to access EMA surveys; (3) basic information about the iPad mini, such as charging, turning the iPad mini on and off, turning up the volume (to hear survey notifications), and finding the home screen; and (4) contact information for the study team. In addition, before the home visit, the parent completed an event-contingent meal survey. This ensured that the surveys were submitted appropriately and helped introduce parents to EMA surveys. The practice surveys were excluded from the analysis. After the second home visit, the iPad mini was taken from the home and the *Family Matters* icon was removed from the home screen to ensure that other participants only used their own unique EMA survey links. Participants' incentives to participate in all components (eg, home visits and EMA) of the *Family Matters* study included an iPad mini and the opportunity to earn up to US $100 for completing all study components.

Types of Surveys

Event-Contingent

Parents were instructed to complete an event-contingent survey (or meal survey) after every meal the study child ate when they (the parent) were present. Parents accessed the meal survey by clicking the *Family Matters* survey icon on the home screen of their iPad mini. This allowed the parent to report on meals they shared together (eg, a family meal) and on meals where only the child ate (eg, an after-school snack where both the parent and child were present). Parents were instructed not to report on meals the child ate where the parent was not present (eg, school lunch). All phase 1 EMA questions can be found in Multimedia Appendix 1. Sample visuals of EMA questions can be found in Figure 1. Survey questions were designed using validated measures and were then adapted for the EMA format. For example, instead of asking "In the last 3 months...," the EMA question would begin, "Since you woke up this morning..." or "Since your last survey...." When appropriate, some survey questions were changed to a *yes* or *no* response format rather than a Likert scale. As shown in Figure 1, survey questions with Likert-scale response options were preset to the midpoint. Times entered by the participant (eg, wake times) were preset to the most likely AM or PM designation (eg, wake times were automatically set to AM). Other preset default response options were decided on a per-question basis by the research team. In addition, some response options were preset based on responses to earlier questions. After responding to the foods served at family meals, participants were asked which food the child ate at the meal; only the foods that were served could be selected. Similarly, the parent had to be present while the child was eating for the meal to qualify as a family meal. Therefore, when asked about who was present at the meal, the parent and the child were shown automatically as present at the meal, and the parent could add additional family members to the list. Participants had to answer all EMA questions to submit the survey; the *Next* button used to reach the next page of questions was grayed out until all questions were answered.

Signal-Contingent

Parents were sent 4 signal-contingent surveys per day. Signal-contingent surveys were spaced so that they began after the parent woke up (reported during the EMA registration; Multimedia Appendix 1). The time between the parents' reported wake and sleep times was divided into 5 blocks to accommodate the 4 signal-contingent surveys and the end-of-day survey, with at least one hour separating each block (eg, a block of time from 8 to 11 AM with the next block starting at noon), so that there would never be an overlap of surveys. Scheduling signal-contingent surveys around the parent's sleep and wake time allowed surveys to be scheduled to accommodate different life situations (eg, working an overnight shift), if needed. Parents were notified via an iPad chime when a signal-contingent survey was ready to be taken. In addition, parents could choose to have an additional prompt either texted to their phone or emailed. Parents had 1 hour to begin the signal-contingent survey on the iPad mini; if participants failed to begin the survey, the signal-contingent survey link would become inactive, although parents would still have the option to complete an event-contingent (eg, meal) survey.

In addition, for the *Family Matters* study, it was important to capture all meals the parent shared with the study child. To ensure that parents captured as many meals as possible, the first question of the signal-contingent surveys (Multimedia Appendix 1) asked the parent if they forgot to report a shared meal with the study child either after waking up or after completing the last survey. If the parent had forgotten to enter a meal survey, they were directed to complete the event-contingent survey first. After submitting the event-contingent survey, they were immediately directed back to complete the signal-contingent survey. As meals are not rare events, it was assumed that parents might forget to initiate event-contingent surveys each time they shared a meal with their child; this prompting strategy allowed the *Family Matters* study to capture additional meals that may otherwise have been forgotten.

End-of-Day

Parents were sent the final (fifth) survey at the start of the final scheduled block (determined by parents' wake and sleep time). As with the signal-contingent surveys, the end-of-day survey began by asking whether the parent had shared a meal with the study child since either waking up or completing the last survey

that had not yet been reported. Unlike signal-contingent surveys, which asked about in-the-moment measures (eg, How stressed are you right now?), the end-of-day survey asked for an overall assessment of the day (eg, Overall, how stressed were you today?). To help ensure that the end-of-day survey was completed, participants were given 6 hours to complete the final survey. The last question of the end-of-day survey asked the parents to assess how difficult it was for them to fill out the surveys during the day (Multimedia Appendix 1). An assessment of respondent burden is an important feature of momentary studies in that it provides information about the demographic and environmental factors that could result in periodic observation gaps or overall low compliance with the study protocol. Although this study is intensive relative to traditional cross-sectional observational studies, respondents reported that they did not experience chronic study burden or increased burden over time. On days when burden was high, participant reports of stress were elevated and burden appeared to resolve over the subsequent days, suggesting that factors other than the study instruments were related to overall burden. The strongest demographic predictor of burden was a first language other than English, suggesting that EMA protocols should anticipate and tailor data collection to diverse population needs [46].

Duration of EMA (Days)

All phase 1 participants (n=150) completed 8 days of EMA. The decision to include 8 days instead of 7 was based on prior research using observational methods, suggesting the need to allow for a *sensitizing period* (eg, one day) for participants to acclimate to the equipment and potentially intrusive measures [47,48]. There were also criteria established for the EMA responses to qualify as a *complete* day. Specifically, participants needed to finish (1) 2 of the 4 signal-contingent surveys, (2) at least one meal survey, and (3) the end-of-day survey. Therefore, all participants had at least 8 meal surveys and 8 end-of-day surveys. In addition, the observation window was extended if the participant was not able to complete the minimum number of surveys. For example, if the participant only completed one signal-contingent survey, an extra EMA observation day was added to their observation window until all 8 days of EMA met the criteria for a complete day. These criteria were established based on the importance of retaining participants from diverse, low-income backgrounds who sometimes cannot finish study requirements given time constraints, resources, acute stressors, or complex life situations. Having 8 full days of EMA data per participating also allowed enough power to detect differences in momentary behaviors by race and ethnicity. However, we also recognize that incomplete days may be due to the very momentary behavior the study is hoping to assess (eg, a high-stress day that limited the participant's ability to fill out EMA prompts). Thus, both complete and incomplete days of EMA were collected, which allowed the use of both data sets as research questions and hypotheses warranted (eg, analysis of foods served at family meals may include all meal surveys regardless of whether they meet the minimum criteria to be a *complete* day).

Resources Used for EMA Implementation

Technology

A computer programmer (third author, MJ) with experience in technology-assisted research methods developed the *Family Matters* programming of EMA surveys. Our programmer had a strong understanding of web design and database architecture. For the *Family Matters* study, built-in internet information services by Microsoft were chosen because the web hosting maintenance was minimal and easy to configure. Razor syntax was chosen as the website's programming language, and Visual Studio was chosen as the development platform for generating the .NET Razor pages. Although there are many tools available that can generate a functional survey, the chosen tools allowed for the level of complexity and control the study demanded at an affordable cost. For phase 1, SMS text message notifications were sent to participants using Twilio, along with a proprietary Windows service. For phase 2, Amazon Web Services was used in place of Twilio to meet the updated privacy policies of University of Minnesota.

Staff Time

Staff members were involved in phase 1 EMA in the following ways: (1) educating participants on how to use EMA and registering them in the EMA system at the first home visit, (2) tracking participants to ensure EMA surveys were completed, (3) remotely trouble shooting EMA issues with participants, and (4) deactivating participants from the EMA system at the end of their observation window.

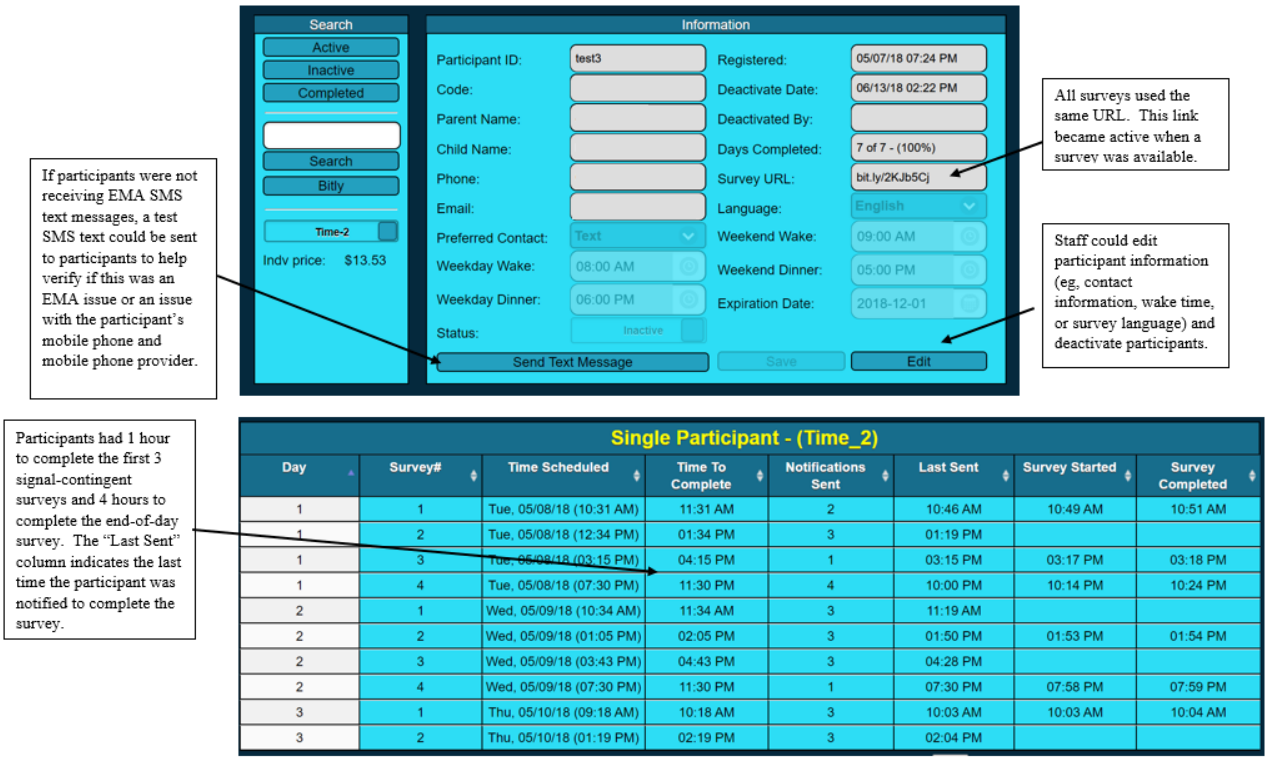
To ensure that the participants were able to meet the minimum criteria for a complete EMA day and for staff to be able to identify any participant's troubleshooting needs, our EMA programmer built a web-based tracker. The staff members were able to monitor participants' EMA progress, including seeing when signal-contingent and end-of-day surveys were scheduled to be sent and when surveys were started and completed. Contact information for the participant, language of the surveys, and the participant's wake and sleep times were also identified. The tracker also allowed the staff to make some changes to the EMA (eg, change the survey language) without burdening the EMA programmer. Figure 2 shows a visual illustration of the EMA tracker.

Using the EMA tracker, the staff members were instructed to contact participants: (1) if the participant did not have a *complete* first day of EMA, to ensure the participant understood the minimum requirements and to identify any troubleshooting and (2) if the participant went 2 days in a row without having a *complete* day to identify any problems or complex situations. In addition, as EMA was part of a larger study design, the staff also contacted the parent by phone during the EMA observation period in order to obtain a 24-hour dietary recall. Once the tracker indicated that the parent had completed 8 days of EMA, a staff member alerted the parent that they had successfully completed the study and deactivated their EMA.

The most common EMA difficulties were some participants' inability to complete EMA surveys while at work, particularly as some participants were not allowed to have the iPad mini with them during their shift. In these cases, the staff worked

with parents on a case-by-case basis. Most parents with difficulties completing surveys due to work were able to meet the minimum requirements (eg, they completed a signal-contingent survey before work and another after their work shift). There were a small number of parents whose work schedules did not allow for the completion of EMA (eg, a nurse working a 12-hour shift). In these rare cases, parents were asked to complete the EMA on nonwork days, and extra days were added to the observation period to ensure 8 days could be completed. Although this information was provided in the registration binder, some parents were unfamiliar with iPads or using a tablet and needed additional remote assistance (eg, how to close a survey tab and return to the home screen).

Figure 2. Depiction of the ecological momentary assessment tracker used in phase 2 of the *Family Matters* study. EMA: ecological momentary assessment.



EMA Compliance and Analysis Considerations

EMA Compliance

Overall, participants completed 8 days of EMA (ie, a minimum of 2 signal-contingent surveys, 1 meal survey, and 1 end-of-day survey), an average of 10.5 days (SD 7.5 days; Multimedia Appendix 2). Somali families had the lowest average completion time (8.8, SD 3.8 days), and Black families had the highest (11.6, SD 6.2 days). Over 40.6% (61/150) of families completed all 8 days in a row without missing any days; 15.5% (23/150) of families missed 1 day and 13.5% (20/150) of families missed 2 days. Racial and ethnic differences were observed in participants' EMA compliance; two-third (16/25, 64%) of Latino families completed EMA without missing any days, compared with only 24% (6/25) of Native American families. Black (10/25, 40%), White (8/25, 32%), and Native American (8/25, 32%) families were the racial and ethnic groups with the highest percentage of participants missing ≥4 days of EMA. The most frequent reason a participant did not fulfill requirements for a complete day was a missed signal-contingent (ie, completed <2) survey; this was true across all racial and ethnic groups. Across all racial and ethnic groups, missing a meal survey was the *least* likely reason a participant did not fulfill the requirements for a complete day. EMA surveys were intentionally kept short to ensure participant compliance. Overall, EMA surveys—regardless of whether they were signal, event, or end-of-day surveys—generally took participants less than 5 minutes to complete.

Regarding meal surveys, participants completed an average of 3.7 (SD 1.5) meal surveys on weekdays and 4.3 (SD 1.6) on weekend days. There was no variation in this pattern across the 6 racial and ethnic groups. As described earlier, participants could complete a meal survey by either (1) self-initiating the survey after sharing a meal with their child or (2) as part of the signal-contingent prompt (eg, if they forgot to submit a meal that was previously eaten). There was no difference in participants' patterns of self-initiating meal surveys in the first half of the observation period compared with the second half (ie, participants did not stop self-initiating meal surveys once they understood that meal surveys could also be taken as part of the signal-contingent survey).

Analysis Considerations

For most of the analysis of phase 1 data, the data set of 1200 days (150 participants × 8 days) was used. However, there were times when using *all* EMA data—not just complete days—was appropriate. For example, a recent analysis of phase 1 EMA data investigated the concordance of foods reported in meal surveys with foods reported through 24-hour dietary recalls [49]. It was not important if the EMA meal survey was part of

a *complete* day; therefore, all meal surveys in the data set were used. Future EMA data analysis should carefully consider whether restricting to only eligible days is necessary or appropriate for the study design; analyses that do not restrict should also consider whether data are missing at random.

EMA data can take both wide and long data formats, resulting in complex data management and analytical needs. As part of the data cleaning and management protocol, the analyst team developed a reference document that contained key information about how to explore the data, investigate missingness, describe panel data frequencies, and merge multiple sources of study data for analysis. The purpose of this document was to establish consistent data integrity procedures to ensure that analysts used descriptive and inferential procedures appropriate for intensive longitudinal data. Furthermore, EMA data collection often exploits *select all that apply* question formats to ensure that a comprehensive momentary assessment is captured. These question types can result in complex, hybrid data structures (a wide and long format) and are preferred to be collected in strictly long formats (ie, one participant survey per row). This minimizes the complexity of dummy coding responses at the analysis stage if the response values are stored in delimited formats. Analysts should also note that the response composition of EMA select all that apply questions will result in data values stored across many columns of data. For example, the first response that is asked can only be stored in the first dummy variable, but the last response value can be stored in any dummy variable position (if the respondent selects only the final response or if the respondent selects all response values, respectively). Study documents should be updated to describe how the raw data format generates complex data structures, and common codes to manage the data should be outlined for consistency.

Adapting EMA in Family Matters Phase 2 From Lessons Learned in Phase I EMA

Overview

In phase 2, 1307 diverse parent and child dyads took a web-based survey at 2 time points, approximately 18 months apart, and approximately half of these families (n=627) were also eligible for enrollment in our EMA subsample. Participants were enrolled into the study between 2016 and 2018. The EMA survey design for phase 2 differed slightly from phase 1 including the following: (1) parents were asked to complete up to 4 surveys per day, including 3 signal-contingent surveys during the day and an end-of-day survey that combined the signal-contingent questions (eg, stress level) and event-contingent meal questions specific to the family's dinner meal; (2) parents had to complete a minimum of 2 signal-contingent and the end-of-day survey for a day to be *complete* and needed to finish 7 complete days; and (3) parents received US $75 for completing 7 days of EMA. These adaptations to our EMA protocol were directly informed by what we learned from phase 1.

Technology, Registration and Training, and Design Changes to Phase 2 EMA

A decision whether to use an iPad mini again or participant's own phones was deliberated for phase 2 EMA. The main concern was whether all participants had access to a smartphone. Ultimately, we decided to use smartphones given some phase 1 participant feedback that the iPad minis were cumbersome. Thus, in phase 2, all participants chose to use their own phones, even though the *Family Matters* study had smartphones available for participants to use. Although a smartphone requirement may be restrictive for some participants, it was not restrictive for our primarily low-income (105/150, 70% of families had incomes of <US $35,000) and diverse sample. This experience aligns with findings from recent research indicating that 98% of Americans in 2020 own a mobile phone, with 81% of them being smartphones [50].

As phase 2 used participants' smartphones, we were unable to use the same approach of placing an icon on the EMA (ie, iPad mini) device and developed a new approach. One approach considered was the development of an app, but there were many reasons why this was not ideal for our study. First, an app would be costly and time consuming to develop, and apps would have to be created for the different mobile phone operating systems used by participants (eg, iOS). In addition, there was concern that participants may have trouble or be hesitant to download the app and that it would require regular updates. Ultimately, the process for phase 2 EMA included participants being sent an SMS text message every time a survey was available, which contained the survey link that the participants followed to access the web-based survey. As there was one unique survey link per participant, participants could follow the link from any SMS text message (ie, not only the most recent one) to access EMA surveys. Participants also had the option to have survey notifications sent to their email addresses if they notified the staff that it was a better fit (eg, participants who worked primarily in front of a computer). Participants were alerted when enrolling in the study that they would receive SMS text messages and would be responsible for any SMS text message charges they incurred through their mobile phone plan.

Registration

Registration for phase 2 EMA was performed remotely and by the participant. After completing the web-based survey, parents who reported more than 3 family meals per week were given the opportunity to participate in an optional EMA substudy. This eligibility criteria aligned with the study aim of examining momentary mealtime routines and behaviors. Participants were able to download a form with substudy information about EMA requirements (eg, number of days and surveys needed) and interested participants were given an access code and directed to a web-based form to consent to the optional EMA substudy; they were then automatically directed to the EMA registration page. To ensure that the participants would receive texted survey links, participants were sent a test SMS text message after registration. Although staff were available to assist if necessary (and could even register participants on the web if needed), overall, participants registered themselves for EMA and understood the requirements (eg, number of surveys needed to complete) without requiring staff assistance. An important lesson learned from phase 2 of *Family Matters* is that participants—including low-income, racially and ethnically diverse, immigrant and refugee participants—are generally able to remotely enroll in an EMA study and understand the study

requirements with little to no staff assistance. Depending on the overall study aims, this remote enrollment option allows for a wider geographical recruitment range and for the study to continue remotely during public health crises (eg, the COVID-19 pandemic).

Staff Time for Participant Tracking

Multiple features were added to the phase 2 EMA to assist both participant compliance and decrease staff time. First, multiple reminder SMS text messages were built into the signal-contingent and end-of-day survey windows. For signal-contingent surveys (expiration of 1 hour), participants received an initial SMS text message with the survey link and an SMS text message alerting the participant of the expiration time. If the survey was not completed, the participant received another reminder SMS text message after 30 minutes and another reminder SMS text message after 45 minutes for a maximum of 3 reminder SMS text messages. For end-of-day surveys (expiration of 4 hours), participants received the initial SMS text message with the survey link; they then received reminder SMS text messages every 45 minutes until the survey was complete or expired, for a maximum of 5 reminder SMS text messages.

Immediately after the end-of-day survey was completed or expired, the participant received another SMS text message with a summary of their study participation information to date, including (1) whether the participant had finished a complete day (ie, at least 2 signal-contingent and end-of-day surveys); (2) how many complete days the participant had done; and (3) if the participant had not finished a complete day, a reminder that additional observation days would be added to the EMA window to allow the participant to complete 7 days. The SMS text message also reminded the participants that they would receive US $75 after completing 7 complete days of EMA.

Regarding staff time, a feature was built into the phase 2 EMA system, where participants were automatically deactivated after 7 complete EMA days were completed. Therefore, unlike phase 1, the staff did not have to actively track each participant every day and manually deactivate. In addition, an email system was set up in which a study email account was emailed daily with the following information: (1) EMA participants who had not finished a complete EMA day on their first observation day, (2) EMA participants who had gone for more than 2 days without finishing a complete EMA day, and (3) the language of the EMA participant. This allowed the staff to easily identify the participants needing to be contacted each day to assist with any EMA difficulties or questions.

EMA Visual Design

As surveys were conducted on participants' smartphones in phase 2, questions were formatted so that the participant did not have to scroll to the right or left to see the full question and response option. Similarly, pages of the survey were designed so that they contained only a small number of EMA questions, which minimized how much participants had to scroll down. Related to the smaller screen of a smartphone versus an iPad mini, the style of the response option (eg, radio button vs checkbox) was carefully considered to promote response ease. For example, questions with a Likert scale had response options provided on a slider (with anchors) rather than a pull-down menu. For the slider, the participant only had to select in the general vicinity of the anchor they wanted to choose (ie, they were not required to push a very specific section of the slider bar).

As participants were registering themselves, we provided instructions in a variety of languages (ie, English, Spanish, Somali, and Hmong) to make this possible. After completing the full web-based survey (in their preferred language), participants were directed to the EMA registration page. Instructions were provided on this page in all 4 languages, and participants were asked to enter their unique access code and then to select a survey language. For phase 2, over 93.3% (585/627) of the sample took EMA surveys in English, 6.2% (39/627) took the surveys in Spanish, and only a few families took the survey in Hmong (1/627, 0.2%) or Somali (3/627, 0.5%). Upon participant request, the staff members were able to change the language of the surveys. In addition, due to less participant and staff contact in phase 2, an information button was added to each question. Participants could select the *i* button and be provided Spanish, Hmong, and Somali translations to the survey questions and response options.

Results

Using EMA methods in the *Family Matters* study allowed for many cutting-edge research questions to be addressed, innovative analyses to be run, and methodological approaches to be advanced. Multimedia Appendix 3 [3,4,13-15,51-55] provides a description of the selected study results highlighting the *Family Matters* research question, analysis used, principal findings, and implications for future research.

Discussion

Principal Findings

Overall, the main aims of this paper were to (1) answer a call in the field to report EMA study designs and (2) to extend prior EMA research by providing a detailed description of the *Family Matters* innovative EMA study design, methodology, protocols, and procedures used to investigate weight-related behaviors of children from low-income and minority households. In addition, lessons learned were also highlighted from both phases of the *Family Matters* study and are shown in Textbox 1 for future research to benefit from the development of EMA best practices and standardization of protocols across studies.

Family Matters demonstrated that EMA was an effective tool for collecting rich weight-related behavior data from participants from a low-income, racially and ethnically diverse, immigrant and refugee sample. In addition, phase 2 established that participants, including non–English-speaking participants, were able to register and complete EMA surveys without one-on-one or in-person staff assistance while using their personal smartphone device. Results from the *Family Matters* study will help inform future research teams using EMA, particularly around diet and physical activity, as they make decisions about the EMA study design.

Textbox 1. Lessons learned from the Family Matters study for future ecological momentary assessment (EMA) studies.

1. Set up and registration

- **Lessons learned**
  - It was feasible for parent participants from low-income, racially and ethnically diverse, immigrant and refugee households (referred to in this textbox as *participants*) to successfully complete the ecological momentary assessment (EMA).
  - Participants were able to complete the EMA via their own smartphones without study provision of such devices.
  - Participants without familiarity with iPad tablet technology were able to easily learn how to operate these devices.
  - Participants preferred receiving survey notifications via SMS text message versus via email.
  - The *Family Matters* study used a computer program designed by an in-house programmer that did not rely on participants downloading an application. This also allowed the programmer to design only one system rather than multiple applications for different smartphone operating systems.
  - Participants were able to register remotely without staff assistance, which included navigating to the EMA registration page, entering an access code, and entering in registration information (eg, phone number and name). This was the case for all study participants, regardless of the main language they spoke (ie, English, Spanish, Hmong, or Somali).
  - Participants who moved into a new time zone during phase 2 needed to have their survey times adjusted, as the initial system was set up using only CST.
- **Applying lesson to future EMA studies**
  - Future studies can feel confident that EMA studies can be carried out in diverse groups, including in non–English-speaking groups.
  - Future studies may be able to rely on participants using their own smartphone devices to complete the EMA; researchers may want to consider having a small budget for providing devices to some participants who may have a mobile phone that is not a smartphone or in case of device failure.
  - Studies providing technology for participants to complete the EMA should consider providing guidance on using the technology (eg, opening web browsers and closing tabs), while at the same time feeling confident that most participants will be able to use mHealth technology.
  - Providing SMS text message notifications for the EMA is likely sufficient, although this may vary depending on the study population (eg, job primarily using a computer).
  - Although participants will become more familiar with applications, some may have hesitancy or trouble downloading an app. EMA application may be a useful tool for future research studies, although it should not feel like a requirement.
  - Although staff should be available to troubleshoot any participant questions or concerns, the *Family Matters* study demonstrated that participants were able to register for the EMA—and understand what to expect (eg, that EMA surveys would start the morning after registration)—without the staff walking them through the process.
  - Future longitudinal studies or ones where participants are located in different time zones should include a time zone question during EMA registration. The adjustment of time zones can then be read and altered by the SMS text messaging service.

2. Tracking participants

- **Lessons learned**
  - The EMA system was set up so that (1) participants were automatically deactivated when they had finished enough complete survey days and (2) if a participant failed to finish a complete day, another day was automatically added on to their observation period.
  - A protocol was designed to alert staff on when to contact participants (eg, if the participant did not finish a complete day on their first observation day). Participants received multiple reminder SMS text messages to complete each EMA survey, and participants also received a summary SMS text message at the end of each day telling them (1) if they had finished a complete day, (2) how many complete days they had done, and (3) a reminder of the incentive amount.
- **Applying lesson to future EMA studies**
  - Having these study design elements automatically built into the EMA computer program significantly reduces staff time (eg, the time spent tracking and deactivating participants), and can lead to participant satisfaction and less participant confusion (eg, eliminates the possibility of sending the participant surveys to finish after the participant has completed all EMA requirements).
  - Having multiple reminders to study participants increases the likelihood that participants will complete surveys. Repeated reminders also reduce the staff time needed to contact participants.

3. EMA survey design

- **Lessons learned**
  - EMA design for phase 2 (completed on participant smartphones) needed to consider how the survey would appear on a smartphone screen rather than how it looked on a computer screen.

- As the EMA is a newer tool for assessing diet and physical activity The *Family Matters* study drew questions from validated surveys and altered them to be EMA-friendly (eg, changing from a Likert scale to yes or no options, changing the question heading to be *In the last month...* to *Since you woke up...*).
- Participants were able to complete a meal survey (ie, providing information about a meal they shared with their child) in 2 ways: (1) self-initiating the survey and (2) as part of the signal-contingent prompt. Over half of meal surveys in phase 1 were completed via self-initiation. There did not appear to be a difference in participants' patterns of self-initiating meal surveys in the first half of the observation period versus the second half.
- Although phase 1 and 2 of *Family Matters* had criteria for what counted as a *complete* day of EMA, data from noncomplete days were kept and were valuable for many analyses (eg, analyses that focused only on meal surveys).
- The web service used during phase 2 of the EMA needed to be changed (from Twilio to Amazon Web Services) to comply with updated privacy policies of the University of Minnesota.

- **Applying lesson to future EMA studies**
  - EMA survey design should be smartphone friendly. For example, the question text should be large enough to be viewed on a phone screen. The question should be designed so that participants do not have to scroll to read the full question or to see the response options. Questions should be on multiple pages rather than having all survey questions on only one page.
  - Researchers should consider adopting the EMA questions already being utilized in EMA survey research. Survey questions for constructs that have not been assessed via EMA should be selected using validated measures (when possible); questions and response options may need to be altered to be more EMA-friendly.
  - For researchers wanting to simplify their EMA design, assessing events (eg, smoking and eating a meal) through signaled prompts rather than participant self-initiation may be a viable option. Depending on the event being considered, researchers may want to consider adding in more signal prompts to catch more events.
  - EMA study designs should capture and retain all data submitted by participants, regardless of whether they meet the full criteria set by the researcher.
  - As the EMA will likely collect identifiable participant data (eg, phone numbers), researchers should be aware of the privacy policies of the institution they are working in to ensure they are compliant.

Considerations for Future EMA Research

One functionality that we built into the design of our EMA event surveys was the ability of the parent to enter a meal survey at the beginning of a signal-contingent survey if they had forgotten to report a meal (event-contingent survey) earlier. This intentional design allowed us to capture any unreported meals that the parent shared with the child in the study. This design was important as EMA studies with racially and ethnically diverse, low-income households are less common; thus, we wanted to ensure that the EMA system was user-friendly to navigate and allowed to collect as much data as possible, within the bounds of the data being accurate. However, there are potential disadvantages to consider in the study design. First, it is not possible to ascertain the exact time of the behavior (ie, meal), although it is possible to determine the window of time the behavior occurred, and there could potentially be a loss of specificity further away from the meal the survey is entered. It is important that signal- and event-contingent surveys be collected in the order they occurred, so they do not affect a retrospective assessment (eg, you would not want participants to submit signal-contingent surveys, ie, report on momentary stress, but enter all event-contingent, ie, meal, surveys in the evening). Future EMA research collecting meal-level data through signal-contingent surveys may be able to increase the level of event-contingent (ie, meal survey) completion by offering multiple ways to complete the survey (ie, individually or as part of the signal-contingent survey), while also having the participant report on the time the meal was eaten when they took the delayed meal survey. Parents also only reported on meals for which both the parents and the child were present. This allowed parents to provide detailed information on the meal; however, this design may not allow for the assessment of overall child dietary intake behaviors as many meals (eg, those eaten at school) were not reported. Another important consideration for future research is related to the differing amounts of time parents are with their child. It may be important to assess the amount of time the parent spent with the child since the last survey to determine if parent behaviors could have had an influence on the child. Future research may wish to involve older children, who may be more reliable reporters than younger children of dietary intake behaviors, in EMA data collection alongside their parents.

Conclusions

EMA is a method that was successfully implemented and improved upon in the *Family Matters* study across both study phases (ie, phase 1 and phase 2), both of which included participants from primarily low-income and racial and ethnic samples. Lessons learned about EMA study design and implementation were also shared so that researchers could benefit from them in their own future EMA studies.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Ecological momentary assessment questions used in phase 1 of Family Matters.
[DOCX File , 25 KB - resprot_v10i12e30525_app1.docx]

Multimedia Appendix 2
Responsiveness of phase 1 Family Matters participants to ecological momentary assessment surveys.
[DOCX File , 25 KB - resprot_v10i12e30525_app2.docx]

Multimedia Appendix 3
Selected results from the Family Matters phase 1 study using ecological momentary assessment data.
[DOCX File , 18 KB - resprot_v10i12e30525_app3.docx]

Multimedia Appendix 4
Peer-review report by the Psychosocial Risk and Disease Prevention Study Section, National Institutes of Health.
[PDF File (Adobe PDF File), 135 KB - resprot_v10i12e30525_app4.pdf]

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Abbreviations

EMA: ecological momentary assessment
mHealth: mobile health

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Protocol

Pandemic Acceptance and Commitment to Empowerment Response (PACER) Training: Protocol for the Development and Rapid-Response Deployment

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Abstract

Background: During a global pandemic, it is critical to rapidly deploy a psychological intervention to support the mental health and resilience of highly affected individuals and communities.

Objective: This is the rationale behind the development and implementation of the Pandemic Acceptance and Commitment to Empowerment Response (PACER) Training, an online, blended, skills building intervention to increase the resilience and well-being of participants while promoting their individual and collective empowerment and capacity building.

Methods: Based on acceptance and commitment therapy (ACT) and social justice–based group empowerment psychoeducation (GEP), we developed the Acceptance and Commitment to Empowerment (ACE) model to enhance psychological resilience and collective empowerment. The PACER program consists of 6 online, interactive, self-guided modules complemented by 6 weekly, 90-minute, videoconference, facilitator-led, group sessions.

Results: As of August 2021, a total of 325 participants had enrolled in the PACER program. Participants include frontline health care providers and Chinese-Canadian community members.

Conclusions: The PACER program is an innovative intervention program with the potential for increasing resilience and empowerment while reducing mental distress during the pandemic.

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KEYWORDS

COVID; COVID-19; coronavirus; pandemic; resilience; acceptance commitment therapy; group empowerment

Introduction

Background

The COVID-19 pandemic has had a devastating impact globally, precipitating a mental health crisis. Early data from a global survey in April 2020 to May 2020 found that 58.6% of respondents exhibited some symptoms of depression [1]. Based on a population-based survey from July 2020, it is estimated that over 50% of Canadians reported worsened mental health, while over 81% of workers surveyed reported significant declines in their mental well-being since the onset of the pandemic [2]. While data on suicide rates is not yet clear, predictive models vary widely, anticipating a 1%-145% increase.

The reported data on mental health are dynamically changing across countries, calling for proactive steps to promote mental health and prevent suicide, especially among the vulnerable [3].

One of the challenges to addressing this mental health crisis is the complexity of the issues. In addition to psychological anxiety and fear brought on by the pandemic itself, the introduced public health measures, such as social distancing and lockdowns, have had a cascade of deleterious psychosocial and economic sequalae on individuals, families, and communities, ranging from social isolation to housing and financial crisis to disruption of access to community supports and services. These measures have a negative impact on social determinants of health and mental health, amplifying existing inequities [4], further exacerbated by COVID-19–related racism, and resulting in poorer mental health [5]. The possible ramifications and fallout of these factors for mental health will continue to unfold for months and years to come.

The Acceptance and Commitment to Empowerment (ACE) Model

To promote resilience and address the multidimensional stressors on mental health, we adapted a resilience building model, the Acceptance and Commitment to Empowerment (ACE) model, for pandemic response. ACE integrates the acceptance and commitment therapy (ACT) [6], an evidence and mindfulness-based intervention, with a social justice–based group empowerment psychoeducation (GEP) [7]. While self-help resources and psychological interventions such as positive reframing, rational thinking, and various coping strategies can be helpful, they may add to a sense of futility in a pandemic when many are faced with external stressors and systemic inequities beyond their control. ACT aims to increase psychological flexibility and adaptability by helping individuals to accept their negative thoughts and feelings rather than challenging them or being entangled by them, get in contact with the here and now as individuals not encumbered by labels and judgments, and find meaning and values through persistent efforts and actions. GEP includes 4 explicit core principles: social justice and equity; empathy and compassion; interdependence; and collective empowerment, fostered through critical reflection, critical dialogue, collaborative learning, and experiential learning. GEP promotes a deeper appreciation of our interdependence in the context of mutual empathy, social justice, and health equity. It empowers individuals to build and tap into their social networks and expand their capacity to engage in mutual support and social activism. Combined, the ACE model has been successfully used to decrease stigma and promote mental well-being in various marginalized populations [7] and adapted for pandemic challenges.

Research Aims

This paper describes the protocol for the development and implementation of the Pandemic Acceptance and Commitment to Empowerment Response (PACER) program. The PACER program was developed during the period of April 2020 to June 2020 and launched in July 2020. As of August 2021, the program was still ongoing, with rolling recruitment and enrollment in cohorts.

Methods

Development of the PACER Program

Constrained by lockdowns, we developed the PACER program to be delivered as an online intervention. The PACER program uses the ACE model as the basis of content development. The program consists of 6, 1-hour, weekly, online, self-guided learning modules accompanied by weekly, 90-minute, facilitated, online group videoconferencing sessions. The online modules are hosted on Moodle, an online e-learning platform with open-sourced coding of activities and exercises. Activities within the PACER modules are designed with the help of an external information technology company in consultation with the research team.

The PACER program modules include a variety of interactive activities, such as reflective writing, guided meditation, and gamified exercises to explore ACE principles and processes. As an example, while most of our gamified exercises do not include a scoring scheme, in one particular acceptance exercise, participants are repeatedly presented with a stressful scenario and asked to select a response from a variety of coping strategies, such as having balanced thinking, doing physical and relaxation exercises, and practicing mindfulness meditation to earn points. Each time any coping strategy is chosen, points are awarded, but this promptly returns the participant back to the starting point of the scenario. The points are actually arbitrary and meaningless, serving only as a behavioral reinforcer to have participants persist in this loop, which continues until the participant finally gives up on finding “the right solution” and chooses the exit option. The debriefing text then guides reflection on a potential trap that we may fall into when we try to avoid and eliminate negative emotions, as many coping strategies may seem rewarding in the short term. In this regard, even mindfulness practice may function as an avoidant behavior. In another exercise, the participant is prompted to categorize people into an in-group versus an out-group to confront their own unconscious process of “othering” and discuss its role in society, including inequities during the pandemic (see Figure 1).

These activities facilitate learning by integrating 3 aspects: the actual present moment experience of the participants’ engagement and interaction online; reflection on personal and communities’ real-life struggles with the pandemic and its sequalae; and the application of ACE theory, principles, and skills. Each module begins with the personal and builds towards a broader collective and systemic perspective. The journey helps participants to connect more deeply with their values and purpose, with others in interpersonal relationships, and with the community at large. The modules increase in complexity across the 6 modules with the final sets of exercises tapping into multiple principles and skills, culminating in developing effective personal and community-level actions to promote individual and collective mental well-being.

Figure 1. Examples of an interactive Pandemic Acceptance and Commitment to Empowerment Response (PACER) exercise.

The weekly online group videoconferencing is led by trained facilitators and provides an opportunity for sharing, collective reflection, and group discussion of the weekly learning activities. It reinforces and broadens the learning, as each participant may have a different interpretation of and insights into the activities, informed by their own pandemic struggles. It also fosters mutual support in dealing with personal and societal pandemic stressors.

Participant Selection and Recruitment

The PACER training program prioritizes 2 populations: frontline health care providers (HCPs) and members of the Chinese-Canadian communities (CH-COM). Frontline HCPs are at high risk of burnout related to increased workload, fear of contracting the illness and spreading it to their family, shifting roles and work protocols, and compassion fatigue in caring for the sick and dying. Members of CH-COM have been experiencing intensified social marginalization, racial discrimination, and pandemic-related stigma in addition to pandemic stress. A Canadian national survey showed that 64% of Chinese-Canadians had experienced some form of racism since the onset of the pandemic [8]. To accommodate differences in lived experiences of both groups, we developed 2 arms of the program. While the content and exercises remain the same for both arms, instructions and examples throughout are adjusted to be more relevant for the intended audiences.

The recruitment of PACER participants is conducted through convenience and snowball sampling. Recruitment methods include outreach to hospital and health care networks and Chinese community agencies using promotional e-flyers. In addition to targeted promotion, recruitment also involved word of mouth, social media (Facebook, Instagram, Twitter, WeChat), and promotional videos posted on YouTube. Eligible participants include anyone identifying as a health care worker and/or member of Asian Canadian communities. Participant enrollment in active cohorts is prioritized based on level of distress and availability to attend the predetermined weekly facilitated discussions. Participants low in distress or are not available for the weekly discussions are put on a waitlist for future cohorts. No eligible participant will be deterred from participation.

Procedure

Eligible participants are invited to indicate their language preferences (English, Chinese Mandarin, Chinese Cantonese), current level of distress, and availabilities to attend weekly discussions in the evenings or on weekends. Following, participants are matched with a cohort led by 2 experienced facilitators. Once enrolled, participants are invited to complete a set of pre-intervention measures. During each week of the 6-week PACER program, participants also complete weekly responses prior to their weekly facilitated discussions. After the completion of the program, participants are invited to a set of self-report measures immediately postprogram and at 3-months follow-up. Weekly and biweekly activity logs are used to track participants' activities in mental health promotion from postintervention to the 3-month follow-up. A focus group will be conducted at follow-up to gather their reflections on their experience of the program. The research ethics boards at Ryerson University, York University, and the University Health Network – Toronto Western Hospital approved the study. All study participants provided informed consent prior to participation.

Measures

To evaluate the effectiveness of the PACER program, participants complete a set of online self-report questionnaires. The questionnaires include demographic and background questions constructed for the purpose of the current study, as well as validated self-report instruments evaluating dimensions of mental health, resilience, and well-being. The measures are described in the following sections.

Demographic and Background Information

Participants will complete information on age, gender, education, ethnoracial identity, status in Canada, professional role(s), workplace setting, and preferred language. Questions are generated for the purpose of the current study.

General Mental Distress

To measure general mental health and distress, participants will complete the General Health Questionnaire (GHQ) [9]. The GHQ is a 12-item, self-report screening tool for general mental distress and general (nonpsychotic) mental health symptoms.

Psychological Flexibility

To measure psychological flexibility, participants will complete the Acceptance and Action Questionnaire II (AAQ-II) [10]. The AAQ-II is a 7-item, self-report measure of psychological inflexibility.

Resilience

To measure resilience, participants will complete the Multi-System Model of Resilience Inventory (MSMR-I) [11]. The MSMR-I is a 27-item, self-report measure of resilience capacity across 3 systems of resilience resources (internal, coping and pursuits, and external).

Empowerment

To measure empowerment, participants will complete the Empowerment Scale (ES) [12]. The ES is a 33-item, self-report measure of empowerment capacity.

Data Analysis Plan

Quantitative data will be aggregated, and descriptive and change-based data will be analyzed using SPSS (IBM Corp, Armonk, NY). Data analyses include descriptive statistics, measures of internal consistency, and analysis of variance. Qualitative data (from focus groups) will be transcribed verbatim. N-Vivo software will be used for data management. Data will be organized and analyzed using thematic and focused descriptive analysis using inductive and deductive approaches.

Results

As of August 2021, 325 participants have been enrolled in cohorts in English, Chinese Mandarin, and Chinese Cantonese. Of those enrolled, 287 have completed the full training, and 38 participants have dropped out due to scheduling conflicts. To date, no adverse events have been reported by participants taking part in the PACER training program. This study is expected to conclude in April 2022.

Discussion

The COVID-19 pandemic has created great mental health challenges. It is imperative to develop accessible and effective interventions to strengthen mental health resilience of affected populations. A wide spectrum of psychological interventions, from psychodynamic therapy to existential therapy to cognitive behavioral therapies, have been proposed [13]. Here, we outlined the protocols for the development and implementation of an online blended learning intervention that combines ACT with GEP to form the ACE model.

Our ACE model is unique in bringing together an individual psychological intervention with a collectivistic social justice intervention. This integration increases its suitability to address an external mass event like the pandemic, which has disrupted social connections, threatened our way of living, and led to worsening of pre-existing inequities and racism. Based on the ACE model's mindfulness approach, there is an emphasis on the acceptance of negative thoughts and feelings, rather than focusing on attempts to avoid or reframe them positively, rationally, or realistically. It presents a palatable approach for many health care professionals who have experienced guilt about their own distress and in the role transition from being a helper to receiving help, with their initial mindset that they ought to have been more competent, rational, and resilient. The ACE model's focus on mindful acceptance also departs from preoccupation with coping, as emphasis on coping strategies may paradoxically add to further stress experienced. In addition, many have expressed frustration and powerlessness in dealing with various health and systemic policies that are a departure from the norm and implemented rapidly in a continuously changing landscape leading to inefficiencies and perceived increased health risks for HCPs and patients, as well as health disparities. Along similar lines, marginalized and discriminated community members report experiences of shame, powerlessness, internalized stigma, and/or a sense of burden to stand up against social injustice. The ACE model encourages a nonjudgmental acceptance stance towards these negative thoughts and feelings, decreasing denial and easing the burden of justification and shame, while identifying the real-world impact of the pandemic, fostering a sense of shared social responsibility, and empowering all for collective action.

Our delivery method is uniquely suited for the pandemic situation. At a time when personal existential issues and larger social justice issues have been elevated to the forefront, the program is designed to foster both individual and collective deep reflection. In addition to being physically safe and pragmatically feasible, the self-guided interactive exercises are innovative in encouraging participants to learn from their own experiences and apply them to issues that are deeply personal, sensitive, or even controversial at a societal level. When these personal experiences are shared and disclosed in a safe space created by the virtual group, participants are empowered and appreciate the powerful mutual learning and support, consistent with the widening of an individual focus to the collective.

We anticipate the data collected will provide important insights regarding the effectiveness of PACER, as well as distinguish the pathways of change in different population groups. The PACER intervention, if found to be effective, may be adapted for other communities and the population at large. While we prioritized frontline HCPs and CH-COM members in this study, we anticipate that PACER can be contextualized for deployment and use with other populations to support their unique and shared challenges. As we complete the study to determine our particular intervention's effectiveness, we advocate for public health and mental health providers to urgently focus more on effective mental health interventions and initiatives that promote

psychological acceptance and flexibility rather than rationalization and advance collective well-being rather than the more limited concept of self-care. With the notion of an independent self being broadened to an interdependent self, the concept of self-care becomes inextricably linked with caring for the communities as a whole. We need to develop a sense of community cohesion while acknowledging our individual differences brought on by differences in power and privilege. This can be likened to not only weathering the same storm together but also being on the same boat that is humanity, even though we need to acknowledge and redress the fact that we inhabit different deck levels.

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Conflicts of Interest

None declared.

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Abbreviations

AAQ-II: Acceptance and Action Questionnaire II
ACE: Acceptance and Commitment to Empowerment
ACT: acceptance and commitment therapy
CH-COM: Chinese Canadian community

ES: Empowerment Scale
GEP: group empowerment psychoeducation
GHQ: General Health Questionnaire
HCP: health care professional
MSMR: Multi-System Model of Resilience
PACER: Pandemic Acceptance and Commitment to Empowerment Response

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Protocol

A Digital Health Platform for Integrated and Proactive Patient-Centered Multimorbidity Self-management and Care (ProACT): Protocol for an Action Research Proof-of-Concept Trial

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Abstract

Background: Multimorbidity is defined as the presence of two or more chronic diseases and associated comorbidities. There is a need to improve best practices around the provision of well-coordinated, person-centered care for persons with multimorbidities. Present health systems across the European Union (EU) focus on supporting a single-disease framework of care; the primary challenge is to create a patient-centric, integrated care ecosystem to understand and manage multimorbidity. ProACT is a large-scale project funded by the European Commission under the Horizon 2020 programme, that involved the design, development, and evaluation of a digital health platform to improve and advance home-based integrated care, and supported self-management, for older adults (aged ≥65 years) living with multimorbidity.

Objective: This paper describes the trial implementation protocol of a proof-of-concept digital health platform (ProACT) in 2 EU member states (Ireland and Belgium) to support older persons with multimorbidities self-managing at home, supported by their care network (CN).

Methods: Research was conducted across 2 EU member states, Ireland and Belgium. A 12-month action research trial design, divided into 3 evaluation cycles and lasting 3 months each, with a reflective redesign and development phase of 1 month after cycles 1 and 2 was conducted. Participants were 120 (60/120, 50% in Ireland and 60/120, 50% in Belgium) older persons with multimorbidities diagnosed with two or more of the following chronic conditions: diabetes, chronic obstructive pulmonary disease, chronic heart failure, and cardiovascular diseases. With permission from persons with multimorbidities, members of their CN were invited to participate in the study. Persons with multimorbidities were provided with ProACT technologies (tablet, devices, or sensors) to support them in self-managing their conditions. CN members also received access to an app to remotely support their persons with multimorbidity. Qualitative and quantitative feedback and evaluation data from persons with multimorbidity and CN participants were collected across four time points: baseline (T1), at the end of each 3-month action research cycle (T2 and T3), and in a final posttrial interview (T4). Thematic analysis was used to analyze the qualitative interview data. Quantitative

data were analyzed via platform use statistics (to assess engagement) and standardized questionnaires (using descriptive and inferential statistics). This study is approved by the ethics committees of Ireland and Belgium.

Results: The trial implementation phase for this 44-month (2016-2019) funded study was April 2018 to June 2019. The trial outcomes are at various stages of publication since 2021.

Conclusions: ProACT aims to co-design and develop a digital intervention with persons with multimorbidities and their CN, incorporating clinical guidelines with the state of the art in human-computer interaction, behavioral science, health psychology, and data analytic methods to deliver a digital health platform to advance self-management of multimorbidity at home, as part of a proactive, integrated model of supported person-centered care.

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KEYWORDS

multimorbidity; digital health; chronic disease; self-management; older adults; integrated care; behaviour change; mobile phone; smart phone; smart device

Introduction

Background

Within the European Union (EU), an estimated 50 million people live with multimorbidity, defined as two or more chronic health conditions [1]. For individuals living with multimorbidity, the self-management of multiple conditions can impose a significant burden [2], with activities that include managing multiple symptoms, medications, information on their conditions, and clinical appointments. In addition, health care services for individuals with multimorbidity are often repetitive (multiple appointments), inconvenient, inefficient (individuals may see different clinicians who give conflicting advice), burdensome, and potentially unsafe due to poorly integrated and coordinated care [3,4]. The outcome for individuals is reduced quality of life, as time and energy are spent managing multiple conditions, limiting their opportunity for social or personal activities [5].

The risk of multimorbidity increases with advancing age, with prevalence rates estimated at 65% in people aged ≥65 years, 85% in people aged ≥85 years, and rising [6]. The rapid aging of the global population brings significant concerns over the sustainability of health services, due to associated increases in health care expenditure, and disparities in the number of practicing health professionals. It is therefore important that efforts are made to explore sustainable digital approaches to support home-based self-management of chronic diseases and multimorbidity. Self-management (or self-care) can be described as an individual's ability to manage symptoms, treatment, emotions, and lifestyle changes as part of living with a chronic condition [7]. Improving best practices around the provision of person-centered care for a person with multimorbidity requires empowering the Person with multimorbidity to self-manage, actively supported by their care network (CN), which primarily involves informal carers (ICs), formal carers (FCs), and health care professionals (HCPs). The CN of a person with multimorbidity plays an important role in diminishing the impact of disease management, which may subsequently improve health outcomes and quality of life [8].

Digital health technologies have the potential to improve and advance home-based self-management for older persons with multimorbidity, yet most digital solutions focus on single-disease management (eg, diabetes) [9,10]. Therefore, digital solutions that address complex disease management and multimorbidity, taking into account the role, views, and needs of the person with multimorbidity and their CN, are also required.

To date, there has been limited research examining the potential of digital health support for multimorbidity management. This includes understanding the challenges faced by people managing multimorbidity, as well as design requirements for digital technologies to address these challenges [11-15]. Although such research is necessary, to the best of our knowledge, research on digital platforms and systems to support multimorbidity has not progressed beyond examining requirements and suggesting design recommendations.

Within the EU, the ICARE4EU program provides the most robust examination of digital or eHealth use to address multimorbidity management within the context of integrated care [16]. Managers of 101 integrated care programs in Europe were surveyed to understand if they had used eHealth (or digital) solutions and, if so, what were the benefits of and barriers for the solutions in relation to multimorbidity care. Of these programs, 85 adopted eHealth solutions, and 42 of these were targeted specifically at older adults. The types of eHealth technologies implemented within these programs included remote consultation and monitoring, self-management tools (including electronic reminders and web-based decision support), health care management technology such as patient databases and e-referral systems, and electronic health records. However, neither detailed descriptions of these technologies nor their evaluations were presented. Furthermore, the authors noted limitations in that HCPs, patients, and their caregivers were not consulted in terms of the availability of eHealth supports within these programs.

With such limited research in the areas of digital health, integrated care, and multimorbidity management, there is a need for large-scale, longitudinal programs or projects to better understand both the complexities of multimorbidity and how digital technologies can be designed, developed, and implemented to support the person with multimorbidity and their CN. The ProACT project, funded by the European

Commission Horizon 2020 programme, brings together a multidisciplinary consortium of 13 European partners for the purpose of developing and evaluating a digital integrated care system to empower home-based, patient-centric care and proactive self-management of chronic conditions for Europe's 50 million persons with multimorbidity.

This paper reports the protocol for the ProACT Horizon H2020 project main proof-of-concept (PoC) trial conducted in Ireland (by the Trinity Centre for Practice and Healthcare Innovation, Trinity College Dublin, NetwellCASALA at Dundalk Institute of Technology and Home Instead Senior Care) and Belgium (by imec at the Studies in Media, Innovation and Technology in the Vrije Universiteit Brussel) between April 2018 and June 2019. Before the PoC trial, the ProACT platform was designed and developed between 2016 and 2018 through an iterative user-centered process involving input from 166 key stakeholders (older people with multiple chronic conditions, carers, and HCPs) across Ireland, Belgium, and Italy [17-21].

Study Aim and Objectives

The study evaluated, at a PoC level, a digital health platform (called *ProACT*) for older persons with multimorbidity to self-manage their conditions with support from their CN. ProACT was implemented at 2 EU trial sites (Belgium and Ireland). The specific aims of the trial were (1) to explore the potential benefits of the ProACT platform for persons with multimorbidity and (2) to obtain feedback from all relevant participants on their experiences using the ProACT platform and on the potential of the platform to improve integration of care and support for multimorbidity disease management.

Specific objectives for all participants were to evaluate the usability, accessibility, and acceptability of the ProACT platform, user adoption and satisfaction with the technology and services, and experiences of participants using ProACT. Additional objectives for persons with multimorbidity were to evaluate the potential impact of the ProACT platform on a range of health, well-being, psychological, and psychosocial outcomes and evaluate the efficacy of ProACT as a behavior change intervention that aims to improve self-management skills for the person with multimorbidity. Additional objectives for IC and FC participants were to evaluate the potential impact of the ProACT platform on their psychological and psychosocial outcomes.

ProACT: Intervention Description

ProACT is a citizen-driven, self-management orientated, digital integrated care platform capable of supporting multiple disease management and well-being parameters (eg, mobility and sleep) on a single user app. The overall platform (Figure 1) consists of the following:

- A kit of home-based health care support tools and off-the-shelf
  measurement and sensing devices (eg, blood pressure cuff, weight scales, smart watch, and home-based sensors).
- A suite of end-user apps and support tools (CareApps; Figure 2). Apps are available for persons with multimorbidity, HCPs, ICs, and FCs.
- A source-agnostic data collection system (CABIE).
- A portal to support (1) management of trials and participants and (2) clinical triage support (Subject Information Management System [SIMS]).
- Cloud-based storage and analytics system (KITE).
- Advanced analytics to provide risk assessment, support person with multimorbidity goal setting, and support person-centric care (CareAnalytics).

Figure 1. ProACT platform overview and data flow.

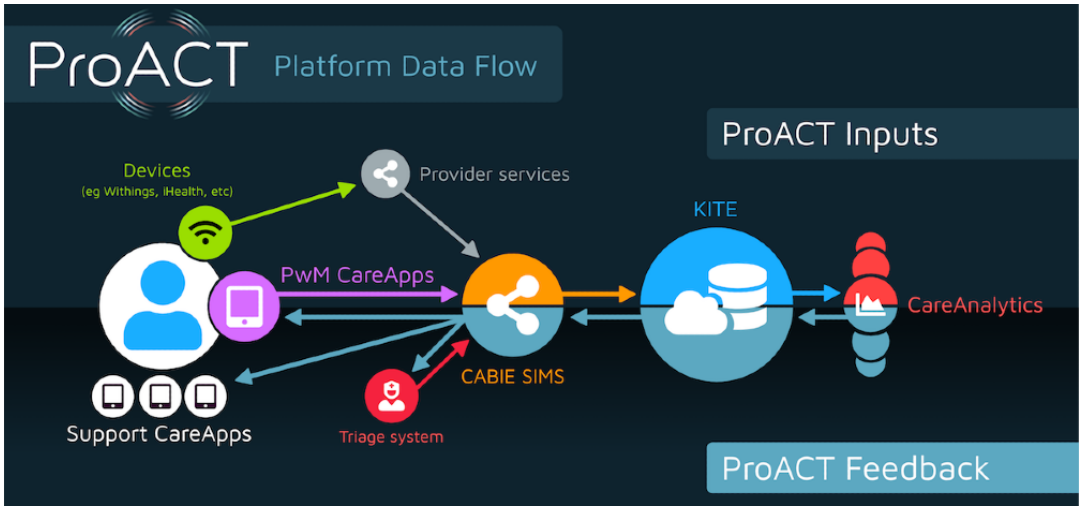
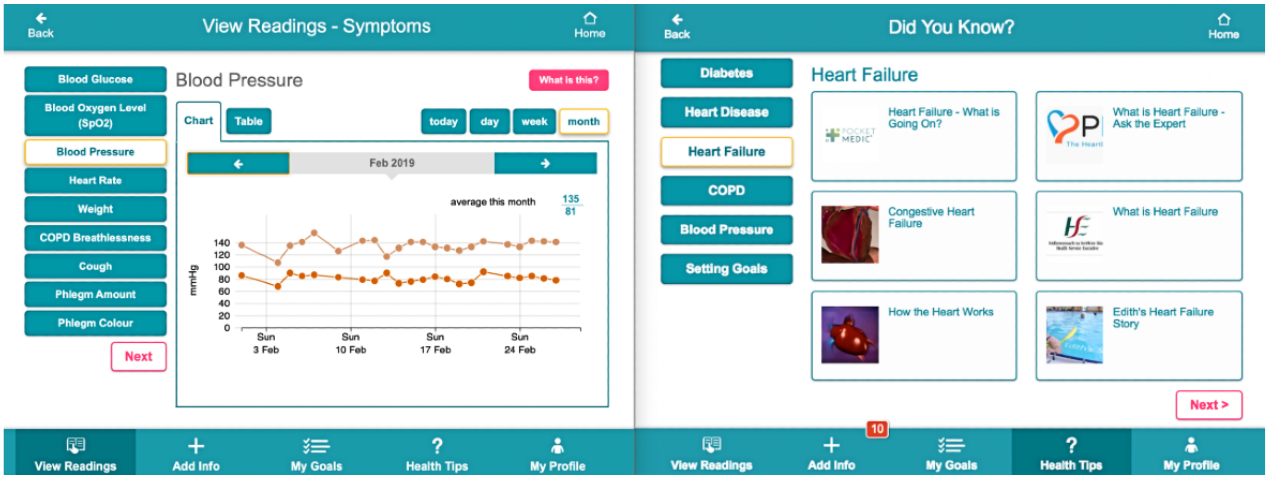


Figure 2. ProACT CareApp View Readings and Did You Know (education) interfaces.



From the person with multimorbidity perspective, the measurement and sensing devices and CareApps are the only platform technologies that they interact with. For CN users, CareApps tailored to their requirements are their point of interaction with the platform. The full list of devices used by the person with multimorbidity is included in Textbox 1.

Within the overall intervention, the primary point of information exchange with the end user (person with multimorbidity or CN support actor) is their CareApp. Textbox 2 outlines the structure and use of each CareApp. Figure 3 provides an overview of the person with multimorbidity home screen co-designed with users. The petal-based interface presents a brief summary of health and well-being data tailored to each person with multimorbidity's condition and self-management preferences. Using a color-coded *traffic light* system, persons with multimorbidity are alerted if their data are below or above their personal thresholds (pink), when they have not taken a reading for five days or more (orange), or when all is deemed normal for the person with multimorbidity (blue).

Textbox 1. Hardware or devices included in the person with multimorbidity ProACT toolkit (customizable according to the preferences and conditions of the person with multimorbidity).

Vital signs monitoring

- iHealth blood glucose monitor
- Withings blood pressure monitor
- Withings weight scales
- iHealth pulse oximeter

Well-being monitoring

- Withings watch (physical activity and sleep)

General

- Tablet device (eg, iPad)
- Broadband connection (supplied where needed)
- Peripheral supplies (batteries, extension leads, etc)

Textbox 2. CareApp components and associated features.

Persons with multimorbidity

- Home screen
  - Provides a quick overview of current health and well-being status, educational tip of the day, and goal progress tailored to individual disease profiles and self-management preferences (eg, blood pressure, step count, blood glucose, and daily questions). Home button and quick links to; view readings, add info; my goals; health tips and my profile (described below).
- View Readings
  - Users can choose to view their data across five key areas: symptoms, sleep, activity, daily question responses, and personal reflections on these responses.
- Add Info
  - Allows for manual entry of data from personal or nondigital devices and presents daily questions around general well-being, anxiety, satisfaction with sleep, and social interactions, as well as symptom monitoring questions for those parameters not measurable by a digital device (eg, breathlessness, sputum color for chronic obstructive pulmonary disease, and edema for Heart Failure).
- My Goals
  - Supports persons with multimorbidity to set personalized, flexible, and collaborative (with their care network) goals around their health and well-being (eg, exercise).
- Tips
  - Tips and educational content relating to conditions and self-management (covers information related to individual conditions; managing multiple conditions; medication management; activity, social, and goal planning, etc) as well as training on how to use devices (including the iPad) and the CareApps.
- My Profile
  - Supports the person with multimorbidity in having control over various aspects of their CareApp, including who they would like to share their data with and how often they would like reminders/alerts to take readings.

Informal carer

- The app view has a similar structure and navigation to the person with multimorbidity app. The home screen is based on a grid rather than a flower-shaped petal and presents a mixture of educational content (this includes the same content as in the person with multimorbidity app along with educational material on providing care to a person with multimorbidity, addressing topics such as self-care and time management) and person with multimorbidity health readings. The app also allows the user to send brief notifications that they have viewed the data and encourage the person with multimorbidity in their self-management practices.

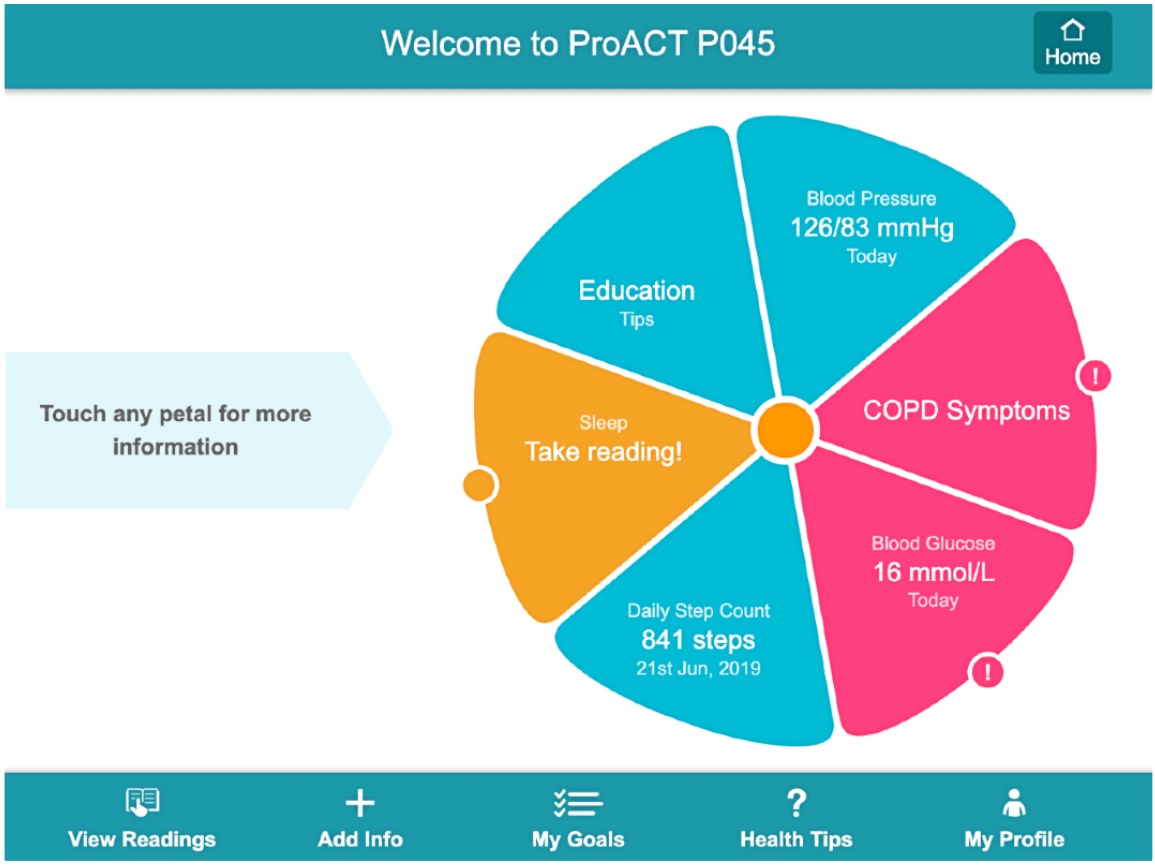
Formal carer

- The app has the same structure and navigation as the informal carer app with similar features. This app is limited so that formal carers can only view well-being data (such as sleep and activity) and not the person with multimorbidity's health (symptom data such as blood pressure, blood glucose, etc) readings, as this was not allowed due to regulations within the formal care organizations at trial locations.

Health care professionals

- The health care professional (HCP) CareApp has similar functionality to the formal carer CareApp in that HCPs can view a list of their patients and with permission, view their readings and their profile. Within this app, HCPs have access to the patient health (eg, symptom data) readings.

Figure 3. Persons with multimorbidity home screen user interface.



Methods

Study Design

The study was a longitudinal (12-month) PoC trial using an action research design and mixed methods approach. Action research is a period of investigation that *describes, interprets, and explains social situations while executing a change intervention aimed at improvement and involvement* [22]. The strength of this approach is the capability to generate solutions to practical problems, while garnering methods to understand the context of care, needs, and experiences of the person with multimorbidity group, drawing upon a range of research methods (eg, participant observation and in-depth interviews), to involve and build relationships with persons with multimorbidity and associated CN support actors. Within the PoC trial, this allowed for modifications to the technology based on quantitative and qualitative data collected from platform use statistics (eg, how often participants engage with the platform), platform data (ie, data coming from sensors and technologies), observational and usability testing methods to understand participant interaction with CareApps; person with multimorbidity and CN responses to interviews, questionnaires, and standardized assessments (eg, to evaluate quality of life, device proficiency, and usability).

Participant Inclusion and Exclusion Criteria

Persons with multimorbidity and their CNs (consisting of ICs, FCs, and HCPs) were eligible for this study. For inclusion, participants with multimorbidity were aged ≥65 years and had at least two of the following conditions: diabetes, chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF), or chronic heart disease or coronary artery disease including hypertension, atherosclerosis, angina, and arrhythmia; were capable of giving written informed consent; had access to broadband services (this refers to regional infrastructure); or lived in an area with sufficient coverage for mobile broadband or internet. The implemented service costs were covered as part of the trial.

CN participants were invited only on the permission of the person with multimorbidity and were required to be aged ≥18 years; to be providing care or support to a participant with multimorbidity; have access to a computer, tablet, or smartphone with an internet connection; and to be capable of giving written informed consent.

Sample

A purposive sample of 120 persons with multimorbidity (60 persons with multimorbidity per trial site in Ireland and Belgium) were recruited to participate in the PoC trial. Although sample size is often cited as a key factor in determining the potential success of a study, this is more relevant for randomized controlled trial studies that seek to answer specific questions regarding the efficacy of interventions (does it work?) and is less relevant for studies related to care and service improvement (how does it work?) [23]. Thus, to determine the PoC sample size, we took a pragmatic approach and reviewed two important factors: (1) it is large enough to provide a reliable analysis of the ecosystem and (2) small enough to be financially feasible. An analysis of the literature suggests that the overall sample size in a PoC, telemedicine and health focused information communications technology trial is low. A review of 1030

studies on telemedicine-based technological interventions for chronic disease management, looking at CHF (436 studies), stroke (422 studies), and COPD (172 studies) between 2005 and 2013 (including 35 systematic reviews and one review of the reviews), suggested that methodologically robust sample sizes for each condition were 17 participants (COPD), 21 participants (stroke), and 19 participants (CHF) [24]. The selected studies were conducted primarily in the United States and Europe.

Ethical Approval and Consent

Ethical approval was granted from participating health service organizations where recruitment took place and from academic partners. Informed consent was obtained on an individual basis in accordance with legal and ethical guidelines at each trial site region, following careful explanation of the study and provision of participant information and informed consent forms for the person with multimorbidity and participating members of their CN. All participants had the right to withdraw from the study at any time without any questions. Following a review of recruitment procedures by ethical committees in Ireland and Belgium, it was agreed that researchers should only contact a person's HCP if they had provided this consent.

Recruitment Procedures

In both Ireland and Belgium, participants were selected by several different methods, depending on which recruitment source they were accessed through, as outlined below:

- HCP and FC services (eg, in Ireland, the Health Service Executive and Home Instead Senior Care, and in Belgium, the hospitals UZGent and OLV Aalst, and the home care organizations Solidariteit voor het Gezin and Rivierenland): participants were selected from the service clinic records or via professional familiarity by HCPs employed directly in the services; HCPs within the services selected any potential participants who met the study inclusion criteria. Research team members did not view health service records to identify participants.
- ProACT *requirements gathering* panel: this research panel consisted of individuals linked to the first phase of the ProACT project, which focused on the design and development of the platform. Phase 1 received ethical approval, and participants consented to be recontacted regarding participation in the PoC trial.
- General practices: participants were selected by general practitioners (GPs) following the same procedures outlined for health professional services. Study information was also left in participating GP waiting rooms. Self-selecting participants who viewed this information could then directly contact the research team. Researchers assessed potential participants to determine whether they met the inclusion criteria (eg, whether they have been diagnosed with the ProACT conditions). If they were unsure, they were asked to check with their GP.
- Relevant older persons and chronic disease networks (eg, diabetes and COPD support groups): participants were self-selected. These organizations disseminated study information to their members, who could then directly contact the research team to participate. The same assessment procedures outlined for general practices were applied.
- Additional recruitment sources in Ireland included social media, radio, and local newspaper advertising; referrals directly from pharmacists; and participants who also referred another person with multimorbidity. Researchers contacted individuals who expressed interest in participating to ensure that they met the inclusion criteria.
- Additional recruitment sources in Belgium included several recruitment agencies (IVOX, Tendens, imec Living Lab, and Zorglab Aalst) via their respective panels, a pharmacy organization, a newspaper advertisement, and participants who also referred another Person with multimorbidity.
- In relation to the additional recruitment channels in Ireland and Belgium, researchers assessed potential participants to determine whether they met the inclusion criteria (eg, whether they had been diagnosed with the ProACT conditions). If they were unsure, they were asked to check with their GP.

Technology Deployment and Trial Setup

Invited person with multimorbidity participants had at least 7 days to review the participant information leaflet and have queries answered before technology deployment, which occurred over 2 visits to the person with multimorbidity's home. All researchers ensured that ProACT technology was deployed correctly and in a consistent manner across trial sites, following a strict deployment plan.

During the first visit, members of the research team obtained written consent from the participants. Each participant received devices depending on their condition profile. Participants also had the option to use any existing device (that they currently use at home) to measure an included parameter (eg, blood glucose monitor) by manually entering readings from the device into the person with multimorbidity CareApp. ProACT sensor devices were connected by Wi-Fi or Bluetooth, and a broadband internet connection was provided for the duration of the trial for any participants who did not have existing broadband in their homes. Participants were trained on how to use their ProACT devices during their initial visit. This included a brief introduction on how to use the ProACT CareApp and associated third party apps (eg, using the Withings HealthMate [25] app to take a blood pressure reading), as it was important that the person with multimorbidity was not overloaded with information on all ProACT technology features during the first visit. Participants were also provided with a paper-based manual, containing detailed instructions for using each device, along with common troubleshooting instructions.

Approximately 1 week after the first visit, the researchers conducted a second deployment visit. Detailed training on the CareApp took place with additional web-based training materials and videos made available through the ProACT CareApp. A study helpdesk, staffed by respective research team members in Ireland and Belgium, was available (from 9:30 AM- 4:30 PM, Monday to Friday) to assist participants with queries and technical difficulties. In both Ireland and Belgium, a dedicated clinical triage service for monitoring vital signs was also available (9 AM-5 PM, Monday to Friday). Triage personnel

(clinical nursing staff) had access to data from all persons with multimorbidities participating in the trial via the SIMS. A protocol for dealing with potential adverse events was developed using triage personnel. This included defining thresholds for abnormal vital sign values for each parameter being monitored. For example, thresholds for high and low blood glucose values were set in the SIMS for participants with diabetes. At the outset of the trial, global threshold values were set for all participants. However, over the course of the trial, such thresholds were often adjusted for individuals based on their normal values. If a participant's vital sign reading is outside the normal threshold, an alert is triggered on the SIMS triage interface, and as noted above, the participant will see a pink petal on their CareApp dashboard (Figure 3). In such instances, the triage nurse calls the participant to discuss the reading and determine whether an escalation is required. In both trial regions, clinical triage was not provided for nonvital sign data (eg, sleep or activity). Participants were reminded that this was a research study and that the triage service would not be considered as a replacement for normal care. In the event that a person with multimorbidity felt ill, they were recommended to seek medical advice or care as they normally would. Persons with multimorbidity were also reminded of this at regular intervals through a pop-up message on their CareApp, as requested by the ethics committees. Following completion of the second deployment visit, the participants began their trial period.

Invited members of the person with multimorbidity's CN were provided with access to their relevant CareApp that they could use on their own devices (smartphones, tablets, or computers). These customized CareApps allowed those in the CN to view relevant data from the participant with multimorbidity and educational materials related to condition management, well-being, and technology use. Participants with multimorbidity chose what data to share with each CN participant. The data viewed by HCP participants via their CareApp were not used to make clinical decisions. This was clearly outlined in the participant consent forms and information leaflets for all trial participants.

Trial Implementation, Outcome Measures, and Data Collection

Overview

The person with multimorbidity CareApp and toolkit were deployed to the person with multimorbidity in their homes for up to 12 months (participants used the app for a minimum of 9 months to cover the three action research cycles), across a 15-month period. Recruitment was staggered across action research cycle 1, as outlined in Figure 4. Introducing participants at various stages in the first action research cycle did not impact the final analysis, as elements of the system were redesigned or developed at 2 separate points, as part of the action research methodology. Invited CN participants also received access to their respective CareApp following nomination from the person with multimorbidity. Outcomes from the trial were assessed using a mix of ProACT platform data (engagement with app and data from sensors), CareApp questionnaires (self-report data on health and well-being), standardized assessments (Table 1), usability testing, and semistructured interviews. Further details of the process for the person with multimorbidity and CN members are shown in Table 1.

Figure 4. Study timeline across action research cycles for persons with multimorbidity.

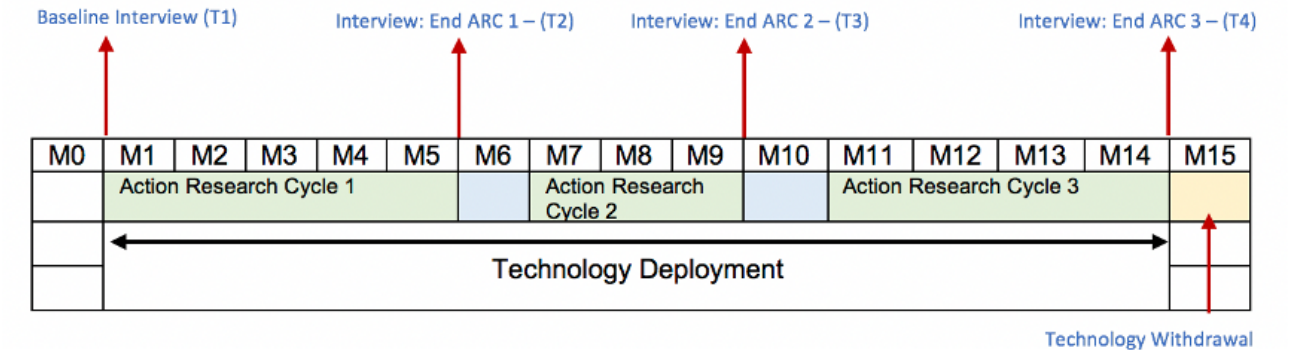


Table 1. Persons with multimorbidity key assessment domains and measures.[a]

Domain	Scale or measure	Description of measure	Assessment time point
Demographics	Self-report questionnaire[b]	• 7 self-report items collecting information on gender; date of birth; marital status; educational level; living alone or with others; employment status; primary occupation	T1
Medication list	Self-report list	• Interviewer recorded a list of the names, dosage, and frequency of each participant's medications. These data were used to initially populate the triage system for nurses, who then managed the ongoing collection and updated medication information	T1
Comorbidity index/disease burden	Multimorbidity assessment by self-report [26][b]	• 22-item list of common conditions or comorbidities: yes or no to indicate presence of conditions; then 5-point Likert scale to assess the extent to which each condition limits daily activities	T1 and T4
Technology use and proficiency	Mobile device proficiency questionnaire [27][b]	• 16-item scale to assess older adults' proficiency with mobile technological devices. Participant-rated ability to carry out different operations (internet, calendar, etc) on a 5-point Likert scale	T1 and T4
Cognitive function	Montreal cognitive assessment [28]	• 30-item scale measuring cognitive function in several domains; total score gives measure of global cognition; cognitive screening test	T1 and T4
Health related quality of life/health outcome measure	The 5-level EuroQol-5D version [29]	• 5-item self-report Likert scale: rate level of problems in five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression • 1-item visual analogue scale: own judgment of health status between 1 and 100 (from "best health you can imagine" to "worst health you can imagine")	T1, T2, T3, and T4
Quality of life	Control, Autonomy, Self-Realization and Pleasure-19 [30]	• 19-item scale measuring quality of life across four dimensions: control, autonomy, pleasure, and self-realization. Developed for an older adult population.	T1, T2, T3, and T4
Illness perceptions	Multimorbidity Illness Perceptions Scale [31][b]	• 22-item scale measuring illness perceptions related to multimorbidity in five dimensions: emotional representations, treatment burden, prioritizing conditions, causal links, and activity limitation	T1, T2, T3, and T4
Self-efficacy	General self-efficacy scale [32]	• 10-item self-report Likert scale: assesses perceived self-efficacy and ability to cope with daily hassles and stressful life events	T1, T2, T3, and T4
Locus of control	Multidimensional health locus of control scale [33]	• 18-item scale assessing beliefs about control individuals have over their own health in three main dimensions: internal control, chance, and power	T1, T2, T3, and T4
Social connectedness	Lubben social network scale [34]	• 18-item version to measure social connection in three domains: family, friends, and neighbors	T1 and T4 (18 item); T2 and T3 (6 item)
Depression and anxiety	Hospital Anxiety and Depression Scale [35]	• 14-item scale to measure depression and anxiety—developed as a screening tool for clinical levels of depression and anxiety	T1 and T4
Sleep quality	Pittsburgh Sleep Quality Scale [36]	• 9-item scale to assess subjective sleep quality: can provide an overall score and domain specific scores	T1 and T4
Fatigue	Functional Assessment of Chronic Illness Therapy Fatigue Scale [37][b]	• 13-item scale measuring feelings of fatigue, weakness, or energy and impact on daily activities	T1 and T4

Domain	Scale or measure	Description of measure	Assessment time point
Physical activity	Rapid Assessment of Physical Activity [38]	• 10-item scale to measure engagement in physical activities	T1 and T4
Usability	System Usability Scale [39]	• 10-item scale (Likert scale item) to provide subjective assessment of the usability of a technology system	T2, T3, and T4
User burden (technology)	User Burden Scale [40][b]	• 18-item[c] self-report scale used to evaluate user burden when engaging with technology. Likert scale	T2, T3, and T4

[a]Measures administered at each assessment time point are a subset of those listed in this table; an indication of the time point for each assessment is indicated in the table below.

[b]These measures were included as part of a paper-based questionnaire sent to participants in advance of the relevant interview.

[c]The original questionnaire has 20 items, but two questions in relation to financial burden were not used due to lack of relevance.

Person With Multimorbidity

Participants with multimorbidity participants were asked to use their CareApp to record information and measure key parameters related to their health and well-being on a regular basis (at their convenience), using sensors/devices and by answering self-report questions presented via the CareApp. They could also use their CareApp to view their recorded data and view educational materials and training videos related to condition management, well-being, and technology use. Adherence to physiological monitoring and use of the ProACT CareApp was monitored via system use statistics and data collected by the ProACT platform.

The persons with multimorbidity's questionnaire or assessment and qualitative semistructured interview data were collected across four time points: baseline (T1 during second deployment visit), at the end of each 3-month action research cycle (T2: month 3; T3: month 7), and in a final posttrial interview (T4: month 12). Figure 4 presents the study timeline for the persons with multimorbidity.

A paper questionnaire containing scales and measures suitable for self-completion was posted to each participant before each interview. This allowed the participant to complete these measures at a time that was convenient to them to reduce participant burden. Interviews were conducted at the participants' homes. The researchers reviewed the questionnaires briefly during interviews and assisted the participants in completing any questions where necessary. Table 2 presents the key assessment domains and measures issued to Persons with multimorbidity across the trial. Semistructured qualitative interviews were also conducted. Themes that were addressed in the interviews included understanding expectations of how ProACT might change health and well-being; persons with multimorbidity's use of ProACT; understanding how ProACT has changed self-management routines or strategies; the impact of ProACT on the role of the CN; frequency of health care use and cost of care; accessibility and usability of ProACT; user satisfaction and effectiveness of ProACT; and technology adoption and perceived future use of ProACT.

Following action research cycle 3, the trial concluded with a 1-month period of phased withdrawal of the technology. The timeline for the withdrawal of the technology was clearly explained to the participants throughout the study to manage participant expectations.

Table 2. Care network participant key assessment domains and measures.

Domain	Measure	Time point	Who
Demographics	Self-report items[a,b] • ICsc: age, gender, education, relationship with persons with multimorbidity, employment status, primary occupation, hours and type of care, and self-rated health • FCsd and HCPse: age, gender, duration of care provided to persons with multimorbidity, and type of care provided to persons with multimorbidity	T1 only	IC[c], FC[d], and HCP[e]
Technology use and proficiency	The Mobile Device Proficiency Questionnaire[a] [27][b]	T1 and T4	IC and FC
Usability	System Usability Scale [39]	T4 (with a subset only)	IC and FC
User burden (technology)	User Burden Scale[a] [40][b]	T4 (with a subset only)	IC and FC
Self-efficacy	General Self-Efficacy Scale[a] [32][b]	T1 and T4	IC and FC
Stress	Perceived Stress Scale [41]: 14-item scale of the degree to which situations in an individual's life are appraised as stressful	T1 and T4	IC and FC
Caregiver stress or psychological impact of caregiving	Caregiver Self-Assessment Questionnaire [42]: 18-item scale to measure the psychological impact (including stress) of caregivers	T1 and T4	IC
Caregiver burden	Zarit Burden Interview [43]: 22-item scale to measure the level of burden experienced by caregivers of patients	T1 and T4	IC

[a]Measures included as part of a paper-based questionnaire sent to participants in advance of the relevant interview.

[b]These measures were included as part of a paper-based questionnaire sent to participants in advance of the relevant interview.

[c]IC: informal carer.

[d]FC: formal carer.

[e]HCP: health care professional.

To assess whether the ProACT CareApps were usable and accessible, we conducted user evaluations with a small subset of users over repeated time points (in line with the action research cycles) during the trial. Participants were asked to conduct a number of tasks and give their opinions and feedback on the app using a *think-aloud* protocol [44]. This involves encouraging participants to verbalize what they are thinking as they use the app to expose potential usability and accessibility issues. Users were video-recorded during the evaluations. The resulting videos were transcribed, annotated, and analyzed by researchers to explore participant interactions with the technology and identify any barriers or difficulties that they encountered. The results of these evaluations were used to update the CareApp interfaces during the trial to enhance the usability and accessibility of the app.

Care Network

Overview

Consenting CN participants came to the trial during the person with multimorbidity's ARC 2 based on referrals from persons with multimorbidity during ARC 1. All users in the CN were provided with relevant data for the participant with multimorbidity participant and relevant training or educational content via their customized ProACT CareApp. These data could be viewed at a time and frequency that was convenient for them. The purpose was to evaluate the experiences of people within the CN using the ProACT platform and to understand whether they would find this type of system and data useful to them in their role, supporting the person with multimorbidity with his/her self-management, care, and treatment plans. Members of the research team collected feedback and evaluation data from people in the CN, as described in the following sections:

Informal Carers

A member of the research team conducted interviews with ICs, either by phone or at a location convenient to the participant at T1 (ie, when the CN participant consented to take part) and T4 (at the end of the trial). While a person with multimorbidity could have more than one IC in their CN who had access to the CareApp, only one, the primary IC, was asked to complete the assessments or interviews. During this interview, the researcher administered scales and questionnaires to collect information on health, psychosocial, psychological, and demographic characteristics (Table 2). A semistructured, qualitative interview was also conducted, covering areas including expectations of the use of ProACT, usability of the CareApp, whether ProACT has benefitted them in their role, and how they felt it benefited the person with multimorbidity. ICs were also asked to complete a short questionnaire to provide feedback on the technology at the end of the trial (T4).

FCs and HCPs

Participants were asked to complete a short questionnaire at T1 (ie, when the CN participant consented to take part) and T4 (at the end of the trial). These questionnaires collected information on the usability and acceptability of the technology, along with

experiences of using the ProACT platform (Table 2). FC and HCP participants also participated in qualitative interviews or focus groups at baseline (T1) and posttrial (T4). Themes addressed were whether ProACT helped in their role, how they felt it benefitted the person with multimorbidity, what would they change about the system, and the usability of the CareApps.

Data Analysis

As a PoC trial, a key outcome is to understand whether a larger trial that makes a definitive assessment of benefit is warranted. Pilot and PoC studies are more about learning than confirming or formally assessing evidence of the impact or benefit associated with an intervention. Therefore, analyses should focus on providing descriptive evidence and indications of the range of possible responses rather than on formal hypothesis testing [45]. Analyses were therefore mainly descriptive and aimed at understanding user experiences in relation to the use of the ProACT platform. Qualitative methods encouraged participants to speak about their experiences of living with and managing multimorbidity and their experience of using ProACT technologies. Quantitative data analysis ensured comparability and consistency of questions across participants and time points.

Qualitative data were analyzed using thematic analysis (TA) to identify and understand emerging themes. An inductive approach was adopted to identify themes at a latent level. An inductive TA is data-driven, as opposed to analyst-driven TA [46]. This approach helps generate novel insights from interview data that may have differed greatly from pre-existing research in the area pertaining to the research questions. This is essential to the action research design of the trial to analyze differences in responses across time points. Furthermore, identifying themes at a latent or interpretative level goes beyond the semantic meaning of the presented data, encouraging interpretative analysis by the researchers. Across the PoC trial locations, a protocol (including in-person and web-based training) was put in place to ensure that the TA followed a strict analytical process, with researchers ensuring transparency and consensus across each step. Individual researchers coded the transcripts according to an established analysis protocol. Pairs of researchers collapsed and categorized codes into themes. Discussions and recoding workshops were conducted to ensure agreement on theme and subtheme names were reached among the wider trial site teams. In Ireland, NVivo for Mac (version 11; QSR International) [47] was used to conduct the coding part of the analysis, while in Belgium, MAXQDA Analytics Pro (VERBI GmbH; [48]) was used. Using different software did not impact the analysis, as the same methodological approach was used at both sites.

Quantitative questionnaire data were analyzed at both trial sites using SPSS statistical software (version 25; IBM SPSS Statistics [49]). The primary analysis was to evaluate changes in scores between the assessment points. Descriptive statistics were used to summarize participant demographic data and general outcomes from the questionnaire data. Sensitivity analysis was performed to treat missing data. Missing data were imputed based on the methods suggested for each questionnaire. In case a standardized method was not reported in the literature, mean substitution, using similar imputations for all questionnaires, was used for all time points, if less than 20% of the data were missing. Initial analyses were conducted to assess the distribution of all variables and check for relevant assumptions, including normality. Given the small sample size at each trial site, the majority of variables violated normality. Therefore, to maintain the intrinsic value of the quantitative data in this circumstance, no transformations were performed, and for further inferential analysis, nonparametric (Friedman and Wilcoxon signed-rank) tests were implemented.

The SIMS component of the ProACT platform supported the analysis of additional data (including sensor data from the devices and engagement with the devices and ProACT CareApps). Metrics of interest for analysis included symptom (eg, blood pressure, blood glucose, SpO_2, and weight) trends or patterns over time; the ratio of alerts to symptom readings over time; trends or patterns in activity and sleep data over time and engagement with various parts or features of ProACT and the CareApp; and responses to self-report questions on health and well-being.

Results

This was a 44-month funded study (2016-2019). The implementation phase was completed in June 2019. In total, 120 persons with multimorbidity (60/120, 50% in Ireland and 60/120, 50% in Belgium) and 73 CN participants (43/73, 59% in Ireland and 30/73, 41% in Belgium) were recruited. The trial outcomes are at various stages in the process of publication from 2021. We believe that the ProACT platform can potentially improve how older adults with multimorbidity self-manage their health and well-being from home, supported by their CN.

Discussion

Summary

Across the EU, there is a growing drive to meet the complex care needs of older people with multimorbidity. eHealth or digital health options are now recognized as potential support [22]. However, EU health care systems are not yet equipped to address the comprehensive care needs of people with multimorbidity [50]. The use of innovative person-centered digital health technologies are increasingly viewed as a means to address the challenge of multimorbid care (eg, tools to support patients' self-management and multidisciplinary collaboration between professionals [51] may play a key role in advancing the integration of health and social care needs). Despite this, research into the design and development of digital health systems, focusing on multimorbidity management, particularly for older adults, is in its infancy.

It is important to re-emphasize that the focus of this research is on multimorbidity (multiple co-occurring chronic conditions, but with a focus on multiple conditions) as opposed to comorbidity (multiple co-occurring chronic conditions, but with a focus on a singular condition) [52], which seeks to advance a multi-country understanding of the challenges for defining, designing, implementing, and evaluating a digital intervention, focused primarily on multimorbidity management across diverse populations. To our knowledge, ProACT is also the first digital

intervention to systematically incorporate (and evaluate) behavioral change and human-computer interaction methods to advance persons with multimorbidity's self-management practices in relation to multimorbidity.

With the mixed methods, action research PoC study of the ProACT platform, we are further addressing the need for increased longitudinal and applied research in the areas of digital health, integrated care, and multimorbidity management. The two primary aims of ProACT are as follows:

- To explore the potential benefits of technological support (ie, the ProACT platform) that aim to improve integrated care and self-management practices for older persons with multimorbidity.
- To obtain feedback from all relevant participant groups on their experiences using the ProACT platform and on the potential for the ProACT platform to improve integration of care and support disease management for older persons with multimorbidity.

Outcomes from trials [53] are positive in terms of user engagement with ProACT and a shift in behavior to adopt this digital intervention. These outcomes will help advance both the state of the art on how to design and conduct research with older persons with multimorbidity and their CN and deliver a new digital health solution to address the challenge of multimorbidity management and care.

Conclusions

Although substantial research has been conducted on the implementation and use of digital health technologies to address single-disease management, a clear gap exists in understanding the requirements for managing multimorbidity from the perspective of older persons with multimorbidity and their CN and how supported self-management happens in practice. The findings from the ProACT PoC trials will contribute significantly to the research in this field. With 120 older persons with multimorbidity and 73 CN participants, the trials have provided a novel multi-stakeholder, multi-country perspective on multimorbidity self-management and integrated care. With a primary focus on qualitative outcomes, the PoC trials have provided detailed insight into the person with multimorbidity's self-management journey facilitated by a digital health platform, longitudinally over 12 months. Outcomes will evaluate the impact of ProACT at a PoC level to determine whether a larger trial, which makes a definitive assessment of benefit, is warranted.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
ProACT Evaluation Summary Report European Commission.
[PDF File (Adobe PDF File), 115 KB - resprot_v10i12e22125_app1.pdf]

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Abbreviations

CHF: chronic heart failure
CN: care network
COPD: chronic obstructive pulmonary disease
EU: European Union
FC: formal carer
GP: general practitioner
HCP: health care professional
IC: informal carer
PoC: proof-of-concept
SIMS: subject information management system
TA: thematic analysis

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Protocol

A Digital Health Innovation to Prevent Relapse and Support Recovery in Youth Receiving Specialized Services for First-Episode Psychosis: Protocol for a Pilot Pre-Post, Mixed Methods Study of Horyzons-Canada (Phase 2)

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Abstract

Background: Psychotic disorders are among the most disabling of all mental disorders. The first-episode psychosis (FEP) often occurs during adolescence or young adulthood. Young people experiencing FEP often face multiple barriers in accessing a comprehensive range of psychosocial services, which have predominantly been delivered in person. New models of service delivery that are accessible, sustainable, and engaging are needed to support recovery in youth diagnosed with FEP.

Objective: In this paper, we describe a protocol to implement and evaluate the acceptability, safety, and potential efficacy of an online psychosocial therapeutic intervention designed to sustain recovery and prevent relapses in young adults diagnosed with FEP. This intervention was originally developed and tested in Australia and has been adapted for implementation and evaluation in Canada and is called Horyzons-Canada (HoryzonsCa).

Methods: This cohort study is implemented in a single-center and applies a pre-post mixed methods (qualitative-quantitative convergent) design. The study involves recruiting 20 participants from a specialized early intervention program for psychosis located in Montreal, Canada and providing them with access to the HoryzonsCa intervention for 8 weeks. Data collection includes interview-based psychometric measures, self-reports, focus groups, and interviews.

Results: This study received funding from the Brain and Behavior Research Foundation (United States), the Quebec Health Research Funding Agency (Canada), and the Canada Research Chairs Program. The study was approved by the Research Ethics Board of the Centre intégré universitaire de santé et de services sociaux de l'Ouest-de-l'Île-de-Montréal on April 11, 2018 (#IUSMD 17-54). Data were collected from August 16, 2018, to April 29, 2019, and a final sample of 20 individuals participated in the

baseline and follow-up interviews, among which 9 participated in the focus groups. Data analysis and reporting are in process. The results of the study will be submitted for publication in 2021.

Conclusions: This study will provide preliminary evidence on the acceptability, safety, and potential efficacy of using a digital health innovation adapted for the Canadian context to deliver specialized mental health services to youth diagnosed with FEP.

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KEYWORDS

psychotic disorders; mental health; telemedicine; young adult; mental health services; e–mental health; virtual care; schizophrenia; eHealth; social support; therapy; psychiatry; psychology

Introduction

Background

Psychotic disorders have a lifetime prevalence of 3% [1] and include symptoms such as delusions, hallucinations, disorganized thoughts and behaviors, poverty of thought and affect, apathy, and deficits in verbal memory and executive functioning [2,3]. The onset of psychosis typically occurs during adolescence or young adulthood (ie, between the ages of 15-25 years), often leading to substantial impairments in social and community functioning, and ultimately derailing transitions toward life goals. Psychosis is associated with three of the top five leading causes of disability in the world (ie, major depression, bipolar disorder, and schizophrenia) for adolescents and young adults [4], incurring substantial costs for the health care system and society in terms of loss of productivity. As such, psychotic disorders have been described in the literature as among the most scientifically challenging and disabling mental disorders [5,6].

Over the past two decades, a specialized early intervention approach has been developed for youth diagnosed with first-episode psychosis (FEP) with the ultimate goal of achieving symptom remission, relapse prevention, and social recovery [7,8]. Many of these programs accept patients with schizophrenia spectrum psychoses and affective psychoses. Specialized early intervention services typically involve medication, psychosocial services (eg, illness education, lifestyle management, employment and education support, or family education and support), and case management [7,8]. The short-term (ie, 1-2 years) benefits of this specialized approach compared to routine care have been reported in several randomized controlled trials, quasi-experimental studies, and reviews of the literature [9-11]. Randomized controlled trials have confirmed that young people treated in a specialized early intervention service have higher rates of adherence; lower relapse and hospitalization rates; better quality of life; and improved outcomes at 12, 18, and 24 months compared to patients in routine care [11-13].

Although the specialized early intervention approach has shown promise in improving outcomes in youth with FEP, the need to develop better psychological, social, and vocational interventions for this population continues to be a priority. This is because there are several clinical challenges associated with treating this population that are of high concern for clinicians, patients, and families. These include high rates of relapse (estimated at 30%) [14,15] and high rates of service disengagement, which range between 20% to 40% across specialized early intervention programs [16,17]. There are also challenges in sustaining improvements in symptoms and global functioning beyond the first 2 years of receiving specialized services [18].

To date, specialized early intervention services have been restricted to models of care that are predominantly delivered in person. However, research suggests that after an initial period of receiving intensive treatment, some youth begin to experience the phenomenon of *overengagement* or *engulfment* by services and prefer a less intensive form of follow-up [17,19]. Moreover, relying entirely on services delivered in person may not be feasible given that specialized early intervention is resource-intensive, with typical case manager-to-patient ratios being 1:25 and services often delivered in the community, which presents a range of challenges including, for example, loss of productivity and lack of access to transportation [20]. Research is needed on new models of service delivery that are accessible, sustainable, engaging, and effective in supporting recovery in youth diagnosed with FEP. This is especially relevant during the first 5 years of the illness as this phase is considered as the “critical period” when clinical and psychosocial interventions have the highest impact [21]. There is also a need for sustainable models of service delivery that can meet the need for psychosocial support beyond the time frame of receiving specialized early intervention for psychosis services.

Information and communication technologies (ICTs) offer a promising avenue for addressing the aforementioned clinical challenges by increasing access and quality of mental health services, and ultimately supporting the process of recovery for youth experiencing FEP [22-25]. These technologies can potentially deliver services using a less intensive and more engaging format that is compatible with the culture of young people growing up in the 21st century. Our prior research conducted in a Canadian specialized early intervention for psychosis setting has shown that more than 90% of youth diagnosed with FEP receiving specialized services have regular access to the internet through computers and mobile devices, and many are receptive to the idea of using these technologies for mental health care [24,25]. However, despite the potential of technology for improving mental health care for youth, this area has received limited research attention in the Canadian

field of early intervention for psychosis. Consequently, few studies exist on the acceptability, safety, and efficacy of digital health innovations to support recovery in youth diagnosed with FEP. Country-specific research on digital mental health care is relevant for advancing policy and practice that is contextualized to the needs of a nation's population. For example, the Canadian health care landscape has particular characteristics that justify locally driven digital mental health service research. According to Martin and colleagues [26], Canada has a health care system that is managed through provincial and territorial insurance plans; a vast geography; and a significant population diversity in terms of density, culture, and language [26]. These characteristics are important considerations for adapting, implementing, and evaluating digital health service innovations in the Canadian context.

The Horyzons Intervention Platform

Members of our team have developed an innovative web-based therapeutic intervention platform, called Horyzons, designed to sustain the treatment benefits of early intervention for psychosis and to promote long-term social functioning [27]. This intervention delivers evidence- and strengths-based targeted psychosocial interventions and is enhanced by a moderated online social networking environment. Youth diagnosed with FEP are guided through interactive games to identify, discuss, and develop key personal strengths in an online environment and in real life to address relapse risk factors and psychological well-being.

Specifically, Horyzons consists of *interactive psychosocial interventions* that are informed by evidence-based psychosocial interventions targeting key risk factors and salient domains in the early recovery process (including psychoeducation, vocational recovery, early warning signs of relapse, depression, social anxiety, personal strengths). Youth with FEP are prompted to practice newly acquired skills through over 350 purpose-developed behavioral activities, which are designed to bridge the gap between online therapy and real-world outcomes (eg, tips on how to use personal strengths to cope with stress, enhance well-being, or improve social connectedness). Horyzons also includes *peer-to-peer web-based social networking* that includes a web feed (or news feed) where youth with FEP and moderators can post comments and information, upload pictures and videos, and *like* different types of content, and includes *moderation* that is conducted by clinicians and peer support workers.

Clinician moderators provide guidance, monitor clinical status, and ensure safety of the social networking environment. Clinician moderators develop brief case formulations that are presented at weekly supervision meetings with the senior clinical research team. Clinician moderators send each youth tailored content suggestions (eg, step or action) weekly based on the young person's needs, interests, and strengths. Suggestions appear on the young person's home page, and they receive a text notification via the intervention platform's SMS text messaging feature. Peer support moderators are young adults with lived experience who have received peer support training and who have been stable and in remission for a minimum of 2 years. Their role includes assisting with orientation to the Horyzons intervention platform, providing support, and fostering engagement. For example, peer support moderators reach out to new users or users that have not logged into the intervention platform after a week. They also post *icebreakers* and comments, *like* the posts of users, and engage in role modeling activities. They receive supervision from the clinical research team. The integrity of the moderation is ensured through a detailed moderation manual, and all moderators participate in weekly to biweekly group supervision sessions with senior members of the team. The intervention platform includes a comprehensive safety protocol following best practices in internet research involving vulnerable people [28], which considers 3 levels of security (ie, online safety, clinical safety, and system security). This safety protocol (including criteria and the process for withdrawal from the study) was successfully used in previous research on Horyzons [27,29].

Research and Development of Horyzons and Canadian Adaptations

A detailed description of the intervention, its development, and its subsequent adaptation for the Canadian context can be found in our previous published work [30-32]. The first version of Horyzons was developed iteratively over a 30-month period following participatory design principles involving patients, clinical psychologists, computer programmers, health informatics experts, web and graphic designers, and professional writers. It was then pilot-tested on a sample of 20 young adults for its feasibility, acceptability, utility, and safety considerations over 1 month [27]. Results showed that there were no dropouts and incidents (ie, adverse events or inappropriate use) during the pilot, and system use was high, with a total of 275 log-ins. Specifically, 70% of participants used the system for at least 3 weeks, 95% used the social networking features, and 60% completed at least 3 therapy modules. Moreover, all participants found the system easy-to-use, 70% considered it to be a useful long-term treatment option beyond discharge from early interventions services, 100% considered it to be safe, 85% would recommend it to others, and 100% reported moderation to be helpful. With respect to potential clinical improvements, 70% considered the therapy modules to be helpful, and 60% reported that Horyzons significantly increased their social connectedness. Paired samples *t* tests also revealed a significant reduction in depressive symptoms at follow-up (d=0.60; *P*=.02) [27]. The safety strategy pertaining to the intervention study addressed both static (eg, personality trait variables) and dynamic factors (mental health status), and results indicated no clinical or security problems related to the use of Horyzons during the pilot study [27,33]. Additionally, a second version of Horyzons was evaluated in Australia within the context of a 5-year follow-up randomized controlled trial [29], with results recently published. Horyzons has also been piloted in the United States, and preliminary analyses of within-group effect sizes demonstrated the greatest improvements in psychotic symptoms (d=0.65-0.81), followed by depressive symptoms (d=0.14-0.30) and social functioning (d=0.18) [34]. Horyzons has also been adapted for young people at ultra-high risk for psychosis, and preliminary research suggests that it is effective in improving social functioning in this population [35].

We recently completed a phase 1 adaptation study of the Horyzons intervention platform in two specialized early intervention clinics for FEP in 1 urban and 1 urban-rural setting, in 2 Canadian provinces [30]. The phase 1 study involved a mixed-methods approach, combining descriptive qualitative and quantitative methods, and was informed by the literature on adaptation of psychosocial interventions [31,36]. Data was collected using focus groups, semistructured interviews, and consultations. The main purpose of the phase 1 study was to determine the types of adaptations needed to the website and the therapeutic intervention protocol before implementing the intervention live. Considering participants' and clinicians' perspectives on the platform, we adapted the Horyzons intervention for Canada (HoryzonsCa). Specifically, adaptations were made to content on employment, study, and volunteer opportunities, and postdischarge information (eg, finding a family doctor); general use and safety features (eg, terms of use, translation of Australian list of problem words to French, safety protocol); and clinical moderation protocol (eg, clinical notes and supervision structure). However, in this phase 1 study, participants had limited access to all the components of the HoryzonsCa intervention; for example, they had access to the therapeutic content modules but not to clinical and peer support moderation nor were they able to communicate with other participants. Their access was also time-limited to 2 weeks. Thus, we designed this phase 2 pilot protocol to assess the acceptability, safety, and potential efficacy of the HoryzonsCa intervention with all features of the intervention accessible to a target sample of 20 to 25 participants over 8 weeks.

In this paper, we describe the research protocol informing this phase 2 live pilot study of HoryzonsCa. The protocol is largely informed by the Technology Acceptance Model (TAM) [37,38], which is a well-established model focusing on individual perceptions pertaining to ease of use and usefulness of a technology, and the eHealth Adaptation Framework [31], which considers broader factors such as language, culture, and context pertaining to localized implementation of an eHealth innovation. Our attention to the adaptation aspects of Horyzons is in alignment with strategies recommended in the literature to better capture complexities pertaining to the implementation of eHealth innovations [39]. Moreover, during our analysis and interpretation of the results, we will also begin to consider models stemming from sociotechnically informed theories of change at the levels of individual, organization, and system, such as the nonadoption, abandonment, spread, scale-up, sustainability framework, which is intended to facilitate reflection on factors influencing adoption, nonadoption, abandonment, spread, scale-up, and sustainability of eHealth technologies [40]. Such reflections will be important to inform the design of a scaled-up evaluation of the intervention, including the types of data that will be important to collect.

Objectives and Hypotheses

The aim of this study is to determine the acceptability, safety, and potential efficacy of HoryzonsCa in supporting recovery in young adults receiving specialized services for FEP. Specifically, our objectives are:

- To determine the acceptability of an online therapeutic platform (HoryzonsCa). *Primary hypothesis:* HoryzonsCa will be acceptable to patients. Our conceptualization of acceptability is partially informed by the TAM [37,38], which posits that attitudes toward using a technology influence intention ("acceptance") to use a technology, which is a direct determinant of behavior [37,38]. The attitude construct is composed of perceived usefulness (an individual's perception that using an information technology [IT] system will be helpful to them) and perceived ease of use (an individual's perception that using an IT system will be free of effort) [38]. Patients' acceptance regarding the use of technologies in health care delivery has been extensively assessed using the TAM model and its derivatives, which highlight the importance of considering factors beyond the individual's attitudes [41-44]. As such, we also include the concept of adoption in our conceptualization of acceptability, which "is defined as the intention, initial decision, or action to try or employ an innovation or evidence-based practice" [45]. Thus, using this combined understanding of acceptability, in this study, the intervention will be considered acceptable if at least 70% of participants provide positive reports on general experience of the platform, 60% provide positive reports on perceived usefulness (helpfulness), 60% provide positive reports on ease of use, and 60% log onto the site at least 4 times over the 8-week follow-up. These percentages are hypothesized based on the results obtained from the original Horyzons pilot study [27]. We will also determine acceptability through qualitatively assessing perceptions of HoryzonsCa in relation to likes, dislikes, perceived barriers and facilitators to using the platform, and ease of use/experiences of navigating and using its key features (eg, various psychoeducational modules or café) and through exploratory analysis of website use analytics.
- To assess the safety of the HoryzonsCa platform. *Secondary hypothesis:* HoryzonsCa will be safe, defined as no adverse events, reports, or incidents (eg, hospitalization, suicidal ideation, or disclosure to treatment team regarding harm) related to use of the platform from baseline assessment to 8 weeks follow-up, and at least 70% of participants report that they agree or strongly agree with the perceived safety of the platform and perceived confidentiality of information shared on the platform. We will also determine safety through qualitatively assessing perceptions of the HoryzonsCa platform (eg, experiences, concerns).
- To assess the potential efficacy of the HoryzonsCa intervention/platform. *Secondary hypotheses:* Participants will show moderate to large improvements (Cohen $d \geq 0.5$) on measures of social functioning (Social and Occupational Functioning Assessment Scale; Personal and Social Performance Scale) and either improvement of 1 point or no deterioration on the Clinical Global Impression Scale, from baseline to 8 weeks follow-up, as our primary foci for assessing potential efficacy. We will also assess for improvements in social support, self-esteem and perceived strengths, and symptoms. The analysis will help determine pre-post effect sizes on a number of variables conceptually targeted by the platform. These effect sizes will be used in

a future clinical trial (eg, randomized controlled trial) for the purpose of statistical power calculation and estimation of sample size.

Methods

Study Design and Setting

This cohort study is implemented in a single center and applies a pre-post mixed methods (qualitative-quantitative convergent) design. Participants are recruited from Prevention and Early Intervention Program for Psychosis (PEPP)–Montreal, the Douglas Mental Health University Institute in Montreal, Quebec. This program provides a comprehensive range of services for young people diagnosed with FEP and follows best practice guidelines for real-world settings [7,8]. Treatment includes psychiatric evaluation and follow-up, modified assertive case management tailored to meet the needs of young patients in the early phase of illness [8] including support toward treatment goals (eg, illness education, return to work or school, and crisis intervention), family support and intervention, and psychosocial group interventions (eg, physical, recreational, recovery, and support).

Participants, Sample Size Considerations, Recruitment, and Orientation Process

The target sample is 20 to 25 participants that are patients receiving services from PEPP-Montreal. This sample size was determined by the following factors: feasibility of participant recruitment within a 2- to 3-month time frame, budget related to staffing of moderators, and ensuring adequate number of active users on the platform for the social networking features to function effectively. This sample size has also shown to be sufficient to pilot-test the feasibility and acceptability of Horyzons, as illustrated in the prior pilot study [27] while also acknowledging the limitation of this small sample size for efficacy testing (which is not the main objective of this pilot study). Participant inclusion and exclusion criteria are presented in Textboxes 1 and 2, respectively.

Textbox 1. Inclusion criteria.

Participants

- Diagnosis of a psychotic disorder (including affective or nonaffective psychoses) by a clinician
- Receiving specialized services for a first-episode psychosis at the recruitment site
- Considered symptomatically stable and capable of interacting on the online platform and participating in focus groups and semistructured interviews, as judged by their primary clinicians (ie, psychiatrist, case manager)
- 18 years or older
- At low or at most moderate severity score (4 or below) on the suicidality item of the Brief Psychiatric Rating Scale, version 4 [46] for the month preceding study entry. This criterion is to minimize risk for the need of urgent intervention regarding comments pertaining to suicidal ideation and plans posted on the social network or to the moderation team (given that the platform is not monitored 24/7) and to reduce potential anxiety or distress in other participants from overexposure to content focused on suicide.
- Able to nominate an emergency contact

Textbox 2. Exclusion criteria.

Participants

- Intellectual disability
- Hospitalized at the time of recruitment
- Unable to speak or read English
- Diagnosis of antisocial personality disorder or borderline personality disorder
- In the acute phase of mania or psychosis to the extent that their mental status may soon require hospitalization or would impede the participant's ability to provide informed consent or to participate in interviews and focus groups

In terms of the recruitment process, a member of the research team met with clinicians at the recruitment site to describe the project, including the rationale, objectives, inclusion and exclusion criteria, and methods. The treating clinicians screened all participants. The treating clinicians referred patients who fulfilled the aforementioned inclusion and exclusion criteria. The treating clinicians provided a copy of the study information handout to prospective participants when introducing the study so that they had time to consider the study and ask questions about it. Once participants completed screening for eligibility, were identified as being eligible to participate, and expressed interest to learn more about the study, they were contacted by a member of the research team to receive further details about the project, their participation, and the informed consent process. A study information brochure was provided to participants as a summary of the information contained in the consent form for user-friendly access to key information about the project.

Participants received detailed information concerning their participation including date, time, and duration of scheduled meetings, interviews, and activities related to study participation. In addition, they were contacted 24 hours prior to any scheduled interviews to confirm their participation. They were contacted according to their preferences either by phone, e-mail, or in

person when attending the clinic. After providing written informed consent, the research assistant administered the baseline measures, the results of which were also used to confirm clinical stability and eligibility to participate. In a subsequent HoryzonsCa Orientation Meeting, participants were oriented to the HoryzonsCa website and provided with login information. Participants were then able to access the website, at their convenience, over a period of 8 weeks. They were encouraged to log into the website at least 1 time per week for a minimum of 15 minutes per visit. Access to HoryzonsCa was in addition to the services that participants already receive from PEPP-Montreal. The Horyzons safety protocol [27] was adapted for this study and included an assessment procedure for risk of suicide attempt. This assessment has been implemented by members of the team in the context of other psychosocial intervention research projects with the same clinical population. All research team members were trained in the safety protocol. Given that it was the first time the website and safety protocol was used in a Canadian context, the results of this study will help identify potential modifications to improve the safety protocol for future research on HoryzonsCa. The details of the adapted safety protocol and withdrawal criteria are provided in Multimedia Appendix 1.

Data Collection

We collected quantitative and qualitative data through interview-based psychometric measures, self-reports, focus groups, and interviews. An initial interview consisted of completing a self-reported sociodemographic questionnaire, the Technology Access, Use, and Competency Questionnaire (TAUC-Q), and a combination of self-reported and interviewer-administered clinical measures (for social functioning, global improvement and therapeutic response, social support, self-esteem and perceived strengths, and symptoms). The TAUC-Q and the clinical measures were also administered during the exit interview at the 8-week follow-up along with the interviewer-administered Horyzons-Canada Acceptability, Usability, Safety, and Impact Questionnaire (HC-AUSI-Q). Participants were also invited to a HoryzonsCa Meet-up and Focus Group during the follow-up period. Multimedia Appendix 2 provides an overview of the schedule of assessments that took place across the duration of the follow-up.

Outcome Measures

Sociodemographic Characteristics and Access and Use of Technology

Participants were asked to complete a sociodemographic questionnaire (self-report) consisting of nine questions regarding gender, age, length of service use, highest level of education completed, ethnicity, vocational status, living situation, marital status, and annual income. Participants' access, use, and attitudes in relation to technology was assessed using the TAUC-Q (self-report), which includes 10 questions regarding participants' access and use of internet and mobile technology (eg, smartphone, computer, social media, text, or email) and perceived competency of technology. Their responses on these questionnaires will allow us to estimate the transferability of our results and to better understand participant experiences, use, and perceptions of the platform.

Acceptability

Acceptability (TAM components of perceived ease of use and perceived usefulness) was measured through the HC-AUSI-Q and website use analytics. The HC-AUSI-Q is an adaptation of questionnaires used in the HoryzonsCa phase 1 adaptation study [30,31], the Horyzons Usability Questionnaire from the original Horyzons pilot study [27], and the Website Analysis and Measurement Inventory [47]. The interviewer-administered HC-AUSI-Q consists of a questionnaire and a semistructured interview that includes 16 close-ended and 10 open-ended questions on perceived ease of use, perceived usefulness, enjoyment, and safety. The questions pertaining to acceptability address the topics of general experience (eg, "I had a positive experience on Horyzons-Canada"), usefulness (eg, "Horyzons was useful to identify my warning signs for relapse"), and ease of use (eg, "Overall, the platform is easy to use"). Acceptability in terms of adoption was assessed using website use analytics (eg, frequency of log-ins and patterns of use over 8 weeks).

Safety

Safety, which considers 3 levels of security (ie, online safety, clinical safety, system security), was assessed using two specific questions (ie, "I felt safe on Horyzons-Canada" and "I felt like the information shared on Horyzons-Canada was confidential") in the HC-AUSI-Q. In addition, any adverse events, reports, or incidents (eg, hospitalization, suicidal ideation, or disclosure to treatment team regarding harm) in relation to the use of the online system were carefully monitored and quantified over the study duration. The causal relationship between adverse events and use of HoryzonsCa was determined based on detailed documentation of each event and through discussion by members of the research and moderation team. All adverse events, reports, and incidents (eg, hospitalization, major deterioration in ability to function) were also submitted to the ethics review board for further examination.

Potential Efficacy

In terms of *primary clinical measures*, *social functioning* was measured using the interviewer-administered Social and Occupational Functioning Assessment Scale that comprises a 100-point single item to assess social and occupational functioning [3] and the interviewer-administered Personal and Social Performance Scale that consists of a 100-point single item to assess functioning in four domains: socially useful activities (including work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors [48]. In terms of *secondary clinical measures*, *global improvement and therapeutic response* was assessed using the clinician-administered Clinical Global Impression Scale that consists of two items to assess global improvement and severity of illness [49]. We also assessed *social support* using the self-reported Multidimensional Scale of Perceived Social Support that includes 12 items (eg, "I get the emotional help and support I need from my family) [50]; *self-esteem and perceived strengths* using the self-reported Self-Esteem Rating Scale that consists of 40 items (eg, "I feel that I am a very

competent person") [51], the self-reported Strengths Knowledge Scale that includes 8 items (eg, "I know what I do best") [52], and the self-reported Strengths Use Scale that consists of 14 items (eg, "I am regularly able to do what I do best") [52,53]; and *symptoms* using the following interviewer-administered assessments: the Scale for the Assessment of Positive Symptoms that consists of 34 items in four symptom domains (hallucinations, delusions, bizarre behavior, and positive formal thought disorder) [54]; the Scale for the Assessment of Negative Symptoms that includes 25 items in five symptom domains (affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality, and attention) [55]; the Brief Psychiatric Rating Scale that includes 24 items assessing psychiatric symptoms such as somatic concern, anxiety, depression, and suicidality [46]; and the Calgary Depression Scale that includes nine items assessing depressive symptoms such as depressed mood, hopelessness, and suicide [56].

Qualitative Measures

Qualitative data on the acceptability, safety, and impact of the intervention was mainly obtained at the 4 weeks follow-up through the *HoryzonsCa Meet-up and Focus Group* discussion meeting.

The research assistant took field notes on any additional comments from participants related to their experiences and perspectives of the intervention during the *HoryzonsCa Initial Interview and Orientation Meeting* (which occur at baseline) and the HoryzonsCa Exit Interview (which occur at the 8 weeks follow-up). Moreover, participants were asked open-ended questions at the end of the HC-AUSI-Q, which were conducted during the *HoryzonsCa Exit Interview*.

At the *HoryzonsCa Initial Interview and Orientation Meeting* (60 minutes), participants completed the baseline measures (as described in previous sections), received an introduction to the website including review of its Terms of Use, and were provided with password information to log into the website using a pseudonym when logged in. They were invited to complete 3 to 5 activities (eg, identifying strengths and values through a card sorting activity and writing a short post in the café) and had the opportunity to ask questions and make comments about the intervention platform. The research assistant took field notes on participants' initial impressions and questions about the website, concerns raised by the participant, and any challenges observed in navigating the intervention platform.

The *HoryzonsCa Meet-Up and Focus Group* (120 minutes) occurred midway through the 8 weeks of follow-up. We invited all participants to this Meet-up and Focus Group Meeting, and aimed to have approximately 4 to 8 participants each session. The focus groups were facilitated by the project lead with the support of a research assistant. Before having a focused discussion on the platform, the facilitator (who does not have any clinical role or therapeutic relationship with the participants) welcomed participants, provided an overview of the meet-up objectives, and provided logistic information (eg, duration of group and scheduled breaks). After that, participants were invited to share their experiences and perspectives of the system, and feedback on factors that support or hinder its use. Specifically, the topics of the focus group were general impressions of the HoryzonsCa intervention platform (eg, likes and dislikes), how easy it is to use, how useful the intervention platform has been for well-being, how the intervention platform can be improved to better meet the needs of Canadian youth, and any other suggestions in implementing and evaluating HoryzonsCa. The interview guides for the focus groups were adapted from our phase 1 adaptation study protocol, which was informed by the eHealth Adaptation Framework [31]. The facilitator encouraged an open discussion on the perceptions of the platform. A moderator was then invited to the room to present participants with the key components of the platform and provide tips on its use. At the end of the meeting, the lead facilitator reiterated the purpose of the focus group, summarized what was said, described the next steps, and gave participants the opportunity to bring up discussion points that were not addressed previously but which were of importance to them. These meetings were audio recorded.

During the *HoryzonsCa Exit Interview* (30 minutes), the TAUC-Q and the clinical measures used for the initial interview and the HC-AUSI-Q were completed. The research assistant took field notes including any additional comments that the participant provided related to the website or participation in the project.

Feasibility Measures

We also collected data on recruitment rates, appropriateness of eligibility criteria, and the project team's experience of preparing for and implementing the intervention (based on team meeting notes) mainly to inform the feasibility and design for conducting a larger implementation study in the future.

Data Management

This study is currently in the data management and analysis phase. The quantitative data from the outcome measures was entered into an Excel file (Microsoft Corporation). All outcome measures at baseline and at the 8 weeks follow-up are either self-reported or interviewer-administered, and those that were completed by the participant were checked by the interviewer for completeness, as sometimes questions are not answered simply because of rushing through, filling in errors, or oversight. Any missing data will be discussed using a team approach to first understand its nature (eg, participant nonresponse, research assistant error in data entry, or participant dropout). We will consider the extent and the type of the missing data (eg, missing completely at random, missing at random, and missing not at random), and then determine the best approach (eg, multiple imputation or regression imputation) to handle the missing data in consultation with a statistician [57]. Once all participants completed the *HoryzonsCa Exit Interview*, website use data was exported to an Excel file.

The qualitative data from the focus group audio recordings will be transcribed and anonymized. The field notes from the *HoryzonsCa Initial Interview and Orientation Meeting* and the *HoryzonsCa Exit Interview* taken by the research assistant will be typed by the research assistant. All qualitative data will be uploaded into the latest version of Atlas.ti software (ATLAS.ti Scientific Software Development GmbH), a coding software package.

Analysis Plan

Following the convergent mixed methods model, the quantitative and qualitative data will first be analyzed separately and then considered for an integrated analysis of the findings [58]. The quantitative data (including website use data) will first be assessed using descriptive statistics (eg, frequencies). Specifically, to evaluate the acceptability and safety of HoryzonsCa, we will analyze quantitative feedback from the HC-AUSI-Q and website use by calculating proportions (ie, percentage of participants who indicate agree or strongly agree for specific items related to acceptability and safety; percentage of participants with at least 4 log-ins over the 8 weeks follow-up). To assess the potential efficacy of HoryzonsCa, paired samples *t* tests will be conducted on social functioning and clinical measures, and within-group effect sizes (Cohen *d*) will be reported for statistically significant changes between baseline and the 8 weeks follow-up. We will make Bonferroni corrections to reduce the inflation of alpha for multiple comparisons and determine a minimal clinically important difference to detect important changes over time. In addition, exploratory analysis of potential meditators and moderators of treatment effects will be conducted; for example, we will analyze the associations between website use and treatment effects to estimate the moderating role of website use. We will conduct the checks of assumptions prior to conducting analysis, including normality of the data, and will transform the data if needed. Two members of the research team (eg, a postdoctoral fellow and a research assistant) will review data quality (eg, missing data) and determine the best approach (eg, multiple imputation) to handle the missing data in consultation with a statistician and senior members of the research team. Quantitative data analysis will be supported using SPSS (IBM Corp; or R [R Foundation for Statistical Computing]).

Qualitative data (including qualitative feedback from the HC-AUSI-Q and the qualitative data from the interviews and focus groups) will be analyzed and reviewed for themes related to acceptability, perceived benefits, safety, barriers, and facilitators of using HoryzonsCa. Two members of the research team will review all the transcripts, codevelop a coding framework, and conduct a thematic analysis [59] in consultation with the project lead. These will be identified based on their salience with the research objectives and in relation to patterned responses. The coding categories will reflect questions asked during the interview and perspectives that emerged frequently in the data. Qualitative data analysis for the focus groups will be supported using the latest version of Atlas.ti software, a coding software package.

Results

This study was funded by the Brain and Behavior Research Foundation (United States), Quebec Health Research Funding Agency (Canada), and the Canada Research Chairs Program (Canada), and was approved by the Research Ethics Board of the Centre intégré universitaire de santé et de services sociaux de l'Ouest-de-l'Île-de-Montréal on April 11, 2018 (#IUSMD 17-54). The study was registered as a clinical trial at [60] (ISRCTN43182105). Recruitment was initiated on May 10, 2018, and data collection occurred between August 16, 2018, to April 29, 2019. A total of 48 individuals were approached for the study, from which 20 were excluded (17 declined to participate, 1 was not reachable, 1 did not meet inclusion criteria, and 1 met exclusion criteria). The 28 remaining individuals provided informed consent and were invited to complete a baseline assessment, from which 4 did not attend for various reasons (eg, no longer interested, no longer attending clinic, or not feeling well). Among the 24 participants that completed the baseline assessment, 3 dropped out of the study before being given access to the intervention, and 1 was excluded from the intervention soon after team discussion of the baseline assessment due to not meeting inclusion criteria (ie, clinical stability). Upon completion of the baseline assessment and confirmation of eligibility criteria, a final sample of 20 participants were given access to the intervention and none of these were lost at 8 weeks follow-up. Participants were recruited over a 9-month duration (which was 3 times longer than our originally anticipated 3-month timeline), with a recruitment rate of approximately 3 participants per month. A total of 9 participants attended the focus group meetings of approximately 120 minutes each session (4 attended more than once). No adverse events related to the intervention occurred during the live pilot implementation. Further details on the results are expected to be submitted for publication in 2021.

Discussion

Importance of This Study

Psychotic disorders can have a profound impact on the individual, their caregivers, and society with regard to a loss of quality of life and productivity. Despite advances in early intervention, there remain ongoing challenges in treating this population, including preventing relapse and service disengagement, and sustaining improvements in symptoms and functioning over the long term. As such, accessible, sustainable, and engaging psychosocial services are needed to optimize care and outcomes for this population. The COVID-19 pandemic and public health guidelines for social distancing have compounded the urgent need for new models of service delivery to provide specialized services to patients with FEP. This study addresses this gap in health service research through leveraging HoryzonsCa, an online intervention with the potential to support recovery and prevent relapse in patients with FEP, during and post COVID-19.

In this paper, we have described the study protocol for pilot-testing HoryzonsCa, and it is the first study to implement and evaluate a live version of this online intervention in a Canadian context. This study is distinguished from previous research on Horyzons, as it is the first to be based on a systematic adaptation process [30,31] that considers geographical, cultural, and health care contexts. There is evidence to suggest that embarking on an adaptation process of an eHealth intervention (eg, considering language, culture, and context) can contribute positively to its adoption and effectiveness [31].

The Canadian context is distinguished from the Australian context in several ways that highlight the importance of

Canadian-specific adaptation and testing of Horyzons. For example, there are differences in terms of history of colonization, such that Australia has a history of British colonization and Canada has both a British and French history, rendering certain health care settings particularly in Montreal to provide care in a bilingual context. This has implications for the adaptability of all features of the website intervention in terms of translation. There are also differences in the use of English terms and colloquialisms [31], and systems-level differences in community resources and how mental health services are organized and delivered. Indeed, based on our phase 1 research, we adapted several aspects of the intervention in relation to these differences, detailed in our previous publication, including but not exclusive to terms and colloquialisms, safety and moderation protocols, need help resources, terms of use, list of trigger words that will automatically be flagged by the system as indicating risk, and change to content and resources pertaining to employment/studying/volunteering to be in alignment with Canadian norms [30].

Furthermore, in comparison to Australia, the Canadian context lags in terms of implementation of digital health innovations [61]. Moreover, peer support legislation, policy, training, and provision is uneven across Canada [62]. These factors influenced our implementation of the intervention, particularly in relation to the hiring and training of the moderation team. For example, in previous Australian research on Horyzons, the clinician moderators were already working at the recruitment site delivering face-to-face services, with part of their time allocated to providing online moderation for Horyzons, whereas in the current context, the clinicians were ambivalent about making online moderation as part of their role, which may be due to the lack of experience and training in the delivering of online interventions [30]. As such, for this pilot study we decided to recruit a moderator external to the setting. Additionally, we had a limited pool of trained and experienced peer support worker workforce to recruit from and had turnover of 2 peer support workers (for reasons unrelated to the intervention) before being able to recruit a peer support worker that completed the duration of the project. However, it is noteworthy that this worker had limited experience in the delivery of online interventions and no employed experience as a peer support worker. As such, this pilot testing provides key information on the factors to consider in the implementation of this complex intervention (including recruitment and training of moderators and participant recruitment, retention, and engagement with the intervention). We will further detail and interpret these aspects of implementation using sociotechnical theory in our upcoming results report. In summary, through this study, we will gain insights into the acceptability, safety, and potential efficacy of HoryzonsCa, as well as key information that will support decision-making regarding scaling up the implementation and evaluation of this online intervention in Canada and abroad.

Strengths and Limitations

There are several strengths to this research. First, in terms of preparing the intervention, we made adaptations to Horyzons to optimize its transferability from Australia to Canada, using a systematic approach and an eHealth adaptation framework, prior to its implementation [30,31]. The mixed methods design in this study is expected to provide an in-depth understanding of user experience and perspectives of HoryzonsCa. This mixed methods approach allows researchers to obtain a comprehensive view about the user experience and evaluate the potential impact of implementing such digital health innovations in Canadian health care settings.

Limitations of this study include a small sample size (N=20) and a single group, pre-post design. Due to this small sample size and a lack of a control group, we may not be able to detect treatment effects and impact of the intervention. Additionally, due to the short duration of follow-up (ie, 8 weeks), our findings regarding the acceptability, safety, and potential efficacy of HoryzonsCa will need to be interpreted with caution. Furthermore, our approach to exclude participants that score as moderately severe to extremely severe on suicidality (ie, due to recent suicidal ideations and behaviors, to mitigate the need for urgent intervention on a platform that is not monitored 24/7, and to reduce potential overexposure to comments that may be disruptive or distressing for other participants in the intervention) is not necessarily supported by predictive research and could even potentially exclude participants who may benefit from such an intervention [63,64]. Future research on HoryzonsCa should consider how such an online intervention platform can facilitate a recovery-oriented approach for all participants despite their score on a suicidality assessment while at the same time optimizing the safety of the online group environment. In addition, although the field of digital mental health is rapidly growing [23,61], we acknowledge that the limited evidence on the implementation of digital mental health interventions for people diagnosed with severe mental health disorders such as psychosis in Canada may limit the scope of our interpretations regarding the results. Nonetheless, the findings will help inform decision-making for scaling up the evaluation on HoryzonsCa to a larger implementation study.

Conclusions

Considering daily use of ICTs among young people and an increasing need for new models of mental health service delivery in the context of the COVID-19 pandemic, research on digital health innovations such as online psychosocial interventions are needed to prevent relapses and support long-term recovery in young people experiencing FEP. However, limited attention has been given to how digital health innovations can be implemented and evaluated in Canada in the context of early interventions for psychosis. In this study, we have reported on the protocol for pilot-testing HoryzonsCa as a follow-up to our phase 1 adaptation study [30,31]. Specifically, this pilot study will provide preliminary evidence on the acceptability (including actual use), safety, and potential efficacy of HoryzonsCa for Canadian young adults with FEP, and an in-depth understanding of user experience and perspectives of HoryzonsCa (eg, perceived barriers and facilitators to using the platform). Our pilot study will inform the development of a research protocol (eg, including pre-post effect sizes on a number of variables conceptually targeted by the intervention, statistical power calculation, or sample size) for a larger implementation study of HoryzonsCa and that also considers sociotechnical factors pertaining to implementation as well as the experiences and

perspectives of clinicians and peer support workers on moderating the intervention.

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Authors' Contributions

SL, MAJ, and JG were involved in designing the overall study, with critical input from RJ and ML. SL, SD, and GE contributed to finalizing adaptations to the intervention and preparing it for evaluation (eg, website use analytics). SL wrote the detailed protocol submitted for ethics review, and GE assisted in preparing materials for protocol implementation. SL and HL prepared the initial draft of the manuscript based on content in the protocol. All authors contributed to revising the current manuscript in a critical way.

Conflicts of Interest

SL reports a recent research grant from Hoffman-La Roche, pertaining to an upcoming phase 3 study on the implementation and evaluation of HoryzonsCa; MAJ, JG, and RJ are coinvestigators on this grant. RJ served as speaker and member of advisory board committees for Pfizer, Janssen, Bristol Myers Squibb, Sunovian, Myelin and Associates, Otsuka, Lundbeck, Shire, and Perdue. He also received grants from Janssen, Bristol Myers Squibb, Otsuka, Lundbeck, Astra Zeneca, and HLS Therapeutics Inc. All of these are unrelated to this study. ML reports grants from Otsuka Lundbeck Alliance, Hoffman-La Roche (pertaining to an upcoming phase 3 study on the implementation and evaluation of HoryzonsCa), diaMentis, personal fees from Otsuka Canada, personal fees from Lundbeck Canada, grants and personal fees from Janssen, and personal fees from MedAvante-Prophase outside the submitted work.

Multimedia Appendix 1
Safety protocol and withdrawal criteria.
[DOCX File , 23 KB - resprot_v10i12e28141_app1.docx]

Multimedia Appendix 2
Schedule of assessments.
[DOCX File , 20 KB - resprot_v10i12e28141_app2.docx]

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Abbreviations

FEP: first-episode psychosis
HC-AUSI-Q: Horyzons-Canada Acceptability, Usability, Safety, and Impact Questionnaire
HoryzonsCa: Horyzons-Canada
ICT: information and communication technology
IT: information technology
PEPP: Prevention and Early Intervention Program for Psychosis
TAM: Technology Acceptance Model
TAUC-Q: Technology Access, Use, and Competency Questionnaire

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Protocol

Prospective Prediction of Lapses in Opioid Use Disorder: Protocol for a Personal Sensing Study

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Abstract

Background: Successful long-term recovery from opioid use disorder (OUD) requires continuous lapse risk monitoring and appropriate use and adaptation of recovery-supportive behaviors as lapse risk changes. Available treatments often fail to support long-term recovery by failing to account for the dynamic nature of long-term recovery.

Objective: The aim of this protocol paper is to describe research that aims to develop a highly contextualized lapse risk prediction model that forecasts the ongoing probability of lapse.

Methods: The participants will include 480 US adults in their first year of recovery from OUD. Participants will report lapses and provide data relevant to lapse risk for a year with a digital therapeutic smartphone app through both self-report and passive personal sensing methods (eg, cellular communications and geolocation). The lapse risk prediction model will be developed using contemporary rigorous machine learning methods that optimize prediction in new data.

Results: The National Institute of Drug Abuse funded this project (R01DA047315) on July 18, 2019 with a funding period from August 1, 2019 to June 30, 2024. The University of Wisconsin-Madison Health Sciences Institutional Review Board approved this project on July 9, 2019. Pilot enrollment began on April 16, 2021. Full enrollment began in September 2021.

Conclusions: The model that will be developed in this project could support long-term recovery from OUD—for example, by enabling just-in-time interventions within digital therapeutics.

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KEYWORDS

digital therapeutics; risk prediction; opioid lapse; mobile phone

Introduction

Background

Opioid use disorder (OUD) is a widespread, intractable disease that devastates the people who suffer from it and their families, friends, and communities. Opioid use is more deadly than other drug use; more than two-thirds of all drug overdose deaths in 2017 and 2018 in the United States involved opioids [1-3]. Improving treatment outcomes for OUD is a critical public health need.

OUD is a chronic, relapsing disease. Many people successfully establish opioid abstinence through pharmaceutical treatments, psychosocial treatments, and peer-support groups [4-7]. These approaches can reduce or eliminate opioid use in the short term but are less effective at supporting successful recovery in the long term [8-10].

Most people with OUD experience setbacks in their recovery. Most people lapse (ie, engage in a single episode of opioid use), and some people who lapse, relapse fully (ie, return to regular, harmful opioid use) [11,12]. Lapses can be triggered by mundane sources such as everyday hassles [13]. Lapses can also occur because maintaining recovery-supportive behaviors is difficult in the long term; over time, people may stop taking medications, engaging with therapy, and attending peer-support groups [14-16]. They may also stop using strategies they learned in treatment and support groups to cope with stress, craving, and other triggers for lapses. These changes in recovery-supportive behaviors over time may increase people's risk of lapses.

Successful long-term recovery requires continuous lapse risk monitoring and appropriately using and adapting recovery-supportive behaviors as lapse risk changes. Ideally, long-term recovery rests on a foundation of general psychological wellness and involves an awareness of, and defense against, the ever-present risk of lapse [14,17-24]. For example, people in recovery may change their routines and learn new psychosocial habits to prevent and overcome drug cravings (eg, avoiding people and places associated with opioid use and engaging in effortful, deliberate coping when cravings arise). To succeed, they may also return to peer-support groups, re-engage with psychosocial treatment, or restart medications when necessary and if their lapse risk increases.

However, lapses can occur after months or years of seemingly successful recovery, and they may often seem to come without warning [9,25-27]. With improved self-monitoring for lapse risk, people may be better able to adapt their treatments, behaviors, and lifestyle to prevent these lapses. Similarly, if treatment providers were able to accurately monitor the lapse risk of patients in their caseload, they may be able to direct their limited resources toward those patients who are at the greatest risk of lapse.

This protocol paper describes research that aims to build a prospective lapse risk prediction model that can facilitate such improved lapse risk monitoring. Specifically, this lapse risk prediction model will generate temporally precise, ongoing lapse probabilities for people in recovery from OUD. Such a lapse risk prediction model can be situated within a digital therapeutic, that is, a software-based treatment platform that aims to prevent disease or manage disease recovery. Digital therapeutics already support people to manage complex, chronic health issues such as substance use disorders (SUDs) by providing a suite of interventions, information, and interactive tools and services that people can access 24×7 on demand [19,28-36]. Digital therapeutic apps on smartphones are also well-positioned for lapse risk prediction because they can use personal sensing methods to collect low-burden, high-quality information that is necessary for lapse risk prediction [37], deliver lapse risk probabilities directly to people in recovery and their app-connected treatment providers, and provide interventions, information, tools, and services at moments of greatest need (ie, *just in time*) and tailor these supports to the characteristics of the person and their context.

We plan to collect all data necessary to develop a lapse risk prediction model within the Comprehensive Health Enhancement Support System for Addiction (A-CHESS), a digital therapeutic for SUD [19,38,39].

In this paper, we first review previous research on lapse risk prediction, highlighting the importance of understanding lapse risk as resulting from a complex interplay of stable and dynamic risk and protective factors [40]. We then review innovative measurement approaches that make collecting information relevant to lapse risk prediction within digital therapeutics feasible. Next, we describe how machine learning statistical approaches can be used for prospective lapse risk prediction. Finally, we describe the methods we will use to develop this lapse risk prediction model. In the *Conclusions* section, we summarize the potential impact of this research.

Lapse Risk Prediction

For more than 30 years, research and treatment communities have sought to understand and predict lapses during recovery from SUD [7,33,41-43]. This work has resulted in theoretical accounts of why people lapse and the identification of traits, experiences, and behaviors that confer risk or protection from lapses.

The traits and other stable factors that confer overall lapse risk or protection relate to people's affective and behavioral tendencies and their history of substance use. People who have a family history of substance use [33], have a long and early personal history of use [44], had severe pretreatment dependence and withdrawal [43], experience more negative emotions than others [33,41,42], struggle with distress tolerance more than others [33,41,42], and have impulsive tendencies [42] are at a greater risk of lapse than others.

However, people's risk of lapse also fluctuates over time [32,33,41,42,44,45]. Thus, stable individual differences alone are not sufficient to predict lapse [7,45-49]. People's behavior and experiences and the monthly, weekly, and daily changes and events in their lives affect their moment-to-moment lapse risk.

The dynamic (ie, temporally varying) factors that confer lapse risk or protection include people's engagement with treatment [50], exposure to use-related cues in their physical and social environments [51], and their wellness, including their stress, cravings, and affective experiences [52-54]. People are at lower risk of lapsing when they attend support groups [55] and take medications as prescribed [56]. People are at higher risk of lapsing when they see people and visit places associated with their past use [51,57], experience job loss [55,56], have more severe pain than usual [51,58], and have more cravings than usual [51-53].

Personal Sensing for Prospective Lapse Risk Prediction

The research described in this paper focuses on prospective lapse risk prediction for clinical implementation. This requires different measurement approaches from those of previous theory-driven research. Earlier research on the theoretical causes of lapses has focused on testing inferences about these causal factors. Testing causal inferences requires measuring (or better

still, manipulating) small numbers of factors. Therefore, this earlier research generally measured or manipulated a select few putative causal factors for lapse once or periodically, depending on how often the factors of interest change (eg, every few months or weeks, daily, or multiple times a day) [59,60]. This research seeks to identify causal factors rather than achieve high predictive accuracy for lapses.

Prospective lapse risk prediction for clinical implementation likely requires measuring many lapse-related factors to account for sufficient variance in lapse outcomes to make accurate predictions. In addition, these factors must be measured frequently enough to capture meaningful variation over time. For example, accurate prediction of the probability of lapse in the next 24 hours may require knowing the status of, and recent changes in, hundreds of factors. Some factors relevant to lapse risk are stable individual differences, but others are dynamic and may change quickly (within hours) or slowly (in weeks or months). Prospective lapse risk prediction requires a measurement strategy that can accommodate continuous, longitudinal measurement of some factors and place minimal burden on people despite capturing information about hundreds of factors.

Self-report methods alone cannot support prospective risk prediction. Self-report is well suited for measuring subjective states, including theoretical causes of lapse, such as affect and pain. However, collecting self-report requires active effort from the individual, which limits the frequency and quantity of factors that self-report can measure.

Recent technological innovations enable measurement approaches that can complement self-report with respect to the need for accurate, prospective risk prediction. Specifically, personal sensing methods leverage sensing technologies in smartphones, wearable devices, social media, and computers to capture information longitudinally about people's naturalistic environments, behavior, social interactions, thoughts, and affect [28,37]. By definition, personal sensing methods provide naturalistic in situ and longitudinal measurement.

Personal sensing methods can be active or passive. Active methods require people to take actions to provide measurement, including self-report. For example, ecological momentary assessments are brief self-report surveys focused on momentary states. People may complete these surveys multiple times per day to provide in situ longitudinal measurement of their subjective experiences. Other examples of active personal sensing include audio or video check-ins, where people describe a positive event in the past, a negative event in the past, or something they are looking forward to in the future.

In contrast, passive personal sensing methods can measure processes with little burden placed on the individual. For example, software monitoring of smartphone call logs and monitoring of geolocation through smartphone location services are both passive personal sensing methods. In some instances, these passive methods can provide lower burden or even privileged access to measure people's behavior or subjective experiences. For example, rather than using self-report surveys to collect information about people's social contacts, exercise, or recent activities, data from people's smartphones can be used as a proxy for these factors. Smartphone call and text message logs can reveal how much social contact someone has had. Geolocation and accelerometer data can be used to estimate people's exercise and activities or even detect long periods of social isolation at home.

Both active and passive personal sensing methods are now possible within digital therapeutic smartphone apps such as A-CHESS. Smartphones house sensors and software that can capture information such as geolocation and movement, audio and video recordings, phone use patterns, call and SMS text message logs, and SMS text message content. Digital therapeutics can access smartphone hardware and software to collect and integrate these data. These raw data form the inputs from which to derive predictors of lapse risk.

Deriving Lapse Risk Predictors

The information that smartphones can collect can produce powerful, theoretically informed predictors of lapse risk. Self-report surveys delivered through smartphones can capture predictors such as people's substance use history, stable tendencies related to risk, and monthly or daily changes in people's craving, affect, experience of stressful or pleasant events, and other risk-related subjective experiences. Geolocation data can capture the frequency and duration of visits to places or movement patterns that may indicate lapse risk (eg, excessive time spent in a location and late-night excursions). Phone call and text message logs can capture the number and pattern of communications with friends or family. The content of people's text messages can indicate their mood, stress, experiences of craving, and other dimensions of their mental health [61]. How often and for how long people use their digital therapeutic app's features can indicate their motivation, commitment, and engagement in recovery-supportive behaviors.

Passive personal sensing information collected from digital therapeutic smartphone apps can be made even more powerful by gathering additional intrapersonal context to better characterize the raw data, for example, by identifying frequent social contacts and asking people for additional information about them. The frequency, timing, and duration of phone calls can be enhanced with self-reported contextual information about relationship closeness and perceived recovery support provided by these contacts. For example, 3 brief morning phone calls to a close friend may signal increased lapse risk, but 3 brief morning phone calls to an internet service provider likely do not. Similarly, patterns in geolocation data can be enhanced with public or self-reported context about type (eg, hospital, bar, restaurant, or a friend's residence) and meaning (eg, recovery supportive and typically pleasant or unpleasant) of the places visited. For example, 5 hours spent at a hospital emergency department may signal increased lapse risk, but 5 hours spent at a recovery-supportive friend or family member's apartment building likely does not.

Critically, contextual information about important people and places can be collected with relatively little burden. Most people have a relatively small, stable set of frequent social contacts and frequently visited places [62-64]. In a previous project, our research group identified a method of collecting this self-reported contextual information. Specifically,

contextualizing information for geolocation and cellular communications data was collected in a brief self-report survey administered monthly over a period of 3 months [65]. After a month of personal sensing data collection, frequent contacts (ie, more than 2 interactions per month) and frequently visited places (ie, places visited more than twice a month) were identified. People answered a brief set of questions about each frequent contact (eg, relationship type; perceived closeness; supportiveness of recovery; typical pleasantness or unpleasantness of interactions; and typical support for, or risk to, recovery) and each place (eg, place type, associated activities, typical pleasantness or unpleasantness of visits, and typical supportive or risk-related effect of visits on recovery). This contextual information can be used to enrich the predictive signal of passively sensed cellular communications and geolocation data.

Modeling Prospective Lapse Risk With Machine Learning

Digital therapeutics can leverage smartphone tools and sensors to feasibly measure and derive risk-related predictors, but accommodating these predictors in a statistical risk prediction model poses a new challenge for prospective lapse risk prediction. Lapse risk is known to relate to a large number of stable and dynamic factors. It is also theorized to result from complex interactive and nonlinear functions of these factors [30,32,33,40,45,66]. Therefore, the statistical models used must support high-dimensional (ie, many predictors) and complex data-generating processes to achieve the high predictive accuracy necessary for clinical implementation. Furthermore, for useful clinical implementation, these statistical models must generalize well when applied to new people and settings and not just those that the model was trained on. Analytic approaches that are typical of theoretical research on lapse risk, such as generalized and multilevel linear models, are not well suited to these challenges. In contrast, machine learning approaches have been developed specifically to achieve these goals [67,68].

High-dimensional sets of predictors pose challenges to many statistical modeling approaches. On the one hand, too many predictors (correlated predictors in particular) may yield overfit, unstable models that vary strongly based on the data used to develop them (ie, high variance), which can compromise model generalizability; on the other hand, too few predictors (as well as other constraints on model characteristics) yield underfit models that may consistently over- or underestimate an outcome (ie, high bias). Machine learning uses various techniques (eg, regularization and hyperparameter tuning) to optimize these bias-variance trade-offs to accommodate high-dimensional sets of predictors while reducing overfitting to the data used for model development. This allows machine learning models to take advantage of high-dimensional predictor spaces to capture complex relationships and patterns learned from these data.

Machine learning also provides rigorous methods to develop and evaluate models in separate data [67]. Cross-validation techniques can be used with a subset of data (ie, the training set) to identify the best-performing model. This best-performing model is selected by cross-validation to maximize its ability to be generalized to new people. This model's performance can then be explicitly evaluated in previously held-out data (ie, the test set) that were not used for model development or selection. This cross-validation procedure allows for more realistic estimates of the performance of the model when it is generalized for use with new people.

Study Objective and Overview

The objective of this study is to develop a highly contextualized lapse risk prediction model that forecasts the ongoing probability of lapse among adults in recovery from OUD. This prediction model will be developed using predictors derived from raw data collected by active and passive personal sensing methods within a digital therapeutic smartphone app, A-CHESS. We will enroll people in their first year of recovery and follow them longitudinally for 1 year. We will recruit a sample that is diverse in their recovery stability, race, ethnicity, and geographic setting (urban, suburban, and rural residence) to provide the raw data necessary to develop a prospective risk prediction model that generalizes well. We will use contemporary machine learning methods to train this prospective risk prediction model and evaluate its performance with new (not previously seen during training) people.

Methods

Participants

We will enroll 480 adults receiving medication-assisted treatment for OUD. We are recruiting these participants using targeted national digital advertising and collaborations with treatment providers at medication-assisted treatment clinics. Our recruitment strategy has been designed to create a diverse sample with respect to recovery stability, demographics (sex, age, race, and ethnicity), and geographic setting (urban, suburban, and rural residence). We do not exclude participants for comorbid SUD or other psychopathologic conditions. To enroll, participants must be aged ≥18 years, fluent English speakers, stable recipients of medication-assisted treatment (defined as taking monthly medication regularly or daily medication on most days or every day) for at least 1 month but no longer than 12 months, and Android smartphone users with an active cellular plan.

We compensate participants for completing brief phone meetings with study staff for initial enrollment and training. Participants earn US $20 per hour for the time they spend in these phone meetings and US $20 for completing training materials. We also compensate participants for completing study tasks, and we award bonuses to participants when they exceed the minimum compliance requirements for study tasks. Participants earn a nominal amount for each daily survey and daily video check-in and are awarded bonuses for completing at least 24 of these per month. Earnings amount to a maximum of US $15 each month for completing daily surveys, US $10 each month for submitting daily video check-ins, US $10 for completing the intake or monthly survey, and US $15 for keeping data sharing (eg, location services and cellular communications) enabled the entire month. In addition to paying participants for completing tasks, we pay US $50 per month to participants' cell phone providers to offset the costs of maintaining a phone plan.

Procedure

Participants are recruited through partnerships with health care systems across the United States and through digital advertising (eg, Facebook advertisements and posts to opioid recovery–relevant subreddits on Reddit). Participants are screened by staff or by completing a brief web-based survey. Interested and eligible participants speak with project staff on the phone to learn more about the study and provide informed consent. Consenting participants provide demographic information, install the app, and complete web-based training.

After enrollment, participants will provide information about themselves and their lapses for a year, information about stable risk-related factors in an intake survey, and information about dynamic risk-related factors through different means. Participants will provide continuous data relevant to some dynamic factors through passive personal sensing of their cellular communications, geolocation, and use of A-CHESS. Every month, participants will actively provide information about dynamic factors through a survey (eg, changes to their housing and employment and information about their mental and physical health and health care). Participants will also provide contextual information about important people with whom they communicate and the places they visit. Every day, participants will provide information about dynamic factors such as their affect, pain, cravings, and motivation by recording a brief (15-30 seconds) selfie-style video check-in and in a brief self-report survey. In their daily self-report survey, participants will also provide information about their lapses (ie, uses of opioids for nonmedical reasons), indicating when they happened by selecting among 6-hour intervals that span their study enrollment. All study data will be collected through A-CHESS.

During the first week of enrollment, study staff will meet with participants by phone to answer questions they have about the study and app and to help them troubleshoot technical issues. Additional meetings with study staff are arranged as needed to resolve technical issues. Training and support materials (eg, infographics and video guides) remain available to participants through A-CHESS. When participants complete the study, discontinue, or withdraw, they will have a brief debrief phone call with study staff.

A-CHESS Digital Therapeutic App

A-CHESS is the digital therapeutic smartphone app that we use in the study. A-CHESS houses a suite of resources and tools for people in recovery from SUD [19,38,39]. The features that A-CHESS offers were designed with guidance from the Marlatt cognitive behavioral model of relapse prevention (Marlatt and George [69]) and self-determination theory (Ryan and Deci [70]). The app aims to reduce relapse risk through features such as a discussion board, guidance on coping with cravings, a library of resources, a gratitude journal, and alerts if a user is near a self-identified high-risk location (see the URL [71] for a detailed description of the app's features).

As of July 2021, A-CHESS has been used by more than 7000 people and 60 treatment centers nationwide. A-CHESS has been developed and refined using techniques from a user-centered design where feedback from key users of the system is sought early and often. User stories and scenarios, participatory design sessions, one-on-one contextual interviews, usability testing, and focus groups have designed and evaluated each of the recovery tools.

A-CHESS provides recovery support to participants enrolled in the study and also collects information relevant to lapse risk using personal sensing methods. A-CHESS administers the self-report surveys and collects passive personal sensing measures such as geolocation and cellular communications (ie, text message content and logs and phone call logs). In addition, the digital therapeutic app has features that support user privacy, such as password protection and adjustable settings for data sharing.

Measures

Overview

Detailed descriptions of the measure items, sources, and administration (eg, instructions) are available on the website [71]. We use these measures to derive predictive features associated with stable individual differences and temporally dynamic risk factors. The granularity of the dynamic risk factors varies across measures from monthly to daily to moment by moment as described below. We collect all measures through personal sensing using A-CHESS on participants' smartphones.

Monthly Survey

The monthly survey includes measures of stable individual differences and dynamic risk factors. There is some variation in the specific measures that are included in different months as described below. However, all monthly surveys take less than 30 minutes to complete on average.

The first monthly survey is an intake survey that is administered shortly after participants enroll in the study. This survey includes measures related to stable individual differences. Specifically, it measures demographics, lifetime substance use history (items adapted from the World Health Organization Alcohol, Smoking and Substance Involvement Screening Test version 3.0 [72]); opioid treatment history; Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, OUD diagnostic criteria for the year before starting medication-assisted treatment [73]; distress tolerance (items selected from the Distress Tolerance Scale [74]); pain catastrophizing (items adapted from the Pain Catastrophizing Scale and Pain Catastrophizing Scale for Children [75,76]); personality traits relevant to psychopathology (Personality Interview Guide from Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Brief Form [77,78]); adverse childhood experiences (items selected from the Adverse Childhood Experiences Questionnaire [79]); and trauma experience [80].

The first and later monthly surveys also include measures related to dynamic risk factors. This includes measures of life circumstances (eg, employment status and living situation); social connectedness (adapted from the Medical Outcomes Study Social Support Survey [81]); romantic relationship quality (items selected from the Relationship Assessment Scale [82]); psychiatric symptoms (items selected from the Behavior and Symptom Identification Scale-32 [83]); pain and anticipated

pain treatment (items adapted from the Wisconsin Brief Pain Questionnaire and the Pain, Enjoyment, General Activity Scale [84,85]); stress (items selected from the Perceived Stress Scale [86]); quality of life (items adapted from the World Health Organization Quality of Life Assessment [87]); substance use (adapted from the World Health Organization Alcohol, Smoking and Substance Involvement Screening Test version 3.0 [72]); opioid use; opioid recovery satisfaction and motivation; other recovery goals; and questions about treatment use, adherence, and perceived efficacy, including questions about medication-assisted treatment, self-help meetings, counseling, psychiatric medication, and detox or other inpatient residential treatment [88,89].

The later monthly surveys also contain questions about the intrapersonal and subjective context associated with people and places with which the participant has frequent contact or visits. The monthly surveys administered at 6 months and the final month of the study also include questions about participant perceptions of the acceptability and burden associated with each of the major categories of personal sensing signals (eg, daily survey, video check-ins, and passive monitoring of geolocation).

Daily Survey

The daily survey includes measures of dynamic risk factors that are collected with greater temporal granularity than in the monthly survey. It becomes available at 5 AM CST and can be completed at any time over the next 24 hours. This survey is brief (16 items) and takes approximately 1 minute to complete.

This survey collects specific reports of the date and time of any recent opioid use for nonmedical reasons that participants have not already reported. These reports serve as the primary outcome for the lapse risk prediction model. Participants also report any other drugs that they have used in the past 24 hours by selecting all that apply from a list of substance categories with examples (eg, alcohol and stimulants). The daily survey includes items related to mood, pain, sleep quality, urges to use opioids, risky situations, stressful and pleasant events, and use of medications associated with their treatment in the last 24 hours. The daily survey concludes with items related to participants' motivation and confidence to continue to avoid using opioids for nonmedical reasons over the next week.

Daily Video Check-In

Each day, participants record a short video check-in using their front-facing phone camera. This video captures their facial expressions and voice as they reflect on recent or expected pleasant or unpleasant events or experiences in the near future. The daily video check-in becomes available at 5 AM CST each day and can be completed at any time over the next 24 hours. It takes less than 1 minute to complete.

Moment-by-Moment Geolocation

We use participants' smartphone location services (accessed through A-CHESS) to passively collect their moment-by-moment geolocation (ie, latitude and longitude). Participants' time-stamped geolocations are updated automatically every 1.5-15 minutes, depending on their movement.

As described previously, we increase the predictive strength of geolocation data by augmenting it with self-reported subjective contexts. Therefore, the monthly survey includes questions about the places that participants frequently visit (ie, 2 or more times per month). We detect these frequently visited places automatically each month through algorithms that review the previous month's geolocation data. For each frequently visited place, participants describe the type of place, what they typically do there, the general frequency of pleasant and unpleasant experiences associated with the place, and the extent to which spending time there supports or undermines their recovery. When available, public information (eg, through OpenStreetMap) about these places will also be used to contextualize these data.

Cellular Communications

Participants' cellular communications are passively collected using A-CHESS. This includes the timestamps of all phone calls and SMS text messages, whether calls and SMS text messages are incoming or outgoing, the phone number of the other party, and the name of the contact if it is saved in participants' phones. For phone calls, the duration of the call is recorded. For SMS text messages, the complete SMS text message content is recorded, excluding any sent or received images.

We potentially increase the predictive strength of the information collected about cellular communications by augmenting it within a subjective intrapersonal context. The monthly survey includes questions about the people with whom the participant has frequent contact (eg, more than 2 calls or 4 SMS text messages per month). We detect these frequent contacts automatically each month through algorithms that review the previous month's cellular communications. For each frequent contact, participants describe the nature of their relationship with the contact, the general frequency of pleasant and unpleasant interactions associated with the person, and the extent to which interactions with the contact support or undermine their recovery.

Digital Therapeutic Use

Participants' overall use of A-CHESS, including engagement with specific recovery support features, will be collected in time-stamped logs. A-CHESS also captures the comments that participants post about recovery-related media, their activity on A-CHESS discussion boards, and the messages they send within the app.

Statistical Analyses

Machine Learning Overview

Machine learning is a subfield of computer science that offers an alternative analytic approach ideally suited for both precise prediction and generalizability [67,68]. Machine learning models can consider high-dimensional sets of predictor variables (ie, features) simultaneously. Using stable and dynamic data sources, we can engineer thousands of features to be used for prediction (eg, individual risk signals, interactions among stable and dynamic risk signals, and intrapersonal change in scores and responses over time). Machine learning models can take

advantage of this high-dimensional feature space to capture complex relationships and patterns learned from the data. However, there is still some cost in including a very large number of features.

In addition, machine learning provides rigorous methods to develop and evaluate models in separate data [67]. Consequently, models generalize well to new data because they are evaluated on out-of-sample prediction. We will use cross-validation techniques with training data to select among a variety of model configurations that differ with respect to the statistical algorithm (and associated hyperparameter values) and feature sets. This approach will allow us to consider models that allow us to restrict ourselves to only passive (ie, low burden) features or remove features with high rates of missing data (as an alternative definition of burden and tolerability). Therefore, we will be able to examine both predictive accuracy and implementation-relevant considerations such as participant burden. We will estimate final model performance in held-out test data.

Feature Engineering and Preprocessing

We will use features (ie, predictors) derived from actively and passively collected personal sensing data to build temporally precise machine learning prediction models for lapse risk for different time intervals (eg, daily and weekly). We will follow general recommended practices for data preprocessing and feature processing in machine learning [67,68]. Although procedures differ to some degree based on the specific candidate machine learning algorithm generally, we will review descriptive statistics for data coding errors, apply power transformations to highly skewed features used in linear machine learning models, center and scale all features (unit variances), and dummy code categorical variables. We will remove features with near-zero variance using standard computations implemented in the tidymodels packages in R [90]. For high-dimensional data sources (ie, natural language), we will evaluate a variety of feature extraction methods that reduce dimensionality (eg, Linguistic Inquiry and Word Count [91], singular value decomposition [92], and Word2Vec [93]). All our candidate machine learning algorithms are tolerant of missing data for events. Specifically, missing data imputation procedures can be applied at the level of the feature representation functions [94,95].

Candidate Machine Learning Algorithms

We will evaluate these features within a small set of candidate contemporary machine learning (statistical) algorithms. These include Random Forest [96,97], Penalized Logistic Regression (Lasso, Sparse Group Lasso, and Elastic Net) [67,97-101], Multilayer Perceptron Neural Networks [102], and Support Vector Machines [103,104].

These algorithms were intentionally selected to be complementary with respect to several key features that may affect their relative performance (eg, parametric vs nonparametric models and linear vs nonlinear models). They also vary with respect to their flexibility, model complexity, and sample size requirements such that they will likely differ in their ability to address bias-variance trade-offs in the prediction of new data, depending on the true population model underlying the observed data [67,68]. Finally, all these algorithms are well established with documented good *out of the box* performance [67,68].

These algorithms vary with respect to the degree of feature selection performed automatically during training. Critically, Lasso and Sparse Group Lasso will yield sparse solutions at the level of individual features and groups of features organized around data sources (eg, moment-by-moment location, cellular communications, and daily survey). If these sparse solutions perform well, they may be preferred because the final model will need fewer data sources with associated easier implementation and lower user burden. We will also manually evaluate model performance with reduced feature sets (eg, dropping daily surveys) for algorithms that do not handle this automatically during training (eg, Random Forest).

Model Training and Evaluation

Model training, hyperparameter tuning, and best model selection will be accomplished in a subset of the data (ie, training set) using repeated grouped k-fold cross-validation. We plan to use a variety of techniques (eg, resampling techniques such as upsampling and Synthetic Minority Oversampling Technique and weighted penalties for minority class) within the training set to accommodate the unbalanced nature of the outcome (lapses are expected to be infrequent). We plan to hold out an independent test set that will not be used for model training or selection. The final performance of the best model configuration will be evaluated on independent data (ie, test set) that were not included in the training set. We will characterize the performance of this best model using standard metrics that are appropriate for unbalanced data (eg, balanced accuracy and area under the receiver operating characteristic curve).

Results

The National Institute on Drug Abuse funded this project (R01DA047315) on July 18, 2019, with a funding period from August 8, 2019, to June 30, 2024. The Institutional Research Board of the University of Wisconsin-Madison Health Sciences approved this project on July 9, 2019. We began enrolling pilot participants on April 16, 2021. These pilot participants met the inclusion criteria and are being used to test all procedures, personal sensing methods, and the implementation of A-CHESS. Full enrollment began in September 2021. We plan to recruit participants for approximately two-and-a-half years.

Discussion

Principal Findings

OUD is a widespread condition characterized by lapses and relapses that can threaten people's lives and well-being even years into recovery. People often fail to anticipate lapses and relapses, resulting in failure to seek support or use effective preventive strategies when they are at risk of lapse. Smartphone technology enables people to access continuing care for recovery through digital therapeutics. Integrating real-time lapse risk prediction within these digital therapeutics has the potential to support sustained recovery by offering treatment or intervention

resources and services to people before a lapse or relapse occurs (eg, just-in-time interventions).

This paper describes the rationale and method of an ongoing, grant-supported project to develop a highly contextualized lapse risk prediction model for people in recovery from OUD. Completing the project will involve collecting information about risk-related factors and lapses from an estimated 480 American adults in recovery from OUD. Information will be collected using a digital therapeutic smartphone app, using both self-report and passive personal sensing methods. The model this project will develop could be used as part of a risk prediction system that would support long-term recovery from OUD, for example, by enabling just-in-time interventions within digital therapeutics.

Bridging the gap between a risk prediction model and a functional risk prediction system that is integrated into a usable digital therapeutic is complex and well beyond the scope of a single R01-supported project. Implementing risk prediction in a way that could prevent lapses requires better, contextualized understanding of the biases in the risk prediction model, effective messaging, costs and benefits of sharing risk predictions with users and treatment providers, and the costs and benefits of different types of information for prediction. Without careful research focused on the details of implementation and without the full understanding and consent of the users, the lapse risk prediction system this line of research aims to produce could cause more harm than good. A system that uses a predictive algorithm to calculate risk from sensitive measures such as cellular communications and geolocations and then communicates that risk to third parties could function as a surveillance system rather than support tool. Furthermore, such a system could perpetuate inequities in recovery (eg, if the algorithm systematically over- or underpredicted lapse risk for people from historically marginalized groups).

Conclusions

To advance collective understanding of these issues and to help inform future research, our project will provide insights about the feasibility, costs, and benefits of different risk prediction systems. For example, our analytic approach involves training sparse models that predict using less information than is available. In addition, our analysis approach will allow us to assess the performance of the models that rely on information that we know or observe to be less burdensome to participants based on both self-reported burden and behavioral compliance.

This project will complete an essential step toward a critical public health goal: improving outcomes among people with OUD. Effective treatments for OUD exist, but the treatments and behaviors required for achieving long-term recovery are challenging to maintain. Knowing when lapses are likely to occur can provide people with information and motivation to engage in recovery-supportive activities and can help treatment providers care for their patients.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the Addiction Risks and Mechanisms Study Section - Risk, Prevention and Health Behavior Integrated Review Group (National Institutes of Health).
[PDF File (Adobe PDF File), 171 KB - resprot_v10i12e29563_app1.pdf]

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Abbreviations

A-CHESS: Comprehensive Health Enhancement Support System for Addiction
OUD: opioid use disorder

SUD: substance use disorder

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Protocol

Investigating the Use of Digital Health Technology to Monitor COVID-19 and Its Effects: Protocol for an Observational Study (Covid Collab Study)

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Abstract

Background: The ubiquity of mobile phones and increasing use of wearable fitness trackers offer a wide-ranging window into people's health and well-being. There are clear advantages in using remote monitoring technologies to gain an insight into health, particularly under the shadow of the COVID-19 pandemic.

Objective: Covid Collab is a crowdsourced study that was set up to investigate the feasibility of identifying, monitoring, and understanding the stratification of SARS-CoV-2 infection and recovery through remote monitoring technologies. Additionally, we will assess the impacts of the COVID-19 pandemic and associated social measures on people's behavior, physical health, and mental well-being.

Methods: Participants will remotely enroll in the study through the Mass Science app to donate historic and prospective mobile phone data, fitness tracking wearable data, and regular COVID-19–related and mental health–related survey data. The data collection period will cover a continuous period (ie, both before and after any reported infections), so that comparisons to a participant's own baseline can be made. We plan to carry out analyses in several areas, which will cover symptomatology; risk factors; the machine learning–based classification of illness; and trajectories of recovery, mental well-being, and activity.

Results: As of June 2021, there are over 17,000 participants—largely from the United Kingdom—and enrollment is ongoing.

Conclusions: This paper introduces a crowdsourced study that will include remotely enrolled participants to record mobile health data throughout the COVID-19 pandemic. The data collected may help researchers investigate a variety of areas, including COVID-19 progression; mental well-being during the pandemic; and the adherence of remote, digitally enrolled participants.

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KEYWORDS

mobile health; COVID-19; digital health; smartphone; wearable devices; mental health; wearable; data; crowdsourced; monitoring; surveillance; observational; feasibility; infectious disease; recovery; mobile phone

Introduction

Background

The COVID-19 pandemic has brought about widespread and drastic changes to people's lives, work, and health resulting from infection by SARS-CoV-2 as well as the public health and social measures (PHSMs) that were introduced to limit the disease. It is important to not only understand how and under what circumstances the disease itself spreads but also understand the holistic impact of the pandemic.

Although many people are resilient to the conditions imposed by the pandemic, previous instances of disease outbreaks [1] and quarantines [2] have been associated with negative psychological outcomes. Postinfection conditions that followed previous coronavirus outbreaks include posttraumatic stress disorder, depression, anxiety, and confusion, among others. Similarly, quarantine has been associated with several conditions, including stress [3], posttraumatic stress disorder [4,5], and depression [4,6]. A longer duration of quarantine is associated with worse psychological outcomes [2]—a potentially pertinent fact given the protracted period of the COVID-19 pandemic. Additionally, the stigma of disease and the hazards that many face may differ among different people in different occupations or sociodemographic groups [7].

More recently, the presence of persistent symptoms following acute COVID-19 illness has received increased attention. Around 20% of people in an Office for National Statistics survey from the United Kingdom who had a positive COVID-19 test result reported symptoms lasting at least 5 weeks, and 10% reported symptoms lasting at least 12 weeks [8]. The symptomatologic groups, which are formed by people with persistent illness following SARS-CoV-2 infection, have not been fully determined. Preliminary studies show a multitude of symptoms with various levels of co-occurrence, including persistent respiratory issues, fatigue, psychological and neurological symptoms, and fever [9-11]. The presence of these long-term symptoms is often referred to as *long COVID*.

Mobile health (mHealth) as a field is well suited to the unique problems that have been encountered during the COVID-19 pandemic [12,13]. The need for social distancing and wide-scale quarantines precludes many studies that require direct physical contact with participants. Apart from the ability to continue where other study and data collection methods have been limited, mHealth technologies also offer various advantages. The pervasive nature of mobile phones and wearable fitness devices allows for a fine-grain, second-by-second level of detail as well as prolonged periods of continuous monitoring, which are useful because although the pandemic has been long in duration, it has often been punctuated by acute events, such as infection or the introduction of public health measures. Moreover, the fine resolution of such data provides a more comprehensive view of a person's health and behavior. Historic fitness, health, and activity records are often connected to a person's web-based accounts. Participants are able to donate such data, which can be used to better understand changes related to participants' prepandemic activities and health, their preinfection status, and the duration required to recover to preinfection baseline. Finally, passive data sets collected in this manner have the benefit of being in a standardized format, regardless of their country or institution of origin, and larger numbers of potential participants can be quickly reached through digital methods compared to those reached through more traditional recruitment strategies.

Various previous and ongoing studies have demonstrated the ability to monitor long-term mental well-being [14,15] and track the prevalence of flu-like disease [16] through the use of remote monitoring technologies (RMTs). Such technologies therefore appear to be a useful lens through which to investigate the COVID-19 pandemic, and multiple initiatives have been set up by several groups [17-19].

Objectives

To investigate some aspects of the COVID-19 pandemic, we launched the Covid Collab study in April 2020. The study is a crowdsourced initiative [20] that will involve remote enrollment. It will use a cross-platform phone app to deliver surveys; allow for the input of COVID-19–related data; and allow participants to connect to third-party sources of wearable data, such as Fitbit LLC. By prospectively collecting regular mental well-being and COVID-19 survey data alongside historic and ongoing health-related wearable device data, we hope to address the following objectives.

We will determine whether remote monitoring can provide data on COVID-19 states with objective, measurable differences. Wearable device data have previously been used to predict the prevalence of influenza-like illnesses [16] and can therefore potentially be used to better understand levels of infection and persistent postsequelae symptoms. We aim to assess the feasibility of detecting acute infections, wellness, and long COVID symptoms at a personal and population level.

We will also stratify and define patterns of symptoms of COVID-19 and any postacute infection illness. Self-reported symptoms and objective measures of activity from wearables will be used to identify any groups or patterns of symptoms, especially those among the nonhospitalized population, which has been less visible and easy to recruit in many studies.

We also aim to identify risk factors and causes of COVID-19, long COVID, and the severity of illness. The incidence of COVID-19 and the likelihood of a person developing persistent symptoms following infection will be investigated with respect to a person's state prior to enrollment, which will be based on sociodemographic information; participants' prior medical histories; and wearable- and phone-derived information, such as activity levels, heart rates, and sleeping patterns.

Finally, we will investigate mental well-being throughout the pandemic. Alongside measures of SARS-CoV-2 infection, we will also collect regular responses to mental well-being surveys. We will describe trajectories of mental well-being in response to illness and PHSMs during the pandemic as well as identify risk and protective factors.

Methods

Study Design

The Covid Collab study is a crowdsourced observational study that will involve remote enrollment. Covid Collab aims to collect wearable device data, phone data, and survey responses from a large number of self-enrolled participants. This is an observational population study with several structures available for particular objectives. Cross-sectional comparisons will involve drawing cases and controls from participants who have and have not reported illness during the course of the study. By conducting individual longitudinal comparisons and participant-specific models, baseline measurements will be compared against measurements from different stages of COVID-19 (ie, acute infection and postinfection) or from periods of interest (eg, vaccination periods and lockdowns).

Recruitment

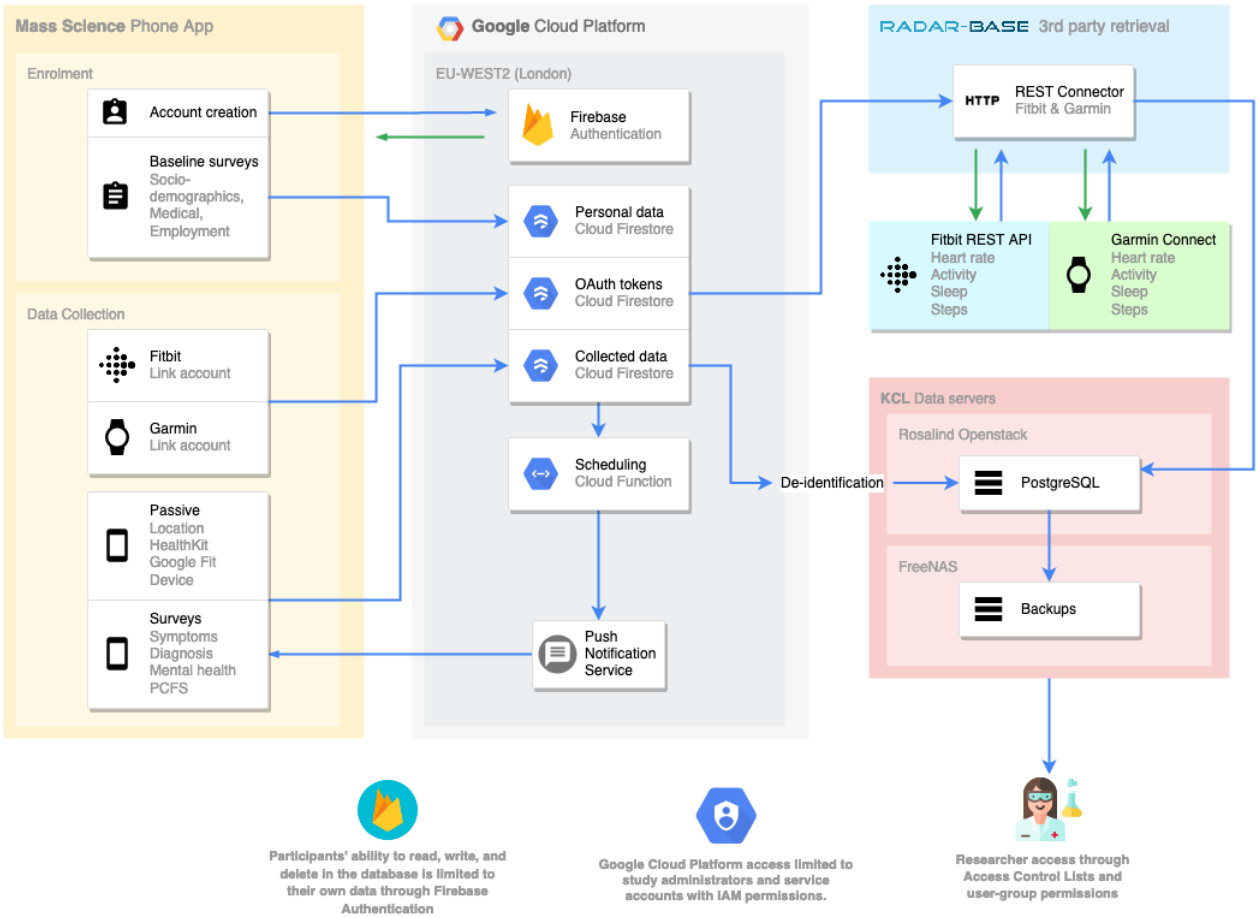
Recruitment started in April 2020 on a small scale, and large-scale recruitment began in June 2020. Given the crowdsourced nature of the study, participants will be able to enroll from anywhere. However, because of the location of our research group, the majority of the promotional activities that have been carried out have targeted people within the United Kingdom. The study is open to enrollment for any person over the age of 18 years who uses a smartphone and, optionally, a wearable fitness device. Participants without a fitness device will still be able to complete COVID-19 and mental health surveys.

Participants will enroll within the Mass Science app—the study app for Covid Collab. During enrollment, the participants will be provided with in-app study information, an in-app consent form, and a basic demographics survey. Directly following enrollment, the participants will go through an onboarding procedure. First, participants will complete a more in-depth demographic survey for collecting information on age, gender, ethnicity, height, weight, previous and existing medical conditions, employment status and whether there has been a change in employment status during the pandemic, and marital status. Second, participants will receive prompts for optionally turning on the location data sharing function in the background of their smartphones throughout their involvement in the study. They will also receive prompts for connecting their wearable device accounts to facilitate wearable device data collection.

Platform and Mass Science App

To facilitate the study, we used pieces of the Remote Assessment of Disease and Relapse (RADAR)–base mHealth data [21] collection platform, alongside services from Google Cloud Platform, as the data collection back end and a custom-built app for remote enrollment and participant interaction (Figure 1).

Figure 1. An overview of the data collection platform that will be used in the Covid Collab study. API: application programming interface; IAM: Identity and Access Management; KCL: King's College London; OAuth: Open Authorization; PCFS: Post–COVID-19 Functional Status; REST: Representational State Transfer.



The Mass Science app is a cross-platform smartphone app that was developed for the Covid Collab study using Flutter. Its key functionalities include providing prospective participants with the ability to enroll in the study; delivering scheduled surveys; allowing participants to input information related to SARS-CoV-2 infection and vaccination; collecting wearable device data either directly from phones or by requesting access to participants' data through third-party application programming interfaces (APIs); and collecting phone data, including location information. The collection of each data type (eg, location) will be optional. This will allow people to provide data that they are comfortable to share.

Google Cloud Platform [22] comprises the majority of the back end. User authentication will be managed through Firebase Authentication (Google LLC), survey scheduling will be managed through Cloud Functions and Firebase Cloud Messaging (Google LLC), and the initial collection of phone data and surveys will be conducted through Firestore (Google LLC).

RADAR-base is a general mHealth data collection platform that has been used in several RMT studies [14,23,24]. It comprises several modular applications. Some wearable device companies provide access to their customers' data through an API (a set of definitions and protocols that ease programmatic access to services). We will use the RADAR-base Representational State Transfer Connector to retrieve wearable device data from the Fitbit Web API (Fitbit LLC) and Garmin Health API (Garmin Ltd).

Procedures and Data Collection

Surveys

A number of baseline, on-demand, and scheduled surveys (Table 1) will be included in the study and completed by participants through the Mass Science app. Sociodemographic and medical information will be collected at baseline. Mental health questionnaires—the Patient Health Questionnaire-8 (PHQ-8) scale [25] for symptoms of depression and the General Anxiety Disorder-7 (GAD-7) scale [26] for symptoms of anxiety—will be made available, and participants will be prompted to complete these questionnaires every 2 weeks. A questionnaire on COVID-19 and long COVID symptoms and a visual analog happiness and energy scale will also be made available. These can be completed on demand, but participants will also be prompted biweekly to complete them. COVID-19 diagnosis and vaccination information can be submitted at any time. Following a reported COVID-19 diagnosis, participants will be prompted to fill in the Post–Covid-19 Functional Status scale [27]. Prompts regarding when a scheduled survey is available will be delivered through Firebase Cloud Messaging push notifications, which will appear as notifications on participants' phones.

Table 1. The surveys that will be collected during the study.

Questionnaires	Purpose	Frequency
Baseline questionnaires		
Covid Collab demographics (Multimedia Appendix 1)	To collect demographic data	Baseline
Covid Collab comorbidities (Multimedia Appendix 1)	To collect data on disorders and comorbidities	Baseline
Scheduled questionnaires		
Post–COVID-19 Functional Status scale [27]	A fast ordinal scale for the evaluation of post–COVID-19 functional status	Fortnightly following diagnosis
COVID-19 symptoms (Multimedia Appendix 1)	To catalog acute-phase and lingering COVID-19 symptoms and long COVID symptoms	Twice weekly and on demand
General Anxiety Disorder-7 [26]	To identify probable cases of anxiety and to determine the severity of symptoms	Fortnightly
Patient Health Questionnaire-8 [25]	To assess the severity and presence of symptoms of depression	Fortnightly
On-demand questionnaires		
Diagnosis (Multimedia Appendix 1)	Self-report diagnosis questionnaire	On demand
Vaccination (Multimedia Appendix 1)	Vaccination survey	On demand

Wearables

Wearable device data will be collected through 2 methods. First, participants can connect their web-based accounts, thereby allowing us to collect data from the wearable vendors' HTTP API. Both Fitbit LLC and Garmin Ltd will provide data access through this method by allowing users to authorize Covid Collab to access their data through the companies' respective APIs. In this case, data can be retrieved directly from a server. Second, we can retrieve data via users' smartphones by using Apple HealthKit (Apple Inc) [28] and Google Fit (Google LLC) [29]. In this case, data will be uploaded to Firestore alongside other phone data.

The exact data types that will be available will depend on the devices that the participants use, what the wearable device manufacturers make available, and what the users choose to authorize when allowing access to their wearable data. Where available, we will collect intraday and summary heart rate, step count, and activity data; sleep data; and other physical and health information, such as height and weight. If a participant does not own a wearable device, they will still be able to provide survey responses and phone data through the Mass Science app.

We expect that some participants will have existing data for the periods of time preceding enrollment and the pandemic. After they connect their wearable device accounts, we will retrospectively collect wearable device data from January 2019, where available. Prospective data will be retrieved as they become available.

Location

Geographic position data will be collected from consenting participants' phones. To reduce battery use, a location point will be recorded only when movement is detected and not when participants are stationary. Raw location data are highly sensitive. As such, they will be stored separately, and only deidentified features and summary statistics will be accessible to researchers. Following a change in stance by the Google Play Store (Google LLC) in January 2021, location collection was discontinued in subsequent updates of the Android app.

Data Enrichment

Analyses will require the enrichment of the data through the incorporation of publicly available data sets. Primarily, this will be performed via the contextualization of location data by using the CORINE (Coordination of Information on the Environment) Land Cover data set [30] and OpenStreetMap (OpenStreetMap Foundation) and via the incorporation of public and social measures from the World Health Organization PHSM database [31].

Data Management

All data will be stored and encrypted, and personal information will be stored in a separate database. Location data will be deidentified via the aggregation of raw geographic coordinates into features. Access to personal information will be limited strictly to study administrators for administration purposes (eg, to delete data at the request of a participant). Researchers' access to the anonymized data set will be limited through access control lists. Participants can choose to allow us to share anonymized versions of their data in a larger public data set, which will be made available at a later date.

Statistical Analysis

Data Exclusion and Absence

As a crowdsourced study involving the optional sharing of different modalities of data, we expect that there may be greater data missingness and participant attrition than those in studies that involve more direct patient contact and engagement. Different objectives may require different exclusion criteria. For example, determining wearable biomarkers for COVID-19 may only require a connected device and a single COVID-19 diagnosis survey, while characterizing trajectories of mental well-being would require multiple PHQ-8 and GAD-7 responses from a single participant.

Rates of participation, adherence, and dropout will be examined with respect to sociodemographics, time points during the pandemic, and participants' concurrent health. Additionally, patterns of user engagement will be characterized to show how participants may interact in similar studies and what drives engagement. User engagement will be determined based on completion rates for the prompted surveys.

Characterizing COVID-19 and Long COVID Symptomology

We will describe and define subgroups for symptoms of COVID-19 and long COVID through the clustering of self-reported symptoms. This will include a time-independent view of all symptoms throughout the illness as well as time-dependent clustering to investigate how the disease progresses. A latent class analysis will be used to group time-independent symptoms. A cluster analysis will be conducted on symptom severity data (4-point Likert scale). The optimal number of latent classes will be selected based on the Bayesian information criterion. Time-dependent symptom clustering will be carried out by using mixture latent Markov models. The classes will be described with respect to the frequency of symptoms and their prevalence in different sociodemographic groups.

Risk Factors for Severe COVID-19 and Long COVID

Risk factors will be assessed by conducting a logistic regression between participants with long COVID symptoms and participants who had COVID-19 but did not experience persistent symptoms. A logistic regression between participants with COVID-19 who self-report severe symptoms (based on a 4-point Likert scale) and those who self-report mild symptoms or are asymptomatic will also be conducted. Predictors will include sociodemographics, smoking status, medical history, and measures of health and behavior derived from the RMT passive data streams (eg, historic and contemporary activity levels and heart rates).

Disease State Classification

By using the identified clusters of symptoms, we will explore RMT parameters that can be used to classify COVID-19. This analysis will involve using conventional machine learning methods, including support vector machines and random forests, in combination with feature selection and fusion approaches, as well as more contemporary deep learning methods.

Trajectories and Classification of Mental Well-being

The primary mental health outcome measures will be the PHQ-8 and GAD-7 for depression and anxiety, respectively, which participants will be prompted to complete every 2 weeks. Additionally, a visual analogue scale for happiness and for energy will be included alongside the biweekly symptoms questionnaire.

Mental well-being will be investigated from several viewpoints. First, we will analyze how mood changes in response to and following a SARS-CoV-2 infection. Second, we will determine how mental well-being has been affected throughout the pandemic for the entire cohort in relation to public health measures and by taking into account levels of activity and information on location (eg, time spent outside, home stay duration, or local population density). Finally, we will assess the feasibility of using machine learning approaches to predict low mood on the basis of passive wearable and phone data.

Results

The Covid Collab study began in April 2020, and large-scale recruitment began in earnest in June 2020. As of June 2021, there are over 17,000 participants. Of those, 11,350 have a connected wearable device, and 16,350 have completed at least 1 survey. An interim analysis is expected to be complete by July 2021. The publication of the final analyses is expected to occur by December 2022 but may depend on the evolution of the COVID-19 pandemic.

Discussion

Remote monitoring is a promising avenue for understanding COVID-19 and the effects of the pandemic. Our study has multiple advantages, including the availability of historic wearable device data, the ability to reach a wide range and large number of people, and the high resolution of data. However, there are also a number of limitations to the study.

Although crowdsourced recruitment is technically open to all, it is likely that there will be bias. The study is only reachable by those who own a smartphone, and a person who already owns a wearable device may be more likely to take part in the study. Both of these populations may be skewed, in some respect, relative to the general population. Moreover, different segments of the population may be more likely to seek out and engage with scientific studies of this kind. For example, within our currently enrolled cohort, 68.6% (11,840/17,255) of participants are female. It will be important to quantify the composition of the cohort and determine how the composition relates to the known COVID-19 incidence rates among different groups, study adherence rates, and data completion rates within the study.

Participant attrition is present in many internet-based studies [32]. As previously mentioned, due to the nature of a study involving remote enrollment and little to no personal interaction, we may expect higher attrition rates than those in studies with different enrollment strategies or methods for promoting participant interaction and engagement [33]. A “history view” screen was implemented in the app. It shows previous mood responses to allow for the direct return of results to participants. However, other studies have used other methods for promoting participant engagement that are not present in our study largely due to development time limitations. Such methods include different notification strategies [34,35] and gamification [36,37].

Another limitation is imposed by the evolving nature of the pandemic and our knowledge of COVID-19; in response to new information, we may be required to change aspects of or add to the protocol. For example, long COVID symptoms and the Post–COVID-19 Functional Status scale were added recently, as more evidence of persistent impairment following SARS-CoV-2 infection has emerged. Time constraints also require us to balance the introduction of features with the need to recruit participants at an earlier stage. For example, the use of the Garmin Health API was recently included in the protocol. This may have limited the prior recruitment of users of Garmin devices. However, current and prospective participants with Garmin devices will still be able to donate historic data connected to their accounts.

There are several similar ongoing studies throughout the world. Although our participants may overlap with those of other studies, each study is fairly well geographically separated. Although we are recruiting participants from throughout the world, as a UK-based group, our outreach and ability to connect with potential participants are greatest in the United Kingdom. Given the similarity of the collected data and the loose alignment of questionnaires, there is potential for collaboration or meta-analysis.

Overall, the introduced study ought to provide an angle through which to view the mental and physical health of a population throughout the COVID-19 pandemic. Using historic and ongoing wearable and mHealth data should allow for more thorough precision health models to be built and enable us to understand how prior lifestyles have affected the risk of developing COVID-19, long COVID symptoms, and mental health issues.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Definitions for the unpublished questionnaires that will be used in the Covid Collab study.
[DOCX File , 11 KB - resprot_v10i12e32587_app1.docx]

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Abbreviations

API: application programming interface
CORINE: Coordination of Information on the Environment
GAD-7: General Anxiety Disorder-7
mHealth: mobile health
NHS: National Health Service
NIHR: National Institute for Health Research
PHQ-8: Patient Health Questionnaire-8
PHSM: public health and social measure
RADAR: Remote Assessment of Disease and Relapse
RMT: remote monitoring technology

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Protocol

Exploring the Intersection Between Health Professionals' Learning and eHealth Data: Protocol for a Comprehensive Research Program in Practice Analytics in Health Care

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Abstract

Background: There is an increasing amount of electronic data sitting within the health system. These data have untapped potential to improve clinical practice if extracted efficiently and harnessed to change the behavior of health professionals. Furthermore, there is an increasing expectation from the government and peak bodies that both individual health professionals and health care organizations will use electronic data for a range of applications, including improving health service delivery and informing clinical practice and professional accreditation.

Objective: The aim of this research program is to make eHealth data captured within tertiary health care organizations more actionable to health professionals for use in practice reflection, professional development, and other quality improvement activities.

Methods: A multidisciplinary approach was used to connect academic experts from core disciplines of health and medicine, education and learning sciences, and engineering and information communication technology with government and health service partners to identify key problems preventing the health care industry from using electronic data to support health professional learning. This multidisciplinary approach was used to design a large-scale research program to solve the problem of making eHealth data more accessible to health professionals for practice reflection. The program will be delivered over 5 years by doctoral candidates undertaking research projects with discrete aims that run in parallel to achieving this program's objectives.

Results: The process used to develop the research program identified 7 doctoral research projects to answer the program objectives, split across 3 streams.

Conclusions: This research program has the potential to successfully unpack electronic data siloed within clinical sites and enable health professionals to use them to reflect on their practice and deliver informed and improved care. The program will contribute to current practices by fostering stronger connections between industry and academia, interlinking doctoral research projects to solve complex problems, and creating new knowledge for clinical sites on how data can be used to understand and improve performance. Furthermore, the program aims to affect policy by developing insights on how professional development programs may be strengthened to enhance their alignment with clinical practice. The key contributions of this paper include the introduction of a new conceptualized research program, Practice Analytics in Health care, by describing the foundational academic disciplines that the program is formed of and presenting scientific methods for its design and development.

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KEYWORDS

digital health; health informatics; practice analytics in health care; health professions education; continuing professional development

Introduction

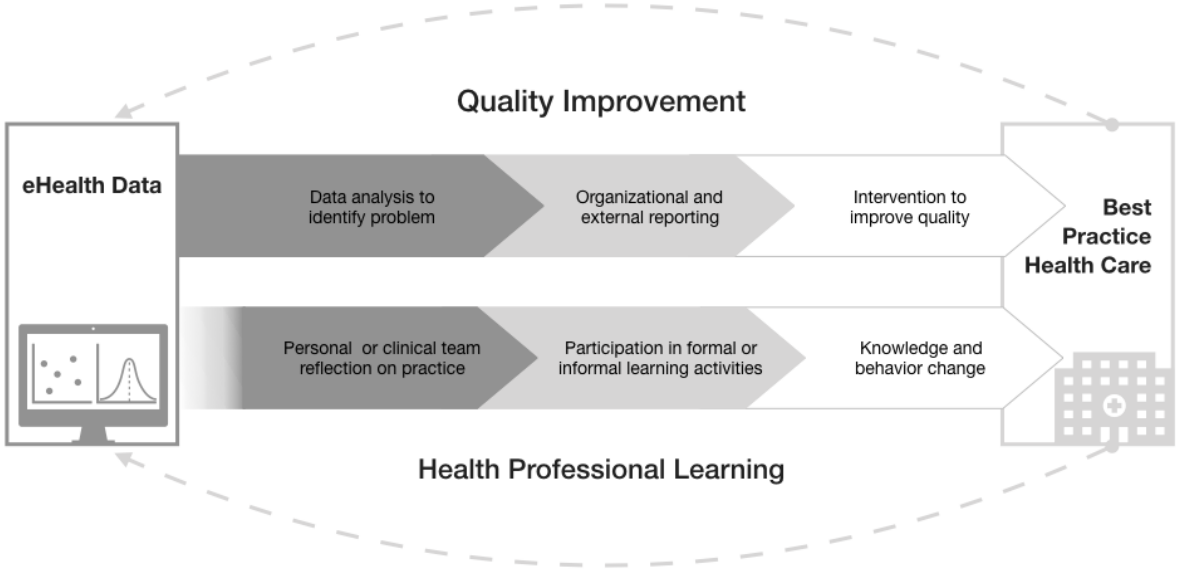
Background

Emerging digital technologies for collecting and using eHealth data have the potential to make data more accessible to individual clinicians, clinical teams, organizations, and the general public. The increasing accessibility of eHealth data provides opportunities for their use in a wide range of applications, including quality improvement activities [1], improving clinical processes [2], and facilitating new approaches to clinical research [3]. These data also have enormous potential to enable self-directed and personalized continuing professional development (CPD) and practice improvement for health professionals based on the data about their own clinical practice [4].

CPD is a cornerstone of health education and has a recognized place in maintaining high-quality care [5]. The principles of effective CPD have been well described in the literature and include being learner-centered, encompassing varied formats and delivery methods, and encompassing lifelong and ongoing assessments to address the needs of individual clinicians [6]. Another core component of health profession education is practice reflection by clinicians and clinical teams. Practice reflection describes the process of revisiting experiences both to learn from them and to understand the complex problems of professional practice [7]. Engaging in practice reflection is highlighted as being essential for health professionals to refresh and update their knowledge [8,9].

Although electronic data are a rich source of information for health professionals' practice, health professionals currently have limited access to their data for this purpose [4]. eHealth data are used by quality improvement teams in many health care organizations to identify variations in the quality of care and lead the process of designing interventions to address this [2,10]. However, this process does not often provide health professionals with an opportunity to actively engage with eHealth data and have an active input in how the data are being used to improve practice. Figure 1 illustrates the disconnect between the processes by which eHealth data are used for quality improvement and how health professionals engage in learning activities.

Figure 1. The difference between the use of eHealth data for quality improvement and health professional learning.



Thus far, a notable gap in health professionals' education and practice reflection is the use of eHealth data contained in clinical data sources such as electronic health records (EHRs), patient administrative systems, and registries. The value of using electronic data, such as that collected by EHRs for training and education, has been acknowledged in the literature [4]. Early research also suggests that clinicians themselves are keen to have more access to their data for personalized training and practice reflection [4]. The increasing need to incorporate clinical data into professional development and training has also been recognized at the government level in some countries [11]. In parallel to this, in some jurisdictions, the health care organization accreditation process now mandates audits and reviews of electronic data as part of the clinical governance process [12].

Despite the growing emphasis on the use of eHealth data to enable practice reflection, there are a number of challenges that need to be considered. A notable challenge relates to data management and ensuring the quality of data used while also considering privacy and security concerns [13]. Concerns about the quality of data collected by health informatics systems such as EHRs include the possibility that they may contain inaccurate or incomplete data, that the data are often recorded for coding

purposes rather than quality improvement or other secondary applications, and that the data often do not indicate a complete clinical story [14]. A recent review of the literature on privacy and security of EHRs showed that health care organizations have a range of concerns regarding the security of data and, in response, implement a range of administrative, physical, and technical safeguards to help address them [15]. In addition, it is important to consider the views of consumers on the privacy and security of eHealth data. The literature on health information exchange has noted that barriers to consumers' consent to health information exchange include privacy concerns, lack of awareness of the value of the contribution of their data, concerns about the data being used for profit, and the lack of easy tools for sharing their data [16,17].

Another challenge the health sector faces in harnessing the full potential of eHealth data is making the data actionable to health professionals in ways that can lead to improvements in quality, outcomes, or cost of care [13]. The application of digital technologies to facilitate better interactions between health professionals and electronic data for a range of professional development and quality improvement applications is a growing area in digital health [18-20]. The term Practice Analytics in Health care (PAH) is proposed to describe this area of digital health, which draws on key learnings from existing disciplines, including quality improvement, health professions education, health informatics, and learning analytics [21]. Broadly, PAH entails the use of integrated eHealth data sets to enable health professionals to optimize, improve, or enhance the value and quality of care. The field is heavily focused on identifying and collecting electronic data that surrounds individual health professionals and clinical teams, which can be used to obtain a snapshot of clinical practice, support individual learning, and enable learning systems. PAH harnesses data to generate new information and health insights that lead to practice reflection by clinicians and ultimately positive health outcomes. The field draws on 3 foundational academic disciplines: health and medicine, education and learning sciences, and engineering and information communication technology. Within these disciplines, there are a number of research specialties that contribute to PAH, including learning analytics [22], human–computer interaction [23], and quality improvement [24,25]. Textbox 1 provides a detailed overview of the research specialties that contribute to PAH.

Textbox 1. Overview of the foundational Practice Analytics in Health care research disciplines.

Academic disciplines and fields of research

- Engineering and information communication technologies:
  - Computer science
  - Human–computer interaction
  - Learning analytics
  - Visualization
  - Data analytics
  - Machine learning
  - Data mining
- Medicine and health:
  - Epidemiology
  - Public health
  - Implementation science
  - Quality improvement
  - Ethics and law
  - Data privacy and security
- Learning sciences and education:
  - Medical education
  - Health professions education
  - Learning analytics

The program described in this paper seeks to understand how health professionals can be supported by digital technology to make effective use of eHealth data to support practice reflection. This will be achieved through a comprehensive research program delivered through a number of discrete doctoral research projects.

Study Aims

The aim of this research program is to make eHealth data captured within tertiary health care organizations more actionable to health professionals for use in practice reflection, professional development, and other quality improvement activities, with the ultimate aim of improving patient outcomes.

Methods

Study Design

The research program described in this protocol is a problem-driven multidisciplinary research program between academic partners and the Digital Health Cooperative Research Centre (DHCRC), and industry partners made up of government and health service organizations. The research program is funded by the DHCRC [26]. Cooperative Research Centres are cofunded by the Australian government, industries, and universities to support applied research and development programs. In the context of this research program, a multidisciplinary team of researchers, scientists, and clinicians has been brought together to identify key industry problems and design a research program that addresses the abovementioned problems.

The multidisciplinary team guiding the delivery of the research program and supporting the project includes academic institutions (2/6, 33%), health care organizations (3/6, 50%), and peak bodies in the Australian health sector (1/6, 17%). The team was engaged early during the problem identification and research formulation stage, aligned with recommendations in the literature on how to undertake multidisciplinary research [27]. The research program will be delivered by a team of academic supervisors, doctoral candidates, and postdoctoral fellows working collaboratively to implement evidence-based solutions to the key problems and identify new knowledge that will address the research program's aims. Supervisor panels were purposely drawn to represent academia, service partners, and active clinical practice.

The research program incorporates scientific theories from implementation science and action research. Action research is based on action, evaluation, and critical analysis of data to drive improvements, and it is commonly used to improve practices in various health care environments [28,29]. This type of research is facilitated by the participation and collaboration of a number of individuals with a common purpose. In PAH, action research is used to enable doctoral candidates to work collaboratively and undertake their research projects simultaneously while also reflecting and adapting based on each other's learnings. Implementation science is the science of methods and strategies that facilitate the use of evidence-based research findings in regular practices by professionals and policy makers [30]. In this research program, implementation theory will be used to ensure that new knowledge created from the doctoral research projects is effectively transferred to tertiary hospitals to change behavior and alter clinical performance. The incorporation of these 2 theoretical approaches is central to ensuring that the program addresses both a research gap and meets the needs of industry partners.

Research Program Development

The research program was co-designed by an academic and industry team supported by a program manager. Academic team members (n=5) brought expertise from a range of specialized research fields from the disciplines of medicine and health, engineering and information communication technology, and education and learning sciences. Industry team members (n=6) included representatives from private tertiary hospitals and representatives from peak national bodies.

To develop the study design, industry representatives who may have interest or expertise in using eHealth data with health professionals were identified from the DHCRC network. A one-on-one meeting with each industry representative and the lead investigator for the research program was conducted to identify key points and research priorities between May and July 2019. Meeting notes were synthesized into a preliminary research program outline by 2 researchers (TS and AJ) familiar with the area. This outline was then circulated to each industry representative who was interested in the research program for feedback.

Industry representatives who indicated continued interest in the direction of the research program participated in a planning workshop in August 2019. This workshop involved an open discussion between academic and industry attendees (n=14) to agree on the final objectives of the program. The workshop also identified the outline of the doctoral projects that would be achievable over the course of full-time candidature and that would meet the priorities of the industry representatives. Feedback from the planning workshop was reviewed and used to turn the research outline into a comprehensive research program road map. The research program was built around 3 streams. The protocol also described 6 objectives for the research program. Table 1 shows the objectives mapped against the 3 streams and the doctoral projects. The research program protocol was circulated to all workshop participants for consideration. Feedback on this document was incorporated into a revised version of the research program protocol.

Table 1. Overview of the 3 research streams in the Practice Analytics in Health care program.

Research stream and objectives	Doctoral project
Stream 1: building capacity for the collection and use of meaningful eHealth data by health professionals	
Understand the readily available data that is most likely to be useful in performance feedback and continuous practice enhancement and explore the ethical considerations of using patient-reported outcomes and the barriers and enablers to health professionals using these data in practice	• Defining clinical practice indicators • Optimizing the actionability of patient-reported experience and outcome measures (future project)
Stream 2: developing tools to optimize the use of complex health data by health professionals	
Determine the acceptability of different tools for feeding back performance data to individual clinicians and health care teams, understand the processes medical practitioners use to make sense of the data presented to them, and understand the ethical and policy implications for organizations and individual clinicians when using eHealth data for reflective practice	• Visualizing performance data • Data sensemaking • Ethical, medico-legal, and policy implications of Practice Analytics (future project)
Stream 3: understanding how Practice Analytics changes the behavior of health professionals and links with professional development	
Explore how performance data can be linked to professional development requirements, clinical governance, and hospital accreditation standards and understand how transition points in clinical careers influence the quality and usability of electronic data for practice reflection	• Understanding the role of performance data in formal and informal professional education • Exploring lifelong learning and career transition points in Practice Analytics (future project)

A final full-day workshop was held with academic and industry representatives (n=17) in February 2020 to review the final scope of the research program and confirm the doctoral projects and other logistical considerations. On the basis of the conclusion of the second workshop, there was a consensus on the 3 streams that would make up the research program. The scope for each of the 4 initial doctoral projects that would be embedded in the research program was also confirmed along with a road map for 3 future doctoral projects.

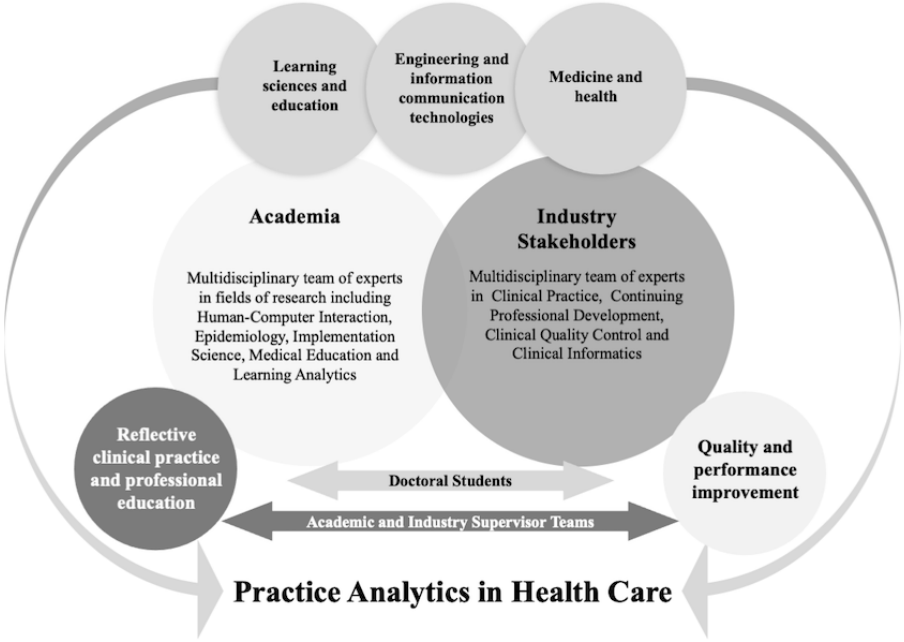
Procedures

The research program will be enabled via an integrated set of doctoral research projects over a 5-year period. Ensuring the privacy and confidentiality of data is a key consideration for the research program. The research program procedures are in place with considerations for the research data being collected and the health data being used. To ensure that all research data are managed appropriately, each doctoral candidate will obtain appropriate human research ethics committee approval, which will require compliance with the National Statement on Ethical Conduct in Human Research [31]. In addition to research data, some projects in the research program may use health data. There are 2 types of health data that will need to be considered for the research program: patient data collected routinely by health care organizations and data about the professionalism of health professionals being used to develop practice reflection tools. It is not anticipated that identifiable patient data will be used in any of the research projects described in this protocol.

Regarding data about health professionals, individual doctoral candidates may use identifiable data. However, the process for accessing and using these data for each doctoral candidate will be approved by the relevant human research ethics committee. No identifiable data will be extracted or used without prior written consent. Finally, because of the importance of data privacy and ethical and legal considerations in the PAH space, the research program has prioritized a specific doctoral project to research these issues (Table 1).

Each doctoral research project is supported by a team comprising, at minimum, a primary academic supervisor with expertise in the research area, an industry supervisor with clinical or technological domain knowledge, and a postdoctoral fellow funded through the program. Figure 2 presents how inputs from academia and industry are harnessed to both design and deliver the Practice Analytics research program.

Figure 2. The collaborative methodology used to develop the Practice Analytics in Health Care research program.



Results

Research Program Design

The process used to develop the research program identified 7 doctoral research projects to answer the program objectives, split across 3 streams. The following section presents a brief description of each doctoral research project and shows their alignment with the 3 streams of the research program. Table 1 shows the objectives mapped against the 3 streams and the doctoral projects.

Stream 1: Building Capacity for the Collection and Use of Meaningful eHealth Data by Health Professionals

Defining Clinical Practice Indicators

This research project is designed to understand how to extract and structure data within health care organizations so that it can be used effectively for performance feedback. It is currently challenging to use eHealth data collected in health care organizations, such as data from patient administrative systems and electronic medical record (EMR), as the systems were not designed to capture data for this purpose. Currently, these systems are not designed with a primary focus on supporting health professional training and practice reflection. As such, it is necessary to explore how to repurpose these data for this project. The project will do this by identifying clinical indicators for individual diagnoses or procedures across different specialties that have clinical validity for the performance profiling of individual clinicians. Once the clinical indicators have been agreed upon by key stakeholders, a data audit will be undertaken to determine whether the quality and completeness of data within an individual health care organization are sufficient to populate each indicator by using routinely collected data.

Optimizing the Actionability of Patient-Reported Experience and Outcome Measures (Future Doctoral Project)

The project will explore the value of a generic set of patient-reported experience and outcome measures to use in informing clinical practice across key disciplines. The project will also explore the value of discipline-specific patient-reported experience and outcome measures and patient survey data sets for informing clinical practice.

Stream 2: Exploring Different Approaches to Make Complex Health Data Actionable for Health Professionals

Visualizing Performance Data

This research project will explore how performance feedback tools are designed to enable health professionals to engage with their data. Research on the design of these platforms for use by health professionals is currently limited. This research project will address this problem by exploring the extent to which a one-size-fits-all solution is viable for feeding back performance data and contrasting it to more personalized approaches. When designing performance feedback tools, personalized approaches to visualizing data could account for factors such as health professional data literacy, different information needs, history of use of the data, and context-specific data use. It will also explore how performance feedback tools can support health professionals who desire a high level of engagement with their data rather than just supporting entry-level needs.

Sensemaking of Data

The overarching aim of the project is to understand how health professionals make sense of data related to their performance. Specifically, the project seeks to investigate how EMR and other health administration data are currently used by health professionals across different health care organizations. Currently, there is little research exploring the processes that health professionals use to make sense of their data, which is a problem because it is a barrier to the more widespread use of electronic data by this cohort. This project will address this problem by exploring the process of data sensemaking across different disciplines and organizational contexts. The project also aims to understand the factors that inform health professionals make sense of information such as emotion and previous experiences. Finally, the project will study how sensemaking informs further action in terms of both CPD and practice.

Ethical, Medico-Legal, and Policy Implications of Practice Analytics (Future Doctoral Project)

This research project is designed to understand the ethical and policy implications for organizations and individual clinicians when using eHealth data for reflective practice. The project will likely explore questions such as how organizations, individuals, and teams respond when data show an individual outlier that needs support and what information must be disclosed outside the organizations. The project will explore the way ethico-legal implications of using data for reflective practice affect engagement by specialists and other health professionals. This includes the nexus between using performance data from performance improvement rather than performance management and in potential litigation.

Stream 3: Understanding How Practice Analytics Changes the Behavior of Health Professionals and Links With Professional Development

Understanding the Role of Performance Data in Formal and Informal Professional Education

This research project seeks to understand how medical regulatory bodies, education providers, and health care organizations can use eHealth data to personalize training programs. This is a challenge for health professionals, medical regulatory bodies, education providers, and other key stakeholders because there is an increasing expectation that health professionals will engage with their practice data for lifelong learning and other professional development activities. The project will address this problem by exploring how eHealth data from health care organizations can be used to better understand the clinical and professional practices of health professionals. Finally, the project will also investigate the attitudes of health professionals to the use of their data for professional development and reflective practice.

Exploring Lifelong Learning and Career Transition Points in Practice Analytics (Future Doctoral Project)

This research project is designed to understand how transition points in clinical careers influence the quality and usability of electronic data for practice reflection. The project will look specifically at the experiences of health professionals as they transition from specialist training to early-career specialty fellowships. It will also look at how data are presented and reported to health professionals in a way that captures knowledge, skills, and professional growth that occurs throughout a clinical career.

Discussion

Overview

This protocol paper provides a description of the term PAH and describes the academic disciplines that contribute to this multidisciplinary field. Furthermore, it presents an overview of the methodology for designing a PAH research program. The research program is the first to bring together academic disciplines combined with industry partners to identify and solve problems they face, increasing the actionability of eHealth data by health professionals for reflective practice and improvement. Finally, the protocol paper outlines how the aims of the research program will be achieved over the course of the program through an intervention that interlinked doctoral projects undertaken by doctoral candidates with diverse skill sets. At the conclusion of the research program, the intervention will have fostered strong partnerships between academic and industry partners; developed new knowledge in the field of PAH to address gaps in the research regarding the extraction, integration, and use of electronic data to change behavior; and translated key findings from the research program to clinical and regulatory settings to change practice.

A problem-driven multidisciplinary approach was foundational in designing the research program described in this protocol. To develop the PAH research program, experts with different perspectives and expertise worked collaboratively to refine the problem to focus on how electronic data within health care organizations could be used to support individual learning and strengthen professional development. The important role of multidisciplinary approaches involving academic and industry experts throughout the process can be challenging; however, through a guided process of discovery, ideation, and development, it can give voice to both health professionals and academic specialists to drive necessary changes [32]. In the area of PAH, multidisciplinary research is essential, as the field incorporates methodologies and approaches from diverse disciplines such as medicine and health, engineering and information communication technology, and learning sciences and education.

A key component of the research program is harnessing individual research projects to deliver an intervention that meets the needs of both academic and industry stakeholders. Each individual doctoral candidate brings knowledge and skills from their own discipline and applies them to answer a specific research question in service of the aims of the Practice Analytics research program. By harnessing principles from action research [28], the doctoral research projects run parallel in a complementary manner. Individual doctoral candidates meet regularly with each other and the larger program team to share their learnings and potentially refine their focus as the needs of the research program evolve. Individual projects are also

embedded with industry partners to enable the health care system to absorb new knowledge from the research. Using discrete research projects that can run independently while also aligning with an overarching program has been established as an effective way of delivering multidisciplinary research [27].

To ensure that individual research projects are aligned with the goals of the PAH program, a number of processes have been implemented. These processes include having touch points with representatives of all industry partners supporting the Practice Analytics program, regular meetings between the academic supervisor team for each candidate, regular meetings between the academic supervisor team and the doctoral candidates, and regular meetings between the doctoral candidates and the postdoctoral fellows. These meetings are augmented with shared web-based repositories of information and serve the dual purpose of acting as coordination tools for the project and facilitating shared communication between all parties. Establishing an overall program management and coordination strategy is a recommended practice for successful multidisciplinary research programs [27].

This research program will need to draw on key learnings from different disciplines to address problems in the PAH field. An example of how this research program leverages research knowledge from diverse disciplines relates to a key challenge in the health sector: making eHealth data more actionable. To date, the health care industry has not fully achieved the potential benefits of using eHealth data to support health professional learning [4]. However, there is acknowledgment in the literature that using cyclic analysis of eHealth data should be incorporated into exemplary health learning environments [33]. Electronic data within health care organizations have not been widely used to support health professional learning for many reasons [34]; however, an important consideration is increasingly that one of the main mechanisms for capturing electronic data is EMRs. Most EMR systems were designed to create a digitized record of an individual's data that can be used by health professionals to provide care to those individuals [35,36] and have limited functionality built into their design to support learning. Although this challenge is relatively new in the discipline of health and medicine, it has something that has been explored in the research area of human-computer interaction within the discipline of engineering and information communication technologies. Human-computer interaction specialists have identified that one of the barriers to developing good interfaces is that the system that is to be used was designed for a different purpose and its function has changed. By translating this knowledge from one discipline to another and between academia and industry, PAH has the potential to rapidly solve a range of problems faced by the health care industry.

Finally, because of the multidisciplinary nature of the research program, it is anticipated that outputs will have an effect not only on health care but also across a range of sectors. The research program will also incorporate established theories from implementation science [30] to ensure that new research knowledge is translated into practice change within the health care sector. At the conclusion of the program, it is anticipated that the intervention will create new knowledge to grow the field of PAH. Furthermore, this new knowledge will be translated into the health care sector within individual organizations to support health care professionals and teams and by regulatory bodies to personalize and strengthen professional development.

Conclusions

The use of a multidisciplinary research program built around core objectives that align with the priorities of both industry and academic stakeholders is a unique approach that aims to unpack the potential of eHealth data to support learning, practice reflection, and other training activities of health professionals, improving the quality of care and patient outcomes. It is anticipated that this program will be extended to specific translational outputs informed by the research findings.

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Conflicts of Interest

Author TS is the Director of Research at Digital Health Cooperative Research Centre. Author AJ is undertaking a postdoctoral research fellowship that is fully funded by the Digital Health Cooperative Research Centre. Authors ST, JK, and DG declare that they have no conflicts of interest.

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Abbreviations

CPD: continuing professional development
DHCRC: Digital Health Cooperative Research Centre
EHR: electronic health record
EMR: electronic medical record
PAH: Practice Analytics in Health care

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Protocol

A Web-Based Service Delivery Model for Communication Training After Brain Injury: Protocol for a Mixed Methods, Prospective, Hybrid Type 2 Implementation-Effectiveness Study

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Abstract

Background: Acquired brain injuries (ABIs) commonly cause cognitive-communication disorders, which can have a pervasive psychosocial impact on a person's life. More than 135 million people worldwide currently live with ABI, and this large and growing burden is increasingly surpassing global rehabilitation service capacity. A web-based service delivery model may offer a scalable solution. The Social Brain Toolkit is an evidence-based suite of 3 web-based communication training interventions for people with ABI and their communication partners. Successful real-world delivery of web-based interventions such as the Social Brain Toolkit requires investigation of intervention implementation in addition to efficacy and effectiveness.

Objective: The aim of this study is to investigate the implementation and effectiveness of the Social Brain Toolkit as a web-based service delivery model.

Methods: This is a mixed methods, prospective, hybrid type 2 implementation-effectiveness study, theoretically underpinned by the Nonadoption, Abandonment, Scale-up, Spread, and Sustainability (NASSS) framework of digital health implementation. We will document implementation strategies preemptively deployed to support the launch of the Social Brain Toolkit interventions, as well as implementation strategies identified by end users through formative evaluation of the Social Brain Toolkit. We will prospectively observe implementation outcomes, selected on the basis of the NASSS framework, through quantitative web analytics of intervention use, qualitative and quantitative pre- and postintervention survey data from all users within a specified sample frame, and qualitative interviews with a subset of users of each intervention. Qualitative implementation data will be deductively analyzed against the NASSS framework. Quantitative implementation data will be analyzed descriptively. We will obtain effectiveness outcomes through web-based knowledge tests, custom user questionnaires, and formal clinical tools. Quantitative effectiveness outcomes will be analyzed through descriptive statistics and the Reliable Change Index, with repeated analysis of variance (pretraining, posttraining, and follow-up), to determine whether there is any significant improvement within this participant sample.

Results: Data collection commenced on July 2, 2021, and is expected to conclude on June 1, 2022, after a 6-month sample frame of analytics for each Social Brain Toolkit intervention. Data analysis will occur concurrently with data collection until mid-2022, with results expected for publication late 2022 and early 2023.

Conclusions: End-user evaluation of the Social Brain Toolkit's implementation can guide intervention development and implementation to reach and meet community needs in a feasible, scalable, sustainable, and acceptable manner. End user feedback will be directly incorporated and addressed wherever possible in the next version of the Social Brain Toolkit. Learnings from these findings will benefit the implementation of this and future web-based psychosocial interventions for people with ABI and other populations.

Trial Registration: Australia and New Zealand Clinical Trials Registry ACTRN12621001170819; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12621001170819, Australia and New Zealand Clinical Trials Registry ACTRN12621001177842; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12621001177842, Australia and New Zealand Clinical Trials Registry ACTRN12621001180808; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12621001180808

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KEYWORDS

implementation science; patient-outcome assessment; internet interventions; acquired brain injury; delivery of health care; caregivers; speech-language pathology

Introduction

Background

More than 135 million people worldwide currently live with acquired brain injuries (ABIs), including traumatic brain injury and stroke [1]. ABIs commonly cause cognitive-communication disorders in which underlying problems with working memory, organization, executive function, self-regulation, or a combination of these, affect the communication skills needed for everyday exchanges such as conversations, explanations, and stories [2]. Cognitive-communication disorders can thus have a pervasive impact on a person's social participation and relationships [3], employment [4,5], and mental health [6], while presenting concurrent health, psychosocial, and economic challenges for their families and communities [7-9].

The growing psychosocial burden of ABI increasingly surpasses the global rehabilitation service capacity to address it [1], including national-scale shortages in public speech-language pathology services to manage communication difficulty [10]. Inversely, families of people with ABI, particularly from rural and remote areas, experience logistical and access challenges when seeking face-to-face health care, leading carers to express their need for locally accessible support [11]. The equitable and scalable delivery of communication rehabilitation for people with ABI is therefore a global health service challenge [1], demanding consideration of alternative and complementary service delivery models to meet the psychosocial needs of this population and their communities now and into the future.

In response to these challenges, an evidence-based suite of web-based interventions known as the Social Brain Toolkit [12] is currently in development. The project was cocreated with stakeholders, including people with ABI and their communication partners, clinicians, partnering organizations, and policy makers. These stakeholders have been attending, and are included in, regular steering and advisory committee meetings. They have provided feedback on early prototypes and have been involved in the planning of implementation strategies and now the formative evaluation of the Social Brain Toolkit products. The aim of the Social Brain Toolkit is to provide scalable communication training to people with ABI and their communication partners, including family members, friends, partners, paid support workers, and clinicians. The Social Brain Toolkit comprises 3 web-based interventions: (1) convers-ABI-lity, a conversation skills training program for adults with ABI and familiar communication partners such as family members, partners, and friends; (2) interact-ABI-lity, web-based communication training for unfamiliar communication partners of people with ABI, such as paid support workers and the general public; and (3) social-ABI-lity, social media training for people with ABI seeking to communicate and connect on the web. interact-ABI-lity and social-ABI-lity are self-directed web-based courses, whereas convers-ABI-lity includes self-directed web-based content between telehealth sessions with a speech-language pathologist. The need for and format of these communication training courses were identified together with stakeholders, including people with ABI and their communication partners, with the aim of improving the quality of life and psychosocial outcomes of people with ABI and their communities.

The communication skills of communication partners can have a positive or detrimental effect on the communication skills of people with ABI [13-15]. Therefore, interact-ABI-lity and convers-ABI-lity deliver an evidence-based [16] intervention known as communication partner training (CPT), which involves training communication partners to facilitate the communication [17] of the person with ABI. CPT is recommended in international guidelines as best practice management of cognitive-communication disorders after ABI [18,19], and the convers-ABI-lity intervention delivers the core therapeutic content of the existing efficacious CPT programs TBI Express [20] and TBIconneCT [21,22]. convers-ABI-lity is a conversion and streamlining of the content of these programs into both asynchronous self-directed activities and synchronous telehealth speech-language pathology sessions. interact-ABI-lity delivers CPT as an asynchronous, self-directed web-based educational intervention.

In addition, the Social Brain Toolkit contains the social-ABI-lity intervention, which provides people with ABI with training in communication through social media. This is because people with ABI who use social media for connection are likely to experience difficulties in web-based interactions that are similar to those experienced in real-world interactions [23]. The social-ABI-lity intervention in the Social Brain Toolkit is an educational intervention based on new recommendations to support and train people with ABI in the safe and effective use of social media, with a view to increasing their social participation, enabling recovery of social communication skills, and promoting a sense of self or identity after ABI [24].

Web-based access to psychosocial interventions such as the Social Brain Toolkit are promising not just for the possibility of improving the scalability and accessibility of interventions, but also for their potential to reduce inequities in access to psychosocial support. Even before global shifts to web-based health care during the COVID-19 pandemic [25], people with ABI frequently accessed language and cognitive training on the web, with older patients and rural residents even more digitally engaged than younger and urban users [26]. When delivered on a national scale, equivalent web-based service delivery models in mental health have demonstrated the ability to overcome entrenched health care access barriers such as socioeconomic and indigenous status, and to enable access to users who otherwise do not access traditional face-to-face care [27,28]. However, web-based service delivery models face numerous implementation challenges. Even clinically effective digital health interventions struggle to be sustained as a long-term service delivery option [29] for reasons beyond their clinical effectiveness, including costs and workflow changes associated with their delivery [30]. Although there is an established and varied evidence base exploring web-based psychosocial interventions [31,32], there is limited implementation science research over and above these clinical trials to determine how these interventions might be successfully implemented and sustained as part of routine clinical care [31]. Therefore, a specific focus on implementation, especially in early research collaboration with end users, has been recommended for future research into web-based psychosocial care [27-31].

Therefore, real-world evaluation of the implementation of the Social Brain Toolkit interventions demands (1) collaborative involvement of end users, (2) a hybrid implementation-effectiveness research design [33] to expedite the incorporation of implementation learnings into intervention design, and (3) a theoretical underpinning in a digital health implementation framework that reflects the complexity of real-world implementation. Thus, this hybrid implementation-effectiveness study will be underpinned by an implementation theory that is both specific to digital health and based on a complexity approach: the Nonadoption, Abandonment, Scale-up, Spread, and Sustainability (NASSS) framework of eHealth implementation [34-36]. This framework will be used to support the more comprehensive identification of real-world complexities in the scale-up, spread, and sustainability of the Social Brain Toolkit.

Aims

In this study, formative evaluation of the implementation of the Social Brain Toolkit by end users in the community will be used to guide intervention development and implementation [37] to support these interventions to reach and meet community needs in a feasible, scalable, sustainable, and acceptable manner. Therefore, guided by domains of the NASSS framework [34,35], in this hybrid implementation-effectiveness study, we aim to answer the following implementation questions:

1. Who uses these interventions and what are their characteristics (domains 1 and 4)? What implementation strategies can be used to improve intervention reach?
2. In what geographical locations and health care and social contexts are the interventions used (domains 3 and 5-6)? What implementation strategies can be used to improve intervention reach?
3. Do users complete the interventions as intended (domain 4)? Why or why not? What implementation strategies can be used to improve intervention adherence and fidelity?
4. How usable is the technology for those completing the interventions (domain 2)? What changes can be made to improve usability?
5. What barriers, facilitators, and workarounds do users experience when completing these interventions (domains 1-7)? What strategies, facilitators, and workarounds can be used to improve future implementation?
6. How satisfied are users with the interventions (domain 3)? What changes can be made to increase user satisfaction?
7. What is the cost of delivering each web-based intervention, and how does this compare with face-to-face delivery (domain 3)?

We seek to determine intervention effectiveness as follows:

1. Do people who complete the interact-ABI-lity course have improvements in their self-efficacy and knowledge about communicating with people with ABI?
2. Do people who complete the social-ABI-lity course have improvements in their self-efficacy and knowledge about communicating safely and successfully on social media?
3. Do people who complete the convers-ABI-lity program have improved communication and quality-of-life outcomes?

Methods

Design

This study uses a prospective hybrid type 2 implementation-effectiveness design [33] and is registered on the Australia and New Zealand Clinical Trials Registry: interact-ABI-lity ACTRN12621001170819 (Universal Trial Number [UTN] U1111-1266-6628); social-ABI-lity ACTRN12621001177842 (UTN U1111-1268-4909); and convers-ABI-lity ACTRN12621001180808 (UTN U1111-1268-4849). The Social Brain Toolkit is well suited to a hybrid implementation-effectiveness design [37] because its interventions present minimal risk [16], with indirect evidence supporting effectiveness [22-24] and strong face validity supporting applicability to a web-based delivery method [21,22]. A prospective hybrid type 2 design especially reflects a collaborative ethos because it allows formative evaluation by end users to inform the refinement and improvement of both the clinical interventions and their implementation processes [37]. Preemptive implementation strategies will be devised during intervention development, including through consultation with people with ABI, communication partners, and clinicians supporting people with ABI, and people with experience implementing digital health [38], as well as reference to current implementation science literature [39]. Additional user-identified implementation strategies will be determined as part of the formative evaluation processes in this study, rather than solely a priori, in keeping with our collaborative ethos and approach.

The deployment of additional user-identified strategies will enable us to identify and potentially address persisting and unanticipated implementation barriers or shortcomings of our preemptive implementation strategies.

Data Collection

To obtain these data, we will use a mixed methods design for both implementation (Multimedia Appendix 1) and effectiveness (Multimedia Appendix 2) [40-42] data collection.

Interviews

Intervention usability and user experience and satisfaction will be formatively evaluated through interviews. The first 30 minutes of the 90-minute interview will involve a think-aloud [43] review of the user interface through screen sharing of the web-based platform. The think-aloud method is a robust and flexible research technique to test usability by providing valuable and reliable information of users' cognitive processes while completing a task [43]. This think-aloud task will be followed by a 60-minute qualitative interview, with interview questions developed using the NASSS framework of digital health implementation [34] to prompt discussion of multiple issues within this time frame (see Multimedia Appendices 3-7 for interview protocols). We will conduct the interviews as soon as possible after a user's completion of the course to facilitate recollection of the intervention experience. We will conduct the interviews individually and with communication partners, depending on participant preference and availability. Data collection will occur entirely on the web, with interviews conducted through secure videoconferencing on Microsoft Teams (Microsoft Corporation) software [44]. The interview will be audio and video recorded using the built-in recording functions of the videoconferencing platform. Interview recordings will be transcribed verbatim for analysis.

Surveys

For all 3 interventions in the Social Brain Toolkit, we will use pre- and postintervention surveys within the intervention platforms to obtain implementation outcomes, including user demographic information, and qualitative and quantitative patient-reported experience measures (Multimedia Appendix 1). We will conduct the surveys completely on the web. The surveys are based on the NASSS framework domains (see Multimedia Appendices 8-10 for survey protocols). We will measure intervention effectiveness using questionnaires that probe patient-reported outcome measures such as self-ratings of confidence in communicating with someone with ABI or using social media (Multimedia Appendix 2).

Analytics

We will collect web analytics (Multimedia Appendix 1) for each intervention over a 6-month sampling frame. This will enable user fidelity and adherence to the interventions to be examined.

Clinical Outcomes

Clinical outcomes (Multimedia Appendix 2) examining the effectiveness of convers-ABI-lity will be collected in a parallel study. As interact-ABI-lity and social-ABI-lity are educational interventions, their effectiveness will be examined by measuring knowledge through preintervention, postintervention, and follow-up multiple-choice questions.

Analysis

Qualitative

To examine effectiveness, 2 experienced speech-language pathologists will review the lists of strategies generated by users of the social-ABI-lity and interact-ABI-lity courses, and code them as appropriate or inappropriate using a consensus rating procedure (Multimedia Appendix 2). To examine implementation, the first author (MM) will conduct deductive content analysis [45] based on the NASSS framework [34] of both free-text survey responses and interview data (Multimedia Appendix 1). Coding will be managed in NVivo 12 Pro (QSR International Pty Ltd) [46] or Microsoft Excel 2016 [47] (Microsoft Corporation) software.

Quantitative

We will prospectively measure implementation outcomes in relation to the following:

1. Preemptive strategies deployed to support the implementation of the Social Brain Toolkit at launch, devised through current implementation evidence [39] and stakeholder input from a separate study [38].
2. Additional user-identified strategies subsequently obtained through formative evaluation of the interventions by end users.

To observe any potential influence of these implementation strategies and factors on implementation success and the time lag of impact, we will record the following:

1. A detailed description of each implementation strategy and its rationale.
2. A detailed timeline of each strategy's deployment.
3. Effectiveness and implementation outcomes over time.

We will calculate descriptive statistics of implementation measures, including user demographic characteristics, satisfaction ratings, percentage completion, and total number of users (Multimedia Appendix 1). We will tabulate descriptive statistics stratified by time and by whether users complete the interventions. Descriptive statistical analysis will be conducted using RStudio software (RStudio Inc) [48].

Clinical assessment data for conversation skills and quality of life (Multimedia Appendix 2) [40-42] will be analyzed using the Reliable Change Index [49] to determine whether individual participants had any clinically significant changes. Patient-reported outcome measures for interact-ABI-lity and social-ABI-lity, such as self-ratings of confidence, will be analyzed using repeated measures analysis of variance, with 3 levels (pretraining, posttraining, and follow-up) to determine whether there is any significant improvement within this participant sample. These data will also be managed using appropriate statistical software such as Microsoft Excel 2016 (Microsoft Corporation) [47].

Finally, theoretically underpinned by the third domain of the NASSS framework [34] examining the value proposition of an intervention, we will use the web analytics data for each

intervention to calculate web-based health care costs and equivalent face-to-face costs using a bottom-up costing approach [50]. With an initial focus on the Australian context from which the Social Brain Toolkit is developed, we will refer to nationally recognized cost guides such as the Australian Medicare Benefits Scheme [51] to obtain relevant unit costs. Costs will be calculated in Australian dollars, with equivalent conversions reported in euros and US dollars, using RStudio software (RStudio Inc) [48].

Rigor

For qualitative implementation data, a second author (EP, RR, LT, MB, or DD) will verify a random 25% of the total codes from the (1) first interview for interact-ABI-lity, (2) first interview for social-ABI-lity, (3) first clinician interview for convers-ABI-lity, and (4) first interview with a person with ABI and their communication partner for convers-ABI-lity. Any discrepancies will be resolved through research team discussion and consensus before the first author (MM) proceeds to code the remaining interviews. Qualitative effectiveness data will be managed by 2 experienced speech-language pathologists through a consensus rating procedure. For quantitative implementation and effectiveness data, a second author (EP, RR, LT, MB, or DD) will review outputs, and the first author (MM) will consult a biostatistician for support as necessary. For quantitative costing data, analysis will be conducted in consultation with a health economist and the clinical research team, with calculation methods, rationales, and references transparently reported. Overall results will be reported according to the Standards for Reporting Implementation Studies [52].

Participants

Inclusion and Exclusion Criteria for Users of interact-ABI-lity and social-ABI-lity

As social-ABI-lity and interact-ABI-lity are publicly available web-based courses, all users of the courses within the sample frame will be included in data collection and analysis of survey and analytic data, with no restrictions of inclusion and exclusion criteria. A minimum of 5 users of the social-ABI-lity course (ie, people with ABI) and interact-ABI-lity courses (ie, communication partners such as paid support workers, friends, and family members) will be invited to participate in further implementation interviews. This number of users interviewed is consistent with the think-aloud methods described in the study design [43], which are used to refine the usability of the courses. The internationally recognized industry standard [53] is for a minimum of 5 users to undergo a formative usability interview evaluation [53], because only so many users are required to identify up to 90% of the usability issues [54] before there are diminishing returns for the product cycle [53]. However, a maximum variation sample of these interviewees will be sought if and where possible.

If people with ABI completed the social-ABI-lity course with the assistance of a friend, partner, family member, or other individual, this person will also be invited through the course user to be interviewed together or individually, depending on individual preference or availability. Therefore, interview participants must meet the following criteria:

1. They must have registered for, and used, at least some modules of interact-ABI-lity or social-ABI-lity, as verified by course records.
2. They must have indicated consent at course enrollment to be contacted for further research participation opportunities related to the course.
3. They must have provided informed written consent to participate in the interview. For users who have an ABI, capacity to consent will be determined during a video call with a qualified speech-language pathologist according to our adapted consenting process protocol that includes relevant questions adapted from the University of California, San Diego, Brief Assessment of Capacity to Consent instrument [55]. People with ABI without the ability to respond correctly to all 5 questions presented using supported communication strategies, as outlined in Multimedia Appendix 11 [55], will be excluded from the study.
4. They must be aged ≥18 years.
5. They must have adequate English proficiency to participate in the study without the aid of an interpreter, with functional reading skills in English.

There are no restrictions on any other factors (eg, gender, clinical experience, or geographical location) for interview participants who have used interact-ABI-lity and social-ABI-lity. Where possible, variation in these factors is preferred to obtain a purposive, maximum variation sample of user experiences of the interventions.

Inclusion and Exclusion Criteria for Users of convers-ABI-lity

Interviews will be conducted with all 10 people with ABI and their 10 communication partners who have completed the pilot version of convers-ABI-lity, as well as the 5 clinicians delivering the intervention. Participants with ABI must meet the following criteria:

1. They must have had a definite moderate-severe ABI at least 6 months previously based on the Mayo Classification Scheme [56] (at least one of the following: loss of consciousness of 30 minutes or more, posttraumatic amnesia lasting ≥24 hours, worst Glasgow Coma Scale total score in the first 24 hours of <13, or evidence of a significant brain imaging abnormality). People with a non–traumatic brain injury (restricted specifically to the etiologies of stroke, hypoxic injury, brain tumor, poisoning, and infection) will also be eligible to participate.
2. They must have been discharged or partially discharged from hospital and be able to spend time at home on a regular basis.
3. They must have significant social communication skills deficits (either self-identified or identified by a usual communication partner).
4. They must have insight into their social communication skills deficits.
5. They must be aged 18-70 years.
6. They must have adequate English proficiency for completing assessment tasks without the aid of an interpreter.

7. They must have functional reading skills in English.
8. They must have a communication partner with whom they interact regularly who is willing to participate in the research interviews and training program.

The exclusion criteria for participants with ABI are as follows:

1. Aphasia of a severity such that it prevents any participation in conversation.
2. Severe amnesia, which would prevent participants from providing informed consent, as evaluated using the University of California, San Diego, Brief Assessment of Capacity to Consent instrument [55].
3. Dysarthria of a severity such that it significantly reduces intelligibility during conversation, as evaluated by the researcher.
4. Drug or alcohol addiction, which would prevent participants from reliably participating in sessions.
5. Active psychosis.
6. Co-occurring degenerative neurological disorder, more than one episode of moderate-severe ABI, or premorbid intellectual disability.

Family members, friends, or paid support workers participating in the study must meet the following criteria:

1. They must regularly interact with a person with ABI (ie, at least once a week). This person with ABI must have had the ABI at least 6 months previously.
2. They must have known the person with ABI for at least 3 months.
3. They must not have sustained a severe ABI themselves.
4. They must be aged ≥18 years.

Speech-language pathologists delivering convers-ABI-lity must meet the following criteria:

1. They must be currently employed in a clinical speech-language pathology role.
2. At least 20% of their caseload must comprise people with ABI.

Ethics

This research has received ethical approval from the University of Technology Sydney (UTS) Health and Medical Research Ethics Committee (ETH21-6111) to conduct interviews with users of social-ABI-lity and interact-ABI-lity. The UTS Health and Medical Research Ethics Committee has also ratified (ETH21-5899) an approval by the Western Sydney Local Health District Human Research Ethics Committee (2019/ETH13510) to conduct interviews with users of convers-ABI-lity and collect demographic and web analytic data for all 3 interventions.

Users of the interact-ABI-lity and social-ABI-lity courses provide their email addresses at registration and indicate whether they consent to participate in follow-up research related to these courses. Consenting users of the courses will be invited to provide informed written consent to participate in a follow-up interview using an accessible, lay-language participant information and consent form. To ensure informed consent, the form will be adapted with visual supports and explained through video call for people with ABI, outlining the full burden and risks of research participation. Screening for capacity to consent is described in the aforementioned inclusion criteria (Multimedia Appendix 11).

Participants with ABI and their communication partners will be paid for their interviews at the 2021 hourly rate recommended by Health Consumers New South Wales [57]. Reimbursement for people with ABI and their communication partners is viewed as critical to recognizing the value of their lived experience of ABI, caring, and health care. It also aims to minimize any undue burden of research participation. Potential participants will be advised of this arrangement in the participant information form to facilitate decision-making around any potential economic burden of participation.

Results

Research Funding

Australian National Health and Medical Research Council Postgraduate Scholarship funding was granted in November 2019, UTS Centre for Social Justice & Inclusion Social Impact funding was granted in April 2021, and icare New South Wales Quality of Life funding was received in November 2019.

Ethical Approval

Ethical approval was received from the UTS Health and Medical Research Ethics Committee (ETH21-6111) on June 29, 2021, and the Western Sydney Local Health District Human Research Ethics Committee (2019/ETH13510) on June 11, 2021, with ratification by the UTS Health and Medical Research Ethics Committee (ETH21-5899) on June 29, 2021.

Participant Enrollment

At manuscript submission on July 13, 2021, 85 participants had enrolled in interact-ABI-lity, with 85 completed entry surveys, 6 course completions, and 8 completed exit surveys. No interview data had yet been collected. Data collection for interact-ABI-lity commenced on July 2, 2021, and is expected to conclude on January 2, 2022, after a 6-month sample frame of analytics. By July 13, 2021, 1 participant had been recruited to participate in the convers-ABI-lity study, with no data yet collected. Data collection is expected to commence on July 26, 2021, and conclude on March 26, 2022. By July 13, 2021, no participant had been recruited to participate in the social-ABI-lity study. Data collection is expected to commence on December 1, 2021, and conclude on June 1, 2022, after a 6-month sample frame of analytics.

Analysis and Findings

Data analysis will occur concurrently with data collection until mid-2022. Results are expected for publication during late 2022 and early 2023.

Discussion

A Dual Focus on Implementation and Effectiveness

As the global burden of ABI grows, our communities and health care system must find a scalable, feasible, acceptable, and accessible health care service delivery solution to address the psychosocial burden of this condition [1]. A concerted focus on implementation is essential to ensure the successful and

sustained uptake of health interventions, without which even efficacious treatments have failed to be adopted, implemented, or sustained [29]. Implementation knowledge should include the perspectives of key stakeholders, while also leveraging existing implementation science theory and evidence, to ensure implementation success.

To this end, we have selected several theoretically informed implementation measures, in addition to measuring the effectiveness of the Social Brain Toolkit. As social-ABI-lity and interact-ABI-lity are educational interventions, their effectiveness will be determined through measures of increased knowledge as well as ecologically valid postintervention measures such as frequency of social media use and confidence communicating with people with ABI. For the CPT intervention of convers-ABI-lity, effectiveness is determined by similarly meaningful measures of quality of life and conversation. The complexity of real-world implementation will be captured using mixed methods, including surveys and interviews exploring user satisfaction and experiences of implementation. For example, our specific survey of whether users are from rural, regional, remote, or metropolitan areas will enable the implementation experiences of these populations to be compared. Given the web-based nature of the Social Brain Toolkit, implementation measures will also include web analytics to identify any need for targeted implementation adjustments or strategies to improve intervention use. As the Social Brain Toolkit comprises technological interventions, think-aloud methods will be used to explore technological usability and provide users with a direct feedback channel to improve user interfaces.

As a prospective study of the real-world implementation of the Social Brain Toolkit, this study will not occur in a closed environment that allows controlled, randomized testing of isolated implementation strategies. Instead, with a theoretical foundation in the real-world complexity of digital health implementation [34], we will measure a comprehensive range of qualitative and quantitative effectiveness and implementation outcomes, and provide a recorded timeline of implementation strategy development and deployment for the Social Brain Toolkit.

Strengths and Limitations

The strengths of this study include a hybrid implementation-effectiveness approach, a mixed methods design with a wide range of implementation measures collected from the outset of implementation, end-user–identified implementation strategies, and a strong theoretical underpinning in a digital health implementation framework. This study is constrained by some technical limitations regarding the collection of analytics, the sample size of the initial limited release of the Social Brain Toolkit interventions, and reliance on self-report for most outcome measures. However, these limitations will be acknowledged in reporting to assist appropriate interpretation.

Conclusions

As people with ABI and their communication partners are the main intended beneficiaries of the Social Brain Toolkit, they have been and are being included from project inception to formative evaluation. Feedback provided by participants will directly inform future iterations of the interventions. Problems identified and recommendations made by users will be incorporated and addressed wherever possible in the next version of the Social Brain Toolkit. Therefore, beneficiaries will see concrete changes to interventions that directly reflect user input. These changes and their rationales will be documented and reported back to users in engaged scholarship that values and empowers stakeholder input through a direct feedback loop. The direct evaluation of the implementation of the interventions by end users in the community aims to ensure that the interventions are sufficiently feasible, acceptable, accessible, scalable, and sustainable to reach those in need of these supports in the community. The results can be used to improve the development and implementation of the Social Brain Toolkit, as well as future web-based psychosocial interventions for people with ABI and other populations.

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Authors' Contributions

This study was designed by MM, EP, RR, MB, and LT. MM prepared the manuscript, and EP, RR, LT, MB, and DD critically revised the manuscript. All authors approved the final version of the manuscript for submission.

Conflicts of Interest

MM, EP, RR, MB, and LT are developers of the Social Brain Toolkit in collaboration with end users.

Multimedia Appendix 1
Overview of prospective implementation data collection.
[DOCX File , 16 KB - resprot_v10i12e31995_app1.docx]

Multimedia Appendix 2
Overview of prospective effectiveness data collection.
[DOCX File , 18 KB - resprot_v10i12e31995_app2.docx]

Multimedia Appendix 3
convers-ABI-lity interview protocol for people with acquired brain injury and their communication partner.
[DOCX File , 16 KB - resprot_v10i12e31995_app3.docx]

Multimedia Appendix 4
convers-ABI-lity interview protocol for clinicians.
[DOCX File , 16 KB - resprot_v10i12e31995_app4.docx]

Multimedia Appendix 5
interact-ABI-lity interview protocol for informal communication partners.
[DOCX File , 15 KB - resprot_v10i12e31995_app5.docx]

Multimedia Appendix 6
interact-ABI-lity interview protocol for paid communication partners and clinicians.
[DOCX File , 15 KB - resprot_v10i12e31995_app6.docx]

Multimedia Appendix 7
social-ABI-lity interview protocol for people with acquired brain injury.
[DOCX File , 15 KB - resprot_v10i12e31995_app7.docx]

Multimedia Appendix 8
Entry surveys for people with acquired brain injury using convers-ABI-lity or social-ABI-lity.
[DOCX File , 15 KB - resprot_v10i12e31995_app8.docx]

Multimedia Appendix 9
Entry surveys for communication partners of people with acquired brain injury using convers-ABI-lity or interact-ABI-lity.
[DOCX File , 15 KB - resprot_v10i12e31995_app9.docx]

Multimedia Appendix 10
Exit surveys for all users of social-ABI-lity, convers-ABI-lity, and interact-ABI-lity.
[DOCX File , 16 KB - resprot_v10i12e31995_app10.docx]

Multimedia Appendix 11
Consenting process protocol, including relevant questions, adapted from the University of California, San Diego, Brief Assessment of Capacity to Consent instrument.
[PDF File (Adobe PDF File), 215 KB - resprot_v10i12e31995_app11.pdf]

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Abbreviations

ABI: acquired brain injury
CPT: communication partner training
NASSS: Nonadoption, Abandonment, Scale-up, Spread, and Sustainability
UTS: University of Technology Sydney

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Protocol

An App-Based Just-in-Time Adaptive Self-management Intervention for Care Partners (CareQOL): Protocol for a Pilot Trial

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Abstract

Background: Care partners (ie, informal family caregivers) of individuals with health problems face considerable physical and emotional stress, often with a substantial negative impact on the health-related quality of life (HRQOL) of both care partners and care recipients. Given that these individuals are often overwhelmed by their caregiving responsibilities, low-burden self-management interventions are needed to support care partners to ensure better patient outcomes.

Objective: The primary objective of this study is to describe an intensive data collection protocol that involves the delivery of a personalized just-in-time adaptive intervention that incorporates passive mobile sensor data feedback (sleep and activity data from a Fitbit [Fitbit LLC]) and real time self-reporting of HRQOL via a study-specific app called CareQOL (University of Michigan) to provide personalized feedback via app alerts.

Methods: Participants from 3 diverse care partner groups will be enrolled (care partners of persons with spinal cord injury, care partners of persons with Huntington disease, and care partners of persons with hematopoietic cell transplantation). Participants will be randomized to either a control group, where they will wear the Fitbit and provide daily reports of HRQOL over a 3-month (ie, 90 days) period (without personalized feedback), or the just-in-time adaptive intervention group, where they will wear the Fitbit, provide daily reports of HRQOL, and receive personalized push notifications for 3 months. At the end of the study, participants will complete a feasibility and acceptability questionnaire, and metrics regarding adherence and attrition will be calculated.

Results: This trial opened for recruitment in November 2020. Data collection was completed in June 2021, and the primary results are expected to be published in 2022.

Conclusions: This trial will determine the feasibility and acceptability of an intensive app-based intervention in 3 distinct care partner groups: care partners for persons with a chronic condition that was caused by a traumatic event (ie, spinal cord injury); care partners for persons with a progressive, fatal neurodegenerative disease (ie, Huntington disease); and care partners for persons with episodic cancer conditions that require intense, prolonged inpatient and outpatient treatment (persons with hematopoietic cell transplantation).

Trial Registration: ClinicalTrials.gov NCT04556591; https://clinicaltrials.gov/ct2/show/NCT04556591

International Registered Report Identifier (IRRID): DERR1-10.2196/32842

(JMIR Res Protoc 2021;10(12):e32842) doi:10.2196/32842

KEYWORDS

caregivers; quality of life; spinal cord injuries; Huntington disease; hematopoietic stem cell transplantation; feasibility studies; self-management; mobile apps; outcome assessment; mobile phone

Introduction

Background

Care partners (ie, informal family caregivers) of individuals with health problems are faced with considerable physical and emotional stress [1-25], often with a substantial negative impact on the health-related quality of life (HRQOL) of both the care partner [1-3,5,7,26-44] and care recipient [14,45-61]. Care partners may suddenly be thrust into this full-time role and are often unprepared. As responsibilities accumulate, they face emergent health risks, including anxiety, fatigue, isolation, sleep problems, and decreased physical activity. Indeed, there is growing recognition that these psychological, social, and physical risks inadvertently affect patient health and well-being (ie, outcomes) [47,53,54,56-59,62-64]. Thus, it is imperative to develop novel interventions to support care partners to ensure better patient outcomes.

Despite the growing awareness regarding the importance of caregiving with the aging US population and evolving health care system, very little action has been taken to understand and improve conditions for care partners [39,40,65]. Thus, family caregiving (ie, care partners) is an urgent public health issue. With a high risk for developing depression, insomnia, and stress-related disorders [21,36-38,66-69], care partners are an ideal population to target for early detection and intervention strategies to treat compromised well-being. Although psychoeducation, skills training, or therapeutic counseling interventions can be effective for care partners, these interventions require intensive time and face-to-face commitment (with trained personnel), which can be prohibitive for an individual who is already overwhelmed by existing caregiving responsibilities and unable to make time for self-care.

Objectives

This pilot study is designed to examine the acceptability and feasibility of an intensive data collection protocol that involves the delivery of a personalized self-management intervention to promote care partner self-care. Care partners from 3 distinct groups will be examined: care partners for persons with a chronic condition that was caused by a traumatic event (ie, spinal cord injury [SCI]), care partners for persons with a progressive, fatal neurodegenerative disease (ie, Huntington disease [HD]), and care partners for persons with an episodic cancer condition that requires intense, prolonged inpatient and outpatient treatment (persons with allogeneic hematopoietic cell transplantation [HCT]). Care partners will be randomized to either the control group, where they will wear the Fitbit (Fitbit LLC) and provide daily reports of HRQOL over a 3-month (ie, 90 days) period (without personalized feedback), or the intervention group, where they will wear the Fitbit, provide daily reports of HRQOL, and receive personalized push notifications for 3 months. The intervention is a just-in-time adaptive intervention (JITAI), that is, an emerging intervention that uses real time data collection to inform and personalize the delivery of the intervention [70,71]. Studies in other populations, including cardiovascular disease, diabetes, mental illness, and smoking cessation, support JITAI's efficacy in improving physical, mental, and social health outcomes [72-76]. We describe the design and protocol of this trial in the following sections.

Methods

Participants and Setting

Overview

Data collection will include a diverse sample of N=60-90 care partners (n=20-30 SCI, n=20-30 HD, and n=20-30 HCT care partners). A care partner is defined as a person who provides physical assistance, financial assistance, or emotional support and who is not a professional, paid caregiver. Participant recruitment and enrollment will take place at the University of Michigan. The study was designed to be fully remote, given the ongoing restrictions related to the COVID-19 pandemic.

Inclusion Criteria

Care partners must be (1) aged at least 18 years, (2) able to read and understand English, and (3) caring for an adult (aged ≥18 years) with medically documented HD, SCI, or HCT. Care partners must be providing some form of care to the person with HD, SCI, HCT. Specifically, care partners must indicate a response ≥1 on the following question:

> *On a scale of 0-10, where 0 is 'no assistance' and 10 is 'assistance with all activities,' how much assistance does the person you care for require from you to complete activities of daily living due to problems resulting from his/her HD/SCI/HCT? Activities could consist of personal hygiene, dressing and undressing, housework, taking medications, managing money, running errands, shopping for groceries or clothing, transportation, meal preparation and cleanup, remembering things, etc.*

Care partners must also have access to necessary resources for participating in a technology-based intervention (smartphone or tablet and internet access) and be willing to use their personal equipment or internet for this study, including downloading the CareQOL app (University of Michigan) and the Fitbit app on their mobile device, and be willing to complete all study assessments for the duration of study participation. Care partners of persons with SCI must be caring for an individual who is ≥1 year post injury and has a medically documented injury. Care partners of persons with HCT must indicate that they are caring for an individual who is receiving, has received, or is scheduled to receive HCT.

Exclusion Criteria

Professional, paid care partners (eg, home health aide) will be excluded from this study.

Recruitment and Screening

Care partners will be recruited through existing clinical databases [77], registries, and relevant patient clinics at the University of Michigan, as well as through a study posting on UMHealthResearch.org and outreach to relevant community groups and organizations. Care partners will be recruited directly or through the person for whom they provide care. Individuals interested in participating will be encouraged to ask questions about the study and their participation, and if they opt to enroll, they will provide informed consent before completing any study assessments.

Study Design

This pilot trial will use a 2-arm, randomized controlled design. Each of the 60 to 90 care partner participants will be randomized to an active *JITAI* arm (n=10-15 care partners of patients with SCI, n=10-15 care partners of patients with HD, and n=10-15 care partners of patients with HCT) or to a control arm (n=10-15 care partners of patients with SCI, n=10-15 care partners of patients with HD, and n=10-15 care partners of patients with HCT). The random allocation of participants to the treatment or control arm establishes the basis for testing the statistical significance or difference between the groups. All participants (regardless of study arm) will complete a baseline assessment comprising several self-report surveys designed to evaluate sample characteristics (ie, demographic information, medical history data, and patient characteristics) and HRQOL (CareQOL measures, as well as other caregiving measures and measures about the functional capabilities of the person with HD, HCT, or SCI). This is followed by a 10-day run-in period to allow for the shipping time of the Fitbit and to provide the participants time to familiarize themselves with the study technology (Fitbit and CareQOL app) and procedures. This period will also allow the study team to troubleshoot any potential barriers or issues that arise before the official start of the home monitoring period. For those who are randomized to the JITAI group, it will also allow for data collection that can be used to inform the intervention messages once the home monitoring period begins. This will be followed by a 3-month (90 days) home monitoring period during which participants will wear a wrist-worn Fitbit (to continuously monitor physical activity and sleep), as well as complete daily real time ratings of HRQOL (ie, single-item assessments of caregiver strain, anxiety, and depression). Those randomized to the JITAI group will have a 50/50 chance of receiving notifications each day during the home monitoring period (intervention details provided below). At the end of months 1 and 2, all participants will also complete a longer battery of self-report surveys on HRQOL (also delivered via CareQOL app), and at the end of 3 months, participants will complete this longer survey battery plus a feasibility and acceptability questionnaire (again delivered via the app).

Study Procedures

Overview

Unless they opt to use their own personal Fitbit, participants will receive a Fitbit for the collection of sleep and activity (steps) data and will download the Fitbit app and study app, CareQOL, on their personal mobile devices (iOS or Android). The CareQOL app will deliver ecological momentary assessments (EMAs) once per day, compile and display data (including those collected on the Fitbit), deliver study notifications, including messages for the participant to complete the daily EMA and other study surveys, and deliver the personalized study intervention prompts to the intervention group (JITAI group).

All study participants will complete 3 EMA questions daily on the CareQOL app. Each participant will be prompted by a push notification in a 5-hour window (based on participant preference) from the app to answer the questions. The EMA questions comprised 1 question on care partner strain (taken from the CareQOL Caregiver Strain item bank), 1 question on anxiety (taken from the Patient-Reported Outcomes Measurement Information System [PROMIS] Anxiety item bank), and 1 question on depression (taken from the PROMIS Depression item bank). These questions will be administered as a computer adaptive test such that each day's item will be based on the previous day's response. Questions are on a 5-point scale, with higher scores indicating more of the named construct.

In addition to the collection of EMA data, the app compiles and displays a graphical summary of historical data for care partner stress (strain), worry (anxiety), sadness (depression), steps (collected by the Fitbit), and hours of sleep (collected by the Fitbit) on a participant dashboard. Participants can view this information for the past week, month, or year (Figure 1). This is available to all participants as a pull—that is, it is available at all times but is accessed only if and when the user chooses to access it.

Care partners will be provided compensation for their participation in this study. Incentives will be identical for both groups (JITAI and control): US $20 compensation for the completion of the baseline assessment, US $10 for completion of each of the end-of-month assessments, US $1 per day for each day that they have EMA or Fitbit data during the home monitoring period, and the option to keep the Fitbit at the end of the study.

Figure 1. Screenshots of the CareQOL app.

Randomization

Blocked randomization will be used to limit bias and achieve an equal distribution of participants to the control and treatment arms. A randomization list will be generated for each condition (SCI, HD, and HCT), and the study statistician will oversee randomization. The participants will be randomized once they are deemed eligible, have provided informed consent, and have completed the baseline assessments. The study coordinator or research assistant who consented the participants will use the appropriate condition's randomization list to assign the participant to the correct study arm. Half of the participants will be randomized to receive the intervention (JITAI; described below); the remaining participants will be in the control group, who will not receive the JITAI but will complete the activities already described in this section. Participants who are randomized to receive the JITAI will have a 50/50 chance of receiving the intervention each day.

Intervention

The JITAI aims to promote behavioral change through motivational messages delivered through the CareQOL app as push notifications. These notifications provide a trigger for participants to initiate or continue behavior change or monitor behaviors (through engagement with the app); they are broadly based on the behavioral activation theory, which posits that negative life events (eg, difficult interactions between the care partner and care recipient and increased care partner stress because of caregiver role overload) trigger negative emotional responses (eg, depression and anxiety) that lead to unhealthy behavioral patterns (eg, poor sleep, decreased exercise, and social withdrawal), which starts the cycle all over again [78]. Specifically, the notifications are designed to foster care partner self-management by targeting behavioral change (ie, through increased physical activity and better sleep habits) and by promoting positive mental health responses (eg, self-efficacy, positive affect, and well-being). Behavioral activation (including behavioral activation delivered via SMS text messaging) is effective for treating both anxiety and depression as *pure* constructs and also for persons who are experiencing a mixture of the two [79-84].

The push notifications are low burden: participants can personalize the administration time (in a 5-hour window), and notifications can be viewed quickly on their phone's lock screen. Participants can also choose not to engage with the notification at the time it is sent if it is inconvenient—they can return to it later if needed.

The JITAI push notifications are aimed at promoting healthy behaviors (physical activity and good sleep hygiene) and improving mood (anxiety, depression, and care partner strain). If a notification is to be sent, the content will be randomly drawn from this pool of messages. Some messages will use participants' data directly in the messages (eg, you walked an average of 8120 steps this week), and most of the messages will be personalized based on data (eg, someone with low steps will get a different message than someone with medium steps than someone with high steps; high-medium-low). Messages comprise one or more of the following types: (1) data feedback, (2) facts, (3) tips, and (4) support. Table 1 provides specific examples of personalized push notifications that will be used in this study.

Randomization of the days the participants receive messages and the messages the participants receive from the pool will be done through the CareQOL app.

Table 1. Examples of personalized push notifications in the just-in-time adaptive intervention.

Feedback domain	Intervention options		
	Low level (below average performance or problems)	Medium level (average performance or problems)	High level (above average performance or problems)
Mental health (depression)	"Your average sadness rating over the last week was XX. Next time you're feeling low, watch your favorite funny movie. Laughter is the best medicine!"	"Your average sadness rating over the last week was XX. When you're feeling low, why not watch your favorite funny movie? Laughter is the best medicine!"	"Your average sadness rating over the last week was XX. If you're ever feeling low, watch your favorite funny movie. Laughter is the best medicine!"
Mental health (anxiety)	"The next time you feel worried, close your eyes and think of a peaceful, relaxing place. Try to imagine as many different sights, sounds, and smells as you can. Continue until you feel more relaxed, then open your eyes slowly."	"Are you feeling anxious? Close your eyes and think of a peaceful, relaxing place. Try to imagine as many different sights, sounds, and smells as you can. Continue until you feel more relaxed, then open your eyes slowly."	"If you ever feel worried, close your eyes and think of a peaceful, relaxing place. Try to imagine as many different sights, sounds, and smells as you can. Continue until you feel more relaxed, then open your eyes slowly."
Mental health (general)	"Is there a friend you haven't talked to in a while? When you feel down, try giving them a call. Talking to friends can help boost your spirits!"	"Is there a friend you haven't talked to in a while? Try giving them a call. Talking to friends can help boost your spirits!"	"Is there a friend you haven't talked to in a while? If you feel down, try giving them a call. Talking to friends can boost your spirits!"
Mindfulness	"Take a few minutes every day to wind down. Even if you don't feel stressed all the time, meditating can relieve built up tension."	"Take a few minutes every day to wind down. Try meditating to relieve built up tension."	"Take a few minutes every day to wind down. Even if you don't feel stressed right now, meditating can relieve any built-up tension."
Physical activity	"This past week, your average daily step count has been XX. Try to increase this if you can!"	"This past week, your average daily step count has been XX. Try to maintain this level, or even increase it more if you can."	"This past week, your average daily step count has been XX. Great job! Try to maintain this level."
Sleep	"You aren't quite getting the recommended 7-8 hours of sleep per night. Try moving bedtime up by 5-10 minutes each night to get closer to this goal."	"You're having a hard time getting the recommended 7-8 hours of sleep per night. We all struggle to get to sleep sometimes. Try moving bedtime up by 5-10 minutes each night."	"If you ever having a hard time getting the recommended 7-8 hours of sleep per night, try moving bedtime up by 5-10 minutes each night."

Outcomes

The primary objective of this study is to establish the feasibility and acceptability of our intensive data collection protocol. Table 2 provides a detailed summary of the study assessments, and Table 3 provides the schedule of activities.

The primary end point will examine survey responses on the feasibility and acceptability questionnaire designed to evaluate our intensive data collection protocol in the full sample. Secondary end points will include attrition and adherence estimates (again across the full sample). Exploratory analyses will be conducted to identify trends for an improvement in HRQOL scores (ie, group differences between the JITAI and control groups at the end of the 3-month home monitoring period, with the hypothesis that the JITAI group will report better outcomes than the control group). Exploratory analyses may also compare important subgroups (eg, care partner groups that differ by diagnosis [SCI, HD or HCT], relationship type [parent vs spousal care partners], sex [male vs female care partners], and according to the functional status of the person they are caring for). Exploratory analyses will use an intention-to-treat approach where the participant will contribute data to the arm they are randomized to, regardless of the amount of data contributed (ie, the duration of participation).

Table 2. Study assessments.

Outcome measure and description of outcome measure	Assessment schedule			
	Baseline	Daily[a]	1 and 2 months (30 and 60 days)	3 months (90 days)
Demographic information				
Study-designed form used to capture demographic data, including age, gender, race, ethnicity, education, marital status, work status, COVID-19 history or status, care partner data, care recipient data, and caregiving demands	✓[b]			
Care recipient medical record information				
Study-designed form with information about the person with SCI[c], Huntington disease, or HCT[d] for whom the care partner is providing care (eg, date of diagnosis, details of diagnosis, and disease stage or severity)	✓			
Caregiver Appraisal Scale [85]				
47 items that assess positive and negative aspects of the caregiving role; 4 separate subdomain scores (perceived burden, caregiver relationship satisfaction, caregiving ideology, and caregiving mastery) can be calculated; higher scores indicate better functioning; reliability and validity supported [86]	✓			
Self-report version of the United Huntington Disease Rating Scale Independence Scale [87]				
Care partner–reported rating provides an estimate of the current level of the independence for the person that they care for; this measure is rated from 1 to 100 in intervals of 5, with higher ratings indicating higher level of independence; reliability and validity supported [88]	✓			
Supervision Rating Scale [89]				
Single rating that the care partner provides about the overall amount of supervision that the person they care for receives; ratings range from 1 to 13, with higher ratings indicating greater levels of required supervision; reliability and validity supported [89]	✓			
TBI-CareQOL[e] Caregiver Strain SF[f] [90,91]				
Assesses perceived feelings of feeling overwhelmed, stressed, and *beat-down* related to the care partner role; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more strain; reliability and validity supported [90-92]	✓		✓	✓
TBI-CareQOL Caregiver-Specific Anxiety SF [90,93]				
Assesses care partner perceived feelings of worry and anxiety specific to the safety, health, and future well-being of the person with TBI[g]; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more anxiety; reliability and validity supported [90,92,93]	✓		✓	✓
PROMIS[h] Sleep-Related Impairment SF [94]				
Evaluates the effect of poor sleep on daytime functioning; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more sleep-related impairment; reliability and validity supported [90,94-99]	✓		✓	✓
PROMIS Fatigue SF [95,100]				
Evaluates self-reported symptoms of fatigue, ranging from mild subjective feelings of tiredness to overwhelming exhaustion that may decrease one's ability to perform activities of daily living; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more fatigue; reliability and validity supported [90,95-98,101-107]	✓		✓	✓
PROMIS Anxiety SF [95,100]				
Assesses self-reported feelings of fear, anxiety, and hyperarousal; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more anxiety; reliability, validity, and responsiveness supported [90,96-98,106,108]	✓		✓	✓
PROMIS Depression SF [95,100]				
Assesses self-reported feelings of sadness and worthlessness; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more depression; reliability, validity, and responsiveness supported [90,96-98,106,108,109]	✓		✓	✓
PROMIS Anger SF [95,100]				

Outcome measure and description of outcome measure	Assessment schedule			
	Baseline	Daily[a]	1 and 2 months (30 and 60 days)	3 months (90 days)
Assesses self-reported feelings of irritability and frustration; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more anger; reliability, validity, and responsiveness supported [90,96,98,108]	✓		✓	✓
NIH[i] Toolbox Self-Efficacy–General SF [110]				
Assesses self-reported confidence in the ability to successfully perform specific tasks or behaviors related to one's overall functioning; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more self-efficacy; reliability, validity, and responsiveness supported [110-112]	✓		✓	✓
Neuro-QoL[j] Positive Affect and Well-Being SF [113]				
Assesses parts of an individual's life that are related to overall life meaning and purpose, well-being, and satisfaction; scored on a *t* metric (mean 50, SD 10), with higher scores indicating greater satisfaction; reliability, validity, and responsiveness supported [113]	✓		✓	✓
NIH Toolbox Perceived Stress [110]				
Assesses an individual's feelings about the nature of events and individual coping resources; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more perceived stress; reliability, validity, and responsiveness supported [110]	✓		✓	✓
PROMIS Ability to Participate in Social Roles and Activities SF [95,100]				
Assesses involvement in one's ability to participate in usual social roles and activities; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more ability to participate; reliability, validity, and responsiveness supported [90,96,98,106,108]	✓		✓	✓
PROMIS Global Health v1.2				
10 items that assess overall physical, mental, and social health; scored on a *t* metric (mean 50, SD 10), with separate scores for physical and mental health (higher scores indicate better health); responsiveness and validity supported [114-118]	✓		✓	✓
COVID HRQOL[k]				
Single item that assesses how concerned the participant is about COVID-19; scores range from 0 to 10, with higher scores indicating greater COVID-19–specific concerns	✓		✓	✓
Single-item Caregiver Strain [90,91]				
Assesses perceived feelings of feeling overwhelmed, stressed, and *beat-down* related to the care partner role; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more strain; reliability and validity supported [90-92]		✓		
Single-item Anxiety [95,100]				
Assesses self-reported feelings of fear, anxiety, and hyperarousal; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more anxiety; reliability, validity, and responsiveness supported [90,96-100,106,108]		✓		
Single-item Depression [95,100]				
Assesses self-reported feelings of sadness and worthlessness; scored on a *t* metric (mean 50, SD 10), with higher scores indicating more depression; reliability, validity, and responsiveness supported [90,96-98,106,108,109]		✓		
Fitbit-based estimate of physical activity				
Fitbit *off-the-shelf* summary physical activity data includes steps, sedentary behavior, and light, moderate, and intense activity		✓		
Fitbit-based estimate of sleep				
Fitbit *off-the-shelf* summary data for total sleep time and time spent in each stage of sleep (awake, rapid eye movement, and light sleep)		✓		
Medical history, medications, treatments, and COVID questionnaire				
Study-specific forms will be used to capture medical history and current treatments or management strategies (medication and nonmedication—eg, exercise and mindfulness) and COVID-19 history	✓			✓

Outcome measure and description of outcome measure	Assessment schedule			
	Baseline	Daily[a]	1 and 2 months (30 and 60 days)	3 months (90 days)
Adverse event or status update				
Self-reported changes in mental or physical health				✓
Feasibility and acceptability questionnaire				
Assesses the experience of the participant with the study methodology and technology, including the CareQOL app, Fitbit, and the JITAI[l]. Items are scaled from 1 to 5 to indicate level of agreement, where *1* indicates *strong disagreement* and *5* indicates *strong agreement*				✓
Optional: semistructured interview (JITAI group only)				
Assesses participant experiences and perceptions of the intervention messages that they received from the CareQOL app				✓

[a]Daily surveys will be administered through the run-in and 3-month home monitoring periods.

[b]Assessment performed.

[c]SCI: spinal cord injury.

[d]HCT: hematopoietic cell transplantation.

[e]TBI-CareQOL: Traumatic Brain Injury Caregiver Quality of Life measurement system.

[f]SF: short from.

[g]TBI: traumatic brain injury.

[h]PROMIS: Patient-Reported Outcomes Measurement Information System.

[i]NIH: National Institute of Health.

[j]Neuro-QoL: Quality of Life in Neurological Disorders.

[k]HRQOL: health-related quality of life.

[l]JITAI: just-in-time adaptive intervention.

Table 3. Schedule of assessments.

Assessments	Pre-enrollment	Enrollment, day 10	Approximately 3 months[a]			
			Run-in[b], days –10 to –1	End of months 1 and 2		End of 3-month assessment, 90 (±7) days
				30 days	60 (±7) days	
SCI[c], Huntington disease, HCT[d] documentation	✓[e]					
Care partner eligibility	✓	✓				
Informed consent		✓				
Demographics and baseline survey		✓				
Caregiver Appraisal Scale		✓				✓
UHDRS[f] Independence Scale		✓				
SRS[g]		✓				
Medical record confirmation CRF[h]		✓				
HRQOL[i] measures		✓		✓	✓	✓
Fitbit and CareQOL app instructions		✓				
Randomization		✓				
JITAI[j,k,l] and control home monitoring			✓	✓	✓	✓
Daily EMA[m,n]						
Feasibility and acceptability questionnaire						✓
Medications, therapies, medical history, and COVID-19		✓				✓
Adverse events reporting						✓
Optional: semistructured interview[o]						✓

[a]Individual participant duration may vary depending on when the participant completes health-related quality of life assessments.

[b]Approximately 10 days in duration, to include time for shipping and at least 3-4 days of data collection.

[c]SCI: spinal cord injury.

[d]HCT: hematopoietic cell transplantation.

[e]Assessment completed.

[f]UHDRS: United Huntington Disease Rating Scale.

[g]SRS: Supervision Rating Scale.

[h]CRF: Case Report Form.

[i]HRQOL: health-related quality of life.

[j]JITAI: just-in-time adaptive intervention.

[k]Active intervention, including personalized push notifications.

[l]Includes daily wearing the Fitbit for sleep and physical activity monitoring.

[m]EMA: ecological momentary assessment.

[n]For both active and control groups.

[o]Optional semistructured interview for the intervention group only; separate consent required.

Data Collection, Storage, and Protection

This project uses multiple electronic data capture and management platforms, such as Research Electronic Data Capture (REDCap; Vanderbilt University), CareQOL, Qualtrics (Qualtrics), Fitbit, University of Michigan Health Information Technology and Services server, Google Cloud, and Amazon Web Services Cloud. All platforms are designed for human subject research and comply with federal and local data and information security practices. The study data entry and study management systems are secured and password-protected. At

the end of the study, all study databases will be deidentified and archived securely at the University of Michigan.

Sample Size Considerations

The main purpose of the current trial is to establish the feasibility and acceptability of an intensive data collection protocol to inform a larger, later-stage effectiveness study on the JITAI in care partners of persons with chronic medical conditions. Thus, this study is designed to provide a point estimate of the effect of the JITAI for the future large-scale trial. Given that there are no formal power analysis calculations for this type of analysis, we have based the proposed sample size on our previous experience conducting these types of trials. Specifically, we believe that approximately 50 participants will provide sufficient numbers and diagnostic diversity to evaluate the feasibility and acceptability of new mobile health apps. Thus, our proposed sample size of N=60-90 care partners (at least 30 per arm and 20 per care partner group) exceeds this estimate and should provide a reasonable range of scores on the HRQOL outcome measures to guide later phase trial work.

Statistics

Sample Descriptive Data

Care partners in each study group (JITAI and control) will be compared descriptively according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [119]. We will use 2-tailed *t* tests and/or analysis of variance to examine group differences for continuous variables (eg, age and HRQOL outcomes). Chi-square or Fisher exact tests will be used to examine group differences for categorical variables (eg, care partner type [SCI, HD, and HCT], sex, ethnicity, race, education, marital status, and relationship to care recipient).

Primary End Point

We will generate frequency counts for each of the feasibility and acceptability questionnaire items (*note:* items are scaled from 1 to 5 to indicate the level of agreement, where *1* indicates *strong disagreement* and *5* indicates *strong agreement*). Descriptive statistics will also be calculated. We hypothesize that this intensive data collection protocol will be both feasible and acceptable for care partners (regardless of group assignment). Feasibility and acceptability will be measured by ≥80% of participants indicating that care partners either *agree* or *strongly agree* that the different study elements are feasible and acceptable.

Secondary End Points

Attrition will be reported as the fraction of participants who will complete the final assessment out of the total number of study participants who completed the baseline assessment. In addition, the completion rates for the EMA assessments, the Fitbit data (ie, steps and sleep), and the monthly surveys will be calculated. Descriptive statistics will be calculated for the missing data across the study. We hypothesize that this intensive data collection protocol will be both feasible and acceptable for care partners (regardless of group assignment). Specifically, we expect ≥80% of participants to complete the study, that ≤60% of participants will be missing data for the daily assessment questions, and ≥80% of participants will complete each of the end-of-month surveys.

Exploratory End Points

We will also conduct analyses to determine if care partners in the JITAI group have better HRQOL at 3 months relative to the control group after controlling for baseline scores. Specifically, we will conduct a series of analyses of covariance to determine if individuals in the JITAI group have significantly better (1) care partner strain (as measured by CareQOL Caregiver Strain), (2) depression (as measured by PROMIS Depression), or (3) anxiety (as measured by PROMIS Anxiety) at 3 months after controlling for baseline scores on each respective measure (eg, analyses looking at 3-month care partner strain scores will control for baseline estimates of care partner strain). In addition, for those participants who will complete the semistructured interviews, we will assess care partners' perceptions and preferences related to the intervention prompts to allow for future adaptations that involve targeting, tailoring, and personalization of these prompts.

Ethics and Dissemination

All study procedures will be conducted in accordance with the US Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR part 46, 21 CFR part 50, 21 CFR part 56, 21 CFR part 312, or 21 CFR part 812) and research best practices. The study procedures have been approved by Institutional Review Boards of the University of Michigan Medical School (application approval HUM00184455 and registered with ClinicalTrials.gov [NCT04556591]). The study results will be reported according to the CONSORT 2010 guidelines and the 2013 CONSORT Patient-Reported Outcomes extension guidelines [120,121].

Results

This study was funded in March 2020 and received institutional review board approval in August 2020. Participant recruitment for this trial began in November 2020 and was completed in June 2021. Dissemination of trial results is forthcoming. We expect to publish the results for the primary outcomes in 2022.

Discussion

Overview

The proposed study aims to investigate the feasibility and acceptability of an intensive data collection protocol that involves the administration of the JITAI intervention to care partners of persons with significant health conditions. This protocol provides a description of the design and methods of this randomized clinical trial.

Although interventions exist to help improve care partners' HRQOL, they are typically time-intensive and expensive and have limited success in improving HRQOL in these individuals. Despite clear advantages in terms of convenience, reach, and scalability with using mobile technologies (including JITAIs) to support healthy behavior change, their clinical utility in care partners remains untested. Furthermore, although much research on care partners has focused on a one-size-fits-all approach to

assessment and treatment, there is a growing body of evidence to suggest that although there are many commonalities in the care partner experience, there are aspects of care that are inherently unique to different care partner groups [122-124]. This study will provide preliminary data that will allow us to begin to explore the commonalities and differences among different populations, specifically care partners (1) caring for a person with a chronic condition that was caused by a traumatic event; (2) caring for a person with a progressive, fatal neurodegenerative disease; and (3) caring for a person with an episodic cancer condition that requires intense, prolonged inpatient and outpatient treatment. These diverse care partner groups not only allow for important between-population comparisons that can be used to inform future trial designs and maximize their impact but also maximize the generalizability to other care partner populations.

Conclusions

In summary, at the conclusion of this project, we will have established the acceptability and feasibility of a low-cost, low-burden self-management intervention to improve HRQOL for care partners of persons across 3 diverse groups of care partners. Ultimately, these pilot data will also provide justification for a larger clinical trial designed to examine the effectiveness of a JITAI in a larger cohort of diverse care partners (ie, those caring for individuals who have survived a disabling traumatic event, are experiencing progressive neurological disease, or episodic cancer conditions). It is our hope that this work will ultimately lead to improved HRQOL of care partners and those they care for.

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Authors' Contributions

NEC provided the first draft of the manuscript, and SWC and SS critically scrutinized the first draft and provided comments. ZW gave specific inputs to sample size considerations and statistical analysis plans, and JAM and AKL gave specific input to the description of the data storage and data storage system function. NEC, SWC, JAM, and SS designed the process evaluation. All authors participated in the design and content of the randomized controlled trial, and all authors read, commented on, and approved the final manuscript before submission.

Conflicts of Interest

None declared.

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Abbreviations

CFR: Code of Federal Regulations
CONSORT: Consolidated Standards of Reporting Trials
EMA: ecological momentary assessment
HCT: hematopoietic cell transplantation
HD: Huntington disease
HRQOL: health-related quality of life
JITAI: just-in-time adaptive intervention
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
SCI: spinal cord injury

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Protocol

Using Interactive Text Messaging to Improve Diet Quality and Increase Redemption of Foods Approved by the Special Supplemental Nutrition Program for Women, Infants, and Children: Protocol for a Cohort Feasibility Study

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Abstract

Background: Children in the United States eat too few fruits, vegetables, and whole grains and too many energy-dense foods; these dietary behaviors are associated with increased risk of obesity. Maternal diet plays a key role in shaping children's diets; however, many mothers have poor diet quality, especially those living in low-income households. The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) is a federal nutrition assistance program that provides mothers and children with nutrient-dense foods, and those who participate have better diet quality. However, many mothers do not redeem all their WIC-approved foods. Thus, there is a need to create effective interventions to improve diet quality, especially among low-income children and families.

Objective: This paper aims to describe the development and protocol for a study to evaluate the feasibility, satisfaction, and preliminary efficacy of a fully automated text messaging intervention as a strategy to improve maternal diet quality and the redemption of WIC-approved foods.

Methods: We describe the use of the framework developed for the description of nonrandomized feasibility studies. Using an observational, prospective cohort study design, we will recruit mothers enrolled in WIC with a child aged ≤2 years. Participants will receive automated SMS text messages aimed at improving the redemption of WIC-approved foods to improve the participants' diet quality for 12 weeks. All outcome measures will be analyzed using descriptive and inferential statistics. Qualitative data will be analyzed using thematic analysis.

Results: Data collection for this study began in March 2021. We expect the study results to be available within 9 months of study commencement. The results will shed light on the feasibility, acceptability, and effectiveness of using automated text messages as a behavior change strategy for mothers enrolled in WIC.

Conclusions: The results of this pilot study will explore whether this digital behavioral intervention, which will deliver nutrition guidance in accordance with the Dietary Guidelines for Americans using interactive self-monitoring and feedback, is feasible and acceptable. This will lay the foundation for a larger evaluation to determine efficacy for improving diet quality in those most at risk for obesity.

Trial Registration: ClinicalTrials.gov NCT04098016; https://clinicaltrials.gov/ct2/show/NCT04098016

International Registered Report Identifier (IRRID): DERR1-10.2196/32441

(JMIR Res Protoc 2021;10(12):e32441) doi:10.2196/32441

KEYWORDS

WIC; diet quality; digital health; text messaging; mothers; postpartum; child obesity; mobile phone

Introduction

Background

The etiology of childhood obesity is multifaceted and is largely influenced by diet quality and the consumption of obesogenic foods [1,2]. Maternal diet is a critical driver of the child's diet and can be a risk factor for childhood obesity [3-5]. Mothers shape the food environment by choosing which foods to buy and demonstrating what foods to eat through their own observed eating behaviors [6]. However, for many mothers, especially those living in low-income households, diet quality is suboptimal [3]. As such, many children consume sugar-sweetened beverages, desserts, and sweets from as early as the age of 4 months [7-11]. Thus, intervening on maternal diet quality during infancy may benefit the eating patterns of both the mother and child and reduce their subsequent obesity risk [3]. However, few interventions focus on improving diet quality for mothers, particularly during the postpartum period.

The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) is a federal nutrition assistance program that supports low-income, nutritionally at-risk pregnant and postpartum women, along with infants and children up to the age of 5 years. In 2020, WIC services were provided to nearly 6.3 million women and young children in the United States [12]. Participants in WIC receive nutrition education, breastfeeding support, referrals to other health and social services, and monthly benefits for specific foods (eg, milk, eggs, bread, and cereal) in specific quantities [13]. WIC also provides a small cash amount for fruits and vegetables *only* (cash value vouchers). Participation in the WIC program contributes to improved diet quality for both the mother and child [14,15], a reduction in the incidence of overweight and obesity [16-18], and cost savings in health care [19].

However, WIC is experiencing a steady decline in caseloads [20]. This may be due to required visits with WIC nutritionists to maintain the recipients' eligibility to continue receiving benefits. At these visits, women have their anthropometrics measured, are educated about infant feeding, and set goals for improving nutrition for themselves and their children. However, there is little follow-up with goal setting between visits, and many WIC beneficiaries report dissatisfaction with the nutrition education sessions, citing them as repetitive, long, or not very useful [21]. In addition, many mothers do not fully redeem their food benefits (ie, purchasing all items in the full quantities assigned), missing out on some of the nutritional benefits the program is designed to provide [22,23]. Efforts are needed to support these required nutrition education sessions and aid in the maintenance of goals, reinforce progress, and problem solve barriers to achieving goals.

Digital health interventions may serve as a scalable, cost-effective, and efficacious way to support mothers enrolled in WIC [24,25]. Nearly all adults (99%) in the United States have a cell phone, and 85% own smartphones; many Americans with lower incomes and those of childbearing age (18-29 years) rely only on smartphones for internet access [26,27]. Many programs have shown promise in successfully using digital technologies among parents to address health issues, including vegetable intake, sedentary behavior, bedtime routines, breastfeeding, and oral health [28-32]. Given their low cost, reach, and dissemination potential, using cell phones to deliver behavioral interventions could bridge gaps in health disparities and enable access to information across sociodemographic groups [25].

Feasibility studies are essential for exploring the relevance and acceptability of interventions [33]. Findings from feasibility studies can help determine whether an intervention should be tested for efficacy. The use of rigorous standards to guide the design and evaluation of feasibility studies is essential, though not often practiced. Here, we describe the use of a framework described by Bowen et al [34], which provides guidance for conducting nonrandomized feasibility studies. Indications for this feasibility trial include a lack of published studies focused on improving the redemption of WIC-approved foods and uncovering the reasons for beneficiaries not redeeming all their WIC benefits.

This paper describes the development and implementation and evaluation plans for *Healthy Roots,* a fully automated, pilot 12-week prospective cohort study of a digital behavioral intervention aimed at improving the redemption of WIC-approved foods to improve diet quality.

Study Aims and Objectives

The aims of this study are as follows: (1) to determine the feasibility of the intervention and (2) to determine the preliminary efficacy of the intervention on changes in maternal diet quality and the redemption of WIC-approved foods. Thus, the primary objectives of this paper are to describe the rationale and design of Healthy Roots using a rigorous framework to enable the reporting of a detailed assessment of the feasibility findings. These findings will guide intervention refinements and inform the appropriateness of a future randomized controlled efficacy trial.

The study has been approved by the Duke Health Institutional Review Board and is registered with ClinicalTrials.gov (NCT04098016). Electronic written informed consent will be obtained from the study participants.

Methods

Overview

The intervention was designed in 2 parts according to questions outlined by Bowen et al [34]. The initial phase focused on answering the question, *Can it work?* We engaged both WIC nutritionists and beneficiaries to conceptualize and design the intervention to answer this question. We used a qualitative approach centered on 2 areas of focus: acceptability and demand, as described in the following sections.

Part 1: Formative Work

Acceptability and Demand

According to Bowen et al [34], assessing acceptability during the intervention design phase allows researchers to understand how the intervention will fit into participants' daily lives. Assessing demand allows us to determine whether WIC beneficiaries will use the intervention to guide their behaviors and choices. Therefore, before conducting the pilot, we conducted in-depth semistructured interviews with parents or legal guardians and caregivers (hereafter referred to as parents) enrolled in WIC (N=13) via telephone. To be considered eligible, the parents must be receiving assistance from WIC, have a child aged ≤2 years, have a cell phone that can receive SMS text messages, and be English or Spanish speakers. To assess the acceptability, parents were asked to list the WIC-approved foods they were most likely to redeem and the foods they were least likely to redeem as well as the reasons affecting their food choices. They were also asked to describe the recipes and cooking methods used to prepare those foods. Parents were asked to specify their thoughts and practices about healthy eating, and how WIC does or does not help them eat healthily. To assess demand, they were also asked questions regarding their digital preferences, such as the preferred frequency of receiving text messages and the desired content of the text messages.

Analysis and Results

We used the Rapid Identification of Themes from Audio Recordings (RITA) procedure to conduct a rapid assessment of the interviews [35]. RITA allows for the expeditious identification of themes without the time-consuming and costly process of transcription, while minimizing the loss of information that often accompanies alternative rapid analysis procedures [36]. We used results from RITA to guide intervention development. We identified the following foods as the most commonly purchased food items: fruits and vegetables, milk, cheese, eggs, and cereal. The reasons behind these purchases include taste, child preferences, health benefits, and use in meal preparation. The least commonly purchased food items were peanut butter and yogurt. Parents typically did not purchase these foods because of child taste preferences and because they come in large packages, increasing their likelihood of going to waste. The parents used various sources to determine how to use their WIC-approved foods, including phone apps, food shows, internet recipes, cookbooks, and family recipes. Most reported cooking and eating at home at least four to five times per week. When asked about healthy eating, most parents noted the importance of consuming high amounts of fruits and vegetables and smaller portion sizes, whereas unhealthy eating was associated with the consumption of processed foods high in sodium or sugar or both. All parents believed that a text messaging program would be helpful in improving their diet quality. The reasons included wanting assistance with eating healthy and using the foods they received in their WIC packages. Parents reported that text messages are an optimal way to reach parents because "nearly everyone has a smartphone" and people send text messages more frequently than emails. As for the content of the text messages, most parents wanted to receive recipes and information about nutritional value, portion control, and meal preparation. The preferred frequency for the text messages varied by about half, with the participants preferring to receive text messages weekly and in the morning.

Part 2: Intervention Development and Implementation

Overview

The second part of the intervention design focuses on answering the question, *Does it work?* [34]. We used results from the formative work to guide the development of the content, frequency, and timing of text messages to ensure that the program matched the preferences and needs identified by the WIC beneficiaries. We used parents' feedback to tailor the goals, tips, and recipes to meet the needs of WIC beneficiaries while aiming to increase their diet quality by increasing the consumption of WIC-approved foods. The intervention is delivered electronically and is fully automated. It was adapted from an evidence-based digital obesity treatment program called the interactive obesity treatment approach (iOTA) [37-43]. iOTA was developed by GGB and the Duke Global Digital Health Science Center and has been tested in previous trials, including adaptation for other populations such as parents of children with obesity [44]. Similar to iOTA, intervention components in this study will be delivered using SMS text messages, interconnected algorithms, and content libraries [45]. Intervention development was also informed by the Social Cognitive Theory to include effective behavior change techniques, such as self-monitoring and goal setting [46,47].

Behavioral Change Goals

Goal creation was guided by formative work and focused on foods identified as being the least likely to be redeemed. In addition, goals were based on their empirical support for improving diet quality, ease of self-monitoring, and concreteness. Goals and tips were developed specifically for WIC beneficiaries using resources recommended by WIC, including guidelines on developing digital tools for WIC participants. WIC nutritionists aided in the development of goals and provided feedback on the message content. Messages were refined based on feedback, and user testing was conducted (N=8); the messages were updated accordingly and finalized by the team's registered dietitians (MCK and NMH).

Each of the 6 goals focuses on a specific set of WIC-approved foods as identified in our formative work. They include nutrient-dense foods such as fruits, vegetables, beans, whole grains, nuts, peanut butter, and leafy green vegetables. See Table 1 for an overview of the goals, the goal tracking questions (ie, self-monitoring), and the optimal answers to the tracking questions. For each goal, the recommended amount and frequency of consumption was guided by the 2020-2025 Dietary Guidelines for Americans [48]. Tips include recipes and simple behaviors to support meeting the goal. All recipe links are from organizations that serve WIC beneficiaries.

Table 1. Healthy Roots behavior change goals and tracking questions.

Ways to increase diet quality	WIC[a]-approved foods	Goal	Tracking question	Optimal answer
Increase fruits	Fruit	For the next 2 weeks aim to eat 2 fruits or more each day	Over the past week, on how many days did you eat 2 fruits or more?	≥2
Increase vegetables	Vegetables	For the next 2 weeks try to eat 3 vegetables or more each day	Over the past week, on how many days did you eat 3 vegetables or more?	≥3
Increase greens and beans	Legumes	Your goal for the next 2 weeks is to eat beans 2 times or more each week	Over the past week, how many times did you eat beans (like kidney, navy, or pinto beans; chickpeas; or lentils)?	≥2
Increase whole grains	Bread, tortillas, pasta, and cereal	For the next 2 weeks eat 3 or more whole grains each day	Over the past week, on how many days did you eat 3 or more whole grains?	≥3
Increase plant proteins	Legumes	For the next 2 weeks eat nuts or peanut butter 3 times or more each week	Over the past week, how many times did you eat nuts or peanut butter?	≥3
Increase dark green vegetables	Vegetables	For the next 2 weeks your last goal is to eat leafy green vegetables (like spinach, lettuce, bok choy, Swiss chard, collards, or kale) 2 times or more each week	Over the past week, how many did you have leafy green vegetables?	≥2

[a]WIC: Special Supplemental Nutrition Program for Women, Infants, and Children.

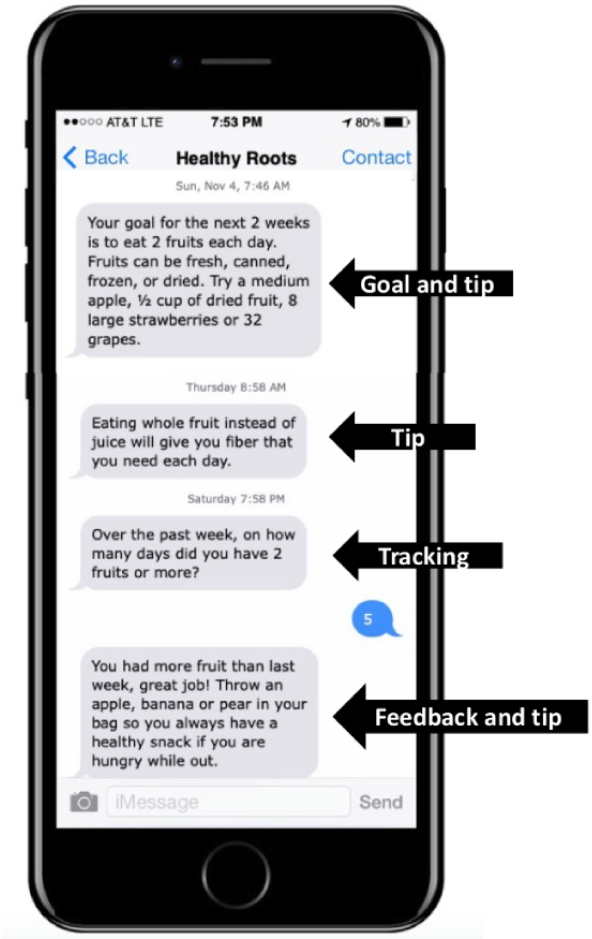
Self-monitoring With Tailored Feedback Messages

Regular self-monitoring is an important predictor of behavior change [49]. To enhance engagement with the intervention and foster behavior change, participants will be asked to self-monitor their behavior weekly via SMS text messaging throughout the intervention period. Participants will receive a text message prompting them to communicate their weekly tracking data; for example,

> *Time to check in. Over the past week, on how many DAYS did you eat 2 fruits or more? Please text only a number (like 1, 2, 5). Do not text words.*

The computer algorithm will then determine which feedback message to send according to the participant's response. Participants who provide self-monitoring data via SMS text messages will immediately receive tailored feedback and a brief skills training message (Figure 1). Feedback messages will describe progress, reinforce successes, offer motivational strategies, and provide short skills training tips. A retry protocol will attempt to reach the participants if the first SMS text message goes unanswered.

Figure 1. SMS text message exchange showing tips, tracking, and feedback.



Population

Demographics

We will enroll mothers aged ≥18 years who have a child aged ≤2 years and who are currently enrolled in WIC in North Carolina, United States. Parents must have a smartphone (ie, a cell phone that can send and receive text messages and access the internet), be willing to send and receive study-related text messages, have an email address they check regularly, have regular access to the internet, and be comfortable reading and writing in English.

Sample Size

Given that this is a feasibility study, we did not use traditional sample size calculations because hypothesis testing is an aim of this study [50,51]. When determining sample size, we consulted the recommendations for good practice in the design of pilot and feasibility studies, where recommendations vary from 12 to 50 participants [52-55]. Thus, we based our sample size on the following objectives: (1) test the integrity of the study protocol, (2) estimate rates of recruitment and consent, and (3) determine the acceptability of the intervention. In addition, because we are also interested in estimating the intake of episodically consumed foods, such as vegetables and whole grains, we chose a slightly larger sample size. For this study, we will recruit a total of 50 parents enrolled in WIC.

Recruitment

We have partnered with 2 different entities for participant recruitment using different strategies. The first is a private, nonprofit health system that operates federally qualified community health centers in North Carolina, United States, which also administer WIC benefits. During WIC encounters, the WIC nutritionists (n=2) will upload the name, phone number, and email address of WIC beneficiaries who are interested in joining the pilot to a secure web-based Duke Box folder. Research assistants will upload this information into REDCap (Research Electronic Data Capture), a secure, web-based software platform designed to support data capture and management for research studies [56,57]. The second recruitment entity is the WIC office from the second most populated county in North Carolina. This county WIC office will include flyers in mailings sent to all new WIC recipients. These flyers will provide information about the pilot study and will include a QR code that parents can scan to take them directly to the screener.

In addition, the Nutrition Services Branch within the North Carolina Division of Public Health, which implements the WIC program for North Carolina, United States, will alert all WIC directors in the state of the pilot study via email. The email will include the flyer with the QR code for WIC directors to distribute throughout their WIC clinics as they see fit. We will also use social media platforms, such as Facebook (Facebook Inc) and Duke University websites, to distribute information

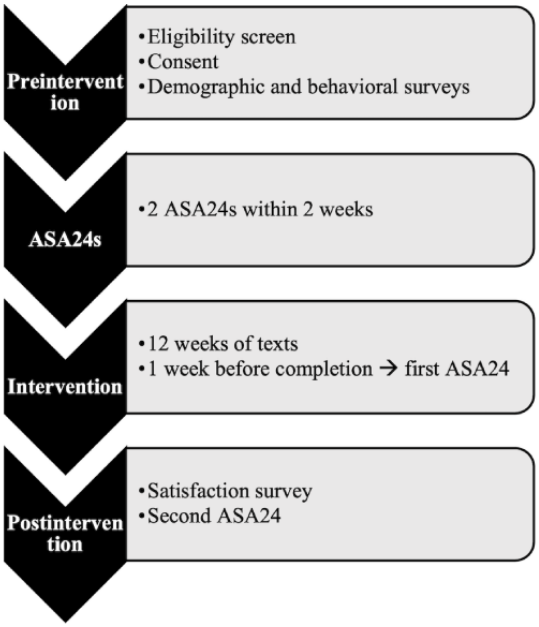
about the study and aid in recruitment. Interested parents can also find a link to the screener from a study-specific website. This website contains the study and contact information for the research team.

Screening, Baseline Assessments, and Enrollment

All study-related processes will be completed electronically to aid in the dissemination potential. The surveys will be administered through REDCap, allowing parents to self-guide themselves through each one. The system incorporates functions such as scheduling surveys and tracking their completion. If surveys are not complete, the system will automatically send reminders via SMS text messages and email, for up to 7 days.

The first survey is the eligibility screener, which includes questions regarding eligibility criteria. As soon as contact information is entered into REDCap by the research assistant, the system will automatically send an email with a link to the web-based screener and will send a SMS text message the following day if not complete. Interested parents will also be able to access the screener by scanning the QR code on the flyer or clicking on the screener link found on the study website and Facebook page. If a parent is eligible, they will confirm their contact information and be directed to a web-based consent form (see Figure 2 for study flow). Once the consent form is electronically signed, the parents will be directed to complete a web-based baseline survey.

Figure 2. Healthy Roots study flow. ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool.



Upon completion of the baseline survey, participants will be asked via email to complete two 24-hour dietary recall assessments administered through the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24) [58]. The ASA24 is a freely available, web-based, self-administered tool developed by the National Cancer Institute and provides comprehensive nutrient data on all foods and beverages consumed during the previous 24-hour period. Parents will be asked to complete 2 separate 24-hour dietary recalls (1 during the week and 1 in the weekend) within 2 weeks of each other. When both ASA24s are complete, parents will be enrolled in the intervention.

Once the participants are enrolled, they will begin receiving SMS text messages. The first text message will include a web link to a study-specific YouTube (Google Inc) channel that includes an orientation video. This 2-minute orientation video informs the participants of what to expect, including surveys they have to complete and the incentives for completing those surveys. They are presented with the study schedule and contact information for the study team and encouraged to reach out with any questions or concerns. Subsequently, participants will receive their first goal, followed by a new goal every 2 weeks until the end of the study for a total of 6 goals. During each 2-week goal cycle, participants will receive 3 tips per week related to that goal. At the end of each week, they will receive a tracking message related to their assigned goal. If they respond, they will receive feedback on their progress. If they do not respond, they will receive an automated reminder. If there is still no response, they will receive a reminder to track the next time and a tip. After 12 weeks, participants will be asked to complete 2 more ASA24s and a satisfaction survey. The participants will receive a gift card after the completion of each ASA24 (n=4) for a maximum amount of US $55.

Data Collection and Outcome Assessments

Self-reported sociodemographic characteristics, including education, age, BMI (kg/m^2), marital status, employment, depression, race, and ethnicity will be collected before enrollment through REDCap web-based surveys (Table 2). REDCap will also be used to capture intervention retention defined as responding to weekly tracking surveys. REDCap will also be used to capture postintervention satisfaction surveys. Research staff will follow up with phone calls and text messages for those who do not complete the satisfaction survey.

Table 2. Schedule of assessments.

Measure	Screening	Baseline	12 weeks
Inclusion and exclusion criteria	✓		
Informed consent	✓		
Sociodemographics		✓	
Food insecurity[a]		✓	
WIC[b] shopping habits		✓	✓
Depression[c]		✓	
Everyday discrimination[d]		✓	
ASA24[e] dietary tracking		✓	✓
Satisfaction survey			✓

[a]2-item screen for food insecurity [59].

[b]WIC: Special Supplemental Nutrition Program for Women, Infants, and Children.

[c]Using personal health questionnaire depression scale (PHQ-8) [60].

[d]Using expanded everyday discrimination scale [61].

[e]ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool.

Primary Outcomes

Feasibility will be assessed using a mixed methods approach across 5 domains based on the framework described by Bowen et al [34] to answer the question *Does it work?*Table 3 provides an overview of each domain and its outcome.

Table 3. Description of feasibility domains for assessment.

Domain	Description	Data source and measure
Acceptability	The extent to which the intervention (delivery and content) is considered relevant, appropriate, or satisfying to program participants and WIC[a] nutritionists	• Quantitative process evaluation and program satisfaction survey with participants • Qualitative process evaluation with participants (n=12) • Quantitative process evaluation with WIC nutritionists (n=4)
Demand or reach	The extent to which the intervention is likely to be used and the reach among the intended population	• Total number of WIC beneficiaries reached to recruit sample size • Time to recruit required sample size • Number of eligible participants needed to recruit required sample size • Number of participants who enrolled and completed the study
Implementation	The extent to which the intervention can be fully implemented as planned	• Number of participants who complete all aspects of the intervention • Number of SMS text messages successfully delivered • Number of participants who respond to each of the SMS tracking messages
Preliminary efficacy	The extent to which the intervention works in making positive changes to diet quality and improved redemption of WIC-approved foods	• Estimated changes in diet quality as measured by the Healthy Eating Index-2015 using ASA24[b] dietary recall data [62] • Changes in self-reported purchasing of WIC-approved foods

[a]WIC: Special Supplemental Nutrition Program for Women, Infants, and Children.

[b]ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool.

Acceptability of the intervention and study procedures will be assessed both quantitatively and qualitatively. Quantitative data will be collected via a poststudy satisfaction survey to assess the acceptability of the message frequency, their timing and content, and perceptions about the use of digital technologies for improving diet quality. We will also survey WIC nutritionists (n=4) to gather feedback on recruitment and thoughts on the program. An embedded qualitative study will obtain the

participants' views and experiences of the intervention. In-depth interviews will be conducted on a sample of at least 12 participants to allow for data saturation when assessing barriers and facilitators to healthy eating [63]. We will use a purposive sampling strategy to ensure that we obtain feedback from both high and low engagers with the intervention to capture all perspectives on participating in the study [64]. Interview guides will be developed to ensure consistency across interviews but also to allow for probing, as deemed appropriate. All interviews will be audio-recorded with responses kept confidential. The participants will receive a US $15 gift card as an incentive.

Reach and demand for the intervention will be measured using administrative and survey data, including participant enrollment, sociodemographics, and retention at the 12-week survey.

Implementation will be assessed through intervention engagement, calculated by dividing the number of days with valid tracking data (numerator) by the total number of possible tracking days (denominator). We will calculate and compare engagement rates by the week. We will create a dichotomous outcome variable comparing high and low engagers using an established cutoff of 80% or more engagement in weekly self-monitoring [65,66]. Bivariate analyses using 2-tailed *t* tests and chi-square tests will be used to examine predictors of intervention engagement. Poisson regression with a robust variance will be used to examine sociodemographic differences among those with higher levels of engagement (80% or more weeks of tracking) and estimate risk ratios and 95% CIs.

Preliminary efficacy will be measured by assessing changes in diet quality and self-reported WIC-approved food preferences. Participants will be asked about their purchasing habits before and after the intervention and the reasons for their choices. The embedded qualitative study will also obtain a more in-depth assessment of changes in WIC food purchases in a subset of the participants. Dietary intake will be measured using the ASA24 recall tool. Participants will be asked via email to complete 2 separate dietary recalls (1 during the week and 1 in the weekend) within a 14-day period before enrollment and again upon study completion, for a total of 4 dietary recalls. These data will be used to calculate a Healthy Eating Index (HEI)-2015 score, which consists of 13 components, 9 of which assess adequacy of the diet, including: (1) total fruit, (2) whole fruit, (3) total vegetables, (4) greens and beans (including peas), (5) whole grains, (6) dairy, (7) total protein foods, (8) seafood and plant proteins, and (9) fatty acids, which is a ratio of poly- and mono-unsaturated to saturated fatty acids. The remaining 4 assess dietary components recommended to be consumed in moderation: (10) refined grains, (11) sodium, (12) added sugars, and (13) saturated fats [62]. For all components, higher scores reflect better diet quality as moderation components are reverse scored. Each component is scored on a density basis rather than absolute scores, either as a percentage of calories or per 1000 calories, allowing use of the HEI for a range of ages and populations. Summed scores of the 13 components yield a maximum total score of 100, with a higher score reflecting greater compliance with the 2015-2020 Dietary Guidelines for Americans [67].

Analytic Approach

Quantitative Data Analysis

Data from this pilot study will be descriptive with outcomes being estimates of variables related to feasibility [34]. Sample characteristics will be described as frequencies for categorical variables and as means for continuous variables. HEI-2015 scores will be summarized as means, SDs, and the percent maximum score ([mean score/maximum score] × 100%]. We will explore intervention effects on changes in HEI score from baseline to 12 weeks using a 2-sample *t* test. We will conduct exploratory analyses to assess differences in HEI scores between low and high engagers using linear regression. A similar analysis will be conducted for changes in the relevant behavioral and psychosocial variables. If the distribution of any outcome is heavily skewed, we will either appropriately transform the data so that it is normally distributed or use a generalized linear mixed model with an appropriate link function. Sensitivity analyses will fit linear mixed models with a full maximum likelihood estimation using all available data to allow for responses to be missing at random, where the missing mechanism may be related to either observed covariates or response variables but not related to the unobserved data. All analyses will be conducted using STATA 14 (StataCorp, Inc).

Qualitative Data Analysis

All interviews with the participants and WIC nutritionists will be audiotaped and transcribed verbatim. In contrast to part 1, which used the RITA method, a 2-stage process will be followed to analyze interview transcripts on an iterative basis for refinement of interview guides and auditing of transcript quality. The first interview transcript will be pilot coded independently by 2 researchers to agree on a coding strategy (ie, to ensure that both researchers are coding consistently and to discuss and resolve any differences). The initial findings of the transcript will be discussed before coding the remaining transcripts. Data from the remaining transcripts will be independently coded by the 2 researchers. This will involve reading and rereading transcripts, identifying themes and subthemes, and mapping these with supporting salient quotes to an appropriate theoretical domain. Content analysis will identify patterns, make subgroup comparisons, and identify relationships within and between major themes using NVivo 12 (QSR International), which is the qualitative data analysis software developed to manage the *coding* procedure [67].

Results

Data collection for this study began in March 2021. We expect the study results to be available within 9 months of the study commencement. The findings will shed light on the feasibility, acceptability, and effectiveness of using automated text messages as a behavior change strategy for mothers enrolled in WIC. The study was approved by the Duke Health Institutional Review Board and registered with ClinicalTrials.gov NCT04098016. Electronic written informed consent was obtained from the study participants.

Discussion

Overview

The postpartum period is an opportune time to provide nutrition support to women as several studies indicate a decrease in diet quality and increased risk for obesity [68-70]. In addition, intervening during the postpartum period has benefits for the child as well; children's development of food preferences and eating habits are heavily influenced by their mothers during this time [71]. However, few studies have explored intervention effects on maternal diet in the postpartum period, particularly among those most vulnerable [72]. Our study offers an opportunity to not only improve retention in WIC and redemption of WIC-approved foods but also improve diet quality, something few studies aim to do [24].

Mothers participating in WIC are a priority population as it is the largest program providing services to improve the nutritional status of women and young children in the United States [73]. Although many women receive nutrition support through WIC, there are many barriers to its uptake, and women may prefer using digital methods to receive nutrition education. Digital health interventions are a scalable and efficacious way to support women enrolled in WIC because mobile phone use is ubiquitous across racial, ethnic, and socioeconomic groups in the United States [27]. A well-designed digital intervention that leverages the reach of WIC has the potential to be cost-effective and scalable to accommodate the disparities in obesity risk among high-risk groups.

Text messaging interventions can be cost-effective as they can reach large groups of people at a low cost per person compared with more complex interventions [74]. The pre- to postnatal period is an opportune time to use text messaging as mothers have a strong need and desire to obtain pregnancy- and child health–related information [75-77]. This is evidenced by the over 1 million subscribers to Text4Baby, a text messaging program that delivers health and safety information about pregnancy and the first year of infancy [78]. Text messaging is an enticing intervention strategy as messages can be stored, read, and answered at the participant's convenience; they are relatively inexpensive, are available for any type of phone, and have had a positive impact on many behavioral outcomes [74,79].

This study uses a rigorous feasibility assessment framework [34] to provide preliminary evidence on how digital technologies can impact engagement and retention in WIC and insight into the adoption potential of digital interventions within the WIC workflow. Seeking input from WIC participants directly, as they are the end users, provides valuable input regarding the development of text message content and support acceptability and engagement with the intervention. Using a framework for investigating feasibility will allow us to further understand the strengths and weaknesses of the intervention idea, that is, acceptability (beneficiaries and nutritionists), demand, implementation, and practicality, along with limited efficacy.

Limitations

A limitation of this pilot feasibility study is the 1-group design and small sample size, which prevents us from making definitive statements regarding its effectiveness. Limitations can be mitigated by the mixed methods approach to the design of the intervention, which will provide useful insights. The study sample might experience selection bias, based on the necessity of having a smartphone and an email address to be able to participate, which may limit the generalizability of the findings. However, 85% of adults in the United States own a smartphone, with higher levels of ownership among adults of childbearing age [27]. Moreover, the collection of data using self-reported measures has limitations in addition to the burden of required measures, such as the ASA24. There may be participants who are unable to respond to the measures without assistance. We will mitigate this with a research assistant who will reach out to those with incomplete data to assist in completion; this may lengthen the process of data collection but will ensure the completeness of data across all participants.

Conclusions

If successful, Healthy Roots will provide evidence to support scalable text message interventions as an appropriate tool to complement existing WIC services. The findings have the potential to inform the National WIC Association on the scalability and translation of the intervention. If the intervention is effective, it could provide benefits at a population-, individual-, and health service delivery–level by improving retention and diet quality with a low-cost, low–resource intensive intervention that can enhance existing models of care. Continued efforts are needed to improve the WIC experience and maximize program efficacy. During the current COVID-19 pandemic, this is particularly important as programs seek alternatives to engage with participants where possible [80]. The results from this pilot study will help explore whether this digital behavioral intervention, which will deliver nutrition guidance for meeting recommendations outlined in the Dietary Guidelines for Americans using interactive self-monitoring and feedback, is feasible and acceptable. This will lay the foundation for a larger evaluation to determine whether this intervention is effective at scale for improving diet quality in those at risk and will help determine the potential for this intervention to be implemented in the existing WIC infrastructure.

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Authors' Contributions

MCK helped with the conceptualization and methodology of the study, original draft preparation, reviewing, and editing. NMH contributed to the original draft preparation, writing, reviewing, editing, and project administration. SJH was involved in supervision, writing, reviewing, and editing. GGB assisted with supervision, writing, reviewing, and editing. All authors have read and approved the manuscript.

Conflicts of Interest

GGB holds equity in Coeus Health and serves on the scientific advisory board of WW (formerly Weight Watchers). These organizations had no role in the study design, data collection, data analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

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Abbreviations

ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool
HEI: Healthy Eating Index
iOTA: interactive obesity treatment approach
REDCap: Research Electronic Data Capture
RITA: Rapid Identification of Themes from Audio Recordings

WIC: Special Supplemental Nutrition Program for Women, Infants, and Children

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Protocol

Harnessing Innovative Technologies to Train Nurses in Suicide Safety Planning With Hospitalized Patients: Protocol for Formative and Pilot Feasibility Research

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Abstract

Background: Suicide is the 10th leading cause of death in the United States, with >47,000 deaths in 2019. Most people who died by suicide had contact with the health care system in the year before their death. Health care provider training is a top research priority identified by the National Action Alliance for Suicide Prevention; however, evidence-based approaches that target skill-building are resource intensive and difficult to implement. Advances in artificial intelligence technology hold promise for improving the scalability and sustainability of training methods, as it is now possible for computers to assess the intervention delivery skills of trainees and provide feedback to guide skill improvements. Much remains to be known about how best to integrate these novel technologies into continuing education for health care providers.

Objective: In Project WISE (Workplace Integrated Support and Education), we aim to develop e-learning training in suicide safety planning, enhanced with novel skill-building technologies that can be integrated into the routine workflow of nurses serving patients hospitalized for medical or surgical reasons or traumatic injury. The research aims include identifying strategies for the implementation and workflow integration of both the training and safety planning with patients, adapting 2 existing technologies to enhance general counseling skills for use in suicide safety planning (a conversational agent and an artificial intelligence–based feedback system), observing training acceptability and nurse engagement with the training components, and assessing the feasibility of recruitment, retention, and collection of longitudinal self-report and electronic health record data for patients identified as at risk of suicide.

Methods: Our developmental research includes qualitative and observational methods to explore the implementation context and technology usability, formative evaluation of the training paradigm, and pilot research to assess the feasibility of conducting a future cluster randomized pragmatic trial. The trial will examine whether patients hospitalized for medical or surgical reasons or traumatic injury who are at risk of suicide have better suicide-related postdischarge outcomes when admitted to a unit with nurses trained using the skill-building technology than those admitted to a unit with untrained nurses. The research takes place at a level 1 trauma center, which is also a safety-net hospital and academic medical center.

Results: Project WISE was funded in July 2019. As of September 2021, we have completed focus groups and usability testing with 27 acute care and 3 acute and intensive care nurses. We began data collection for research aims 3 and 4 in November 2021. All research has been approved by the University of Washington institutional review board.

Conclusions: Project WISE aims to further the national agenda to improve suicide prevention in health care settings by training nurses in suicide prevention with medically hospitalized patients using novel e-learning technologies.

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KEYWORDS

suicide prevention; hospital; training; e-learning; artificial intelligence; implementation science; user-centered design; task-shifting; quality assessment; fidelity

Introduction

Background

Suicide is the tenth leading cause of death in the United States, with >47,000 deaths in 2019 [1]. Most people who died by suicide had contact with the health care system in the year before their death, both in general medical and in acute care settings, and frequently for reasons other than behavioral health [2-4]. Therefore, to better reach patients in general medical settings, the National Action Alliance for Suicide Prevention designed an agenda that prioritizes training a wide range of health care providers in suicide prevention [5]. There is increasing awareness of *occult* or hidden suicidality or suicide risk among hospitalized patients presenting for medical reasons, surgeries, or traumatic injury. When implemented in acute medical care settings, universal suicide screening programs routinely identify patients at risk for suicide who would otherwise have gone unnoticed [6-10]. For instance, a study conducted with patients seen in emergency departments (EDs) across 8 hospitals and 7 states observed twice the rate of suicide risk detection after implementing universal screening [11]. Many medically hospitalized patients are known to have risk factors for suicidality, such as high rates of behavioral health conditions [12-14]. Hospitalization experiences, such as being admitted to an intensive care unit, are known to increase the risk factors for suicidality, including posttraumatic stress disorder (PTSD) and depression [15], and reasons for hospitalization, such as traumatic injury, are known to place patients at a greater risk of suicide following discharge [16]. Therefore, the Joint Commission, which provides oversight, standards, and guidelines for health care organizations nationally, recommends screening for suicide risk among medically hospitalized patients and mitigating risk with strategies such as suicide safety planning [17]. To support patients identified as at risk of suicide in these hospital settings, we aim to develop Project WISE (Workplace Integrated Support and Education), which includes research to develop an e-learning training in suicide safety planning enhanced with novel skill-building technologies that can be integrated into the routine workflow of nurses serving patients hospitalized for medical or surgical reasons or traumatic injury.

Continuing Education for Health Care Providers in Suicide Prevention

There has been a proliferation of e-learning and in-person continuing education programs designed to train a workforce that has otherwise been naïve to suicide prevention. State licensing boards are increasingly requiring health care providers to complete several hours of suicide-prevention continuing education at least once, if not routinely, every several years [18,19]. *Gold standard* evidence-based training approaches aim to improve both knowledge and skills about suicide and how to intervene and include some form of didactic training (in-person or web-based) with a demonstration or modeling of suicide prevention skills, opportunities to practice these skills, and expert coaching and feedback on practicing these skills [20-22]. Many also target attitudes for increasing willingness and motivation to engage in suicide-prevention activities, given that stigma, anxiety, and unhelpful myths about suicide are common among the general population and professionals [23,24]. In addition, evidence-based continuing education harnesses what is known about how adults learn in real-world environments, such as allowing clinicians to be self-directed and solve real-life problems [25,26].

Although evidence-based training and suicide-prevention continuing education approaches exist (eg, the Question, Persuade, and Refer Gatekeeper training and LivingWorks Applied Suicide Intervention Skills training for safety planning [27,28]), peer-reviewed research on training outcomes is limited with regard to the impact of training on skills [29-31]. Even less is known about how well the trainees apply and maintain these skills in routine intervention delivery; this is a concern, as skills frequently drift from higher to lower quality following training, and this drift is a critical barrier to the sustainment of evidence-based practices [32].

Using Technology to Enhance the Scalability and Sustainability of Continuing Education in Suicide Prevention

Our research is designed to address 2 common and related barriers to the widespread implementation of effective continuing education and the transfer of what was learned from the training to practice in health care settings. The first is the need for efficient and low-cost training that targets skill-building for suicide-prevention activities. The gold standard methods for training require considerable provider and expert trainer time for didactics, skills practice, fidelity or quality assessment,

and feedback or coaching sessions [22,32,33]. Therefore, continuing education generally requires taking large amounts of time away from work at considerable financial costs to the trainee and their employer. Busy providers and organizations with limited access to resources for training may opt to engage in briefer and less costly training such as web-based didactics [34], although didactics alone are insufficient for provider behavior change [22].

The second barrier is the lack of efficient tools to evaluate the quality of trainee suicide-prevention skills, both for training and skill maintenance purposes. Quality refers to the extent to which an intervention is delivered well enough for it to achieve its expected effects [35]. Traditional methods of quality assessment for psychosocial interventions are not scalable in routine training and quality improvement contexts [22,32,33]. These methods rely primarily on humans to convert complex qualitative data (eg, transcripts or observations of recorded interactions) into simplified and summative quantitative information [36], which is labor-intensive and expensive, requiring a well-trained and reliable coder to code samples of skills practice.

Advances in technology are promising for reducing the barriers to implementing effective, evidence-based training and reaching the full spectrum of health care providers who may engage patients in suicide-prevention activities. Although web-based learning platforms with didactic content are routinely available for provider training in psychosocial interventions [34], more recent innovations using computer technologies allow the trainees to practice relevant skills using simulated training environments, replacing human effort with computer technology to facilitate skill practice with feedback on their performance [37-41]. We designed Project WISE to develop and implement web-based, technology-enhanced suicide-prevention training for nurses serving patients hospitalized for medical or surgical reasons or traumatic injury. The training is designed to be effective, efficient, and ultimately low-cost. To be most widely scalable, the training will be flexibly designed with components that can be integrated into a routine workflow in a clinical setting.

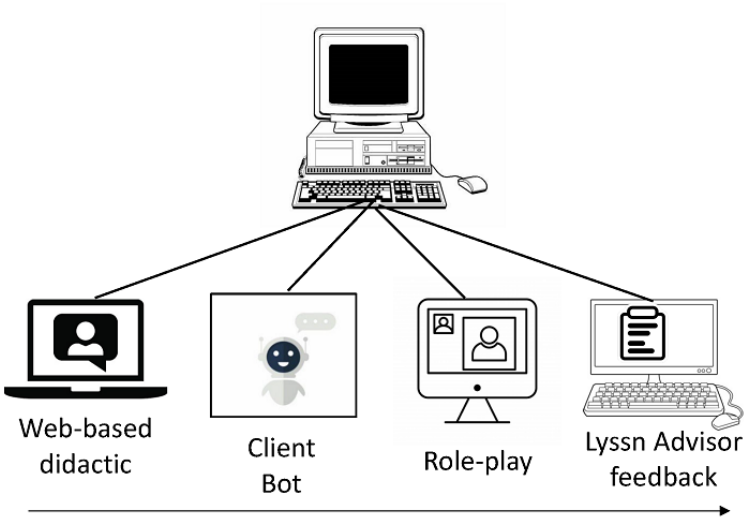
Project WISE: Technology-Enhanced Training in Suicide Safety Planning

The Joint Commission recommends suicide safety planning for patients in hospital settings at risk of suicide. Suicide safety planning can be a brief, 30- to 45-minute intervention in which a provider works collaboratively with a patient to identify a multistep plan for coping with suicidal thinking and urges to prevent suicidal behavior [42,43]. Coping strategies include ways to distract from suicidal thinking and seek help from others, both through social support and professional help. A provider helps the patient identify experiences, thoughts, or feelings that commonly lead to suicidal thoughts so that the patient knows when to engage in the safety plan. Safety plans also include strategies for limiting access to lethal ways to die (eg, locking firearms). Suicide safety planning requires providers to effectively use general counseling skills [44], including empathic listening to understand patients' experiences, reflection of this understanding, and the ability to work collaboratively with patients to generate useful and relevant safety strategies. Research shows that collaboratively developed safety plans are of higher quality [45,46]. In a recent study of veterans seeking emergency services for suicidality, suicide safety planning was associated with a 50% reduction in suicidal behavior over 6 months [47]. Safety planning with active US army soldiers seeking emergency behavioral health care was effective in reducing suicide attempts as compared with contracting to not engage in suicidal behavior (5% vs 19%) [43].

Project WISE's e-learning training in suicide safety planning includes several components consistent with adult learning principles and effective practices for training in evidence-based interventions (Figure 1). The training will take 2.5 to 3 hours and begin with a web-based didactic training that includes a demonstration of safety planning. Much of the content for the didactic is publicly available from the Joint Commission resources on suicide safety planning, and other content is crafted for nurses by the first author (DD). The 1-hour didactic training may be completed over ≥1 session, with the intention of having it done within 1 week.

Following the didactic training, nurses will complete a 30-minute role-play practice with a conversational agent called Client Bot, developed by Lyssn. Trainees may complete this training in one sitting or across multiple sessions. The Client Bot technology uses machine learning and artificial intelligence to simulate interactions with a patient in text format, providing the opportunity for trainees to practice general counseling microskills (eg, reflective statements of what a patient says or means and open questions to elicit a patient's perspective and interests) and receive real-time feedback on performance and coaching on the use of these skills. Microskills training is known to be an effective method for improving counseling skills during counseling sessions [48], and Client Bot has successfully trained novice counselors to generate empathic reflective statements and ask open-ended questions [39]. Practice with the Client Bot is also expected to help increase confidence in inquiring about and discussing suicidality with simulated and real patients.

Figure 1. Project WISE (Workplace Integrated Support and Education) e-learning training in suicide safety planning. The webinar includes didactic training and demonstration of safety planning. Client Bot allows for practice with feedback in counseling microskills. Role-play includes practice in doing safety planning with a patient actor. Lyssn Advisor feedback includes review of computer-generated feedback for empathy and collaboration skills and a recording of the role-play.

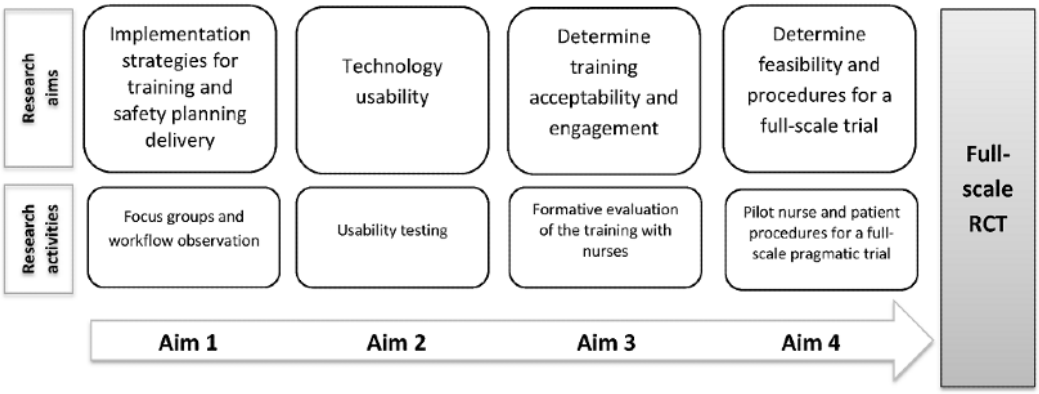


Following the didactic webinar and microskills practice, trainees will practice suicide safety planning with a human actor role-playing a medically hospitalized patient at risk of suicide. Such simulated patient interactions are common in medical training and clinical skills evaluation [49]. The 30-minute role-play will be completed using videoconferencing software and will be recorded. The recording will be processed through a system called Lyssn Advisor, developed by Lyssn, that uses speech signal, natural language processing, and machine learning to first convert the audio content to a transcript and then assess the provider's quality of general counseling skills based on the transcript text [40,50]. The feedback will provide information on the quality of general counseling skills, such as using a collaborative, empathic style with the patient. The Lyssn Advisor system generates a confidential feedback report accessible via the internet at the trainee's convenience. The trainee will be encouraged to spend approximately 30 minutes reviewing their report and parts of their role-play and to use the feedback to inform their counseling style in future simulated or real patient suicide safety planning interventions. Trainees will be welcome to spend more time with the Client Bot if they would like to practice microskills after receiving computer-generated feedback through the Lyssn Advisor system. In routine deployment of the training, we expect that trainees will have the option to engage in additional role-plays and obtain feedback on these role-plays.

Project WISE Research Aims

Much remains to be known on how best to integrate the novel conversational agent (Client Bot) and automated feedback (Lyssn Advisor) technology for skills training into continuing education for health care providers and how to optimize the transfer of skills learned for the greatest impact on patient outcomes. Project WISE includes developmental and pilot research to inform the refinement and deployment of e-learning training as well as the design of a future large-scale pragmatic trial. The future trial will examine whether hospitalized medical, surgical, or traumatically injured patients at risk of suicide have better suicide-related postdischarge outcomes if admitted to a unit with nurses trained using technology-enhanced training in suicide safety planning as compared with those admitted to a unit with untrained nurses. Our interdisciplinary team will use concepts and methodology from implementation science, adult learning theory, user-centered design, and suicide-prevention research to conduct the 4 research aims (Figure 2): (1) identify strategies for the implementation and workflow integration of both the technology-enhanced training as well as the delivery of suicide safety planning with patients, (2) adapt the existing Client Bot and Lyssn Advisor technologies to train nurses in general counseling skills for use in suicide safety planning, (3) conduct a formative evaluation of the training with nurses to assess training acceptability and engagement with the training components and technologies and inform the iterations of the training, and (4) assess the feasibility and pilot procedures for a cluster randomized trial evaluating the impact of the training on patient outcomes.

Figure 2. Project WISE (Workplace Integrated Support and Education) research aims. RCT: randomized controlled trial.



Methods

The methods specific to each study aim have been described in the following sections. All procedures were approved by the University of Washington institutional review board.

Setting and Population

The Project WISE research takes place at a level 1 trauma center, which is also a safety-net hospital and academic medical center. Nurses there are required to complete 6 hours of suicide-prevention training at least once for state licensure and universally screen all patients admitted to the ED and inpatient units for suicidality. The Columbia Suicide Severity Rating Scale (C-SSRS) triage version [51] was adopted by the hospital and implemented as part of the universal screening protocol in the ED in October 2019 and on inpatient units in July 2020. The usual care for patients screening as high risk includes suicide precautions such as ensuring that the environment is safe from lethal means, having a patient monitor sit with the patient, and notifying the medical team, who would request a consult from the hospital psychiatry service. Low- or moderate-risk patients are provided suicide-prevention resources at discharge (eg, crisis line) and may request to see a hospital social worker. Units serving medical, surgical, and traumatic injury patients will be recruited to participate. Unit managers will help facilitate the recruitment of nurses and have agreed to have the research team recruit patients. On the basis of prior research with local and similar trauma centers, it is anticipated that nurses will predominantly identify as female and White [52] and that the patients will predominantly identify as male [53] and White [54].

Aim 1: Focus Groups and Contextual Inquiry

Design

Aim 1 combines implementation science and user-centered design methods to collect qualitative and observational data to identify the strategies for implementing both nurse training and the transfer of learning from training simulations to the conduct of suicide safety planning with actual patients. Aim 1 includes the conduct of 3 to 6 focus groups with nurses serving medical, surgical, or trauma inpatients (n=4-6 per group) to assess the barriers to and facilitators of engaging in the training and delivery of suicide safety planning with hospitalized patients using the Theoretical Domains Framework (TDF) [55]. The TDF synthesizes 33 theories with relevance to provider behavior change associated with implementing an evidence-based practice, resulting in 14 domains covering individual-, setting-, and organizational-level variables that are relevant to both training engagement and training transfer [56,57].

Aim 1 also includes the user-centered design method of contextual inquiry and task analysis, with 3 nurses to observe and inquire about actual nursing workflows [58]. Task analysis includes shadowing nurses as they demonstrate their current practices, including preparing and documenting patient encounters, their information technology interaction, and their workflow. Data collected will include field notes of observations and audio recordings of real-time discussions with nurses on workflow integration of both the training components and the delivery of safety planning with patients. Real-time questions will further assess the TDF constructs (eg, emotions and beliefs about capabilities).

In addition to these research activities, members of the team will meet with various hospital stakeholders for guidance and input on Project WISE, suicide-prevention initiatives, and the implementation of research activities. A key stakeholder group is a committee that approves and advises research projects that involve nurses and nursing services. Decisions about nursing research also occur at the unit level; therefore, the team will engage unit nurse managers in planning for research activities.

Plan of Analysis

Focus groups will be audio recorded and transcribed for analysis, which will include a qualitative content analysis [59] to identify the presence, absence, and specific characterizations of potential implementation barriers and facilitators based on focus group data. A priori themes will be identified, and an initial coding scheme will be developed based on TDF constructs and then refined after reviewing each transcript. The transcripts will be coded by 2 coders. Discrepancies will be resolved by consensus and estimates of interrater reliability will be calculated [60]. The findings may be presented through narratives, tabular representations of themes with illustrative quotes, and thematic counts. The Atlas.ti (ATLAS.ti Scientific Software Development, GmbH) computer program [61] will assist with the analysis [62,63]. The contextual inquiry will result in task flow diagrams of key user processes, which are detailed, visual

depictions of the steps a user takes to complete a task with the technology, and identify a workflow for engaging patients in safety planning.

Aim 2: Usability Testing

Design

A user-centered design methodology will be used to update the user interfaces of both the Client Bot and Lyssn Advisor technologies for nurse end users and inform the instructional support provided to nurses regarding how to use the technology. We will conduct usability testing with nurses, followed by the completion of a brief questionnaire to obtain their feedback on the novel technologies. The 3 nurses will interact with the Client Bot and the Lyssn Advisor feedback report. For Client Bot, a 15-minute session will include text-based *chatting* with a simulated, suicidal patient. Nurses will be instructed to use general counseling microskills, including asking open-ended questions and making empathic reflections on what the client has said. Throughout the chat session, nurses will be provided immediate, adaptive feedback when they use these skills and encouragement to do so when they do not. The first author will observe the nurses interacting with the Client Bot system and record their experiences. Nurses will also be asked to verbalize their thought process as they interact with the technology (eg, *concurrent think-aloud protocol* [64]). These nurses will also be asked to interact with a sample version of the Lyssn Advisor feedback system based on a sample suicide safety planning intervention, again using the *concurrent think-aloud protocol*, and providing feedback on the provided information and the manner in which it is presented. Usability will also be measured with the System Usability Scale (SUS) [65], a 10-item Likert scale survey that has been widely used in usability research as a measure of user satisfaction.

Plan of Analysis

The research team will make observations during the usability testing sessions and use video recordings of the sessions. The team will document misunderstandings, frustrations, technology errors or problems, participant errors, what went well in using the technology, successes in using the system, and suggestions made by the participants. Usability will be indicated with a target SUS score of 68 out of 100. Changes will be made to the user interface to achieve sufficient user satisfaction ratings based on the feedback from usability testing.

Aim 3: Formative Evaluation of the Training

Design

For the formative evaluation of e-learning training with nurses, we will assess the acceptability of and engagement with the training components and technologies using longitudinal survey research, observation of nurse performance in suicide safety planning, and end-of-evaluation focus groups. The evaluation will be registered at ClinicalTrials.gov.

Procedures

A total of 20 nurses from the participating acute or intensive care units will be recruited by the research team to participate. They will be invited to complete all the training components (Figure 1), including the web-based didactic training and demonstration of suicide safety planning, practice of counseling microskills with the Client Bot, a 30-minute role-play practice with a patient actor, and computer-based feedback on this practice through the Lyssn Advisor system. Completion of all training components is expected to occur within 1 month; however, nurses may access these materials at any time during the 6-month study follow-up period.

Evaluation activities will include a series of surveys (before training, after training, and at the 6-month follow-up) and an end-of-study focus group to collect data on the acceptability of the training and technology and barriers to and facilitators of the implementation of the training and suicide safety planning delivery. In addition, nurses will complete a series of standardized patient role-plays to assess their skills in suicide safety planning before and after interacting with each of the novel technologies. A follow-up role-play will occur 6 months after completing all the training components.

Measures and Variables

Demographics

In the baseline survey, the nurses will be asked about their demographics (eg, gender, race or ethnicity, and age), length of their current employment, training background, and experience with suicide prevention.

Acceptability of the Training

In follow-up surveys, the nurses' training and technology acceptability will be assessed using the SUS [65] and open-ended questions to elaborate on what contributes to their responses on the SUS. The SUS has 10 statements that are responded to on a Likert-type scale ranging from 0 (strongly disagree) to 4 (strongly agree). The scores range from 0 to 100, with higher scores indicating greater acceptability (usability). The SUS has demonstrated good internal consistency, reliability, and concurrent validity with other usability measures [66].

Training Completion and Technology Use

Training completion and use of the technology will be assessed with self-report surveys after training and at the 6-month follow-up. This will include questions about whether and when the participants used the Client Bot and Lyssn Advisor feedback system and how they used it in their training and practice. The didactic portion will have embedded knowledge questions to track the completion of didactic content. Use data will also be collected by the Client Bot and Lyssn Advisor systems, which will comprise how often the nurses accessed the program, times of day for use, how long the nurses spent on the program, and the features that they used.

Motivation for Training and Delivery of Suicide Safety Planning

A measure of nurse motivation to use the training materials, including the technology, will be asked at each survey time point. This will include variables such as the nurses' interest in the material, technology, and willingness to persist when challenged by practicing skills and receiving corrective feedback. The motivation to use general counseling skills to conduct collaborative safety planning with patients (ie, transfer

of training [56]) will be assessed by adapting measures from the TDF (eg, beliefs about capabilities and consequences, behavioral intentions, and negative emotions) [55].

Suicide Safety Planning Quality

The quality of the use of general counseling skills and safety planning skills will be assessed using standardized patient role-play assessments. Nurses will complete four 30-minute role-plays over the course of the evaluation. Role-play scenarios will be developed that allow nurses to practice the full range of safety planning skills with a willing, hospitalized patient who has previously experienced a suicidal crisis. A role-play will be used as part of the training and for providing evaluation data as it will be uploaded to the Lyssn Advisor system for nurses to review their performance. All role-plays will be conducted by a patient actor via video web-conferencing software, recorded, and assessed for general counseling skill quality using the Lyssn Advisor system. The Lyssn Advisor system codes for provider empathy and collaboration, consistent with the Motivational Interviewing Skill Code [67].

The postwebinar, posttraining, and 6-month follow-up role-plays will be assessed for quality of the safety planning intervention by the first author using the Safety Planning Intervention Rating Scale [68]. The scale scores range from 0 to 20, with higher scores indicating greater quality of safety planning (eg, whether the key components were done and how well they were done). Self-reported perception of skills will be assessed via surveys at baseline, after training, and at 6 months after training using methods modified from previous research on training clinicians in evidence-based psychotherapy [69]. Specifically, nurses will report their self-perceived level of skill on a Likert-type scale for engaging in components of the safety planning intervention covered in the Safety Planning Intervention Rating Scale.

Implementation Barriers and Facilitators

Implementation barriers and facilitators will be assessed for both engaging in training and using the skills learned with patients via nurse surveys at baseline, after training, 6 months after training, and at end-of-study focus groups. Questions will be designed using the TDF (eg, beliefs about consequences, role and identity, and environmental context and resources).

Plan of Analysis

Quantitative data will be viewed graphically and analyzed descriptively. Qualitative open-ended responses to questions will be summarized into common themes, or their content will be analyzed as appropriate. Acceptability of the training will be indicated by a target score of 68 out of 100 on the SUS. We will observe the rates of training completion per training component, and follow-up assessments will explore reasons for noncompletion based on self-report. The findings will be used to inform iterations to improve the acceptability of and engagement with the training. Focus groups will be content analyzed using the same methods as described for aim 1 and will be used to inform the implementation of the training and suicide safety planning with patients in a future trial.

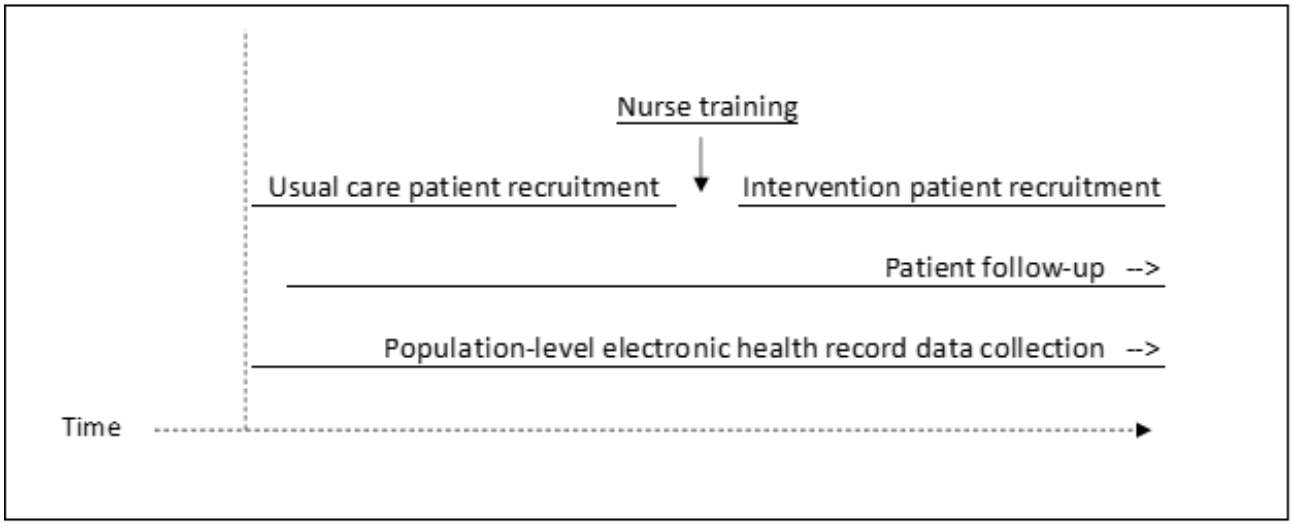
Aim 4: Pilot Procedures and Feasibility Assessment for Conducting a Full-Scale Pragmatic Trial

Aim 4 will inform the design of a cluster randomized trial, including whether to use a parallel or stepped-wedge design [70], measurement approaches, and sample size determination to obtain adequate statistical power.

Design

In the future full-scale trial, randomization will occur at the hospital unit level, and patient recruitment will occur for a period before and after the training of nurses in the unit on suicide safety planning, resulting in usual care and intervention group samples, respectively (Figure 3). Nurse training outcomes will also be assessed longitudinally in the future trial, and aim 3 provides pilot data related to the feasibility of retention and the assessment of training outcomes for nurses.

Figure 3. Anticipated timing of patient enrollment, nurse training, and data collection at the unit level for a future full-scale cluster randomized clinical trial evaluating the impact of the training on patients' suicide-related outcomes.



We will pilot the longitudinal follow-up of a sample of patients identified as at risk of suicide based on the C-SSRS triage version, including the assessment of feasibility for recruitment, retention, and self-report of suicide-prevention service use and

suicide-related outcomes over 6 months. We will also pilot the collection of electronic health record (EHR) data linked to patients to observe what is documented in the EHR regarding suicide-prevention services received while at the hospital and patient outcomes (eg, readmission for suicidal ideation or behavior) over the follow-up period. Data may be abstracted directly from the EHR by the research team or collected from a data warehouse.

There are limited data on suicide screening results for patients hospitalized for medical or surgical reasons or traumatic injury. A study implementing the C-SSRS with hospitalized trauma patients observed a 4% rate of positive screens [10]. With an estimated 6000 trauma patients in the study hospital per year [71], we might expect 20 potential participants per month on trauma units alone. To better estimate potential recruitment rates, we will collect deidentified population-level data for C-SSRS screening in acute and intensive care over a 1-year period. EHR data collected naturalistically in the course of clinical care are commonly harnessed in pragmatic trial research [72]. For instance, it is possible to collect data on suicide-related hospital visits, such as admissions for self-inflicted injuries or suicide attempts. Such outcomes can be collected for the entire population of patients seen during a specific time frame and could be used to provide a population-level estimate of the effect of introducing suicide safety planning training on hospital units, as opposed to relying solely on an estimate from a subsample of the population followed over time. Therefore, we will develop and pilot procedures for collecting population-level deidentified EHR data to pragmatically assess suicide-prevention service delivery for hospitalized patients (eg, documentation of a psychiatry consultation for suicide risk, suicide risk assessments, and documentation of safety plans) and suicide-related patient outcomes (eg, ED admissions for suicidal ideation and hospital admissions for self-inflicted injury).

Procedures

A total of 40 adults aged ≥18 years admitted to the hospital for medical or surgical reasons or traumatic injury will be recruited based on having a positive C-SSRS triage screener result (moderate or high) as recorded in the EHR. Exclusion criteria will be patients unable to consent to the research, such as because of cognitive impairment or active psychotic symptoms, prisoners, and non–English speaking patients. Enrolled patients will complete a baseline survey and provide detailed contact information for follow-up purposes. At the end of the enrollment process, patients will be provided with national crisis line resources. All participants will receive usual care for suicide risk, which may include the removal of lethal means from a patient's hospital room, designation of a person to sit with and monitor the patient for safety purposes, or referral to the hospital-based psychiatry consultation service for evaluation and referral.

Patients will complete the study measures via surveys at baseline, 1 month, and 6 months. Surveys may be completed via self-report or interviews with the research staff. To address safety concerns, the surveys will incorporate procedures from the University of Washington risk assessment protocol [73]. For self-report surveys, certain responses indicative of active suicidal ideation will trigger contact from the research staff to follow-up on safety concerns. EHR data relevant to the injury event and initial and follow-up clinical care will also be collected, such as C-SSRS screening results, documentation of suicide-prevention interventions in the hospital, International Classification of Diseases codes for suicidal ideation and self-inflicted injury associated with their inpatient hospitalization, and readmissions to the hospital for suicidal ideation or behavior during the 6-month follow-up period. Subsequent visits to any ED in the state will also be observed using the ED information exchange system [74].

Population-level deidentified data for medical, surgical, or traumatic injury patients will be collected from the hospital data warehouse and will include the collection of state-level death records data that are integrated with these EHRs. The team will identify potential sources of clinical data related to suicide such as reasons for patient admission, services delivered, and patient clinical characteristics and work with data warehouse biomedical informaticians to locate and pull these data from the warehouse.

Measures and Variables

Demographics and Clinical Characteristics Related to Hospitalization

Patients will complete self-report demographic questions on information such as their gender, race or ethnicity, age, and socioeconomic status. Clinical characteristics of their hospitalization will be abstracted from the EHR regarding suicide screening results, services received during the hospital stay, International Classification of Diseases-10 codes associated with their stay, and admission diagnosis or reason for hospitalization.

Columbia Suicide Severity Rating Scale

The C-SSRS triage version [51] will be asked for each patient upon admission to the study hospital's ED or inpatient unit. There are 6 yes or no questions to assess the past month's suicidal ideation severity and lifetime and the past 3 months' preparatory behavior or suicide attempt. On the basis of these responses, patients will be determined to be at low risk, moderate risk, or high risk. The presence of a detailed plan, suicidal intent, preparatory behavior, or suicide attempt in the past 3 months will result in patients being considered at high risk. The C-SSRS is recommended as a screening tool by the Joint Commission [75].

Hospital-Based Suicide-Prevention Services

We will assess the suicide-prevention activities conducted during the patient's hospitalization via EHR documentation and patient self-report at the 1-month assessment. Patients will also self-report their perception of what was helpful or not helpful with regard to these activities at both follow-up assessments.

Suicide-Related Outcomes

Patients will self-report suicidal ideation and behavior using the Self-Injurious Thoughts and Behaviors Interview–revised (SITBI-R) [76]. EHR and ED readmission data for visits related to suicidal ideation and self-inflicted injury will also be assessed.

We will use a subset of items from the SITBI-R to assess suicide ideation, suicide planning, preparatory behaviors, suicide threats and gestures, aborted suicide attempts, interrupted suicide attempts, and suicide attempts [76]. Questions regarding the age of onset, frequency of thought or behavior, duration of thought or behavior, urge or intensity, and future likelihood of thought or behavior engagement will be asked. Items responses include Likert-type ratings and open-ended and multiple-choice options. The measure has demonstrated good test-retest reliability and convergent validity with an existing measure for use both as an interview assessment and self-report in a web-based survey format. The SITBI-R will be asked at all time points.

Patients will self-report self-efficacy to avoid suicidal behavior at each time point using the Suicide-Related Coping Scale [77]. This scale includes 17 items rated on a Likert-type 5-point scale ranging from 0 (strongly disagree) to 4 (strongly agree). The items assess the knowledge of and confidence in using internal coping strategies and external resources to manage suicidal thoughts and urges to decrease risk and avert suicidal crises (eg, when I am suicidal, I know of things to do by myself that help me feel less suicidal; I know which friends or family members to contact to help take my mind off my suicidal feelings).

Behavioral Health Service Use

Patient behavioral health service use will be collected via self-report and EHRs, when available. Questions will assess whether, how often, and what types of services patients used for reasons of mental health and substance use or addiction. Lifetime and previous month assessments will occur at the 1-month follow-up, and previous 6 months' assessment will occur at the 6-month follow-up.

Behavioral Health Symptoms

Patients will be asked about depression and anxiety at each assessment. Self-reported depression symptoms will be assessed using the Patient Health Questionnaire 9-item version [78], a well-validated and reliable measure that assesses the severity of depressive symptoms according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) criteria [79]. Items are rated on a scale from 0 (not at all) to 3 (nearly every day) and summed for a total score, with higher scores indicating more depression. A score of ≥10 indicates clinically significant depression symptoms. Self-reported anxiety symptoms will be assessed using the General Anxiety Disorder 7-item scale [80], a well-validated and reliable measure that assesses the severity of generalized anxiety based on the *DSM-5*. Items are rated on a scale from 0 (not at all) to 3 (nearly every day) and summed for a total score, with higher scores indicating greater levels of anxiety. A score of ≥10 indicates clinically significant generalized anxiety symptoms.

Patients will be asked about their trauma history and posttraumatic stress symptoms at the 1-month follow-up and posttraumatic stress symptoms at the 6-month follow-up. Patients will self-report on [81] whether they have experienced the 16 events in the Life Events Checklist for DSM-5 and then select which event was the *worst* event that they would report on in the PTSD Checklist for DSM-5 (PCL-5) [82]. The PCL-5 asks patients to report how bothered they have been by 20 symptoms consistent with the *DSM-5* diagnostic criteria for PTSD, with item responses ranging from 0 (not at all) to 4 (extremely). The items are summed so that higher scores indicate greater severity of PTSD symptoms. The PCL-5 has demonstrated good internal consistency, test-retest reliability, and convergent and discriminant validity. A cutoff score between 31 and 33 indicates clinically significant symptoms.

Patients will be asked about alcohol and substance use using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) developed for the World Health Organization. The ASSIST has demonstrated good concurrent, construct, and discriminative validity, as well as test-retest reliability [83,84]. Patients will report on alcohol and nonprescription drug use at each time point. The ASSIST includes 8 questions to assess use frequency, severity, and related problems. Items are summed so that higher scores indicate a greater risk of problems associated with use and cutoff scores that indicate low-, moderate-, and high-risk stratification.

Plan of Analysis

Regarding the longitudinal, observational study of patients, quantitative data will be viewed graphically and analyzed descriptively. Qualitative open-ended responses to questions will be summarized into common themes or content analyzed, as appropriate. The rates of recruitment of at-risk patients will inform the sample size needed and length of data collection periods for a full-scale trial. Feasibility of retention will be indicated by 80% follow-up rates with participants. We will examine the feasibility of collecting self-report and EHR data linked to patients and the feasibility of locating and pulling EHR data related to suicide-prevention services and outcomes in a data warehouse. Problems with feasibility will be addressed and incorporated into the full-scale trial planning.

Results

Project WISE was funded in July 2019. As of September 2021, we have completed data collection and preliminary analyses for the focus groups (N=27) and usability testing (N=3). We anticipate that the publication of these findings will be in spring 2022. Workflow observation of nurses on the unit will occur during aims 3 and 4. We will begin enrolling nurses and patients for aims 3 and 4 in November 2021, and we anticipate the completion of data collection by November 2022.

Discussion

Principal Findings

Project WISE is a response to the increasing rates of suicide in the United States and calls for health care settings and providers to play a greater role in suicide prevention [5,85]. The findings will inform the development of technology-enhanced training in suicide safety planning and the design and procedures for a fully powered cluster randomized trial to evaluate the impact of this training for nurses on patients' suicide-related outcomes. In all phases of the research, Project WISE takes a pragmatic approach, both in terms of what is developed and deployed as well as how the impact of the training on patients will be evaluated. There are several pragmatic considerations for a

future trial design. This includes planning for a design that randomizes medical, surgical, and trauma units by cluster and the collection of data at the unit level. Although EHR data are highly pragmatic, procedures for collecting these data can vary greatly by health care system and setting [86]. This pilot research will provide critical insight into how best to capture data from the local hospital data warehouse for population-level assessment of service delivery targets and patient outcomes. Patient-reported outcomes are frequently collected alongside EHR or administrative data in pragmatic trials. We will collect patient-reported outcomes in a future trial and will pilot pragmatic web-based longitudinal data collection procedures. This includes using a self-report measure of suicidal ideation and behavior previously used in web-based research and piloting both independent and interview-based completion of surveys. Finally, recruiting patients using the C-SSRS triage version screening data has pragmatic appeal in the study site as nurses will have this information available in routine care with a usual care workflow to address patient safety concerns. We recognize that enhancing usual care by having nurses engage in suicide safety planning may not be readily generalized to other hospitals without the existing infrastructure for suicide risk screening.

Project WISE is situated within a larger movement to improve the population impact of behavioral health care through alternative models of service delivery. The challenges of reaching the full population of people in need and the disparities in received care among racial or ethnic minority populations are well-documented [87,88]. This movement has gained even greater momentum in the recent context of the COVID-19 pandemic, which has led to societal- and individual-level changes such as increased social isolation, unemployment, and fear of contracting the virus, which are expected to result in a greater need at a population level to help with depression, anxiety, substance use problems, and suicidality [89,90]. A service delivery model that Project WISE aligns with is integrated care. Integrated care refers to patients receiving behavioral health and medical care within the same service setting and is known to reduce access and stigma barriers by serving patients where they are already being seen [91]. Consistent with the integrated care model, Project WISE encourages providing some suicide-prevention services in the hospital setting, thereby not requiring patients to make it to outpatient referrals before getting help with suicidality. As many suicidal patients will not make it to outpatient referrals [92], safety planning with their nurse may be the only immediate practical help with suicidality these patients receive.

Project WISE also promotes a task-shifting approach, which moves the intervention delivery to health care workers with fewer mental health care qualifications but who can be trained in a short period to effectively deliver these interventions [93,94]. Task-shifting increases the availability of resources by reducing reliance on specialty providers who are generally costlier and less available. Inpatient medical, surgical, and trauma care nurses are already on the frontlines working closely with patients with behavioral health needs, and there is increasing recognition that nurses want and need additional training to effectively support these patients [12,95]. Engaging patients in suicide safety planning does not require having advanced mental health training, and as a brief intervention, it is particularly well-suited for a task-shifting approach in a hospital setting with nurses. The premise of Project WISE is that nurses who are already screening for suicidality, working closely with patients, and helping patients prepare for discharge from the hospital are ideally positioned—with some additional support and education—to engage patients in safety planning.

Project WISE was born out of research on how to effectively and pragmatically train frontline trauma center providers in brief evidence-based counseling interventions [52,93,96]. From these experiences, it was clear that the gold standard training models developed through implementation science [32] could be challenging to implement in routine care environments and that accessible, flexible, and efficient skill-building approaches are needed. This need led us to harness novel artificial intelligence–based technologies for the skill-building components of the Project WISE training. Advances in computing power have allowed the field of artificial intelligence to flourish in the past 20 years, and the use of artificial intelligence is quickly becoming normative across medicine for a variety of purposes [97,98]. Although these technologies can be costly to develop initially, they can be highly pragmatic and cost-effective for subsequent deployment [99]. The Lyssn Advisor technology is past the initial development phase and is being deployed in outpatient behavioral health settings, with ongoing research to evaluate its impact [39,41]. Advances in study technologies are ongoing. Project WISE technologies currently focus on training in general counseling skills, also known as *common factors*, that are important across counseling or psychological interventions [44]. However, applications of the automated coding technology are now being developed to assess the quality of the unique aspects of interventions, such as cognitive-behavioral techniques, that are believed to also cause change in patients and improvement in patient outcomes [100]. Future development on the quality of suicide-prevention interventions such as safety planning may become available and incorporated into future research.

To ensure that nurses will engage with the Client Bot and Lyssn Advisor technologies, Project WISE incorporates user-centered design principles and methods, such as usability testing. However, the role of user-centered design is integral to the overall approach of the research. In particular, Project WISE aims to integrate the methods, models, and principles from user-centered design and implementation science. Implementation science is the study of processes and strategies that integrate evidence-based interventions into usual care settings, and provider training is one of the common and well-studied implementation strategies [101]. User-centered design is the process of designing products with the involvement of those who will use the product and incorporate their needs and preferences into the design [102]. Both fields are concerned with getting innovations into routine practice and appreciate the importance of the intervention delivery context. However, an important difference is that implementation science has traditionally focused on how to move innovations into routine practice after the innovation has been developed, whereas user-centered design does so during the development process. Project WISE takes the stance that the implementation strategy

of training must itself be designed with input from the end user while taking context into consideration. The planned research ensures that nurses' perspectives and hospital setting constraints are integral to developing and deploying the training.

Although not an explicit focus of Project WISE, findings from implementation science also underscore that training is necessary but insufficient to ensure that providers are able to deliver a high-quality, evidence-based intervention over time, a problem that can be assuaged with occasional feedback on performance or refresher training [32]. The automated coding technology used in Project WISE can be harnessed for this purpose, and future research could examine how to most effectively use the technology specifically for the purpose of managing drift. The problem of drift speaks to the potential need for booster training, and the intention behind the workplace integrated training model of Project WISE is to make such booster sessions readily accessible.

Conclusions

Project WISE includes developmental and pilot research for a technology-enhanced skills-based training that can be integrated into the routine workflow of nurses to support them in engaging medical, surgical, or traumatically injured inpatients in a brief suicide-prevention intervention. Project WISE is designed to uncover the challenges and opportunities in engaging nurses in e-learning training, as well as the feasibility of a future pragmatic trial. Therefore, the procedures and components of the resulting full-scale trial may look different from those proposed in this pilot research. Regardless, much will be learned about suicide prevention with hospitalized patients, the role of nurses in this work, and how nurses engage with novel training technologies. As such, Project WISE is expected to help further the national agenda of implementing suicide prevention in health care settings and inform best practices for meeting the needs for provider training that will be required to reach this goal.

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Authors' Contributions

All authors made substantial contributions to the conception and design of the research detailed in the study protocol. DD drafted the manuscript, and KAC provided a critical review of the manuscript. All authors reviewed the final manuscript.

Conflicts of Interest

DCA, MJT, and TH are cofounders with equity stakes in the technology company Lyssn, which is focused on tools to support training, supervision, and quality assurance of psychotherapy and counseling.

Multimedia Appendix 1
NIMH Peer-Review Summary Statement.
[PDF File (Adobe PDF File), 159 KB - resprot_v10i12e33695_app1.pdf]

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Abbreviations

ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test
C-SSRS: Columbia Suicide Severity Rating Scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ED: emergency department
EHR: electronic health record
PCL-5: Posttraumatic Stress Disorder Checklist–5
PTSD: posttraumatic stress disorder
SITBI-R: Self-Injurious Thoughts and Behaviors Interview–revised
SUS: System Usability Scale
TDF: Theoretical Domains Framework
WISE: Workplace Integrated Support and Education

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Protocol

Co-designing an Adaption of a Mobile App to Enhance Communication, Safety, and Well-being Among People Living at Home With Early-Stage Dementia: Protocol for an Exploratory Multiple Case Study

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Abstract

Background: There is a growing interest in using mobile apps to support communication, safety, and well-being. Evidence directly from people with dementia regarding the usability, usefulness, and relevance of mobile apps is limited.

Objective: This paper describes the protocol of a study that will evaluate an app designed for supporting communication, safety, and well-being among people living with dementia. The study aims to understand if the app can enhance safety through improved communication among users.

Methods: The study will use participatory qualitative methods over 3 cycles of evaluation with co-designers (service users, their families, and care practitioners). The study will be developed in partnership with a specialist home care service in England. Purposive case selection will be performed to ensure that the cases exemplify differences in experiences. The app will be evaluated in a walk-through workshop by people living with early-stage dementia and then trialed at home by up to 12 families in a try-out cycle. An amended version will be evaluated in a final walk-through workshop during cycle 3. Data will be collected from at least 4 data sources during the try-out phase and analyzed thematically. An explanatory multiple case study design will be used to synthesize and present the evidence from the three cycles, drawing on the Normalization Process Theory to support the interpretation of the findings.

Results: The study is ready to be implemented, but it was paused to protect vulnerable individuals during the COVID-19 pandemic in 2020. The findings will be particularly relevant for understanding how to support vulnerable people living in the community during social distancing and the period following the pandemic as well as for providing insight into the challenges of social isolation that arise from living with dementia.

Conclusions: Evaluating a mobile app for enhancing communication, safety, and well-being among people living with dementia contributes to the key ambitions enshrined in policy and practice—championing the use of digital technology and supporting people with dementia to live safely in their own homes. The study will involve co-designers living with dementia, so that the voices of service users can be used to highlight the benefits and challenges of assistive technology and shape the future development of apps that enhance safety by improving communication.

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KEYWORDS

design research; co-design; dementia; mobile app; communication; safety; mobile phone

Introduction

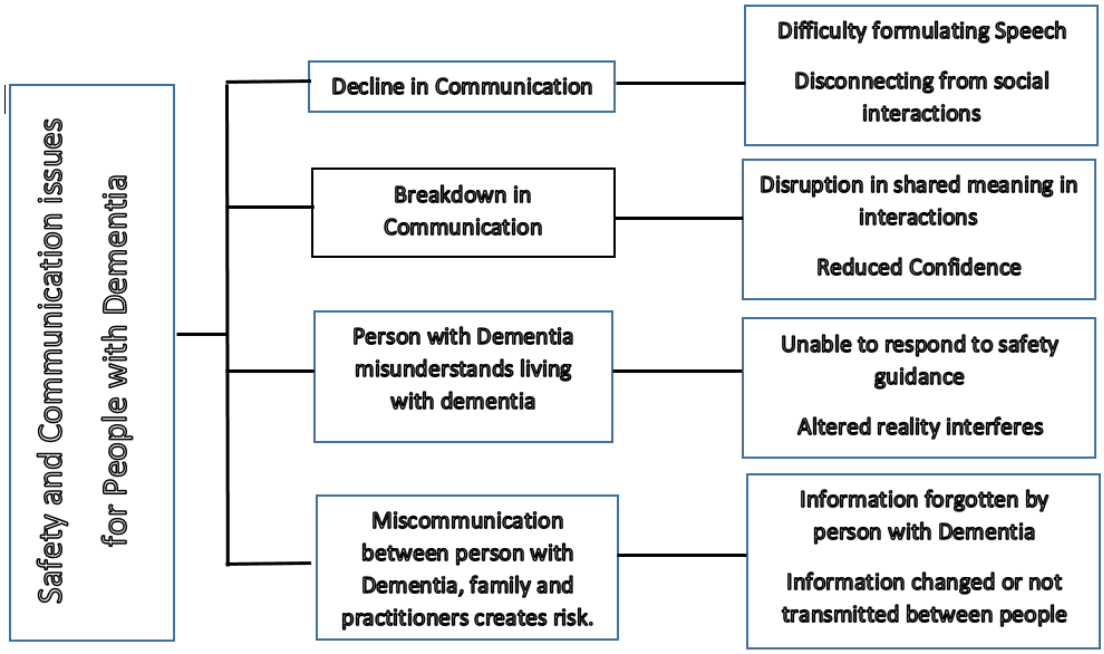
Background

This paper presents the protocol of a study that will examine an app that is used and managed by people living with dementia and their families to improve communication and thereby reduce risks and enhance safety. Many people living with dementia have complex health and well-being needs that require carefully balanced support plans that need to be implemented across multiple settings where care takes place [1]. Complicated care regimes involving a range of people, together with variable or deteriorating cognitive abilities that affect communication, can pose significant risks for people living with dementia. Confusion can be compounded by complex health and social care systems that are difficult to navigate [2,3], and this can add to potential risks to safety. Minimizing the risks associated with the poor management of health among people living with dementia is a priority for governments [4] and family carers [5]. The rapid development of digital technology has enhanced timely communication in society and offers innovative ways to support communication, safety, and well-being for older people [6,7]. Previous studies that investigated the role of digital technology in supporting safety for people living with dementia focused mainly on passive monitoring for people with late-stage dementia [8]. Fewer examples of interventions for people living with dementia take account of the outcomes that they and their families identify as priorities [5]. In research that has gathered user views of safety in primary care, people have identified the importance of basic physical needs, such as being clean, comfortable, safe, and secure at home, but have also emphasized social and emotional concerns, such as feeling respected and being able to see, hear, and understand in order to communicate with others [9].

Safety for People Living With Dementia

Dementia is a neurological condition that is typified by a decline in brain function and structure and affects cognitive processing, such as memory, communication, and the control of physical movement [10]. There are different forms of dementia, and these are characterized by specific symptoms and the progression of the disease. However, the characteristics of progressive confusion, difficulty with managing routine activities, and limited communication are always evident and are often associated with the reduced awareness of risk and increased tendency to have accidents. For example, in 2012 to 2013, 18% of short-stay emergency admissions to hospitals among people living with dementia in England were related to injuries [11]. A number of safety issues have been reported in the literature [12], including injuries (eg, those related to falls, the ingestion of dangerous substances, sharp objects, fires and burns, etc), behaviors (eg, the act of wandering and getting lost, the inability to respond rapidly to a crisis, aggressive behavior, etc), and the misuse of medication [13]. The progressive nature of dementia, together with the process of distancing oneself from social interaction (which is linked to limited cognition and communication), may deepen an individual's vulnerability and susceptibility to compromised safety, as illustrated in Figure 1.

Figure 1. The relationship between communication issues for people living with dementia and safety.



The principal management of the condition involves alleviating the symptoms in order to maintain an active life, so that people living with dementia can frequently continue to live independently and safely with support from family and friends in their own homes [14]. Thus, there has been a shift in emphasis from finding a cure for dementia to seeking life-enhancing strategies for supporting people with dementia from within their homes (ie, strategies that are based on the unique contexts of their lives). Such an approach emphasizes relationships and interactions with family and the wider community, as embodied in the concept of personhood [15,16] and relationship-centered care [17]. Service users value positive and trusting relationships with care professionals and effective communication when they consider patient safety in primary care [9] and endorse the importance of enhancing these factors for people living with dementia.

Implications of Communication Difficulties for Safety Specific to People Living With Dementia

Relationship-centered care depends on effective interaction and communication between people living with dementia and those in their social network; this includes interactions among professionals, formal carers, family, and friends [18]. The cognitive deficits that are present in people living with dementia will always be associated with declining language and communication skills, with distinctive difficulties and strengths being evident in the early, middle, and late stages of dementia (Textbox 1). Early-stage dementia [19]—a term that is frequently used to refer to people who are at the beginning stage of cognitive impairment, irrespective of the type of diagnosis—is characterized by mild problems in communicating as well as forgetfulness. These occur in the context of continuing independence in daily living [20]. Specific patterns of communication difficulties that are linked to types of dementia have been identified [21,22], but 3 general features need to be considered when developing an intervention to improve communication. First, communication is a social act that depends on interaction and conversation rather than on a simple transaction of information (ie, receiving information from and providing information to people living with dementia) [23]. Communication breakdown results from the interplay between two individuals—an individual with declining language skills and their conversation partner—suggesting that an intervention must enhance the interactions between people living with dementia and others in their social world. This applies to both verbal and written communication. Second, changes in sensory skills, such as visual and auditory acuity, affect the way that communication is scaffolded [23]; it would be a mistake to assume that audio and written words, for example, automatically augment communication. Third, people living with dementia undergo changes in how they experience reality, such as increasing confusion and disorientation as the condition progresses, that affect how they interpret the world. This also affects their ability to understand what they themselves, as well as people in their social network, say. Enhancing communication to support patient safety has been identified as 1 of the top 10 priorities by care practitioners and service users [24]. However, there is little empirical or theoretically backed evidence underpinning the best approaches to designing an intervention that supports communication with people living with dementia [23,25] and enhances safety [26].

Textbox 1. Characteristics of communication difficulties and strengths in dementia [23].

Communication and cognitive difficulties

- Early-stage dementia
  - Mild difficulty with remembering names and places
  - Difficulty with abstract language and conversation
  - Mild difficulty with memory and visuospatial activities
  - Occasional lapses in attention
- Middle-stage dementia
  - Increasing difficulty with word finding and the reduced use of "content" words
  - Difficulty with understanding complex instructions
  - Increasing difficulty with memory, attention, and the maintaining of a topic of conversation
  - Difficulty with organizing and planning
- Late-stage dementia
  - Significant difficulty with expressing needs
  - Inappropriate verbal and vocal productions
  - Lack of any speech in some cases
  - Severe difficulty with understanding spoken language
  - Severe memory difficulties
  - Difficulty with maintaining attention

Communication and cognitive strengths

- Early-stage dementia
  - Talks in full sentences and maintains conversation appropriately
  - Maintains an understanding of concrete language
  - Aware of difficulties
- Middle-stage dementia
  - Conversational turn-taking is maintained
  - Able to read aloud and understand familiar written phrases
  - Maintains familiar, overlearned skills such as brushing hair and drinking from a cup
- Late-stage dementia
  - Appropriate affective responses to sensory stimuli and music
  - Able to cooperate with appropriate cues (touch, vision, and emotion)

Dementia and Assistive Technology

Assistive technology has become a central element of policy and guidance for improving the care of people living with dementia [4,27,28], although issues of adoption by people living with dementia remain challenging [29]. Assistive technology can operate as an aid for maintaining or improving a person's functioning or independence [30]. The Alzheimer's Society [31] suggests that these technologies can serve the following three roles: (1) supportive technologies that enable people to complete tasks, (2) responsive technologies that manage risk and raise alarms, and (3) preventative technologies that prevent harm and raise alarms. Assistive technologies can take the form of simple low-tech equipment, such as walking aids, or high-tech aids that make use of digital technology to offer support.

The largest growth in the use of assistive technology for older people has focused on safety and security in the community [29]. However, these technologies often come in the form of passive devices, such smoke detectors, that do not require participation by people living with dementia. Studies investigating assistive technologies that require active involvement and engagement with devices have indicated that people living with dementia do not use the safety-related features of assistive technology devices. Even when a digital assistive

device has been codeveloped with people living with dementia, there appears to be a disparity between acceptance and use [32,33]. A recent scoping review reported on the importance that older adults place on expressing their identity as one of independence, self-reliance, and competence, which influences their decisions about adopting technological solutions [34]. The cultural meaning attached to digital devices is evident in society; one item (eg, a smartphone) can symbolize independence and modernity, while another (eg, alarms) may symbolize stigma and dependence [34]. Using devices may be perceived by some people as an action that reinforces negative identities and ageist stereotypes [35].

Smart mobile and wearable technology, in the form of apps, can help overcome any issues of user acceptability resulting from assistive technology being "concealed" in everyday technology such as smartphones. Such integrated technology therefore allows for the real-time monitoring of health variables and social aspects of an older person's life [36]. Taken together, these characteristics offer promising outcomes. However, the proliferation of apps for health care has not been matched by robust research, and major criticisms have been aimed at the limited evaluation of clinical outcomes [30,37]. Principles for developing and applying app technology are emerging [30], with personalization being expressed as a priority [30,38]. Other essential considerations include the quality of the content, usability, the matching of apps to users' health literacy levels, and security and privacy issues [39].

Hear Me Now App

In England, the National Health Service has created a library of apps and web-based tools that aim to help people manage their health and well-being [40]. They have been approved in terms of clinical safety, data protection, security, and usability. However, at the time of writing this paper, there are only 2 apps in this library that are specific to dementia. Although a general web search indicates a proliferation of apps, few have been evaluated [41]. The Hear Me Now (HMN) app (formerly the My Health Guide app) [42] was developed to help people with learning disabilities and those who support them be in control of their health and well-being information. People can use the app to explain their needs and concerns, help them understand how to act on advice given by health and social care professionals, keep and share information about themselves and their needs, and record consultations to listen to them again at a later date. Furthermore, HMN supports care practitioners in understanding an individual's needs better by providing quick access to key information that facilitates communication and interaction with app users.

Normalization Process Theory

HMN depends on interacting components, such as users' understanding; the usability of the app; and the app's adoption, which is contingent on individual, group, and organizational behaviors. It can be considered to be a complex intervention [43]. The Normalization Process Theory (NPT) was developed to improve people's understanding of how complex interventions work. The theory looks beyond the workability of systems [44] and instead looks at issues such as the effects that eHealth interventions have on the roles and responsibilities of all those involved, how interventions affect interactions between service users and care practitioners and the outcomes of service users, and implications for care practitioners. The NPT is a middle-range theory that explores issues of how interventions work in practice in more depth. It provides a framework for conducting multifaceted analyses to understand the actions and interactions influencing implementation and how new interventions and practices come to be normalized in health and social care contexts. Conversely, it can aid with the explanation of why technologies fail to be routinely adopted when they are implemented in organizational contexts [45]. There are 4 key constructs that can be applied to service users and care practitioners who use digital apps. First, the construct of *coherence* is used to describe the way individuals understand the meaning of a new technology and its associated practices. Second, the construct of *cognitive participation* explains the relational work that is needed to sustain a community of practice for a new intervention. Third, the *collective action* construct signifies the operational work required to enact new practices. Fourth, the *reflexive monitoring* construct applies to the appraisal of new practices. The NPT examines the processes of changes that occur in individual and collective behaviors and allows the dynamics of human agency to be connected to a given context. The theory has explanatory power; thus, it can be used to understand the work that is required for the adoption and integration of new interventions.

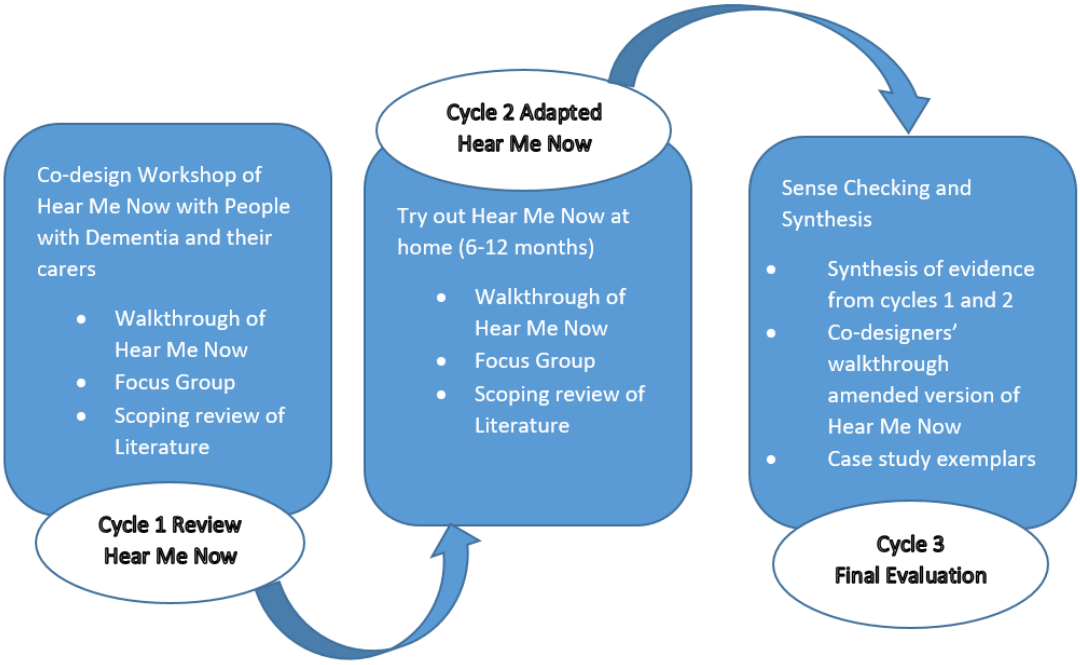
The aims of our study are to (1) evaluate the usability, usefulness, and relevance of HMN among people living with early-stage dementia who live in the community; (2) examine the benefits and challenges of using HMN to enhance the management of health, safety, and well-being; and (3) determine if adaptions are required in HMN and how these adaptations should be designed.

Methods

Study Design

We will conduct a formative evaluation based on the principles of design research [46,47] by involving co-designers (service users, their families, and care practitioners) in 3 evaluation cycles, in which data will be collected over 18 months (Figure 2). There will be a 6-month preparation phase, during which patient and public involvement and engagement strategies will be used before the evaluation commences. Co-design studies involve designers and nondesigners working together to design, or potentially redesign, a product. In this study, the digital design company Maldaba, which is experienced in designing HMN for people with a learning disability, will be working with people living with dementia, care practitioners, and researchers to redesign the app [42]. The previous evaluation of the app showed that HMN was used for creating appointment reminders, documenting information about an individual, recording medical information, and noting people's feelings. The results suggested that the app was easy to operate, but the availability of support was an important factor in the adoption and use of the app. Furthermore, users had a preference for using the app to interact and converse with individuals in their informal support networks [48].

Figure 2. Cycles of Design research Hear Me Now.



Multiple individual case studies will be used to record and report in-depth evidence of the app's usability, usefulness, and relevance among people living with dementia, and a number of sources of data (eg, interviews, demographics, analytics, etc) will be used to help us understand an individual participant's case. Yin's [49] 6-stage case study process will be used, together with other guidance [50], to support the rigor of the design. Case studies are valuable for exploratory and explanatory purposes and are suited to contemporary phenomena for which "how" and "why" questions are posed. They are particularly appropriate for research questions that are posed to understand and evaluate the complexities of implementing and adapting an existing intervention with a new group of service users. Purposive case selection will be conducted to ensure that the cases illustrate a variety of contexts. Data will be analyzed by using deductive and inductive approaches.

The research will be conducted over 24 months and involve the following steps:

- Preparation (months 1-6): develop an understanding of issues and processes with patient and public involvement and engagement strategies, negotiate arrangements with partners, obtain ethical approval, set up an advisory group, and prepare walk-through workshop
- Cycle 1 (months 6-12): the collection of data for review and the remodeling of HMN in a walk-through workshop with up to 24 co-designers (people living with dementia, carers, and care practitioners)
- Cycle 2 (months 12-18): recruiting and working with up to 12 co-designers with dementia and up to 12 people from their health and social networks
- Cycle 3 (month 18): final walk-through workshop and sense-checking event with co-designers (end-of-project workshop)
- Reporting (months 18-24): written report, dissemination with co-designers, impact activities

The Intervention: HMN

HMN is a user-led app that collates users' preferences so that users can engage with the app in a relevant and personalized way (ie, according to their own needs and experiences). App users (and their families) are able to build a customized profile containing relevant information that they can control, such as information on how best to communicate with others, personal interests and concerns, and essential information. Information can be captured and presented in different formats, such as audio, text, and visuals, and written content can be verbalized to users via the app simply by clicking the text-to-speech icon. The key features (Textbox 2) of the intervention were identified during development and evaluation with people with a learning disability [48].

Textbox 2. Key features of Hear Me Now.

App users control the content

- Users have control over how the app is used by creating boxes to store things that are important to them. Boxes can be labeled by using photos or text.

Enables flexible use

- Each box can store content that is captured as text, pictures, videos, or audio.
- Content can be created by using the app, and users can add content that is already stored on their device.
- Written content can be verbalized to users by clicking on a text-to-speech icon

Enables personalization

- The app prioritizes "important things about me," thereby enabling users to build a life story that can be shared with other people when they attend appointments or social events.
- App users can personalize the app. This includes adding a profile photo, changing the color and font size of text, creating reminders, and using an in-app personal ID number for security.

Contains an appointment facility

- The app includes an appointment facility for creating appointments.

Contains contact information and a sharing facility

- Users can record the details of friends, family, and carers and can share their boxes with anyone in their contact list. Contacts are notified via email and can log into the Hear Me Now web interface on their browser. The web interface lets contacts do the following:
  - Stay in touch with the app user's latest activities
  - Suggest content additions for the boxes they can see (app users will be able to accept or decline additions)
  - Send app users alerts (the app user will see the alert next time their app synchronizes with the server)

Able to store documents

- Documents can be uploaded to the app and stored in 1 place

Participants

Participants will be recruited, together with partners who deliver home care, from the northwest of England over 12 months based on the inclusion and exclusion criteria outlined in Textbox 3. Participants with early-stage dementia (as identified by people living with dementia and their carers) who live at home will be introduced to the study by home care practitioners, who routinely visit people with dementia living at home. They will provide study information leaflets and introduce the researchers to the families of people living with dementia who express an interest in participating in the study. The sampling will be purposive in order to have participants with varied experiences of dementia, backgrounds, and living arrangements.

Textbox 3. Inclusion and exclusion criteria.

Inclusion criteria

- Medical diagnosis of dementia
- People living with early-stage dementia
- Living in own home or extra care housing
- Experiences symptoms of memory loss and cognitive changes but lives independently
- Adequate vision and motor skills for managing a tablet computer
- Supported by family carer and/or formal carers
- General health is stable and well managed
- Able to converse in English

Exclusion criteria

- No diagnosis of dementia
- People living with late-stage dementia
- Living in a care home
- Extensive cognitive confusion
- Unable to handle a tablet computer
- Receiving no support from carers
- Experiencing regular bouts of acute illness
- Limited spoken English

As the data collected from each participant will be predominantly qualitative (data will be drawn from a number sources for detailed case studies), a total of 12 participants with dementia will be recruited, together with family members who offer support (spouses, partners, and children), formal carers, and regular care practitioners (up to 24 in total). Formal carers and care practitioners will be those who have routine involvement with the person with dementia (at least 1 contact per week).

Data Sources and Data Collection for Case-Based Evidence

Design research is conducted iteratively in collaboration with co-designers. Formative evaluations provide the opportunity to improve the design of an intervention and are integral to the design process. Three iterative cycles of review, formative evaluation, and redesign will be conducted (Figure 2) by using a range of data sources to triangulate the evidence. In the first cycle, a workshop for a walk-through of the current app will be conducted in the community with people with early-stage dementia, their carers, and care practitioners to review the current version of HMN. This will involve investigating the usability, usefulness, and relevance of the app. The walk-through method is a part of the user experience design process that is used in software development. It involves a step-by-step process in which technology users, as they deploy an app, observe practicality, note users' comments, and seek a detailed narrative of use [51].

The walk-through will be conducted remotely (where possible) with the assistance of carers and support staff. It will involve qualitative data collection methods, including the observation of app use, interviews for gathering data on individuals' experiences with using the app, and focus groups conducted via videoconferencing for examining the collective views of service users. Each set of data will be analyzed thematically. Potential changes and recommendations for the redesign will be discussed and enacted by the app developers [42].

The second cycle will involve 12 people with dementia who live independently and associated family members and care practitioners using the app during everyday life. Each case will be contacted (2 contacts over 3-6 months) to collect a range of data as participants use the app within their homes. This will be done remotely or by care practitioners visiting families (Textbox 4). The third cycle will involve the analysis of the data from cycle 2 together with the data generated at the final walk-through and sense-checking workshop, which will include people living with dementia, their families, and care practitioners.

Textbox 4. Summary of data sources and data collection details for cycle 2.

Usage logs

- Usage data (the frequency of use and length of time using the app) will be collected from all participants during the data collection period (in collaboration with the developers).

Semistructured interviews

- One-to-one semistructured interviews with people living with dementia, people in their social networks, and professionals will be conducted at 2 time points to assess the initial and ongoing use of and experiences with the app over a time frame of up to 12 months. These interviews will be adapted appropriately to the cognitive status of individuals with dementia and undertaken by using videoconferencing software or phones to ensure participants' safety during the pandemic. Researchers will undertake appropriate training to conduct interviews with people living with dementia. Interviews will be recorded and uploaded to NVivo (QSR International) for automated transcription.
- The interviews will be conducted by using a topic guide, which will be based on the objectives of the Hear Me Now app, along with questions for exploring the potential of the app to facilitate communication with health and social care professionals. The topic guide will be used flexibly in interviews, and emerging themes will be explored in subsequent interviews in accordance with the conventions of qualitative data collection.

Observation of app use

- In order to obtain contextual data on people using the app in different contexts, we aim to observe up to 12 people living with dementia (with or without key people in their social networks) in each setting (homes and extra care housing). We will observe participants using the app via videos of a prearranged visit when people living with dementia receive an episode of care. Observations will focus on the interactions between people living with dementia and a regular formal carer or professional, such as the admiral nurse. These will be carried out by conducting remote data collection and analyzed in a structured format. The analysis will be augmented by using field notes from the initial observations of video interactions.

Review of documents uploaded to app

- Documentary data will be collected in the form of photographs, drawings, and other visual data. Participants will decide whether they want to produce these materials for research purposes, and if so, they will choose the formats that are the most relevant to them. More formal documents, such as relevant notes of meetings (case conferences) or action plans, will be collected. Documentary data will be summarized by using structured forms that are based on the key features of Hear Me Now.

Data Analysis

The qualitative data analysis will be conducted via an abductive approach [52], thereby enabling a continuous dialogue among theory, data from users' experiences, and existing models of engagement. This approach allows for the conduction of inductive and deductive analyses, which ensure that findings are based on both new empirical evidence and previous evidence. This will align well with the iterative design process and the cycles of evidence collection and redesign for the HMN app. The analysis will be conducted by two researchers who are trained and experienced in qualitative research. Interviews and focus groups will be audio recorded, transcribed, and analyzed thematically to identify key themes [53]. Participants' use of the app during interactions with family and care practitioners in their usual settings will be recorded via direct, nonparticipant observation by using a structured template and field notes. These will be also be analyzed thematically [54]. NVivo (QSR International) software will be used to support the management and analysis of data. In keeping with qualitative research conventions, the involvement of the user participants will provide the opportunity to conduct sensemaking exercises to assure the participants of the trustworthiness and credibility of the data analysis and interpretation. The app developers will form part of the research team; they will provide their expertise to support the interpretation of findings, identify areas for redesign, and prepare amended prototypes for evaluation during the cycles of the design research process. A framework analysis will be conducted to collate and analyze the data for the case studies in order to describe, explain, and compare the similarities and differences among cases. The comparison with NPT constructs should provide further depth to the conceptual analysis, and this will contribute to the final evaluation of the HMN app for people living with dementia.

Patient and Public Involvement and Engagement

The study will use participatory methods for involving patients and the public in the study as part of the design process. For the purposes of maintaining governance and ensuring the involvement of professionals in the co-design (in keeping with the 2018 guidance from the National Institute for Health and Care Excellence) [55], we will establish a "critical friends" group for guidance in designing the study. This will consist of a person living with dementia, a care practitioner, and an academic experienced in dementia research. The trustworthiness and credibility of the findings will be enhanced through the involvement of external partners in peer-review and sense-checking research plans, the dissemination of findings, and data interpretation. Specific tasks will include commenting on the study design and study documents, developing and conducting the data collection and analysis processes, and disseminating the findings.

Ethics and Governance

We are following ethical guidance from the University of Manchester ethics committee and have obtained approval in accordance with their standardized system. The recruitment, data transfer, and data storage processes are in accordance with the legislation and guidance from the research institute. Written informed consent will be obtained from all participants, and

arrangements are in place for anonymizing and securely storing obtained data. The study participants will be at the early stage of dementia and will have the capacity to consent. If the participants' capacity to consent changes during the research cycles, researchers will adopt the Mental Capacity Act Code of Practice and work alongside experienced care practitioners to ensure that appropriate checks are in place. The study will be managed on a day-to-day basis by a project management group consisting of experienced researchers who will meet monthly to make plans and monitor progress. A "critical friends" group will be established to provide guidance for the development of study materials, conduction of analyses, and interpretation and dissemination of findings.

Results

Digital technology is developing rapidly, and using apps to manage the many elements of daily life is becoming routine. Given the context of social distancing, which was introduced to combat the COVID-19 pandemic in 2020, it is particularly urgent to understand the views of people living with dementia and those in their social and care networks regarding the use of an app that focuses on supporting communication, safety, and well-being. Our study will enable us to evaluate HMN's usability and its value for people living with dementia and identify adaptions for improving the app's implementation. The study will consider how using the app might contribute to communication and potentially contribute to improving safety through a personalized approach to recording health and well-being issues that are important to people living with dementia in the community. The study will also contribute to methodological innovations, as it will involve illustrative, NPT-informed case studies of how an app is used by people at home. This will provide the basis for an explanatory model of the relationship among factors such as communication, social and health care networks, cognitive strengths and weaknesses, and the enhancement of safety in the community.

Ethics approval was obtained from the University of Manchester Ethics Committee (reference number: 2020-8665-13751). Participants will give written consent to participate in the study and consent to the publication of anonymized data. Supporting data will be made available upon request from the corresponding author.

Discussion

Evaluating a mobile app for enhancing communication, safety, and well-being among people living with dementia contributes to the key ambitions enshrined in policy and practice—championing the use of digital technology and supporting people with dementia to live safely in their own homes. The study will involve co-designers living with dementia, so that the voices of service users can be used to highlight the benefits and challenges of assistive technology and shape the future development of apps that enhance safety by improving communication.

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Authors' Contributions

The design of the study was developed by all of the authors. KD and BNO jointly led the drafting of the manuscript. All of the authors critically reviewed the drafts of the paper and agreed on the final version.

Conflicts of Interest

None declared.

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Abbreviations

HMN: Hear Me Now
NPT: Normalization Process Theory

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Protocol

Investigating the Implementation of SMS and Mobile Messaging in Population Screening (the SIPS Study): Protocol for a Delphi Study

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Abstract

Background: The use of mobile messaging, including SMS, and web-based messaging in health care has grown significantly. Using messaging to facilitate patient communication has been advocated in several circumstances, including population screening. These programs, however, pose unique challenges to mobile communication, as messaging is often sent from a central hub to a diverse population with differing needs. Despite this, there is a paucity of robust frameworks to guide implementation.

Objective: The aim of this protocol is to describe the methods that will be used to develop a guide for the principles of use of mobile messaging for population screening programs in England.

Methods: This modified Delphi study will be conducted in two parts: evidence synthesis and consensus generation. The former will include a review of literature published from January 1, 2000, to October 1, 2021. This will elicit key themes to inform an online scoping questionnaire posed to a group of experts from academia, clinical medicine, industry, and public health. Thematic analysis of free-text responses by two independent authors will elicit items to be used during consensus generation. Patient and Public Involvement and Engagement groups will be convened to ensure that a comprehensive item list is generated that represents the public's perspective. Each item will then be anonymously voted on by experts as to its importance and feasibility of implementation in screening during three rounds of a Delphi process. Consensus will be defined a priori at 70%, with items considered important and feasible being eligible for inclusion in the final recommendation. A list of desirable items (ie, important but not currently feasible) will be developed to guide future work.

Results: The Institutional Review Board at Imperial College London has granted ethical approval for this study (reference 20IC6088). Results are expected to involve a list of recommendations to screening services, with findings being made available to screening services through Public Health England. This study will, thus, provide a formal guideline for the use of mobile messaging in screening services and will provide future directions in this field.

Conclusions: The use of mobile messaging has grown significantly across health care services, especially given the COVID-19 pandemic, but its implementation in screening programs remains challenging. This modified Delphi approach with leading experts will provide invaluable insights into facilitating the incorporation of messaging into these programs and will create awareness of future developments in this area.

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KEYWORDS

mobile messaging; digital communication; population screening; SMS; implementation

Introduction

In England, there are currently 11 different population screening programs that are involved in the detection of conditions as varied as abdominal aortic aneurysms and thalassemia [1]. Each year, over 10,000 lives are saved as a result of these different screening programs [2]. However, screening services are facing increasing challenges in the way they operate. Governance issues, poor interoperability of systems, and capacity concerns have negatively impacted on the effectiveness of services [3]. In 2018, these factors all contributed toward a national incident, where 120,000 women failed to receive their final mammogram appointment [4]. Moreover, there are now increasing concerns regarding falling uptake of screening invitations for conditions such as breast cancer across the United Kingdom [5]. Similar trends are also seen across the world, including in the United States and Canada [6].

Collectively, screening programs in England invite 15 million people annually; however, on average, only 10 million people take up the invitation [7]. This performance differs significantly between the individual programs. While diabetic eye screening is consistently well attended, uptake of cervical cancer screening is falling, with a 6.8% lower uptake in 2020 than in 2019 [8,9]. These trends are likely to be exacerbated as a result of COVID-19, in which screening services were ceased, leading to a backlog of millions of tests [10]. One way in which some services have attempted to address these concerns is by using mobile messaging.

Mobile messaging encompasses a range of text and multimedia messaging platforms through mobile devices and includes SMS and multimedia messaging service. It has been widely used in several industries, including banking and retail, and is often seen by the public as a less intrusive and more convenient means for communication, as compared to phone calls [11]. In one survey, 69% of respondents across all age groups wanted to be able to contact businesses by text [12]. Within health care, its use as an adjunctive means of communication between health care professionals and patients is also growing. Both primary and secondary care services use messaging in a variety of ways, including confirming appointments, as reminders, and for health promotion campaigns. Moreover, as with the COVID-19 pandemic, mobile messaging has been shown to be an effective and acceptable means of providing public health information, when direct access to hospital or health care services is limited [13]. Within screening programs, the use of mobile messaging, predominantly SMS, is well established as a reminder tool. SMS reminders in breast cancer screening have been shown to increase attendance by 5% [14]. Furthermore, research has shown that by altering the content of these messages it may be possible to improve declining uptake rates [15]. The formal cross-program adoption of mobile reminders is, therefore, one of the foremost recommendations in the United Kingdom's Independent Review of Adult Screening Programmes [7].

Adopting mobile messaging, whether for reminders or health promotion in this context, however, provides a unique set of challenges. Unlike individual general practitioner (GP) practices, regional screening hubs will send hundreds of thousands of messages annually [16]. These large target populations consist of a diverse range of people with differing health literacy levels, awareness of screening services, and communication needs. There are already concerns that mobile messaging may exacerbate inequalities among different socioeconomic groups, thereby creating a technological divide; on a population scale, this possibility is much greater [17]. Furthermore, in some programs, screening is not undertaken through the GP practice or a known health care service, but by a screening hub. An individual may be contacted by a service they have never interacted with previously and, therefore, may lack trust in the provenance and content of the message. Moreover, if messages are not sent from the GP practice, this also introduces potential security issues that need consideration, as it is not always possible to verify mobile numbers of previous nonattenders or new invitees. Above all, screening is a choice, and a clear balance is needed between facilitating patients to attend screening, but not coercing them to attend. The message content, therefore, should also differ from messaging for outpatient appointments, which may have been requested directly by the patient or by proxy. There is, however, a paucity of guidance about how screening services can use mobile messaging appropriately.

Of the few published frameworks on the use of mobile messaging in health care, the predominant focus is on the use of mobile messaging in a single service (eg, a GP practice) or on the provision of general content-based recommendations only [18,19]. Therefore, they fail to provide guidance on the aforementioned breadth of areas of contention faced by population screening programs. The aim of this study is to use a modified Delphi approach to determine the opinions of experts in the fields of preventative care, screening, health communications, and academia, and to draw a consensus on the key issues and ways mobile messaging can be implemented into population screening. Through this process, we will aim to create an expert-derived list of current recommendations for services, as well as highlight areas to inform the future direction of mobile messaging in this context. This study is registered on the Open Source Framework as the SMS and Mobile Messaging in Population Screening (SIPS) study [20].

Methods

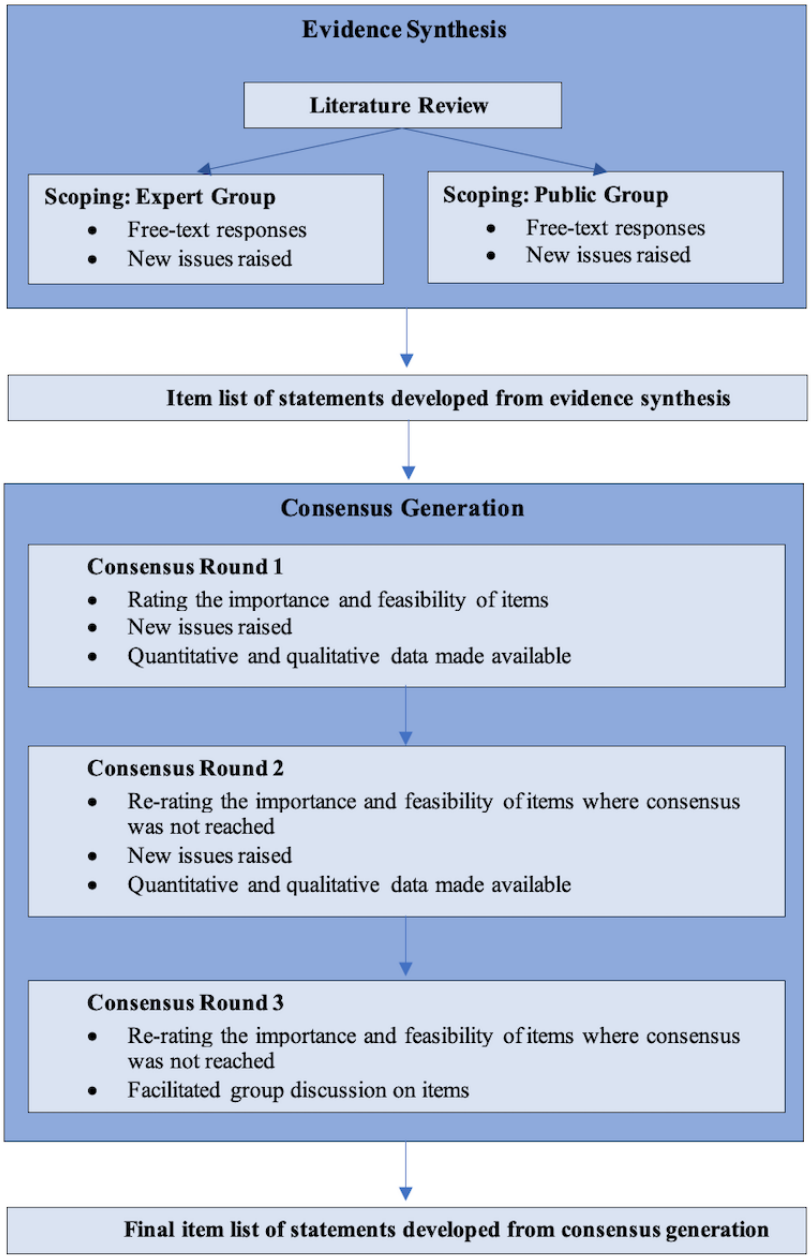
Study Design

The study was developed using a modified Delphi approach, which aims to integrate opinions from stakeholders and experts in the field [21]. Delphi exercises have been used in a variety of health care and technology contexts, such as medical artificial intelligence reporting guidelines [22]. Unlike other consensus group methods, such as the nominal group technique (NGT), Delphi methods lend themselves to being conducted remotely, which is a necessity given current social distancing constraints [23]. Moreover, unlike the NGT, the Delphi technique can be used to synthesize the viewpoints of a large group of experts from a variety of backgrounds, as is required with several different population screening programs [24]. While there are concerns regarding the reproducibility of the results from Delphi studies, the attrition during the process, and issues with validity,

it remains one of the most widely used means of deriving expert-level consensus [25]. One of the reasons for these criticisms is the paucity of best practice guidance or standardization when undertaking Delphi methodology. It is accepted, however, that through an iterative process, in which individuals are sequentially asked to rate items and guided to amend these ratings in light of feedback from the collective response, the Delphi process can effectively derive consensus. By recruiting individuals with a breadth of related experience and ensuring the anonymity of responses, it enables a wide range of results applicable in several allied fields to be elicited, without a single voice or group dominating [26]. This is particularly important with population screening in which each program has its own messaging infrastructure, delivery system, and needs. If the results were to favor one of the groups more than the other, ultimately, it would make the findings of this study less applicable.

The procedure for this modified Delphi study will be undertaken in two parts: evidence synthesis and consensus generation (Figure 1).

Figure 1. Diagram demonstrating the stages of the study, including the primary outcome.



Ethics

The Institutional Review Board at Imperial College London has granted ethical approval for this study (reference 20IC6088). All public and expert participants will be required to provide informed consent for each part of the study and have the freedom to withdraw consent at any stage.

Part 1: Evidence Synthesis

Overview

To develop a list of items of interest for experts to deliberate on for the consensus rounds, a literature review will be undertaken. This will be supplemented by an online expert and public scoping exercise.

Literature Background

A review of literature published from January 1, 2000, to October 1, 2021, in both academic and nonacademic forums was undertaken to inform the development of this protocol and determine the areas that require addressing in the consensus. A search of PubMed, MEDLINE, Embase, and Google Scholar databases was undertaken using various terms, including the following: "mass screening," "population screening," "abdominal aortic aneurysm," "diabetic retinopathy," "cervical cancer," "cervical smear," "mammography," "colonoscopy," "sigmoidoscopy," "newborn hearing," "thalassemia," "sickle cell," "congenital abnormalities," "chorionic villus sampling," "amniocentesis," "lung cancer," "chest x ray" in conjunction with "mobile, cell, phone messaging," "short message service," "multimedia messaging service," and "text messages." Terms were combined using the Boolean operators "OR" and "AND," as appropriate. A full list of search terms can be found in Multimedia Appendix 1. Duplicates were removed and studies were imported into the review software Covidence. Two authors (AA and VS) independently screened titles and abstracts to check for relevance to the research question. Disagreements were discussed until resolution was reached.

Additional articles relevant to health care messaging were also found using grey literature, including publications from health care organizations, such as Public Health England, the National Institute for Health and Care Excellence, and the US Food and Drug Administration. Again, these documents were screened by the two independent authors, with disagreements discussed. Included articles were reviewed and the data were extracted to provide evidence for higher-order domains of interest relating to messaging in screening, provide individual items for inclusion into the scoping stage, and highlight areas of contention.

Scoping Exercise: Experts

An online scoping questionnaire based on evidence generated from the literature review will be undertaken to determine whether there were any notable areas of omission and areas for further consideration, and to help generate an item list for the consensus round. This scoping questionnaire will be framed according to six domains of interest elicited from the literature review: content, timing, delivery, evaluation, security, and future considerations. The scoping exercise is designed to elicit unrestricted free-text responses from individuals, with prompts given under each of the six headings to guide answers. Experts will be given the freedom to respond in any way that suits them, including providing examples of different types of messages and links to evidence to support their point. The scoping questionnaire will be delivered online independently to a group of experts (see Expert Recruitment section below), who will be encouraged to use their experience and appreciation of available guidance.

Free-text responses will then be examined using a thematic approach. Authors will first familiarize themselves with responses, sorting them according to the higher domains to which they pertained. Both authors will then independently code each response and derive recurring subthemes and disagreements. These subthemes will be discussed among the wider group of authors, and an item list will be generated. Through discussion, disagreements will be resolved on whether an item should be included or regarding the wording of a particular item.

Patient and Public Involvement and Engagement Group

Population screening messages directly impact the public. It is, therefore, important to appreciate and include the experience of members of the public, in order to highlight areas that may not have been previously addressed by experts or the existing literature. Members of the public will be recruited through the existing affiliations of authors, as well as via the online health and social care research platform VOICE. Participants will only be included if they are over 18 years of age and based within England at the time of the study. Members of the public will be asked to provide their own experiences with health care messaging within screening programs through free-text responses. This will mirror the themes from the expert questionnaire and will include jargon-free prompts, developed in discussion with representatives of the VOICE platform. Input from this Patient and Public Involvement and Engagement (PPIE) group will be used to ensure that items are relevant to the public, with the consensus list amended following this review. The responses will be mapped to the finalized item list derived from the expert consensus by two independent authors. If an item does not map onto an existing item, it will be added as an additional item under the appropriate higher domain. Quantitative data (ie, frequencies [eg, 50% stated that item X was important] and rankings [eg, item X is more important than Y]) and qualitative data (ie, summarizing quotes) will also be elicited from the public free-text responses. These will be included under the corresponding item during the consensus generation process. These public responses will be used to provide further guidance for the experts during the consensus rounds and to ensure the public perspective is included.

Part 2: Consensus Generation

Expert Recruitment

Experts recruited to participate in the scoping and consensus stages will be from a broad range of intersecting specialties, such as academia, clinical medicine, screening administration, health care consultancy, behavioral science, industry, and public and population health. Input from a diverse array of sectors ensures that findings are widely relevant and reduces the chance of omission of important areas of discussion. To be included, experts require professional experience in one of the 11 active screening programs in the United Kingdom, or in the Targeted Lung Health Checks program, which is currently being piloted. While no strict definition of an "expert" is used, authors will recruit only individuals who hold prominent regional or national roles within their field, have evidence of impact within that area, or have conducted prominent academic research into screening programs. As this study focuses on UK screening programs, and because other countries conduct screening differently, an international group of experts will not be contacted at this stage. In keeping with previous Delphi studies, no sample size calculation has been conducted, as the resultant consensus findings are related to the experience of the individuals, as opposed to the number recruited [27,28]. We plan to recruit a minimum of 20 experts across the

aforementioned specialties, as this number has previously been shown to provide reliable judgments [23]. Invited individuals will be agreed on through discussion between all authors, with disagreements discussed until these have been resolved.

Consensus Rounds

Two rounds will be conducted in order to gain consensus on the items. Specifically, participants will be asked to rate (1) the importance and (2) the feasibility of incorporating each item into mobile messaging for population screening. Importance is defined as a characteristic that is fundamental to the effective use, governance, or development of messages from or for the screening service. Feasibility is defined as a message characteristic that can be easily incorporated into the current system without significant cost, time, or logistical difficulty. Each item will be listed under one of the six higher domains. For each item, experts will respond on a 5-point Likert scale for importance (ie, 1 = extremely important, 2 = important, 3 = neither important nor unimportant, 4 = unimportant, and 5 = extremely unimportant) and feasibility (eg, 1 = absolutely feasible, 2 = feasible, 3 = neither feasible nor unfeasible, 4 = unfeasible, and 5 = absolutely unfeasible). Additionally, as not all items will be relevant to each screening program, a sixth option of "not relevant" will be added in. Question logic will ensure that if an individual selects this option, they will not be able to rate the feasibility or importance of that particular item. Within the first consensus round, data from the previous PPIE group and the National Cyber Security Centre will be provided to experts to aid their decision making.

While there is no formal accepted definition of consensus, within this study, we have predefined the threshold at 70% [29]. Items that more than 70% of experts deem "extremely unimportant" or "unimportant" and "extremely unfeasible" or "unfeasible" (scores of 4 or 5) will be excluded from subsequent rounds. Items that achieve more than 70% consensus as "extremely important" or "important" and "extremely feasible" or "feasible" (scores of 1 or 2) will be included in the final core item list for discussion. Items that do not reach these thresholds of consensus will be put forward to the next consensus round. Furthermore, participants will have the option to add free-text responses or suggestions for further items to be included, which will be available to vote on in the next consensus round. This second consensus round will have the same format as the first, but will include new items suggested from round 1. Moreover, the aggregated responses from round 1 will be made available for each item. Through this feedback on the collective response, it is hoped that consensus on the remaining items can be achieved. Items will be treated similarly to the first round, with those deemed important and feasible put forward to the final core item list. Items that are found to be important but not feasible, following the second consensus round, will be considered "desirable" and will be placed on a separate list for discussion at the consensus meeting. However, items that are voted to be feasible but not important will be excluded, given their lack of utility for screening services.

Consensus Meeting

The final round will be a consensus meeting, held online due to the current social distancing constraints. This meeting will be facilitated by the authors of the study in order to provide a structured means of interaction between individuals and to enable all members to have their voices heard. Furthermore, the use of a consensus meeting provides experts the opportunity to provide justification of their viewpoint and seek clarification where necessary. Previous research has highlighted this modification of the original Delphi methodology as more effective and collaborative [30,31]. The aim of this meeting is to develop a finalized list of important and feasible items to guide mobile messaging use in population screening programs. To achieve this objective, attendees at the meeting will first be presented with the results from the second consensus round. Any item that has not reached a consensus will then be discussed and voted on again using the 5-point Likert scales for importance and feasibility. All items that have reached a positive consensus at any point throughout the process will then be discussed further for consideration into the final recommendation. This recommendation will consist of items that experts agree are important and currently feasible for incorporating into screening program messaging. A separate list of items that are considered important but not feasible will also be included. These will be considered aspirational or desirable qualities that could guide future developments in this area.

Data Availability

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

Results

The literature review is underway. A final list of feasible and important items to consider in population screening programs will be published in 2022. In addition to publishing this work in a peer-reviewed journal, we aim to make this work available to screening services in England through presentations and online posts. In this way, we hope stakeholders will easily have access to, and be able to benefit from, the lessons derived from this study.

Discussion

The use of mobile messaging has grown significantly across health care services, especially given the COVID-19 pandemic. While its use in population screening programs (eg, as reminders) has been supported by policy makers and patients alike, the implementation of messaging remains challenging. Screening programs pose a unique set of challenges to the use of messaging regarding the content, timing, delivery, evaluation, and security of messages. Moreover, as the digital literacy of the population continues to grow, how future technologies can be integrated must also be considered. This is particularly important as messaging functionality develops further, with the increasing penetrance of technologies such as rich communication services. These services allow for more complex messaging (eg, sending location services and higher-resolution multimedia) to be undertaken and, therefore, it is increasingly important for screening services to have guidance on how best to implement them [32]. There is, however, a paucity of information regarding the application of messaging systems in screening. We hope this modified Delphi approach with leading

experts will provide invaluable initial insights into facilitating the incorporation of messaging into these programs and creating awareness of future developments in this area. Furthermore, we hope our findings will enable comparisons with screening services internationally, in order to determine the most effective means of using mobile messaging to facilitate attendance.

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Authors' Contributions

AA and VS undertook the literature search and the full-text data extraction. AA and GJ undertook the creation and conduct of the scoping item list. AA, GJ, HA, AS, and NJW all developed the methodology, recruited participants, and generated the consensus item lists. AD oversaw the conduct of the project, providing guidance and support that enabled the study to be completed. All authors have read and approved the manuscript.

Conflicts of Interest

AD is Chair of the Health Security Initiative at Flagship Pioneering UK Ltd. Flagship Pioneering had no role in the development, conduct, or analysis of this study.

Multimedia Appendix 1
Supplementary material, including search strategy for evidence generation.
[DOCX File , 15 KB - resprot_v10i12e32660_app1.docx]

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Abbreviations

GP: general practitioner
NGT: nominal group technique
NIHR: National Institute for Health Research

PPIE: Patient and Public Involvement and Engagement
SIPS: SMS and Mobile Messaging in Population Screening

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Protocol

Complicated Odontogenic Infections at 2 District Hospitals in Tonkolili District, Sierra Leone: Protocol for a Prospective Observational Cohort Study (DELAY)

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Abstract

Background: Deficits in global oral health care are paramount, and complications of odontogenic infections constitute a considerable global health problem, particularly in low-income countries. A high mortality rate has been observed for patients who have been admitted with complicated odontogenic infections to our facilities in Tonkolili District, Sierra Leone, although exact data have not been published yet. Data regarding who in this region is at risk and why are lacking.

Objective: The Dental Abscess Study (DELAY) aims to prospectively investigate morbidity and mortality from complicated dental abscesses and to analyze patients' characteristics and microbial findings to examine predisposing factors for poor outcomes. In particular, the incidence and the clinical and microbial characteristics of complicated odontogenic infections, as well as the sociodemographic data and comorbidities of affected patients, will be studied to develop improved management algorithms based on circumstance-specific factors.

Methods: Patients who present with complicated dental infections requiring hospital admission in Masanga Hospital or Lion Heart Medical Centre will be consecutively selected for possible inclusion in the study (starting on September 4, 2021) over a study period of 1 year, and individual routine follow-ups will be conducted at least 3 months after discharge. The results of standardized questionnaires will be obtained, and clinical measurements as well as medical photos will be taken. Standard laboratory tests (eg, full blood count and HIV status tests) will be performed, and pus specimens will be examined. Local treatment guidelines will be adhered to, and data on medical and surgical treatment as well as data on outcomes will be collected. The study results will be reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria. Routine follow-ups will take place at 1 and 3 months postdischarge.

Results: The DELAY protocol was endorsed by the Masanga Medical Research Unit's Scientific Review Committee on June 16, 2021, and ethical approval was granted on July 5, 2021, by the Sierra Leone National Ethics Committee. The funding of the budgeted study costs was approved by Dental Health International Netherlands in August 2021. The projected start date of data

collection was September 4, 2021, and the study period will most likely last for 1 year. As such, data collection is expected to be complete in November 2022.

Conclusions: The aim of our prospective observational cohort study is to gain more knowledge about complicated odontogenic infections in Tonkolili District, Sierra Leone, to further improve treatment strategies.

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KEYWORDS

complicated odontogenic infection; dental abscess; deep neck space infection; Ludwig angina; necrotizing fasciitis; prospective observational cohort study

Introduction

Background

Globally, one of the main reasons for visiting a health care facility is dental infection [1,2]. Odontogenic infections can be the result of dental caries, periodontitis, pericoronitis, or complications from dental procedures and can result in the formation of dental abscesses [3]. Both children and adults can be affected by odontogenic infections, and underprivileged groups are especially at risk [4]. Appropriate dental care services are lacking in most low-income countries, and shortages of human resources as well as unmet dental health needs have been reported from Sierra Leone [5,6]. If odontogenic infections are left untreated, dental abscesses can form, which can result in complications such as Ludwig angina, retropharyngeal spread, mediastinitis, necrotizing fasciitis, osteomyelitis, and intracranial abscesses. These complications are associated with high mortality rates [7-10]. The first therapy of choice for abscesses resulting from deep neck space infections (DNSIs) is incision and drainage treatment, and antibiotics are a cornerstone of DNSI treatment [11]. However, due to the inappropriate, widespread use of broad-spectrum antibiotics, pathogens that cause oral infections have become more resistant to antibiotic treatment [12]. A flowchart specifying the criteria for admitting and identifying patients with infections that have a high risk of secondary complications was proposed by one study [13]. Another study developed a risk assessment scale and management algorithm for DNSIs [14]. Although the management algorithm was deemed useful for that particular cohort, which was recruited from a high-income country, it does not seem to be feasible for low- and middle-income country environments where advanced medicotechnological instruments, such as fiberscopes, are not readily available. To the best of our knowledge, up-to-date data on the prevalence, characteristics, and management of complicated dental abscesses in Sierra Leone have not been published yet. As such, our study—the Dental Abscess Study (DELAY)—will prospectively investigate morbidity and mortality from complicated dental abscesses and analyze patients' characteristics and microbial findings to identify predisposing factors for major complications.

Hypothesis and Research Objectives

In our study, we hypothesized that extensive odontogenic infections are a frequent and potentially life-threatening clinical problem in Tonkolili Province, Sierra Leone. Current diagnosis, treatment, and outcome management methods require improvement. As such, our study will address the general and specific objectives provided in Textboxes 1 and 2.

Textbox 1. General objectives.

Objectives

- To study the incidence of complicated odontogenic infections at 2 district hospitals in rural Sierra Leone
- To study the clinical and microbiological characteristics of severe odontogenic infections
- To study the comorbidities, complications, and outcomes of extensive odontogenic infections
- To develop improved management algorithms based on circumstance-specific factors

Textbox 2. Specific objectives.

Objectives

- To assess the prevalence and severity of cases presenting with complicated odontogenic infections requiring hospital admission
- To describe the study population based on sociodemographic information and clinical presentation
- To determine the causative agents and the resistance spectrum of complicated odontogenic infections
- To define risk factors of the severity and sequelae of odontogenic infections (ie, dental abscess formation, cellulitis, phlegmon, necrotizing fasciitis, osteomyelitis, mediastinitis, and the need for cricothyroidotomy) based on sociodemographic information, clinical presentation, and HIV status
- To correlate the physical examination findings with disease severity and outcomes
- To correlate the microbial findings with disease severity and outcomes
- To retrospectively assess antimicrobial therapy appropriateness and to develop locally relevant antibiotic treatment guidelines for odontogenic infections
- To propose improved health service algorithms that match locally available resources to patients' needs (ie, after the primary data analysis)

Methods

Study Design

The DELAY is a prospective longitudinal cohort study that will be conducted at 2 rural district hospitals in Sierra Leone and will include any cases that are eligible for inclusion, as per the inclusion and exclusion criteria. The study will have a 1-year enrollment period between September 2021 and August 2022. Study participants will routinely be followed up for 3 months.

Disclaimer

It is important to indicate that standard local treatment guidelines will be adhered to, regardless of whether patients decide to participate in the DELAY. Given that there will be no interference with the routine treatment modalities, oral consent was considered to be appropriate. That notwithstanding, written informed consent (or thumb-printed consent from illiterate participants) will be documented in a separate form. This consent encompasses consent for the initial examination and all follow-up examinations, including the taking of medical photos. At any point during the study, consent can be withdrawn.

Study Sites

Masanga Hospital is a 120-bed general district hospital that serves a population of around 440,000 people. Masanga is a remote town located in the Kholifa Rowala Chiefdom of the Tonkolili District in Sierra Leone's Northern Province. The hospital offers inpatient and outpatient services related to internal medicine, pediatrics, surgery, and obstetrics and gynecology and is transitioning from a nongovernmental organization–supported hospital to a fully governmental hospital.

Lion Heart Medical Centre (LHMC) is a 70-bed general district hospital in Yele—a town in the remote south of the Tonkolili District. LHMC serves a catchment population of around 100,000 people who are mainly from the Gbonkolenken, Valunia, and Kamajei chiefdoms. LHMC offers inpatient and outpatient services related to internal medicine, pediatrics, surgery, and obstetrics and gynecology. LHMC too is a nongovernmental organization–supported hospital that is transitioning to become a government-supported hospital in the coming years.

Population

The study population will be selected consecutively from patients who present with complicated odontogenic infection requiring in-hospital admission to 1 of the 2 district hospitals in Tonkolili District—Masanga Hospital or LHMC—from September 4, 2021, to August 31, 2022 (this period is subject to prolongation depending on the number of study participants). Consequently, the study population will most likely consist of, but will not be limited to, Sierra Leone citizens from the Tonkolili District.

Inclusion Criteria

In order to be eligible to participate in this study, a patient must meet the following inclusion criteria: (1) the in-hospital admission of any patient due to the clinical suspicion of a complicated odontogenic infection (eg, DNSI, necrotizing fasciitis, cellulitis, dental abscess formation, osteomyelitis, and mediastinitis) and (2) the provision of documented informed consent by a patient or a legal representative.

Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participating in this study: (1) a swollen neck resulting from any cause other than odontogenic infection (eg, goiters, congenital cysts, and trauma), (2) oral and neck infections resulting from any cause other than odontogenic infection (eg, isolated peritonsillar cellulitis, tonsillitis, isolated osteomyelitis, trauma, or infection after trauma), and (3) the inability of a patient or a legal representative to provide informed consent.

Sample Size

A formal case size calculation has not been conducted, as there is no effect-modifying intervention that can be compared against a therapeutic (clinical) gold standard. The DELAY is an observational study for informing future larger studies on odontogenic infection. We aim to include at least 300 patients from both locations combined. However, we propose the inclusion of 350 patients in the study to account for possible missing data and losses to follow-up.

Data Collection

On admission, study information will be provided to individuals (or their primary caretakers) who are apparently eligible for inclusion, and informed consent will be sought. Subjects who consent and are found to be eligible after checking the inclusion and exclusion criteria will be assigned unique participant identification numbers (PINs). In Masanga Hospital (in the village of Masanga), the first patient will be assigned the PIN "M001," the second patient will be assigned the PIN "M002," and so forth. In LHMC (in the town of Yele), the first patient will be assigned the PIN "Y001," the second patient will be assigned the PIN "Y002," and so forth.

After PIN assignment, a standardized questionnaire will be completed. The questionnaire contains questions about patients' characteristics (eg, age, sex, past medical history, and socioeconomic status), clinical symptoms (eg, the start and duration of complaints), and health behaviors (eg, consultation with a traditional healer and dental care). A physical extraoral and intraoral examination will be performed at and during admission and at discharge. These will include measurements of the interlobar distance [15], Adam distance [16], and interincisal distance at maximal mouth opening [16,17] (Table 1).

Details on the clinical conditions of patients upon admission (eg, vital signs, airway patency, and AVPU [Alert, Responsive to Verbal Stimulus, Responsive to Pain Stimulus, Unresponsive] scale scores), as well as suspected complications (eg, sepsis, cervical necrotizing fasciitis, and mediastinitis), will be noted. If a patient has provided consent, a medical photo will be taken. Standard laboratory testing will be conducted depending on the availability at the study site and will include hemoglobin tests (Masanga and Yele), white blood cell count tests (Masanga and Yele), malaria rapid testing, hepatitis B surface antigen tests, and HIV testing (Masanga and Yele).

If applicable, a pus swab will be taken and sent to the laboratory at the University Hospital of Münster, Germany, for culture and bacterial cell count tests as well as antibiotic susceptibility testing. Moreover, a pure pus sample will be taken and stored locally in a freezer. A bacteriology lab is under construction at the Masanga site—a development that has been delayed due to COVID-19 epidemic circumstances. Provided that the on-site bacteriology laboratory becomes operational during the study period, which is likely to be the case, the samples will be tested there, and the results will be validated at the Münster collaboration site. If blood culture material becomes available at the local level during the study period, blood cultures will be collected. Treatment will be provided in accordance with standard local treatment guidelines; we will not wait for antibiotic susceptibility results before the start of antibiotic therapy, given the long shipping times. As the local laboratory will most likely not be certified during the study periods, and as the results from the Münster reference laboratory will only become available after an individual patient's acute treatment period, laboratory results will not be used to modify treatment.

Data on treatment will be collected on the date of admission (eg, the use of antibiotics and planned surgeries) and on the day(s) of surgery (ie, if a surgery will be performed). Additionally, several outcome parameters will be measured on the day of admission; on postoperative days 1, 2, and 7 (in cases where surgery has been performed); on discharge; and at both routine follow-up visits. These will include the interlobar distance, the maximal interincisal mouth opening capacity, and the Adam distance. On discharge, additional data on outcomes will be collected (eg, the state of wound closure, the presence of facialis paresis, and mortality), and medical photos will be taken.

Follow-up visits will take place on postdischarge weeks 4 and 12. If necessary, additional follow-up visits will be conducted. A standardized questionnaire regarding current symptoms will be taken at follow-up visits, during which a physical examination will be performed and a photo will be taken.

Further specifics on which parameters will be recorded during admission, discharge, and follow-up can be found on the case record form in this study protocol (Multimedia Appendix 1).

Table 1. Clinical measurement definitions.

Measurement	Anatomic site of measurement	Time of measurement	Tools used
Interlobar distance [15]	From the tip of the tragus to the gonion and to the contralateral tip of the tragus	• Upon admission • Postoperative days 1, 2, and 7 • Follow-up weeks 4 and 12	Tape measure
Maximal interincisal mouth opening capacity or trismus [16,17]	From the incisal edge of the maxillary central incisor to the incisal edge of the mandibular central incisor	• Upon admission • Postoperative days 1, 2, and 7 • Follow-up weeks 4 and 12	Vernier caliper
Adam distance [16]	From the laryngeal cartilage to the vermilion border of the lower lip at rest	• Upon admission • Postoperative days 1, 2, and 7 • Follow-up weeks 4 and 12	Tape measure

Data Capture and Entry

Paper versions of the informed consent forms will be filled out and stored on-site upon admission. Data will be collected and stored on-site on paper case record forms by trained research staff. During the data collection phase of the study, all variables will be entered on a research computer by using Microsoft Access at each separate study site (offline database). Data will be double entered by 2 different researchers on 2 separate forms and subsequently matched to identify errors.

All medical photos taken during the study will be encoded by using the following file name format: "PIN_contact moment." In the *contact moment* field, 1 of 4 labels will be used, as follows: "A" (admission), "D" (discharge), "F1" (follow-up visit 1 after 1 month), and "F2" (follow-up visit 2 after 3 months). An example file name of a photo that is taken upon the admission of a theoretical study participant in the Masanga study site would be "M005_A.png." Medical photos will be stored on a hard drive during the data collection period. After the study period, all study data will be stored for a minimum of 15 years in 1 database at the Masanga Medical Research Unit (MMRU).

Data Analysis

Microsoft Excel and SPSS (IBM Corporation) will be used for the analysis of the data. An exploratory analysis of the variables and descriptive statistics of the data will be carried out. Study parameters will be assessed from an etiologic perspective. For data consistency, certain groups might be excluded from the data analysis (eg, neonates). The description of the distribution of each variable will be made based on measures of central tendency (mode, mean, and median) and measures of dispersion (variance, SD, and maximum and minimum values). Pearson chi-square tests and Kaplan-Meier curves will be used to analyze the study objectives. Logistic regression analyses as well as Cox regression models will be conducted to assess the predictive value of patients' characteristics and microbial findings on outcomes.

Ethical Considerations

Patients will be approached by the researchers after admission to the hospital and will be asked to provide informed consent after they have received and studied the patient information (Multimedia Appendix 2). This consent will include permission to publish anonymized (nonidentifiable) picture material. Since treatment will be performed according to the local guidelines, participation in the study will not influence the treatment that patients receive. Informed consent files (Multimedia Appendix 3) will be kept at the MMRU and at LHMC, as will the patient-reported questionnaires. Study participants can leave the study at any time for any reason if they wish to do so, without any negative consequences for the care provided. The investigator can decide to withdraw a participant from the study for urgent medical reasons.

Results

Ethical Clearance

The study was scientifically scrutinized and endorsed by the MMRU's Scientific Review Board on June 16, 2021, and was granted scientific and ethical clearance by the Sierra Leone Ethics and Scientific Review Committee, Freetown, on July 5, 2021.

Funding

Major contributions (salaries, accommodations, and consumables related to routine care) will be made as in-kind contributions by the participating centers. In August 2021, Dental Health International Netherlands approved the funding of the budgeted costs of the study (Table 2) after endorsing the study protocol. The Center of Tropical Medicine and Travel Medicine (of whom MPG is the head) serves as a sponsor of the study and serves as the guarantor for the funding (up to the sum described in the budget; Table 2), so that the study can be initiated right after approval.

Table 2. Budget calculation (includes both study sites).

Budget items	Cost (€)[a,b]
Personal protective equipment	1167.70
Data collection materials	114.80
Reimbursement follow-up visits	1600
Additional fees	
Sierra Leonean ethical approval (students)	161.35
Open-access publication fees[c]	1500
In-kind contributions	
Microsoft Access and SPSS (IBM Corporation)[d]	N/A[e]
Personnel from Masanga Hospital and Lion Heart Medical Centre	N/A

[a]A currency exchange rate of €1=US $1.14 is applicable.

[b]The total cost was €4543.85 (plus 10% overhead: €4998.24).

[c]There might be open access publication costs for the manuscript; hence, this cost factor was included in the calculation. The Center of Tropical Medicine and Travel Medicine, Amsterdam University Medical Center, serves as guarantor for eventual costs not being covered otherwise.

[d]These contributions were provided by the Masanga Medical Research Unit.

[e]N/A: not appliable.

Data Collection

The projected start date of data collection was September 4, 2021, and data collection is expected to be complete in November 2022. A timeline is presented in Table 3.

Table 3. Timeline.

Task	December 2020 to April 2021	May 2021	June 2021	September 2021 to August 2022	September to November 2022	December 2022	January 2023	February 2023
Study protocol, CRF[a], IC[b] form, and PIF[c]	✓[d]	✓						
Funding	✓	✓						
Scientific Research Committee		✓	✓					
Protocol revision			✓					
Sierra Leone ethical council			✓					
Data collection				✓				
Data collection during follow-up contact				✓	✓			
Data analysis					✓			
Present data to local authorities						✓	✓	
Paper writing							✓	✓

[a]CRF: case record form.

[b]IC: informed consent.

[c]PIF: patient information folder.

[d]A checkmark indicates that the task will be performed during the specified period.

Reporting of Study Results

Study results will be reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [18] for the reporting of prospective cohort studies. Study results are planned to be presented at the community level and during scientific meetings. One or several papers intended for publication in peer-reviewed journals will be prepared timely.

Discussion

As only insufficient data are available in literature databases concerning the prevalence, characteristics, and management of complicated dental abscesses in Sierra Leone, our study aims to provide further information to improve treatment strategies.

Acknowledgments

The funding of budgeted costs was approved by Dental Health International Netherlands (DHIN). DHIN has not been involved in the study design.

Conflicts of Interest

FS has received funds from Pfizer Germany to support susceptibility testing of ceftazidime/avibactam in the last 36 months. No further conflicts of interest reported.

Multimedia Appendix 1
Case record form.
[DOCX File , 327 KB - resprot_v10i12e33677_app1.docx]

Multimedia Appendix 2
Patient information folder.
[DOCX File , 64 KB - resprot_v10i12e33677_app2.docx]

Multimedia Appendix 3
Informed consent form.
[DOCX File , 128 KB - resprot_v10i12e33677_app3.docx]

Multimedia Appendix 4
Peer-review reports from the Masanga Medical Research Unit (MMRU).
[PDF File (Adobe PDF File), 204 KB - resprot_v10i12e33677_app4.pdf]

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Abbreviations

AVPU: Alert, Responsive to Verbal Stimulus, Responsive to Pain Stimulus, Unresponsive
DELAY: Dental Abscess Study

DHIN: Dental Health International Netherlands
DNSI: Deep Neck Space Infection
LHMC: Lion Heart Medical Centre
MMRU: Masanga Medical Research Unit
PIN: Participant Identification Number
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Incorporating African American Veterans' Success Stories for Hypertension Management: Developing a Behavioral Support Texting Protocol

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Abstract

Background: Peer narratives engage listeners through personally relevant content and have been shown to promote lifestyle change and effective self-management among patients with hypertension. Incorporating key quotations from these stories into follow-up text messages is a novel way to *continue the conversation*, providing reinforcement of health behaviors in the patients' daily lives.

Objective: In our previous work, we developed and tested videos in which African American Veterans shared stories of challenges and success strategies related to hypertension self-management. This study aims to describe our process for developing a text-messaging protocol intended for use after viewing videos that incorporate the voices of these Veterans.

Methods: We used a multistep process, transforming video-recorded story excerpts from 5 Veterans into 160-character texts. We then integrated these into comprehensive 6-month texting protocols. We began with an iterative review of story transcripts to identify vernacular features and key self-management concepts emphasized by each storyteller. We worked with 2 Veteran consultants who guided our *narrative text message* development in substantive ways, as we sought to craft culturally sensitive content for texts. Informed by Veteran input on timing and integration, supplementary educational and 2-way interactive assessment text messages were also developed.

Results: Within the Veterans Affairs texting system *Annie*, we programmed five 6-month text-messaging protocols that included cycles of 3 text message types: narrative messages, nonnarrative educational messages, and 2-way interactive messages assessing self-efficacy and behavior related to hypertension self-management. Each protocol corresponds to a single Veteran storyteller, allowing Veterans to choose the story that most resonates with their own life experiences.

Conclusions: We crafted a culturally sensitive text-messaging protocol using narrative content referenced in Veteran stories to support effective hypertension self-management. Integrating narrative content into a mobile health texting intervention provides a low-cost way to support longitudinal behavior change. A randomized trial is underway to test its impact on the lifestyle changes and blood pressure of African American Veterans.

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KEYWORDS

texting; African American; hypertension; self-management; mobile phone

Introduction

Background

Uncontrolled hypertension is common among African Americans, leading to higher rates of cardiovascular morbidity and mortality [1]. High prevalence and inadequate control of hypertension in this group contribute to persistent disparities in stroke, heart failure, peripheral artery disease, and end-stage renal disease [2,3]. Disparities in hypertension control may derive from differential rates of diagnosis, treatment titration, and patient factors, including medication adherence, lifestyle changes, self-monitoring, and engagement with the health care system. Due in part to experiences of racial discrimination (personal and historical), African Americans routinely express lower levels of trust in the health care system. Thus, to promote sustained behavior change, hypertension self-management interventions designed to support African American patients must be personally relevant [4] and acknowledge and address mistrust in the health care system.

Peer narratives, also referred to as *storytelling*, can provide personally relevant messages, helping address mistrust and cognitive resistance arising from concerns about treatments or medical information [5]. In contrast to clinical recommendations that may be perceived as abstract or disconnected from daily experiences, peer narratives provide real-world examples of behavior embedded in daily lived experiences [6]. Peer interventions have been used to support African Americans in achieving effective hypertension self-management [7-10] and storytelling can play an important role in this support. When a patient is engaged in a story, their attitudes and intentions can be influenced by features from the story, and this engagement is often mediated by personal identification with the storyteller.

In our previous work, African American Veterans shared stories of struggles and strategies related to hypertension self-management, which we video-recorded [11]. We found that patients who viewed story videos were more likely than those who viewed an educational DVD to be engaged emotionally and report intent to change behaviors [12]. However, we found that this one-time intervention did not translate into a sustained improvement in blood pressure. Therefore, we sought to provide additional longitudinal support.

Text messaging has proven to be an effective and inexpensive way to communicate with patients longitudinally [13] and shows promising results as a means of supporting hypertension control [14]. A randomized feasibility texting intervention conducted among African Americans [15] with uncontrolled hypertension found trends toward improvements in medication adherence, as well as systolic and diastolic blood pressures. A larger text-messaging randomized trial addressing hypertension treatment adherence in over 1300 South Africans showed small but significant improvements in blood pressure after a 12-month intervention [14]. A small trial of text messaging paired with electronic medication tray reminders showed significant improvement in the number of African American and Hispanic participants who achieved blood pressure control after 6 months [16]. Several larger randomized trials are underway to further explore text messages as a means of supporting hypertension control for African Americans.

Objective

In this paper, we describe the process by which we developed text message content and texting protocols aimed at incorporating the voice of African American Veteran storytellers [17]. Our goal is to extend the impact of our previous peer storytelling intervention by *continuing the conversation* through engaging, personally relevant text messages adapted from the Veterans' video-recorded stories.

Methods

Overview

We designed our text messages for use in a Veterans Affairs (VA)–based text-messaging platform, *Annie* [18]. Our multidisciplinary team included physicians (SLC, HSG, JAL), sociolinguists (BGB, CP), anthropologists (GMF), experts in informatics (SLS, SLC), self-management behavior specialists (KLD, SEM), qualitative analysts (DAM, SEM, KLD), and African American Veteran consultants (Rodney Calloway and Paula Smith-Benson). We began text message development by identifying key concepts in hypertension self-management that emerged from our previously recorded Veteran stories. We then used these key concepts to guide the development of 3 distinct text message types (narrative, educational, and interactive). Throughout this process, we sought input from 2 African American Veteran consultants to improve the cultural sensitivity and relevance of narrative text messages to support our goal of designing messages that transmitted each Veteran voice with authenticity and respect. Social Cognitive Theory (SCT) [19] informed our approach to framing messages aimed at enhancing self-efficacy, with the goal of ultimately influencing health behaviors.

Below, we describe the texting platform we used and our approach to developing the 3 text message types: (1) *narrative* texts, (2) educational texts, and (3) interactive messages assessing self-efficacy and behavior related to hypertension self-management.

Using the VA-Based Text-messaging Platform

Annie is an SMS text-messaging system in the Department of VA, which is available to support routine clinical practice. Providers can access a secure dashboard and choose from a menu of texting protocols intended to promote self-care for Veterans enrolled in VA health care. Veterans can receive text messages directly on their phones or through a VA mobile app downloaded into their smartphones. Existing texting protocols provide motivation, education, and, in some cases, an invitation to monitor the status of their chronic illness (eg, reporting blood sugar readings) [20]. The *Annie* text-messaging system is not intended to be monitored by providers and delivers an error message if free text is sent in by a Veteran (or if any response at all is sent in for noninteractive messages).

The *Annie* system contains templates for one-way and 2-way texts that allow for the customization of timing and content. Each message is limited to a maximum of 160 characters and must include the word *Annie* as an identifier. Short URLs can be included in the text. Response options for 2-way texts cannot be open-ended and must be preprogrammed into the system. We worked closely with a few VA researchers experienced in the use of this platform as well as with VA operational partners to understand the constraints imposed by *Annie* and to construct messages that optimized available opportunities.

Key Content Area Identification

In our previous work, we created video-recordings of 5 stories (each about 5-8 minutes long), told by African American Veterans who had successfully managed their uncontrolled hypertension [12]. The development of these narrative videos has been well described previously [11] and included the identification of key content areas (Table 1). During that work, we sought to maintain authenticity and the voice of the storyteller, while also describing small specific behavioral action steps, bringing them together in a video-recorded story designed to engage and maintain viewer attention.

Table 1. Key content areas and description.

Key area	Description
Salt intake	Veterans describe strategies and contextually situated stories of how they managed salt intake
Talking with your physician	Veterans describe reasons why honest communication with providers is important
Take your medicine	Veterans describe strategies and motivation tools in taking their prescribed medicine
Exercise	Veterans talk about specific strategies to increase exercise
Stress management	Veterans describe tools and tactics to manage stress
Monitor your blood pressure	Veterans tell stories of ways they monitored their blood pressure
Diet or nutrition	Veteran storytellers describe how they improved their diet or learned more about the importance of nutrition
Faith or church or community	Veterans share how their faith, church or community is a source of support or motivation for them and their health
Alcohol or smoking or challenges	Veterans share their experiences with alcohol, smoking, etc and how they addressed these challenges

Narrative Text Development

Overview

Narrative text messages are text messages that incorporate content from Veteran stories aligned with the key content areas outlined in Table 1. To develop content for the narrative text messages in this study, we sought to identify microstories within these longer narratives. We took a multistep approach beginning with (1) review of transcripts (GMF, KLD, SLC, SEM, CP, BGB, and SLS) from patient stories and selection of quotations aligned with previously identified key content areas, (2) followed by creation of 160-character messages capturing the Veterans' voices (GMF, SEM, SLC, CP, KLD, BGB, and SLS), each aligning with a key content area [11]; and (3) finally, solicitation of feedback from Veteran consultants.

For example, (Table 2), we created a text message focused on the Key Content Area of Faith or Church or Community as follows: In step (1), a Veteran storyteller's transcript captures his description of a wish to *give back* to other Veterans and contribute to his community because *I've been through it too*. Although this message is not specific to hypertension self-management behaviors, it was chosen for its potential to reinforce the recipient's identification with the storyteller and to strengthen the message of this key content area, which focuses on gaining support for healthy behaviors through one's social network. In step (2), we identified and extracted a few words that exemplified this message. In step (3), the Veteran consultant reviewed this message during a feedback session and suggested modifications.

Table 2. Examples of narrative text messages (adapted from quotations from African American Veterans sharing stories about how they manage their hypertension).

Hypertension self-management key content area	Direct quotation from unedited video transcript[a]	Draft text message	Examples of ways that narrative content and Veteran input were used to modify texts	Final
Low sodium diet	"*Basically, I don't have any salt, plain salt in my house. S-salt substitute, seasoning*, uh, a low salt, *anything with, that's low salt* in there**,***I use that*, you know. It's not as strong as the salt that I usta take but still crave, you're given that, all, *keep me from craving for regular salt*, you know."	"*Annie-BP*: Willie says-basically I don't have any salt, plain salt in my house. Salt substitute, seasoning, anything that's low salt-I use that."	• Informed by narrative content, we incorporated the concept of craving • The Veteran used this concept several times in the narrative to emphasize the role played by salt substitute	"*Annie-BP*: Willie says-basically I don't have any plain salt in my house. Salt substitute or seasoning keeps me from craving for regular salt."
Faith or church or community	"*I'm a Veteran tryin' to give back to a Veteran***.** If I'm, they-they gave to me, you know, a new, a-await in life, you know, but homeless vets, the Veterans are homeless out here today and my thing is to try to do for our homeless myself at one time and, uh, uh, different things I went through in life, *I can basically relate to the 'nother Veteran because I've been through it, too***.** So that's what I do now is house homeless vets and then we have pro-, uh, programs for, like posttraumatic stress and we all talk about PTSD."	"*Annie-BP*: Willie says: I'm a Veteran trying to give back to a Veteran. I can relate because I've been through it too."	• Informed by Veteran consultant feedback, we deleted: I can relate because I've been through it too. • Our consultant felt this would be understood by another Veteran without needing to be stated.	"*Annie-BP*: Willie's doing something he loves to do while helping others in the community. Willie says: I'm a Veteran trying to give back to a Veteran."
Exercise	"I began to see that it was affectin' a lotta things in my life so I decided to do somethin' about it, and that's why I call it a journey...That's what I do. *I do little stuff that adds up to big stuff...And I do it every day*, cuz like I said, there's not, it's nothin' strenuous, you know what I mean?...I do a whole lotta little stuff that I think adds up to somethin' big, you know...I do, *I do a lotta little stuff that adds up to big stuff, you know.*"	"*Annie-BP*: Richard talks about his BP: it was affectin' a lotta things in my life so I decided to do somethin' about it. I do a lotta little stuff that adds up to big stuff."	• Informed by Veteran consultant feedback, we adopted standard spelling, while trying to keep the cadence of the Veteran voice. • Our consultant observed that professionally typed transcriptions can reflect the bias of the transcriber. Including nonstandard spelling may offend those who personally experienced stigmatization related to their speech patterns.	"*Annie-BP*: exercise doesn't have to mean a big lifestyle change. Richard says, I do little stuff that adds up to big stuff and I do it every day."

[a]Italicized text corresponds to sections either paraphrased or directly quoted in text message.

Review of Story Transcripts and Selection of Quotations

We began our text message development by iteratively reviewing the transcripts of video-recorded Veteran stories. Two study team members reviewed the 5 unedited video transcripts (one from each Veteran storyteller). The transcript review included (1) identification within each story of key concepts in hypertension self-management and key narrative elements; and (2) selection of longer transcribed segments containing quotations conveying these key hypertension concepts, key narrative elements, or linguistic phrases characteristic of the storyteller. These longer (usually multi-sentence) excerpts from storyteller transcripts were then categorized based on key concepts. We initially selected and categorized longer segments because we wanted to ensure that we captured the full context of quotations. We did this to avoid misrepresenting the intended idea when (in subsequent steps), we pared down the wording to fit in a brief text message. In some cases, longer excerpts were categorized as relevant to multiple key hypertension self-management concepts, and text messages were adapted from these for more than one key concept area.

Creation of 160-Character Text Messages

In these longer segments, we then highlighted smaller sections of quoted text that contained key story elements, key hypertension self-management concepts, or linguistic phrases that had either been repeated throughout the story or were evocative of the storyteller's unique personal style. We sought concepts that could be succinctly communicated and examined.

We considered whether we could delete text to shorten the message without distorting the intended meaning and whether there were ideas that would be better communicated by paraphrasing because of the structure of the quotation.

We began drafting potential text messages based on this review, often writing out 2 or more possible versions. As our ultimate goal was for these text messages to be delivered after study participants watched the 5-to 8-minute video-recorded versions of our storytellers, we also noted whether the excerpted text reflected a section that had been included in the final edited video (although we did not require that text messages be derived solely from segments included in the video).

Our multidisciplinary team met weekly as a group to review the text messages that were created, identified favorites by consensus, and edited iteratively for character count and flow. Our Veteran consultants also met with a team member separately to allow for more in-depth feedback. The diversity of training and expertise on this team enhanced our ability to look at the nuances of texts and their implications. Some video-recorded Veteran storytellers did not address all the key concepts (or the storyteller addressed the concept in language, not lending itself to incorporation into a 160-character narrative text). Our planned intervention requires participants to watch all 5 videos, and then select a single storyteller they prefer. This choice will then inform assignment to the corresponding texting protocol, which will include quotes from the participant's preferred storyteller. Our goal was to cover all the key concepts for each storyteller protocol. Therefore, we used narrative messages from another Veteran storyteller to cover the missing concepts. When we performed this step, we included wording to distinguish the quotation. For instance, instead of *Morris said* we used *a Veteran who shared his story with us said:* as in the example: "ANNIE-BP: *A Veteran who shared his story with us said*: I was enjoying the smoke but also I was hurting myself at the same time. If I wanted to live, I had to give up cigarette smoking."

Feedback From Veteran Consultants

We invited one of our consultants (coauthor RC) to view storyteller videos and give inputs for our process of creating texts. Our goal was to design messages that conveyed each Veteran's voice with authenticity and respect. As an African American Veteran himself, RC guided us in our efforts, helping us improve the cultural sensitivity and relevance of our narrative text messages.

We asked RC for reactions to individual storytellers and enquired which story segments and themes were most memorable. These responses helped inform the selection of quotations from the unedited transcripts. RC reviewed drafts of narrative texts as we created them and guided our choices on (1) language structure, (2) word choice and tone, and (3) fidelity to storyteller voice. For each of the 5 storytellers whose stories were developed into text messages, RC met with us for multiple 1-hour periods over several weeks, reviewing every narrative text message. For an additional perspective, we invited our second Veteran consultant (Paula Smith-Benson) to provide additional feedback. Her input was focused on a story told by our female Veteran storyteller; therefore, Ms Smith-Benson reviewed only a subset of narrative messages.

Educational and Interactive Text Development

Alongside our narrative text messages, we developed educational and interactive text messages corresponding to each key content area.

Educational Messages

Educational messages incorporated content from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention [21]. Each message focused on one of the key content areas outlined in Table 1 (eg, for salt intake: "ANNIE-BP: You can also reduce salt by avoiding the saltshaker. Avoid sea salt and garlic salt too—try substitutes instead: Mrs. Dash or fresh herbs for flavor").

Interactive Text Messages

Interactive text messages were 2-way messages that asked a question, prompted a reply, and sent a follow-up comment. These had several purposes: motivation, patient engagement, data collection, and education. We adapted questions from validated scales [22,23] where available. Guided by SCT [24], we assessed (1) participants' confidence in their own ability to carry out a hypertension self-management task (self-efficacy) and (2) participants' actions toward effective self-management (behavior). Interactive text messages often provided content-specific resource links to educational sites (eg, the American Heart Association) or VA webpages.

Interactive text responses were developed using preset phrases (Table 3). For self-efficacy: "How confident are you that...Text NA 1 (not confident), NA 2 (somewhat), or NA 3 (very) to reply." For behavior performed across a number of days per week: "How many days this week have you...Text ACT 0, ACT 1 up to ACT 7 to reply." Automated and rapid turnaround follow-up text message responses were developed, containing encouragement and additional information tailored to acknowledge the reply.

Table 3. Examples of interactive text messages.

Interactive text sent and patient response	Condition	Automated texts acknowledging response
Self-efficacy —"*Annie-BP*: how confident are you that you can make small daily changes to increase your activity? Text EX 1 (not at all), EX 2 (somewhat) or EX 3 (very) to reply"		
EX 1, EX 2	When reply received	"*Annie-BP*: thanks for letting us know. To learn more about exercise opportunities, check out (URL provided)"
EX 3	When reply received	"*Annie-BP*: That's great! If you'd still like to learn more about exercise opportunities, check out (URL provided)"
No reply or reminder	N/A[a]	"*Annie-BP*: how confident are you that you can make small daily changes to increase your activity? Text EX1 (not at all), EX2 (somewhat), or EX3 (very) to reply."
Behavioral—"*Annie-BP*: How many DAYS this week have you done a specific exercise other than what you do around the house or at work? Text ACT 0, ACT 1 up to ACT 7 to reply."		
ACT 0, ACT 1, ACT 2	When reply received	"*Annie-BP*: Getting exercise is hard & support helps. Ask your care team: is VA MOVE! right for me? Options include teleMOVE and mobile apps. (URL provided)"
ACT 3, ACT 4, ACT 5, ACT 6, ACT 7	When reply received	"*Annie-BP*: Good work! To support exercise routines, ask your care team: is VA MOVE! right for me? Options include teleMOVE & mobile apps (URL provided)"
No reply or reminder	N/A	"*Annie-BP*: How many DAYS this week have you done a specific exercise other than what you do around the house or at work? Text ACT0, ACT1, ACT2 up to ACT7 to reply"

[a]N/A: not applicable.

Content Influenced by Texting Protocol Structure

Our text message content development was further guided by the development of a structure for a 6-month texting protocol (Multimedia Appendix 1). Each 2-week block addressed a single key concept (Table 1) in hypertension self-management and contained 8 text messages spaced across 14 days. As detailed below, informed by Veteran input, we incorporated a structured combination of the 3 message types (narrative, educational, and interactive) into each block. Texts were designed to be delivered consecutively. The automated response for the first interactive text (delivered at the start of a 2-week block) suggested a website with further information on the content (providing resources for self-guided education); the response for the second interactive text (sent at the end of the 2-week period) provided suggestions for accessing additional VA resources (Table 3). Thus, interactive texts acted as *bookends*; messaging in some instances also built across multiple texts within the 2-week period.

Results

Overview

Within the VA texting system *Annie*, we programmed five 6-month text-messaging protocols that included cycles of 3 text message types: (1) narrative messages, (2) nonnarrative educational messages, and (3) 2-way interactive messages assessing self-efficacy and behavior related to hypertension self-management (Multimedia Appendix 2). Each of the protocols corresponds to a single Veteran storyteller, allowing the Veterans to choose the story that most resonates with their own life experiences. Veteran consultant input played a pivotal role in the content and design of our final protocols.

Incorporating Veteran Consultant Feedback on Cultural Sensitivity of Text Messages

Both Veteran consultants felt strongly that our approach to narrative text development should include direct quotations from our Veteran storytellers as was our original intent. Working directly from professionally typed transcriptions of our Veterans' stories, we initially crafted texts that sought to adhere closely to the language of the transcription, in the belief that this would be the best way to share the voice of our storytellers. Hence, consistent with the sociolinguistic concept of phonological variants that stay true to actual voices [25], colloquial or informal spellings such as *hafta* and *gotta* were initially included, as were verbs with the final *g* omitted and replaced with an apostrophe (eg, runnin', eatin'). In an effort to convey the linguistic choices of our Veteran storytellers through our text messages, we also crafted text messages that included sentences with the vernacular features used by the speakers in the delivery of their stories.

RC provided important feedback on these choices. He addressed the subjectivity of our professionally typed transcriptions, pointing out that when he listened, he did not hear *hafta* ("I heard *have to*") and that transcribing language in this way can reflect the bias of the transcriber. "You should write it how I hear it," he advised. He emphasized that if we included quotations with colloquial spelling, we might achieve an effect that was the opposite of what we intended. "They'll think you made a mistake, or they'll be offended." RC further pointed out that Veterans receiving our text messages may have personally experienced stigmatization related to their speech patterns, which could influence their interpretation of a text message using nonstandard spelling. Finally, he reminded us of our obligation in seeking to serve the African American Veteran community: to keep in mind that some of our intended text message recipients have likely suffered from disparities in access to high-quality education, and that we should use standard

spelling to avoid perpetuating these disparities through our texts. Taking all these points into account, we modified all our narrative text messages to adopt standard spelling while trying to keep the cadence of the Veteran voice.

Incorporating Veteran Consultant Feedback on Text-messaging Protocol Structure

Our Veteran consultant (RC) helped define the strategy for integrating educational and narrative texts into the protocol. He suggested that, for each key concept in hypertension self-management, we begin by providing educational text messages for 1 week without referencing the Veteran storyteller (*to see if they can do it themselves* and *give them a little space*). He suggested bringing the storyteller's voice back into the conversation after the first week. Thus, following a week of educational texts, our protocol includes a week of narrative texts intended to draw recipients back into the story, using messages that have personal relevance to *continue the conversation*. RC also provided specific feedback on the order in which narrative messages should be presented, seeking to maintain a narrative arc within the week wherever possible.

By incorporating Veteran feedback on text message content and protocol structure, our team refined our overarching structure for a 6-month texting protocol. We outlined a 26-week protocol with 9 key content area blocks. We repeated 2 content areas (salt intake and taking medicine) using identical content when repeating blocks. These were chosen for repetition because of their wide applicability across our intended target population and abundant content from Veteran story transcripts. To further support opportunities for self-reflection and to periodically renew engagement, we included a check-in week after every 4 key concept blocks (every 8 weeks); this check-in week was composed entirely of interactive texts. We intended this check-in primarily for motivational purposes but secondarily planned to use it to assess the sustenance of self-management behaviors. Each check-in week began with the same overarching assessment of self-efficacy ("How confident are you in managing your BP? Text CONF1 (not at all confident), CONF2 (somewhat), or CONF3 (very) to reply") and then repeated 3 behavioral assessments used in the preceding 8 weeks, inviting reflection on performance of behaviors over *this week* (eg, asking participants to reflect on their performance over the check-in week).

With input from our Veteran consultant, we determined that the timing of the texts would be 11 AM and 3 PM to account for off-shift as well as day shift workers. Pilot testing is planned to ascertain the acceptability of using the default timing (as opposed to customized) and to assess the usability of the interactive components of the texting protocol.

Discussion

Principal Findings

Our goal was to design a text-messaging protocol that preserved the voice of our storytellers while conveying authentic and respectful messages to African American Veterans in support of their hypertension self-management. We used 3 complementary strategies to accomplish this goal. First, we built directly on our previous work on the use of storytelling to support behavior change. The use of the VA Annie texting platform for research purposes is still a nascent field of study. Our second strategy was therefore focused on understanding and responding to the constraints imposed by the Annie system while taking advantage of the opportunities afforded by this nationally available system. This adaptation was made possible through the guidance offered by a few VA researchers experienced in the use of this platform as well as from VA operational partners. Finally, our third strategy was to pay careful attention to the inputs provided by our Veteran consultants to design both content and a texting structure informed by cultural considerations.

This work builds on previous work on the use of storytelling to support hypertension management in African Americans. Previous research has advanced the theory and empirical evidence for using peer narrative communication (storytelling) to promote patient engagement and hypertension self-management [26]. Schoenthaler et al [26] combined the information-motivation-behavioral theory with qualitative feedback from African Americans with hypertension to tailor their mobile health intervention. We were informed by SCT in our development of both text message content and texting protocols. Interactive text messages were designed to *bookend* a 2-week focus on a key content area. The 2-weeks begin with an interactive text assessing self-efficacy, following which we provided one week of educational messages intended to support behavioral capability and self-regulation using friendly and encouraging language. In the second week, narrative messages convey the voice and sentiments of the storytellers with the intent of incentivizing and reinforcing health behaviors by referencing the actions of participants' preferred storytellers. SCT focuses on interactions among people, their behavior, and their environment. We used this approach to connect the hypertension control strategies of the storytellers to those of the participants in the context of their daily routines.

In a randomized trial conducted in a safety-net hospital in Birmingham, Alabama, an intervention based on video-recorded stories by African Americans led to significant improvements in blood pressure at 3 months among those with uncontrolled hypertension [27]. In our previous work, we translated these findings to the VA, developing and testing video-recorded Veteran narratives shown to African American Veterans during VA clinic visits [12]. We demonstrated significant differences in intention to change hypertension self-management immediately after viewing the stories; the effects on blood pressure were not sustained, with 6-month outcomes revealing only modest benefit (3.1 mm Hg) versus control (P=.06). Our findings highlight the need to focus on longitudinal support to sustain the storytelling effect, which prompted us to explore the opportunities presented by the nationally available VA texting platform, Annie.

Similarly, others have developed text-messaging protocols tailored to a target population [15,26,28-30]. Including the target population in the design can help ensure that the intervention is culturally relevant [26]. Tailoring messages that align with theory and are tailored to be culturally relevant show promise to be more effective than standard care [28]. Barsky et al [29]

developed a text-messaging intervention comparing active hypertension management versus passive health behavior messages, and found that this approach helped patients in remote areas feel connected and supported [29]. Others have found text messages supporting hypertension control to be both a feasible and an acceptable format for African Americans [15], with the potential to improve adherence [31]. Other studies working to design text-messaging protocols to support African Americans with hypertension sought to design culturally appropriate messaging, a goal that we shared. Our strategy aligned with those of other studies insofar as we sought inputs from our end-user population (Veteran consultant input); other studies made modifications to enhance the cultural sensitivity of the messages [29] and elicited end-user feedback through focus groups [15] or qualitative interviews [26]. According to our review of the literature, our approach to designing messages to support hypertension self-management in African Americans is unique in its incorporation of Veteran's voice and story. In addition, longitudinal data, such as those proposed in our study, are still required [26].

Constraints placed by the Annie texting platform required creativity to improve our texting design in some instances; in other cases, these platform limitations are expected to introduce challenges at the implementation stage. The requirement that the word *Annie* be included in every text for identification purposes prompted us to *brand* our emails (each begins with *Annie-BP*) which may facilitate recognition and decrease the likelihood of these messages being confused with any others. With a limited character count, this requirement occasionally forced us to cut down messaging or spread a concept over several messages (spaced across days). Interactive texts have strict requirements for formatting responses (and lack the ability to be customized to provide automated guidance when the response is incorrect). This requirement is expected to pose challenges for less technically proficient Veterans, particularly when texting protocols must be initiated virtually. There is currently no easy way to change the time of delivery of all messages across a multi message, multiday protocol; timing must be changed manually (message-by-message) to accommodate Veteran preferences, introducing the possibility of programming errors when implemented in real time (eg, during enrollment of a Veteran). We are working with our Veteran consultants to select times with broad acceptability and have provided this feedback to VA operational partners as a possible update to Annie that would allow for more Veteran-centered choices in future work.

Inputs from our consultants, both African American Veterans, were instrumental in the development of this text message content and protocol. The development of culturally sensitive messaging is critical for health care and public health messages [32]. Mobile health programs for behavior change reflect opportunities to reach underserved populations in real time in a relevant, sustainable, and scalable manner [33]. Amid the current COVID-19 pandemic, text message programs that seek to convey personally relevant and culturally sensitive messages of support represent a potentially valuable way to reach out to otherwise isolated Veterans. If such messages help our Veterans feel connected to their health care team, this delivery may be an important way to enhance trust during this difficult time and could have additional long-term benefits.

Our protocol is being piloted using methods adapted in the setting of the current COVID-19 pandemic; we are reaching out to the Veterans and delivering the intervention to them virtually rather than following our original study design (ie, we are no longer asking them to come in-person to the clinic). Participants will be invited to watch 5 storyteller videos and then select their preferred storyteller. This selection will guide the assignment of the texting protocol. After the pilot and refinement of the protocol as needed, we will conduct a 2-site randomized controlled trial to determine if our *continuing the conversation* protocol can improve not only intentions, but also blood pressure control. If successful, our storyteller video and texting package can provide access to culturally sensitive health care messaging for African American Veterans who have difficulty controlling their blood pressure but who are unable to come in-person to the clinic.

Conclusions

Incorporating quotations from the stories of African American Veterans and including African American Veteran consultants on our team allowed us to create culturally sensitive, 6-month text-messaging protocols aimed at supporting effective hypertension self-management through greater engagement and behavioral change.

Practice Implications

Text-messaging platforms provide important tools to continue conversations and provide sustained cues for behavior change. By addressing inequities in health care delivery and access and by supporting the promotion of healthy behaviors, our planned intervention seeks to address several key VA priorities. We hope that our findings will also have broader applicability and reach beyond our Veteran population. A memorable story stays with the listener as an inspiration and guide. Our *continuing the conversation* video and texting package aims to weave the storyteller's messages into the everyday life of the text recipients, reminding and reinforcing them as our recipients engage in the numerous daily decisions that will impact their blood pressure and their lives.

Acknowledgments

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second Veteran consultant, Paula A Smith-Benson, BSN, MSN, RN, CTRC, Major, United States Air Force (Ret), who reviewed selected draft text messages for one storyteller and provided valuable inputs.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example 6-month texting protocol.
[PNG File , 1692 KB - resprot_v10i12e29423_app1.png]

Multimedia Appendix 2
Continuing the Conversation 9-week example protocol.
[DOCX File , 23 KB - resprot_v10i12e29423_app2.docx]

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Abbreviations

SCT: Social Cognitive Theory
VA: Veterans Affairs

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Protocol

Utility of a Machine-Guided Tool for Assessing Risk Behavior Associated With Contracting HIV in Three Sites in South Africa: Protocol for an In-Field Evaluation

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Abstract

Background: Mobile technology has helped to advance health programs, and studies have shown that an automated risk prediction model can successfully be used to identify patients who exhibit a high probable risk of contracting human immunodeficiency virus (HIV). A machine-guided tool is an algorithm that takes a set of subjective and objective answers from a simple questionnaire and computes an HIV risk assessment score.

Objective: The primary objective of this study is to establish that machine learning can be used to develop machine-guided tools and give us a deeper statistical understanding of the correlation between certain behavioral patterns and HIV.

Methods: In total, 200 HIV-negative adult individuals across three South African study sites each (two semirural and one urban) will be recruited. Study processes will include (1) completing a series of questions (demographic, sexual behavior and history, personal, lifestyle, and symptoms) on an application system, unaided (assistance will only be provided upon user request); (2) two HIV tests (one per study visit) being performed by a nurse/counselor according to South African national guidelines (to evaluate the prediction accuracy of the tool); and (3) communicating test results and completing a user experience survey questionnaire. The output metrics for this study will be computed by using the participants' risk assessment scores as "predictions" and the test results as the "ground truth." Analyses will be completed after visit 1 and then again after visit 2. All risk assessment scores will be used to calculate the reliability of the machine-guided tool.

Results: Ethical approval was received from the University of Witwatersrand Human Research Ethics Committee (HREC; ethics reference no. 200312) on August 20, 2020. This study is ongoing. Data collection has commenced and is expected to be completed in the second half of 2021. We will report on the machine-guided tool's performance and usability, together with user satisfaction and recommendations for improvement.

Conclusions: Machine-guided risk assessment tools can provide a cost-effective alternative to large-scale HIV screening and help in providing targeted counseling and testing to prevent the spread of HIV.

Trial Registration: South African National Clinical Trial Registry DOH-27-042021-679; https://sanctr.samrc.ac.za/TrialDisplay.aspx?TrialID=5545

International Registered Report Identifier (IRRID): DERR1-10.2196/30304

(JMIR Res Protoc 2021;10(12):e30304) doi:10.2196/30304

KEYWORDS

machine learning; predictive risk; modeling; algorithm; HIV status; HIV; risk assessment; South Africa

Introduction

A recent study by Nguyen et al [1] showed that albeit the current progress achieved by some African countries in the effort to work toward reaching the Joint United Nations Programme on HIV/AIDS (UNAIDS) targets of human immunodeficiency virus (HIV) testing, the prediction shows little chance in achieving this by 2030. None of the African countries analyzed shows a high probability of achieving the targets; however, only three countries still have a chance of attaining this, with a probability below 50%. This may suggest that countries heavily affected by HIV may require substantial efforts, such as increased support from global organizations, to make progress toward the UNAIDS targets. Additionally, there is a need to find and make more effective changes in the previous strategies for encouraging behavioral interventions to increase condom usage, and strengthen HIV programs in many of the most affected countries. HIV-screening programs therefore are largely invested in preventing HIV transmission by promoting regular testing and continuous development of innovative prevention methods and messages [2,3]. Mobile technology has played a role in advancing health programs [4,5], and studies have shown that an automated risk prediction model can successfully be used to identify patients who exhibit a high probable risk of contracting HIV [6-8]. One of these studies demonstrates that with the use of machine-guided risk assessments, the process of pre-exposure prophylaxis (PrEP) initiation can become more efficient and suitable.

Although identifying persons who are at high risk of contracting HIV should enable a more targeted and cost-effective approach for prevention programs, universal screening programs are costly and labor intensive and do not have as high a success rate in identifying high-risk individuals [6,9].

Supervised learning is used to train machine learning models by using patient traits as inputs. There are two broad categories of patient traits:

1. Generic patient traits, such as age, gender, disease history, and more
2. Disease-specific traits, such as sexual behavior in the context of HIV

In the supervised learning paradigm, we need to know the ground truth to train the model, which in this case is a medical outcome, such as a diagnostic test result. The relationship between patient traits and outcomes can be analyzed by measuring the performance of the model [10,11].

A risk assessment tool is a set of simple and easy-to-understand questions *that* are answered by the participant(s), and based on the responses, a risk probability is calculated. The questions are related to demographics, sexual behavior, sexual history, personal behavior, lifestyle, and medical history. The questions are scientifically designed based on the HIV correlation data from published research and clinical trials. The tool makes use of scientific algorithms to determine the risk probability and *provides* the outcome as low risk, medium risk, or high risk. Diagnostic assistive assessment is performed on a mobile device by the patients themselves, thus eliminating external influences and hence providing more accurate information.

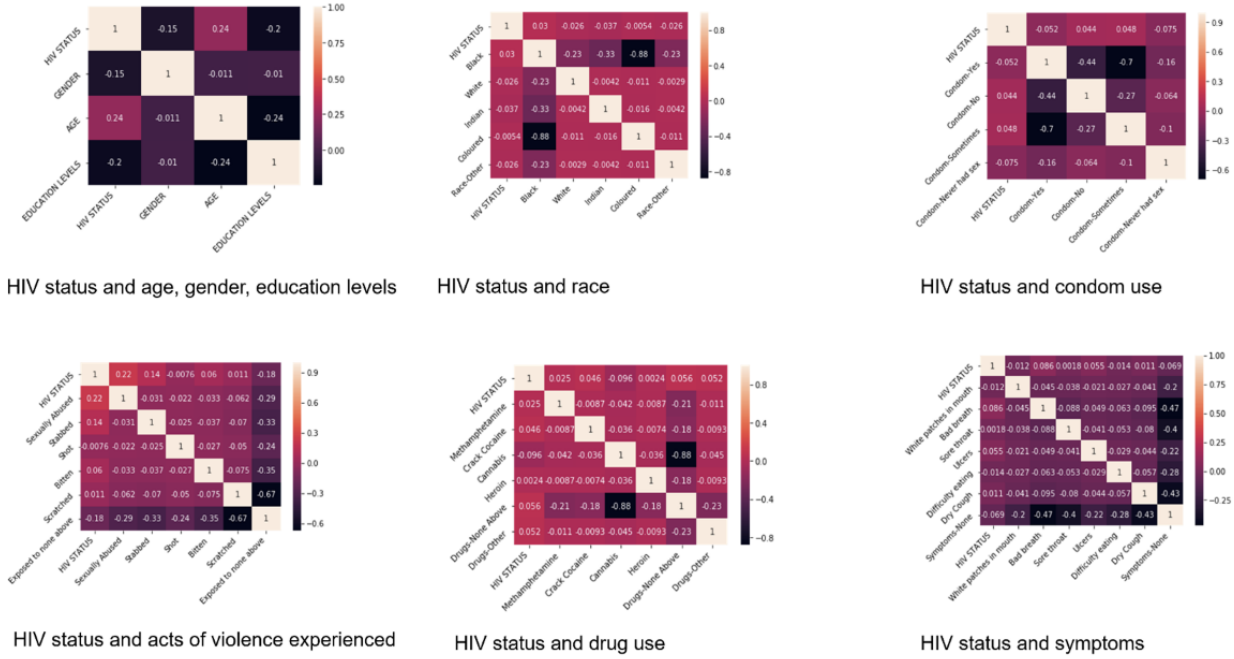
In 2019-2020, a feasibility study was conducted with over 1000 participants at the Wits Reproductive Health and HIV Institute's (WRHI) HIV self-testing assessment and research (HSTAR) Africa site in Johannesburg, South Africa. This study sought to understand the correlation between HIV status and factors such as demographics, sexual behavior and history, personal behavior and lifestyle, and symptoms, individually.

Analysis of the data collected from this feasibility study showed correlations between HIV status and all the variables. The main inference made was that patients can be grouped based on multiple factors as follows:

- Primary features (demographics)
- Secondary features (lifestyle)
- Tertiary features (sexual behavior)
- Auxiliary features (symptoms)

Examples of the detailed analysis are shown in Figure 1.

Figure 1. Examples of correlation between HIV status and selected features. Note: +1 shows a strong positive correlation, –1 shows a strong negative correlation, and 0 shows no correlation between the variables. HIV: human immunodeficiency virus.



Methods

Objectives

The primary objective of this study is to assess the participants' risk behavior using an automatic machine-guided tool and compare these results to HIV outcomes. The secondary objectives are:

- To evaluate the participants' interaction with the tool in terms of effectiveness and efficiency, that is, successful/unsuccessful completion and difficulty using the tool
- To assess the ability of the participants to correctly comprehend and complete specific behavioral questions on a digital platform
- To understand user experience and satisfaction with the overall process and recommend improvements for machine-guided tool development

The study is registered on the South African National Clinical Trial Registry (www.sanctr.gov.za; DOH-27-042021-679) and was approved by the University of Witwatersrand Human Research Ethics Committee (HREC; ethics reference no. 200312) on August 20, 2020.

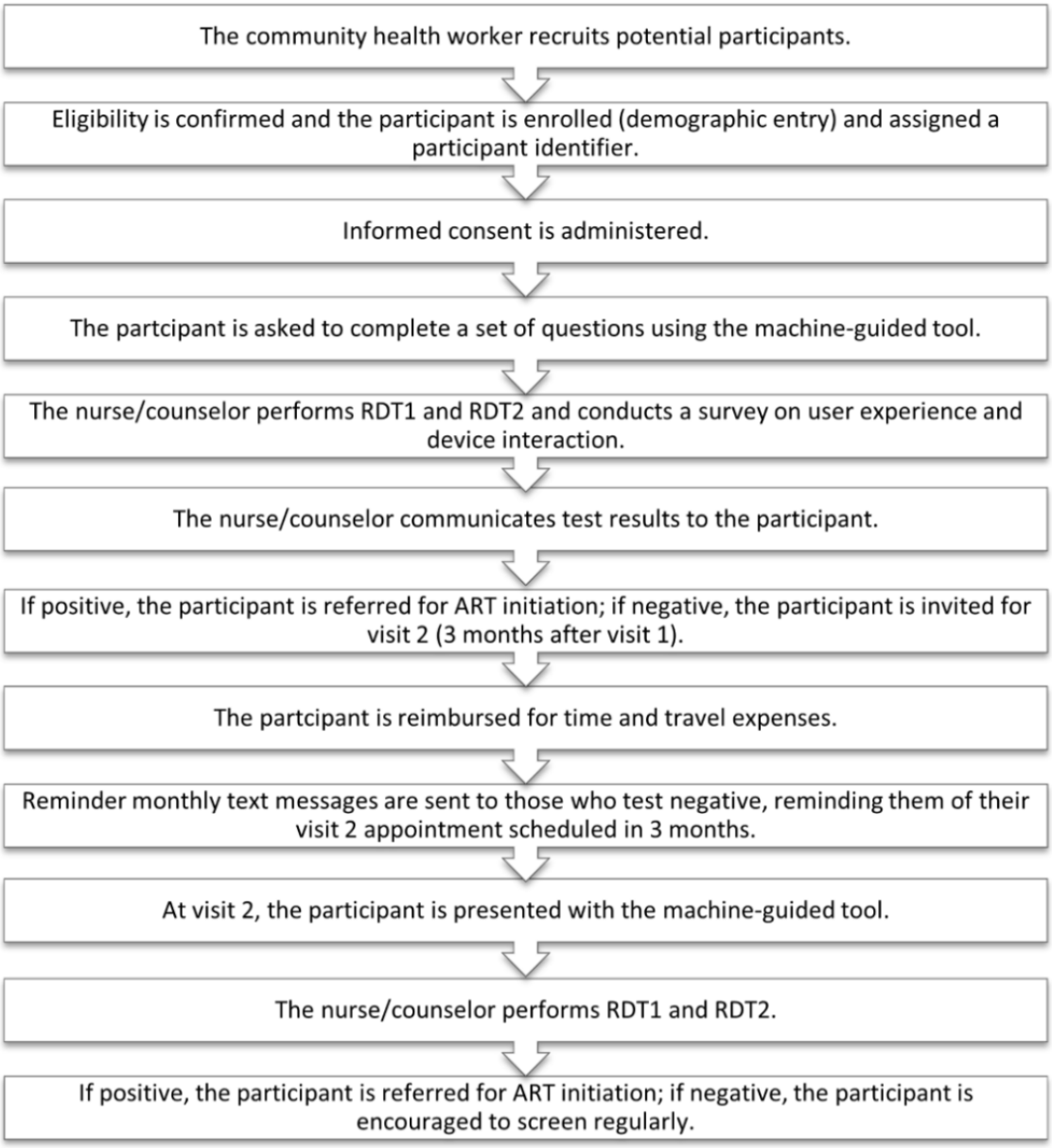
Design

In this longitudinal, supervised learning study, the data collected will be split into a training set and a validation set and the data used to validate the model will not be used in the training of the model, which will eliminate the need for a control group. This study will build on the feasibility study described before. The major variable shift is from a clinic-based setting to an in-field setting, which includes rural and semirural sites.

During the evaluation, the untrained user will be assessed thoroughly for process success or difficulty by a silent, non-interacting nurse/counselor. Overall, the process will include (1) completing a series of behavioral questions on an application system without the assistance of trained staff (assistance will only be provided on user request); (2) HIV testing being performed by the trained nurse/counselor (for comparator data to the risk assessment scores); and (3) communicating test results and completing a survey questionnaire developed to collect data on user experience.

All participants will have two rapid HIV tests performed. In the event of a positive HIV diagnosis, the participant will be referred for clinical treatment and care. If a participant tests negative, they will be found eligible for visit 2, which will occur 3 months after visit 1. At visit 2, the participant will follow the same process as that completed at visit 1 (Figure 2).

Figure 2. Flowchart of the study process from recruitment to confirmatory testing. ART: antiretroviral therapy; RDT: rapid diagnostic test.



Study Population

This is a general population study of adult males and females who are self-reported HIV negative or have an unknown HIV status in order to assess the capability, from device interaction, of identifying those who are potentially at high risk for contracting HIV. Recruitment will take place in different geographical regions using multiple recruitment methods, increasing the chances of the study population being representative of the general population.

Study Site

Participants will be recruited from three districts situated in three provinces: (1) Tshwane, Gauteng; (2) Gert Sibande, Mpumalanga; and (3) Ugu, Kwa-Zulu Natal. The participating sites comply with all local government requirements for HIV testing and reporting. All sites will receive necessary approvals prior to enrolling participants.

Sample Size

A purposive sample of 600 participants across all sites (200 per site) will be recruited for this study. In machine learning, the required sample size for a study has not developed into a clear-cut methodology and requires data to compare model performance to relative data size. Therefore, the initial feasibility study maximized on available funding to determine an initial sample size for method validation and to allow for the ability to use the initial sample to compare the performance of the model to the sample size. As seen in Figueroa et al [12], 80-560 samples were required to reach a root-mean-square error below 0.01. A sample size of 600 based on the observations of Figueroa et al [12] will facilitate comparison between model sample size and model performance in order to inform further investigations and machine learning model development. As the device is intended to be used by both males and females from the general population, this assessment aims to recruit as close to a 50% breakdown per gender as possible.

Inclusion Criteria

This study is open to individuals 18 years of age or older who meet the inclusion criteria. No potential participant will be excluded because of race, gender, ethnicity, or sexual orientation.

People volunteering to be enrolled in this study must meet the following criteria:

- Understands and signs the written informed consent form
- Is able to complete the required testing on the allocated testing day(s)
- Agrees to provide an accurate medical history and the required specimens for two fingerprick blood tests
- Is able to speak and read English
- Is ≥18 years of age
- Is willing to provide the required information for the algorithms
- Is HIV negative or has an unknown HIV status

Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

- Are known to be HIV positive
- Have received any experimental HIV vaccine
- Are currently on a PrEP regimen or any HIV treatment
- Cannot provide legal identification for age verification
- Have any condition that, in the opinion of the facilitator, would make them unsuitable or unsafe for enrollment; interfere with the completion of the assessment, consent form, and questionnaire; or bias the outcome, for example, being unable to see/read by forgetting to bring reading glasses, being intoxicated, or having acute illness

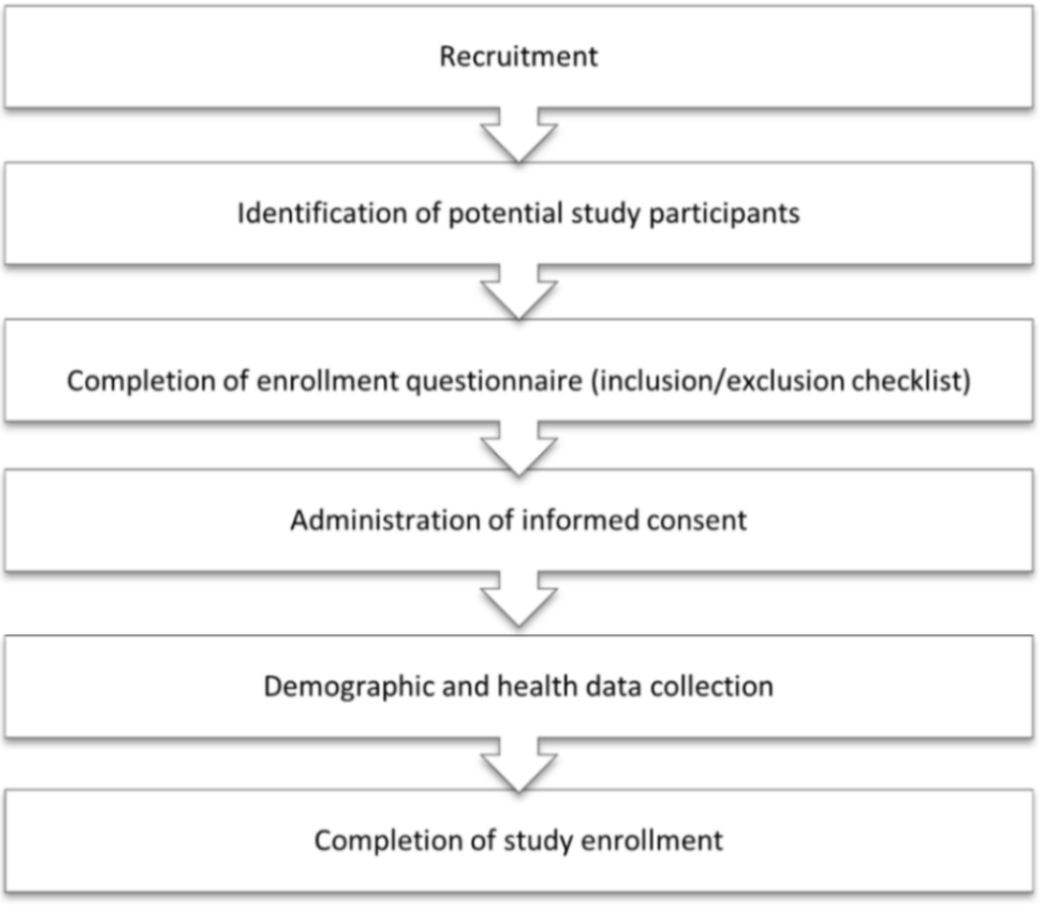
Blinding of Results

This will be a blinded study. Participants will not be aware of their risk assessment scores. There will be no randomization of participants, as all participants will be required to interact with the machine-guided tool. This study will make use of supervised learning in which the data set will be collected and then used to train and test the machine learning model that has been created. The data will be collected in a specific area, and selection will be random. The data, however, will be split into training and validation data using a randomized split algorithm commonly found in statistical and data processing languages such as R and Python.

Recruitment

Participant selection will be recruitment based related to clearly defined inclusion and exclusion criteria described before. Selected participants will be required to sign an informed consent form. Project staff will be required to fill data collection forms and study questionnaires that include participant demographic information about age, education, language preference, and a brief medical history. Participant recruitment follows a serial process, as shown in Figure 3.

Figure 3. Flowchart of participant recruitment and study enrollment.



Community-based recruitment: Participants will be recruited by community health workers stationed at a mobile testing unit using regulatory body–approved study-designed recruitment materials. Additional recruitment methods will be used, such as outreach activities within the community and appearance at community events and local malls.

Word-of-mouth recruitment: Participants will be encouraged to tell others about the study. Once potential participants have been identified through the recruitment modes, they will be approached and informed about the study and the role they will play in the study procedure. The objectives, rationale, eligibility requirements, and procedures of the study will be explained to the participants and will highlight that participation is purely voluntary. The risks and benefits of participation in the study and the rights of participants in the study will also be discussed. The participants will be encouraged to ask questions to ascertain their level of understanding and asked to take flyers home with them to inform other potential participants. Potential participants who meet inclusion criteria will be scheduled and directed to the testing site.

Enrollment Questionnaire: Inclusion/Exclusion Checklist

An enrollment questionnaire will be administered to establish successful qualification for enrollment. The questionnaire will clearly outline the inclusion and exclusion criteria. If participants satisfy all the inclusion criteria and none of the exclusion criteria, eligibility for enrollment will be confirmed. Enrollment questionnaires will be available in English and will capture information such as participant identification, name and surname, date of birth, nationality, employment status, and recruitment site. Information such as participant initials, date of birth, gender, date of enrollment, and reason for exclusion will be captured on an enrollment log. Once a participant has qualified for enrollment and has signed the informed consent form, the participant will be assigned a unique identification number. Volunteers who do not satisfy inclusion criteria will be documented and reported as exclusions. Further, the reason for enrollment failure will also be recorded.

Selection and Withdrawal of Study Participants

Participants may voluntarily withdraw participation at any time. In this case, the principal investigator (PI) will acquire all study-related information and the reason for withdrawal will be documented. The information and data collected prior to participant withdrawal from the study may be used for research by the PI or sponsor. This information may be used without identifying any personal information as agreed upon in the informed consent form unless the participant provides a written request prohibiting/limiting the use of their study data.

The PI may decide to limit or withdraw participation of any participant at any point in the study. Further, the sponsor may close the study prematurely for any reasons, including administrative decisions.

Informed Consent

Prior to any research processes taking place, potential participants will be provided with information about the study, enabling an informed decision regarding further participation. If the participant voluntarily accepts participation, a regulatory body–approved informed consent form will be administered. The form will contain general information about the study and specific information regarding sample collection and all other study procedures.

Potential participants will be encouraged to ask questions to ensure the entire process is clearly understood. Prospective participants will also be informed that they may reject the specimen collection procedure and withdraw from the study at any time. Participants must agree to and submit their informed consent forms (along with demographic data; see below) prior to formal enrollment in the study.

Informed consent will be offered after verbal explanation of the study procedures in English by designated staff. If a participant is found to be unable to read or write, no further consent procedures will be undertaken.

Demographic and Health Data Collection

All enrolled participants will have the following demographic data captured:

- Initials
- Date of birth
- Age
- Gender
- Nationality

The participant background information captured will include:

- Employment status (employed/unemployed)
- Years of schooling and level (≤grade 7 primary schooling level/≥grade 8 primary schooling to ≤matric level/≥Technikon, university, and university plus)
- Reading/writing impairment
- Language preference
- HIV status (if known)
- Approximate date of last HIV test

Participants may choose to report their medical health history, which will be documented and archived for statistical review. Information will include:

- Self-reported HIV status:
- Unknown status/never been tested
- Negative status
- Self-reported medical conditions:
- Diabetes
- Hypertension
- Visual impairment
- Pregnancy
- Other

Testing Procedures

Subject Tool Evaluation

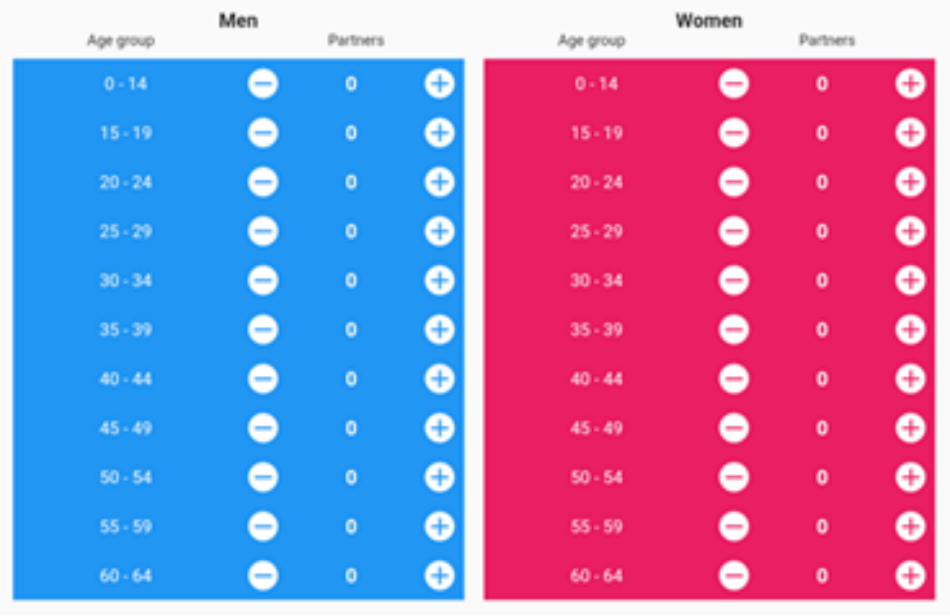
After the consenting procedures, enrollment questionnaire, and demographic data have been collected, each participant will be invited into a private area (tent, gazebo setting) and introduced to the clinical staff (nurse/counselor), who will describe the study process. The digital tool interaction is to be completed

under the direct observation of the study staff. The nurse/counselor will verbally guide the participant as follows: "This is the part of the study in which you will be asked to use the study product. With this product, you can begin to answer the questions yourself. I will be available to answer any questions or explain further if you require assistance, but would prefer that you try and use the tool on your own. When you are finished, you can let me know and we will proceed to testing."

Each participant will be presented with a tablet that has the application installed and will be requested to complete the set of questions listed below:

1. Please select your gender.
   - Male
   - Female
   - Transgender
2. Date of birth:
3. Please select your race.
   - Black
   - White
   - Indian
   - Colored
   - Other (please specify)
4. What is your education level?
   - Primary school
   - High school
   - Diploma or certificate
   - Tertiary
   - None of the above
5. What is your occupation type?
   - Informal (different employers, depending on job) How long working away from home (remote)? 1 week per month 2 weeks per month 3 weeks per month 1 month or longer Working in the same city/area where you live (local)
   - Formal (permanently employed and same boss) How long working away from home (remote)? 1 week per month 2 weeks per month 3 weeks per month 1 month or longer Working in the same city/area where you live (local)
   - Unemployed (no job)
6. When was the last time you tested for HIV?
   - 0-3 months
   - 3-12 months
   - More than 12 months
   - Never tested
7. Do you use a condom during sex?
   - Yes
   - No
   - Sometimes
   - I have never had sex.
8. Please select the gender and age of all sexual partners with whom you had sex in the past 3 months.
   - Number of partners and age groups (Figure 4)
   - No sex in the past 3 months
9. Which of the following sexual activities have you performed in the past 6 months?
   - Anal receptive (you receive penis in anus)
   - Anal insertive (you insert penis in partner's anus)
   - Vaginal receptive (you receive penis in vagina)
   - Vaginal insertive (you insert penis in partner's vagina)
   - Oral receptive (your partner sucks your vagina/penis)
   - Oral insertive (you suck partner's vagina/penis)
   - None of the above
10. Have you gone through any of the following in the past 6 months?
    - Sexually abused
    - Stabbed
    - Bitten
    - Scratched
    - None of the above
11. Have you experienced/noticed any or many of the following?
    - Weight loss of more than 5 kg over 3 months
    - Persistent cold and flu in the past 6 months
    - Persistent diarrhea and fatigue in the past 6 months
    - Recurring night sweats in the past few months
    - White patches in mouth
    - Bad breath
    - Sore throat
    - Ulcers
    - Difficulty in eating
    - Dry cough
    - Wet cough for more than 3 weeks in the past 1 year
    - Blood in cough in the past 1 year
    - Persistent fever or chills for no known reasons in the past 1 year
    - Persistent shortness of breath or chest pain in the past 1 year
12. Have you experienced/noticed any or many of the following?
    - Genital warts (small bumps on genitals)
    - Genital herpes (genital pains or sore genitals and open sores on genitals)
    - Gonorrhea (bacterial infection: white or yellow liquid visible in genital region)
    - Syphilis (rash on the body or painless sore on genitals, rectum, or mouth)
    - Gonococcal (painful urination and abnormal discharge from penis or vagina)
    - None of the above

Figure 4. Number of partners and age groups selection box.



A trained nurse/counselor will proceed to perform two rapid HIV tests and communicate the results to the participant. If the results are HIV positive, the participant will be counseled and encouraged to commence antiretroviral therapy at a clinic of their choice. If the results are HIV negative, the participant will be eligible for visit 2 (3 months after visit 1) and will be issued with an appointment card. If the results are discordant, the nurse/counselor will be required to repeat testing. Additionally, the participant will be sent visit 2 appointment reminders through text messages monthly.

Confirmatory Procedures

HIV status will be confirmed using the rapid diagnostic kits in-use (First Response HIV 1-2-0 and Alere DetermineHIV-1/2) at the testing site. If the confirmatory rapid test is HIV positive, the participant will be referred to a clinic of their choice for treatment and care.

In the event the second rapid test shows a negative result, the HIV status will be considered indeterminate, and all tests will be repeated (Textbox 1) [13].

Textbox 1. Interpreting test results. RDT: rapid diagnosis test.

RDT1 (positive) + RDT2 (positive) = positive
RDT1 (negative) + RDT2 (negative) = negative
RDT1 (negative) + RDT2 (positive) = indeterminate (repeat test)
RDT1 (positive) + RDT2 (negative) = indeterminate (repeat test)

Data Analysis

The study endpoints for this trial are concerned with the proportion for concordance of the participants' risk assessment score with the confirmatory test results.

An interim analysis of the results will be reviewed after visit 1 has been completed. All the recorded risk behavioral scores will be analyzed for any correlation between HIV testing outcomes.

In addition, the analysis plan will include an evaluation performed at visit 2, identifying cases where an initial nonreactive test (at visit 1) has resulted in a change to a reactive test result (at visit 2).

Machine Learning Algorithm

The first phase of this machine-guided diagnostic study will be used to compare potential supervised learning algorithms to determine which algorithm is the most robust in variable variation. The algorithms that will be compared are K-nearest neighbor, logistic regression, neural network, random forest, support vector machine, and XGBoost. These models will be compared using a confusion matrix by comparing sensitivity, specificity, accuracy, precision, and negative predictive value. When comparing models, the relative risk of a false negative versus a false positive will be taken into consideration to minimize the risk of potentially high-risk patients not being flagged for further screening.

Error and Failure Rates

Critical errors occur when participants make operational errors during interaction with the machine-guided tool. Project staff will aid participants, if needed, to ensure accurate completion of all behavioral questions that contribute directly to risk assessment scores.

The failure rate (cases where the risk score is high and the test result remains negative for both visits) will be identified and reported as the number or a percentage of failed cases of the total number of cases completed in the study.

It should be noted that failure due to critical errors (participants not being able to successfully complete the digital assessment) will not be included in the analysis.

The type of behavioral questions and the weighted score for each will be monitored and evaluated for continuous improvement and refinement purposes.

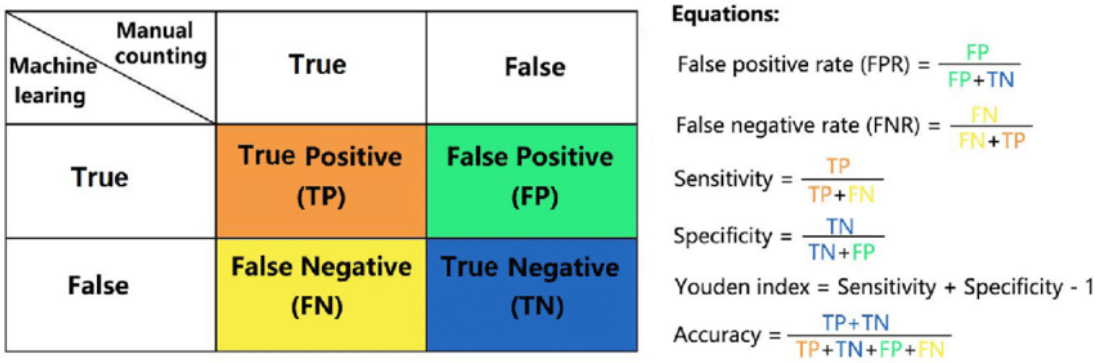
Missing Data

The study will use electronic data capture for each participant, which requires that each question be completed before moving on to the next. This will eliminate the possibility of missing data during the data collection section of the study. Any participant record with missing results for a HIV test will be removed from the study.

Sensitivity Analysis

The performance of the model will be analyzed using the validation data set from the data split using a confusion matrix (Figure 5) that will allow for the calculation of sensitivity, specificity, and accuracy.

Figure 5. Confusion matrix with classification metrics [14].



Interaction Between Variables

A bivariate analysis will be performed for each variable to investigate the relationship between the respective variable and HIV status. This will then further be used in feature engineering.

Post Hoc Analysis

In machine learning, post hoc analysis is not commonly performed, and a comparison of model performance through the analysis of a confusion matrix and confidence curves offers an alternative to conventional omnibus tests [15].

Skewed Data

The participants enrolled in this study who are either HIV negative or of unknown HIV status will cause a lower HIV prevalence in the sample data set. However, this will be done so as to remove the possibility of participants who are HIV positive creating a bias in the supervised learning, as these people may have altered behavior due to being HIV positive, which may result in risk reduction behavior, reducing the sensitivity and accuracy of the model. The skewed data set will be accounted for in the second phase of the study, where participants will perform two visits, including a follow-up HIV test, which will allow for the analysis of a comparison to the predictive ability of the machine learning model created in phase 1.

Secondary Objectives

The usability of the tool will be measured through direct observation. The study staff will complete a checklist and note whether each participant was *successful* or *unsuccessful* in using the tool. They will also note whether the participant was able to complete the behavioral questions via electronic data collection.

User satisfaction will be recorded by a study team member via a series of yes/no questions to obtain an overall satisfaction score. Additionally, recommendations will be captured as free text and coded during analysis.

Data Management

Data management will be undertaken by the HSTAR staff. Data will be collected on paper (questionnaires, informed consent forms) and on tablets (demographic data collection) and will be transmitted daily to the research site data staff. A data capturer will enter the paper-based data into an in-house-developed electronic database within 2 days. Data quality control will be managed daily by the project team.

Confidentiality

All documents, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by regulatory authorities.

> *The PI or designee and the study team may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. All computers are password-protected, and records can only be accessed by permitted study staff.*

Record Retention

All correspondence relating to this study will be kept in appropriate study folders. Records of participants, source documents, and questionnaires pertaining to the study will be kept on file. Essential documents will be retained until at least 2 years after the last approval of a marketing application in an

International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of product development. These documents will be retained for a longer period, if required by the applicable regulatory requirements. If an investigator moves, withdraws from the study, or retires, the responsibility for maintaining the records will be transferred to another person who is willing to accept the responsibility.

Data Reporting

Data reporting will be performed by the program manager and study consultants. A research report will describe the study area, study population, and execution of the research and present the study results. The report will present both qualitative and quantitative discussions on the outcomes of the study.

Biannual progress reports will be submitted to the University of the Witwatersrand Human Research Ethics Committee (HREC) for the duration of the study. Annual recertification will be obtained from the HREC. Upon completion or premature termination of the study, the PI will provide the HREC with a summary of the study's outcome and any other regulatory authorities with any reports required.

Other Study Procedures

Investigator Documentation

Prior to study commencement, the PI will be asked to comply with ICH E6(R1) 8.2 by providing the following essential documents, including but not limited to:

- An original signed investigator agreement page of the protocol.
- An HREC-approved informed consent form, samples of site advertisements for recruitment for this study, and any other written information regarding this study that will be provided to the participants.
- HREC approval.
- Curriculum vitae of the PI and each investigator. They will be signed and dated by each investigator at study start-up, indicating that they are accurate and current.

Quality Control and Study Monitoring

Quality control of the study will be performed following the standard operating procedures developed for the study and those generic to the implementing organization. The project manager will assume overall responsibility for ensuring all procedures are adhered to and quality controlled.

A study monitor will be contracted. The study monitor will have the obligation to follow the study closely. In doing so, the study monitor will visit the study facility at periodic intervals, in addition to maintaining necessary telephonic and email contact. They will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the PI and study staff.

All aspects of the study will be carefully monitored for compliance with applicable government regulation with respect to current ICH good clinical practice (GCP) guidelines and current standard operating procedures.

Protocol Amendments

Protocol amendments will be prepared by the PI. These amendments will be submitted in writing to the HREC for approval prior to participants being enrolled into the amended protocol, except where it is necessary to eliminate an immediate hazard to participants or where the changes involve only logistical or administrative aspects of the clinical study. This will be fully documented.

Examples of amendments requiring approval are:

- A significant change in the study design
- An addition or deletion of a test procedure for safety monitoring

The requirements for approval will in no way prevent any immediate action from being taken by the investigator or the sponsor in the interests of preserving the safety of all participants included in the study. If an immediate change to the protocol is deemed necessary by the investigator and is implemented by them for safety reasons, the PI will be notified and the HREC will be informed within 10 working days.

Protocol Violations and Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the HREC and agreed to by the PI or designee. Deviations usually have an impact on individual participants or a small group of participants and do not involve inclusion, exclusion, or primary endpoint criteria.

A protocol violation occurs when there is non-adherence to the protocol that results in a significant additional risk to the participant, when the participant or PI or designee fails to adhere to significant protocol requirements (inclusion and exclusion criteria) and the participant is enrolled without prior approval, or when there is non-adherence to regulations or some ICH GCP guidelines.

The PI or designee will document and explain in the participant's source documentation any deviation from the approved protocol. The PI or designee may implement a deviation from or a change of protocol to eliminate an immediate hazard to trial participants without prior HREC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments will be submitted to the HREC for review and approval.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. The PI or designee will be notified in writing by the monitor of violations and deviations. The HREC will be notified of all protocol violations and deviations in a timely manner.

Adverse Events and Adverse Device Event Reporting

Adverse events will be captured, and line listings provided. Any serious adverse event or adverse device event that may occur will be reported to the PI. Depending on the severity of the

adverse event, the PI is obliged to report the event to the HREC. All serious adverse events will be reported by the PI.

Inspection of Records

The PI or designee and institutions involved in the study will permit study-related monitoring, audits, HREC reviews, and regulatory inspections by providing direct access to all study records.

Study Termination

Although there is every intention to complete the study, the implementing organization reserves the right to discontinue the study at any time for clinical or administrative reasons. The end of the study is defined as the date on which the last participant completes the last visit.

Dissemination

De-identified results will be disseminated through community engagements, study reports, and peer-reviewed publications and conference presentations. All outputs will be produced in compliance with donor requirements.

Results

This study received ethical approval from the University of Witwatersrand HREC (ethics reference no. 200312) on August 20, 2020, and has been funded by the Bill & Melinda Gates Foundation (OPP 1204282). As an ongoing study, data collection has commenced and is expected to be completed in the second half of 2021. At the end of this study, we will be able to report on the performance and usability of the machine-guided tool, that is, the accuracy of the tool to identify people who are at high risk of contracting HIV and how easy participants find it to successfully interact with the digital platform. Lastly, the results of this study will report on user satisfaction and their recommendations for improvement. The results will be disseminated by the first quarter of 2022.

Discussion

Importance of Principal Findings

To the best of our knowledge, this would be the first evaluative report on a machine-guided tool for assessing the risk behavior associated with HIV acquisition in the South African context. South Africa has a high burden of HIV, and less than 90% of the population knows its HIV status [16]. Despite the large financial investment in the country, prevention of HIV infection remains a challenge [17]. In evolving economic landscapes and contexts that necessitate employment of innovative approaches to addressing HIV, machine guidance has the potential to offer a cost-effective, focused solution to identify priority populations for HIV prevention and treatment. Our study will provide evidence for this approach as a possible solution to tackling HIV risk and identification.

Machine guidance and artificial intelligence have proven useful in the health sector and are being used in many branches of medicine, including gastroenterology and hepatology [18], oncology [19,20], and infectious diseases [21,22]. For HIV, the potential benefits of engaging in machine-guided identification include immediate and private HIV test results, which may encourage frequent testing of individuals in high-risk groups who would otherwise refrain from testing due to the unknown risk factors associated with susceptibility to acquiring HIV. Although many health ministries make available free testing for HIV in a clinical setting, this machine-guided identification removes the need for spending time visiting a clinic and waiting for results, which is particularly critical where public testing facilities require long-distance traveling.

Nguyen et al [23] highlight the importance of understanding high-risk behaviors (eg, multiple concurrent partnerships, unprotected sex, and needle sharing) and demographic characteristics of people newly diagnosed with HIV/acquired immunodeficiency syndrome (AIDS). It is crucial for health programmers to consider this information as they design strategies for preventing HIV acquisition and transmission. With an earlier diagnosis, individuals are empowered to identify and modify their high-risk behaviors, potentially reducing the number of new HIV infections. This empowerment of consumers is not just limited to modifying lifestyle decisions but also involves being proactive in their health care decisions, which include adherence to clinic appointments and HIV treatment adherence (crucial to the prevention of viral rebound, treatment resistance, and the success of HIV management programs) [24,25].

The risk probability of contracting HIV may positively impact the effectiveness of universal testing and treatment by directing limited testing/treatment resources to the highest-risk groups, the number of people knowing their HIV status, the number of people linked to services, decision making and follow-up costs, reduction in duplication of tests, identification of high-risk self-harm cases, and PrEP initiation.

Conclusion

Machine-guided risk assessment tools can provide a cost-effective alternative to large-scale HIV screening. This will be beneficial in providing directed counseling and testing to prevent the spread of HIV.

Acknowledgments

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Authors' Contributions

Conceptualization: CFJF and LA; funding acquisition: KH; writing—original draft: CFJF, LA, and STL-E; writing—review and editing: MM, MP, KH, SM, AK, and STL-E. All authors have read and agreed to the published version of the manuscript. The data sets that will be collected during the study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AIDS: acquired immunodeficiency syndrome
ART: antiretroviral therapy
GCP: good clinical practice
HIV: human immunodeficiency virus
HREC: Human Research Ethics Committee
HSTAR: HIV self-testing assessment and research
ICH: International Conference on Harmonization
PI: principal investigator
PrEP: pre-exposure prophylaxis
RDT: rapid diagnostic test
UNAIDS: Joint United Nations Programme on HIV/AIDS

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Protocol

Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER): Protocol for a Multisite Longitudinal Cohort Study

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Abstract

Background: Workers critical to emergency response and continuity of essential services during the COVID-19 pandemic are at a disproportionally high risk of SARS-CoV-2 infection. Prospective cohort studies are needed for enhancing the understanding of the incidence of symptomatic and asymptomatic SARS-CoV-2 infections, identifying risk factors, assessing clinical outcomes, and determining the effectiveness of vaccination.

Objective: The Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER) prospective cohort study was designed to estimate the incidence of symptomatic and asymptomatic SARS-CoV-2 infections, examine the risk factors for infection and clinical spectrum of illness, and assess the effectiveness of vaccination among essential workers.

Methods: The RECOVER multisite network was initiated in August 2020 and aims to enroll 3000 health care personnel (HCP), first responders, and other essential and frontline workers (EFWs) at 6 US locations. Data on participant demographics, medical

history, and vaccination history are collected at baseline and throughout the study. Active surveillance for the symptoms of COVID-19–like illness (CLI), access of medical care, and symptom duration is performed by text messages, emails, and direct participant or medical record reports. Participants self-collect a mid-turbinate nasal swab weekly, regardless of symptoms, and 2 additional respiratory specimens at the onset of CLI. Blood is collected upon enrollment, every 3 months, approximately 28 days after a reverse transcription polymerase chain reaction (RT-PCR)–confirmed SARS-CoV-2 infection, and 14 to 28 days after a dose of any COVID-19 vaccine. From February 2021, household members of RT-PCR–confirmed participants are self-collecting mid-turbinate nasal swabs daily for 10 days.

Results: The study observation period began in August 2020 and is expected to continue through spring 2022. There are 2623 actively enrolled RECOVER participants, including 280 participants who have been found to be positive for SARS-CoV-2 by RT-PCR. Enrollment is ongoing at 3 of the 6 study sites.

Conclusions: Data collected through the cohort are expected to provide important public health information for essential workers at high risk for occupational exposure to SARS-CoV-2 and allow early evaluation of COVID-19 vaccine effectiveness.

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KEYWORDS

COVID-19; SARS-CoV-2; incidence; vaccine effectiveness; cohort study; health care personnel; first responder; essential and frontline workers

Introduction

SARS-CoV-2, the virus causing the COVID-19 global pandemic, has rapidly spread throughout the world and has led to over 3 million deaths since December 2019 [1,2]. Evidence from prospective cohort studies is critical for understanding the incidences of symptomatic and asymptomatic SARS-CoV-2 infections, identifying risk factors, assessing clinical outcomes, and determining the effectiveness of vaccination. Studies have suggested that the incidence of asymptomatic SARS-CoV-2 infection is high, but it is unclear whether or not individuals remain asymptomatic throughout their infection [3,4]. Additionally, while rare, reinfection has been documented among healthy adults with an indication of diminishing severity that may require systematic monitoring to identify asymptomatic infections [5]. Moreover, emerging variants of SARS-CoV-2 are causing concern and have been associated with an increase in the incidence of infection and may have implications for COVID-19 vaccine effectiveness [6-8]. Research is needed to improve our understanding of SARS-CoV-2 to better inform public health policies that may help protect essential workers and their patients, co-workers, customers, and household members, as well as others in the community, as they respond to the pandemic.

Essential workers, including health care personnel (HCP), first responders, and other essential and frontline workers (EFWs), serve in vital roles requiring direct interaction with the public to maintain the minimum requirements for a functional society. HCP include physicians, physicians' assistants, nurse practitioners, dentists, medical assistants, medical technicians, nurses, nursing assistants, occupational therapists, pharmacists, and nonclinical personnel, including but not limited to social workers, receptionists, etc. First responders are workers in care or public contact response roles, including emergency medical technicians, firefighters, law enforcement, security guards, and other responders to emergency situations. EFWs are those not in HCP or first responder occupations, who perform work that cannot be executed from home and cannot be done without contact with other people. These include grocery store clerks, food service workers, those in certain agricultural and manufacturing occupations, hospitality employees, transportation and construction workers, and school teachers, among others. In a pandemic, these workers provide direct patient care, respond to the public need for assistance, and maintain critical public and private services. Work-related risks and exposures in essential workers differ from those in the general public, placing them at higher risk for exposure, infection, and transmission of SARS-CoV-2 [9-14]. The increased risk of infections, such as influenza, has previously been recognized for HCP and first responders, but few studies have been conducted to assess EFW infection risk or adherence and attitudes toward personal protective equipment (PPE), the use of which has been recommended as part of the COVID-19 pandemic response. A comprehensive assessment of these broad occupational categories is needed to understand infection risk, appropriate control measures, and COVID-19 vaccine effectiveness.

Vaccination against COVID-19 is an important tool for reducing both SARS-CoV-2 infections and the morbidity and mortality impacts associated with these infections. The Advisory Committee on Immunization Practices identified certain essential workers (particularly HCP and first responders) for earlier receipt of COVID-19 vaccines, making this population a high priority for studies evaluating vaccine effectiveness in preventing SARS-CoV-2 infection and transmission [15].

We designed a prospective cohort study entitled "Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER)" for estimating the incidences of asymptomatic and symptomatic infections and reinfections of SARS-CoV-2 in essential workers and for the rapid evaluation of COVID-19 vaccine effectiveness and immunogenicity against SARS-CoV-2 infection. In addition to these 2 primary objectives, data from the RECOVER study will be analyzed to assess a set of secondary objectives, including the risk factors for infection, the clinical spectrum of illness, the severity of

infection after vaccination, and vaccine effectiveness against secondary infections within households.

Methods

Study Design

The RECOVER study has been designed to enroll and follow approximately 3000 essential workers for at least 18 months in 6 states. The primary objectives are to (1) estimate the incidences of asymptomatic and symptomatic SARS-CoV-2 infections and reinfections, and (2) evaluate COVID-19 vaccine effectiveness in preventing symptomatic and asymptomatic SARS-CoV-2 infections. Additional objectives include examining individual and occupational predictors of infection, and characterizing the clinical spectrum of COVID-19 illness. We also examine the association involving serum concentrations of per- and polyfluoroalkyl substances (PFAS), a component of some fire-suppression foams that has been associated with reduced immune response to vaccination [16]. Finally, we evaluate humoral and cellular immune responses to infection and vaccination, and estimate secondary infection rates within the households of vaccinated and unvaccinated RECOVER participants (Textbox 1).

The RECOVER study is funded by the US Centers for Disease Control and Prevention (CDC). The CDC and Abt Associates made key decisions on the study design, with scientific and operational input from investigators at each of the 6 study sites. Marshfield Clinical Research Institute in Marshfield, Wisconsin advised on laboratory methods for respiratory specimens in the study, and the CDC advised on the laboratory methods for serologic specimens. All study sites use a common protocol and data collection instruments approved by their institutional review boards (IRBs), as well as standard operating procedures.

Textbox 1. Objectives of the RECOVER (Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel) study.

Primary objectives

- Determine the frequency of SARS-CoV-2 infection and COVID-19 illness among essential workers using both molecular and serologic diagnostic tests.
- Identify and describe SARS-CoV-2 reinfections among essential workers with prior SARS-CoV-2 infection as confirmed by reverse transcription polymerase chain reaction and/or SARS-CoV-2 serum antibody detection.
- Assess the effectiveness of SARS-CoV-2 vaccines in preventing SARS-CoV-2 infection and COVID-19 illness in essential workers. Examine vaccine effectiveness for different vaccine exposures, including different vaccine types and full versus partial adherence to recommended vaccine doses and timing.

Secondary objectives

- Assess the incidence of primary symptomatic and asymptomatic laboratory-confirmed SARS-CoV-2 infections in essential workers by examining observed frequencies within the context of characterized source populations.
- Examine the individual, occupational, and environmental predictors of SARS-CoV-2 infection and of asymptomatic infection versus symptomatic COVID-19 illness in essential workers.
- Describe the clinical characteristics and outcomes associated with COVID-19 in essential workers.
- Characterize the duration and severity of illness and examine the sociodemographic and health characteristics associated with prolonged or severe illness in essential workers.
- Determine the impact of COVID-19 on the indicators of functioning, including missed work, ability to complete normal work and home activities, and working while ill in essential workers.
- Determine the proportion of COVID-19 illnesses that are medically attended and examine the factors associated with seeking medical care and treatment in essential workers.
- Compare illness characteristics and duration among essential workers with primary infection versus reinfection with SARS-CoV-2.
- Evaluate the kinetics of immune responses to SARS-CoV-2 infection by comparing immune indicators from sera collected before or during illness with those collected after illness in essential workers.
- Examine antibody correlates of protection against SARS-CoV-2 reinfection in essential workers.
- Examine the duration of viral RNA detection associated with symptomatic COVID-19 illness in essential workers.
- Examine the interindividual variability in the magnitude and duration of viral RNA detection in essential workers.
- Assess the infectiousness of prolonged virus shedding in essential workers.
- Identify essential workers' familiarity with personal protective equipment and other infection control measures or facility policies related to SARS-CoV-2, COVID-19, and pandemic response.
- Compare molecular diagnosis relying on different respiratory specimen types (eg, anterior nasal swabs versus saliva).
- Examine the association between serum concentrations of per- and polyfluoroalkyl substances (PFAS) in essential workers and the manifestations of COVID-19 illness and immune response to SARS-CoV-2 infection, including risk of reinfection and COVID-19 vaccine effectiveness.

Additional pandemic vaccine objectives

- Assist in the evaluation of the immunogenicity of pandemic SARS-CoV-2 vaccines by collecting sera from essential workers before and after vaccination and performing serologic and cellular immune response testing.
- Examine whether vaccine effectiveness is modified by sociodemographic characteristics, occupation, health status, or other risk factors in essential workers.
- Examine whether vaccination modifies COVID-19 illness severity, duration, and infectiousness (or viral shedding) among essential workers with breakthrough infections.
- Characterize the knowledge, attitudes, and practices related to new COVID-19 vaccines and examine the associations of knowledge, attitudes, and practices with subsequent vaccination behaviors (including vaccine refusal, hesitancy, or incomplete adherence to vaccination recommendations) among essential workers.
- Determine the association of serum PFAS concentration with SARS-CoV-2 infection, COVID-19 illness, and SARS-CoV-2 antibodies in essential workers.

Exploratory objectives

- Examine the kinetics of the immune response to SARS-CoV-2 infection through serial sampling of sera in essential workers.
- Examine the kinetics of viral shedding associated with SARS-CoV-2 infection and COVID-19 illness in essential workers.
- Examine individual heterogeneity in the use and host response to COVID-19 therapeutics and vaccines in essential workers.

- Examine cell-mediated immune responses (B cells, and CD4 and CD8 T cells) to SARS-CoV-2 infection in essential workers.
- Estimate the secondary attack rate of SARS-CoV-2 infection within households of essential workers.
- Estimate the effectiveness of available vaccines or antiviral prophylaxes and treatments to prevent secondary transmission within the households of essential workers as they become available.

Setting

The RECOVER study consists of 6 health care system–based and academic research and hospital-based partner institutions with experience recruiting HCP and first responder cohort populations. Most of these study sites also serve as the usual source of medical care to a large proportion of the local community population, including essential workers, and are uniquely positioned to rapidly identify and recruit participants. The RECOVER study network includes the University of Arizona in Tucson, Arizona; Baylor Scott and White Health in Temple, Texas; Kaiser Permanente Northwest in Portland, Oregon; the University of Miami in Miami, Florida; St. Luke's Hospital in Duluth, Minnesota; and the University of Utah in Salt Lake City, Utah (Table 1).

Table 1. RECOVER (Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel) study sites and site characteristics.

Variable	University of Arizona	Baylor Scott & White Health	Kaiser Permanente Northwest	University of Miami	St. Luke's Hospital	University of Utah
Geographic area of the site	Tucson, Arizona	Temple, Texas	Portland, Oregon	Miami, Florida	Duluth, Minnesota	Salt Lake City, Utah
Participant catchment area	Pima County, Arizona	Bell County, Texas and cities of Temple, Belton, and Killeen, Texas	Northwest Oregon from Eugene, Oregon to Longview, Washington	Miami-Dade, Broward and Palm Beach Counties, Florida	Within 100 miles of Duluth, including northwest Wisconsin	Within 60 miles of Salt Lake City, Utah
Study population composition goal	14% HCP[a] 37% first responders 49% EFWs[b]	70% HCP 10% first responders 20% EFWs	68% HCP 11% first responders 21% EFWs	9% HCP 64% first responders 27% EFWs	68% HCP 11% first responders 21% EFWs	45% HCP 29% first responders 26% EFWs
Communication of reverse transcription polymerase chain reaction results to participants	Study staff call with positive results; positive and negative test results sent by mail	Study staff call with positive results; positive and negative results added to participant's EMR[c] as a patient message	Study staff call with positive results; positive and negative test results sent by mail	Study staff call with positive results; positive and negative test results sent by email	For HCP, occupational health reports to participants. For first responders and EFWs, staff call with positive test results	Positive and negative test results emailed to participants
Communication of reverse transcription polymerase chain reaction results to the state or local health department	Positive and negative test results submitted to Arizona Department of Health Services	Positive test results submitted to Bell County Health Department	Positive and negative test results submitted to Oregon Health Authority and Washington Department of Health	Positive and negative test results submitted to Florida Department of Health	Positive test results submitted to Minnesota Department of Health or Wisconsin Department of Health	Positive and negative test results submitted to Utah Department of Health
Primary recruitment method for HCP and first responders	Recruiting from an existing Firefighter Cancer Cohort study and the University of Arizona Antibody Testing Initiative, as well as via fire station, police department, hospital, and clinic site visits	Recruiting from volunteers of previous research studies and employees within the Baylor health system via hospital and clinic site visits, targeted emails, and phone calls	Recruiting from volunteers of previous research studies and employees with Kaiser medical coverage via targeted emails and phone calls	Recruiting from an existing Firefighter Cancer Cohort study, as well as via fire station, police department, hospital, and clinic site visits	Recruiting from employees within the St Luke's health system and surrounding area first responder companies via targeted emails to team leaders, emails to employee lists, and phone calls	Recruiting from employees within the University of Utah health system and surrounding area first responder companies via targeted letters to team leaders, emails to employee lists, and phone calls
Primary recruitment method for EFWs	Recruiting from employer groups via site visits, employer contacts, and the Arizona Antibody Testing Initiative	Recruiting from various local worker groups associated with existing university partners via emails and local radio advertisements	Recruiting from the population with Kaiser medical coverage via targeted emails and phone calls	Recruiting from various local worker groups associated with existing university partners via in-person outreach and email invitations	Recruiting from various local worker groups via social media, calls, emails, local radio advertisements, and current participant referrals	Recruiting from various local worker groups associated with existing university partners via social media, emails, and local radio/media advertisements

[a]HCP: health care personnel.

[b]EFW: essential and frontline worker.

[c]EMR: electronic medical record.

Eligibility Criteria

Eligible essential workers include HCP, first responders, and EFWs who meet the following criteria: age at least 18 years; current work in a health care, first response, or another essential or frontline occupation; work for at least 20 hours a week; direct contact with people, defined as being within 3 feet of other people as part of job responsibilities; willingness to receive and respond to SMS text messages; and willingness to provide medical history via electronic medical record (EMR) access or health-related questionnaires. This study's definition of "direct contact" (within 3 feet) does not require physical contact, but it is physically closer than that in the definition used to describe any contact for SARS-CoV-2 exposure (within 6 feet) to reflect

high exposure conditions common to essential responder occupations [17]. Potential participants are excluded if they work less than an average of 20 hours per week, have already received a COVID-19 vaccine, or have participated in a COVID-19 prevention or treatment investigational trial in the 3 months prior to screening for the study.

Recruitment

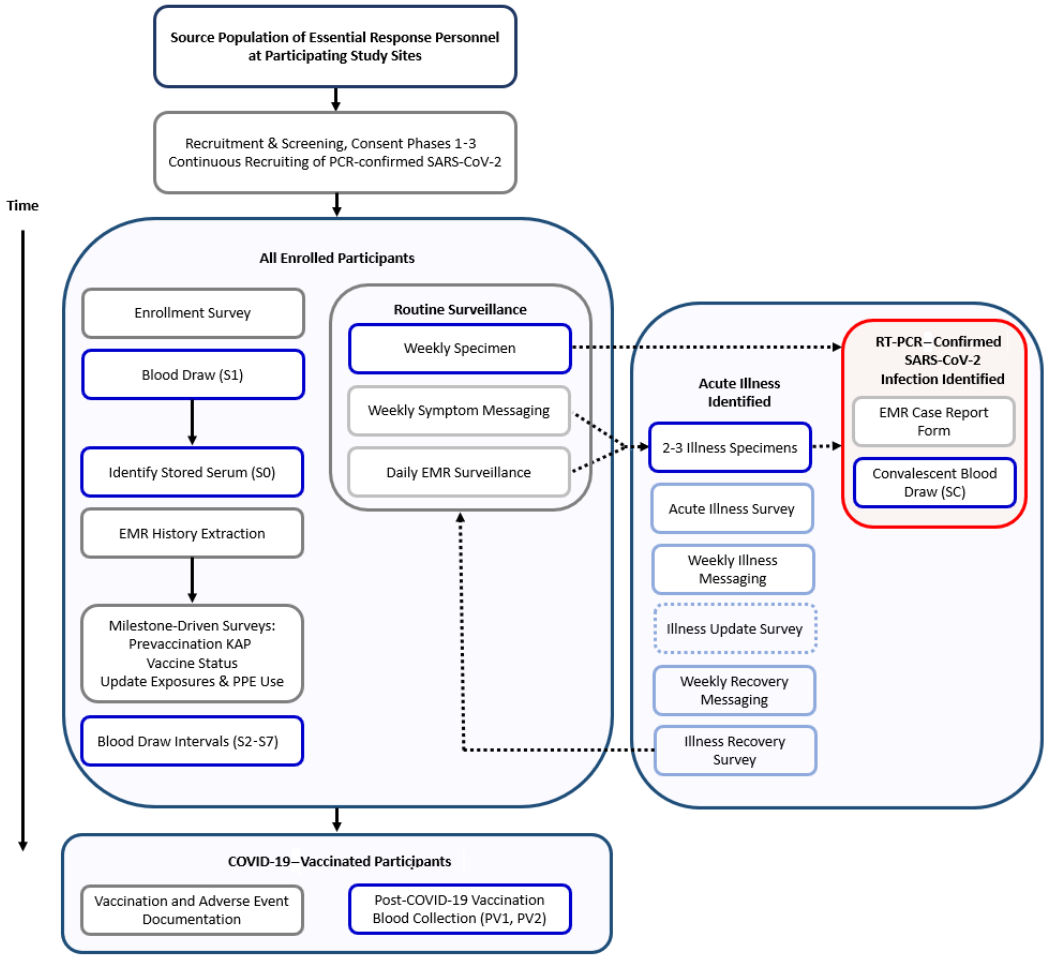
To minimize potential biases and ensure a diverse population of essential workers, each study site aims to enroll 500 to 700 participants using a 3-phase stratified recruitment approach according to sex, 2 age groups (18-39 years and 40+ years), and 4 occupational categories (primary HCP, support HCP, first responders, and EFWs). Primary HCP are physicians (Doctor of Medicine or Doctor of Osteopathic Medicine), physician assistants, dentists, and nurse practitioners, since these are typically underrepresented occupations in cohort studies of HCP [18]. Support HCP are all other personnel not included in the primary category. Each study site aims to recruit a minimum of 20 participants per occupation, age, and sex stratum. While sites are not required to incorporate racial and ethnic diversity directly into recruitment strata, targeted outreach for recruitment in diverse communities is conducted.

To gather the most information about protective immunity and reinfection over time, phase one recruitment includes HCP and first responders with current or any prior reverse transcription polymerase chain reaction (RT-PCR)–confirmed SARS-CoV-2 infection; HCP and first responders with an available baseline sera sample collected as a part of other research efforts; and HCP and first responders in difficult-to-fill recruitment strata, defined as particular ages or sex strata that are underrepresented at certain study sites (eg, female first responders). Phase two recruitment includes all other HCP and first responders to reach at least 400 participants per study site. Phase three recruitment includes EFWs, with a minimum of 100 enrollees per site. Recruitment and enrollment at each study site began in early August 2020. Site-specific methods for recruitment are provided in Table 1.

Data Collection

Data collection and site-level data management are conducted using Research Electronic Data Capture (REDCap), a browser-based metadata-driven software system (Vanderbilt University) [19]. Data collection occurs through SMS text messaging on the Twilio platform that integrates directly with REDCap, internet-based surveys, or telephone calls from study staff [20]. An overview of the study methods and data collection instrument delivery is provided in Figure 1.

Figure 1. Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER) study activities. EMR: electronic medical record; KAP: knowledge, attitudes, and practices; PCR: polymerase chain reaction; PPE: personal protective equipment.



Enrollment Data

Following informed consent, participants are asked to complete an online survey to assess sociodemographic characteristics, occupation and work responsibilities, health status and behaviors, self-reported medical history, and use of PPE (Table 2). To further establish exposure levels, the health care setting and age of patients attended are collected, and both HCP and first responders are further asked about performing aerosol-generating procedures. All participants are asked to estimate exposures to persons, including patients, coworkers, and the public at work or in any setting, and to potential SARS-CoV-2 infection, as well as their PPE utilization.

Table 2. RECOVER (Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel) study data collection activities.

Variable	Screening	Enrollment	Weekly active surveillance	Follow-up survey 1	Follow-up survey 2	Acute illness surveys	Electronic medical records[a]
Essential worker status	Yes	No	No	No	No	No	No
Sociodemographics	Yes	Yes	No	No	No	No	Yes
Household size and age distribution	No	Yes	No	No	No	No	No
Occupation	Yes	Yes	No	Yes	Yes	No	No
Location of work	No	Yes	No	No	No	No	No
Patient care responsibilities (HCP[b] only)	No	Yes	No	No	No	No	No
Typical hours worked	No	Yes	No	No	No	No	No
Health status and risk behaviors	No	Yes	No	Yes	Yes	No	No
Recent care for acute respiratory illness	No	Yes	No	Yes	Yes	No	Yes
Chronic medical conditions and pregnancy	No	Yes	No	Yes	Yes	No	Yes
Assessment for current CLI[c]	No	No	Yes	No	No	No	No
SARS-CoV-2 testing history	Yes	No	Yes	No	No	No	Yes
COVID-19 diagnosis history	Yes	No	No	No	No	No	Yes
Medical care for COVID-19	Yes	No	No	No	No	No	Yes
Contact with confirmed or suspected COVID-19	No	Yes	Yes	Yes	Yes	No	No
Contact with patients, customers, or the public	No	Yes	Yes	Yes	Yes	No	No
PPE[d] utilization	No	Yes	Yes	Yes	Yes	Yes	No
PPE concerns	No	Yes	No	No	No	No	No
Knowledge, attitudes, and practices related to new COVID-19 vaccines	No	No	No	Yes	Yes	No	No
COVID-19 vaccination status	No	No	No	Yes	Yes	No	Yes
Influenza vaccination status	No	No	No	Yes	Yes	No	No
Employee records of illness absence	No	No	No	No	No	No	Yes

[a]Electronic medical records are available at the Baylor Scott & White Health, Kaiser Permanente Northwest, St. Luke's Hospital, and University of Utah sites.

[b]HCP: health care personnel.

[c]CLI: COVID-19–like illness.

[d]PPE: personal protective equipment.

Follow-Up Surveys

Approximately every 3 months after enrollment, participants are sent a follow-up survey to allow them to update information on their health status, job characteristics, potential exposures to COVID-19, and use of PPE. These surveys also assess participant knowledge, attitudes, and practices regarding COVID-19 vaccines; participant intention to be vaccinated; and, after each vaccination dose, any adverse reactions. Influenza vaccination status is assessed separately by self-report (including type of vaccine, lot number, and date of vaccination)

starting approximately 2 months after the seasonal influenza vaccines become available each year.

Active Surveillance

Study participants are followed weekly for the duration of the study period with active surveillance for SARS-CoV-2 infection and symptomatic COVID-19–like illness (CLI). Participants are contacted by SMS text message to determine the presence of one or more of the following symptoms of CLI in the past 7 days: fever, cough, shortness of breath, sore throat, diarrhea, muscle or body aches, and change in smell/taste. In October 2020, the case definition was modified to include chills based on an evolving understanding of the symptoms associated with COVID-19 [21-23]. These questions serve as a baseline for when participants are subsequently asked exposure and PPE utilization questions through the weekly active surveillance SMS text message, such that data are collected monthly.

Participants who report no CLI are asked 1 of the following 4 rotating questions about contacts and sleep in the past 7 days: (1) hours spent in direct contact with persons with suspected or confirmed SARS-CoV-2 at work, (2) hours spent in direct contact with other people at work, (3) hours spent in direct contact with people outside of work, and (4) quality of sleep. Each question about contact is followed by asking about the percentage of time they wore PPE. Participants are then reminded to collect their weekly respiratory specimens and ship them to Marshfield Clinical Research Institute for testing.

Participants who report experiencing CLI are asked to self-collect the standard respiratory specimen, an additional anterior nasal dry foam swab, and a saliva sample. The participant is sent an acute illness survey, including questions regarding symptoms since onset, self-rated health today, ability to perform normal activities, and medical utilization. The survey also asks about direct contact within the past 7 days with known or suspected COVID-19 cases at work and outside work, direct contact with other people, and PPE use during those contacts. The weekly SMS text messages are modified to assess if their illness is continuing and to gauge their ability to conduct normal activities. Participants who report continuous symptoms ≥7 days after illness onset are asked to complete an illness update survey to assess new symptoms, illness severity, and medical utilization.

Once participants report that they are no longer experiencing illness symptoms, they are asked to complete an illness resolution survey to assess symptoms, severity of illness, and medical utilization over the course of the illness, and to estimate their current recovery progress (defined as feeling 0%-100% of “normal”). Until a participant reports ≥90% recovery progress, the weekly surveillance messaging will continue to ask about recovery progress. Once a participant reports ≥90% recovery, the weekly messaging will return to the standard question set.

Acute illness may also be reported any time during the week to study staff. At study sites with EMR capabilities, acute illness may also be identified through daily monitoring of medical visits for an acute respiratory illness.

EMRs

When available, data from EMRs are abstracted and extracted to count medical visits for acute COVID-19 illness, identify influenza and COVID-19 vaccination data, and assess chronic medical conditions for the 12 months prior to enrollment and through the end of the study. The EMR extraction uses International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes for all ambulatory medical encounters and all hospital admissions. Chronic medical conditions and vaccination status are assessed by self-report for participants with or without access to EMR data.

COVID-19 Vaccination Data

COVID-19 vaccination status is assessed through multiple methods to ensure complete and near real-time data capture, which is a critical component for scheduling postvaccination blood collection and monitoring for receipt of additional doses. Participants are asked in advance to proactively self-report if they are scheduled for COVID-19 vaccination or to contact local study staff as soon as possible after receipt of each vaccine dose. Throughout the study, participants receive brief periodic surveys via SMS text message links to report vaccination. Additionally, sites query participants’ EMR and their state immunization information system to obtain COVID-19 vaccination status or history. If COVID-19 vaccination is self-reported, participants are asked to send a digital photograph of the vaccination card provided at vaccination using secure file transfer. Study staff cross-check vaccination information received from multiple sources to ensure accuracy.

Household Transmission Data Collection

To assess the transmissibility of SARS-CoV-2 in vaccinated and unvaccinated individuals, all members of a RECOVER participant’s household (adults and children) are asked to join the study for a 10-day period if an RT-PCR–confirmed SARS-CoV-2 infection is identified in the RECOVER participant. These daily household study activities began in February 2021. Once a SARS-CoV-2 infection is confirmed, participants with at least one other household member are contacted by study staff to enroll both the RECOVER participant and their household members into this component of the study. Data collection activities include a brief enrollment interview to ascertain demographics, vaccination status, and prior SARS-CoV-2 infection among household members. All enrolled household members are asked to self-collect a mid-turbinate nasal swab each day for 10 days, regardless of infection status. On a daily collection form, participants are asked to indicate the day their specimen was collected and the presence or absence of CLI symptoms.

Retention and Adherence

Study sites implement several strategies to increase retention among their enrolled participants. These include robust incentive programs that vary by study site within the confines of local IRB requirements, monthly newsletters with aggregated study data and results, and opportunities for participant feedback on study activities. When possible, study sites also combine study activities within a single contact or visit to reduce participant

burden and increase retention. For example, a visit for a blood draw may also include catching up on any missed survey instruments and collecting the weekly respiratory specimen so the participant does not have to personally ship the specimen that week.

Study sites regularly monitor participant adherence to main study activities, including through automated reports on missing weekly surveillance swabs, automated survey reminders, phone calls to the participants to collect missing information, and mailed letters detailing missed activities. Upon consecutive poor adherence to study activities, study staff reach out to the participants to identify possible solutions, such as changing their specimen shipping procedures, adjusting the day or time of their weekly surveillance survey, or altering the location for their blood collection appointments. If adherence remains low after these modifications or there is general nonresponse from the participants, they will be considered for withdrawal from the study.

Laboratory Methods: Respiratory Specimens

Each week, participants collect a mid-turbinate nasal specimen using a flocked swab placed in viral transport medium (VTM). Upon the onset of CLI symptoms, participants self-collect a mid-turbinate flocked nasal swab in VTM, as well as a dry foam anterior nasal swab and saliva. Participants are provided with training and materials for the self-collection of each specimen type at enrollment. When collecting saliva, participants are instructed to avoid eating, using tobacco products, or brushing their teeth for 30 minutes prior to collection. They then deposit approximately 2 mL of saliva into a collection tube with a funnel. Participants are given written and visual detailed instructions for collecting, storing, and submitting specimens by dropping them off at a specified location, having them picked up by an at-home courier, or shipping them according to guidance and specifications from the US Food and Drug Administration.

All respiratory specimens are shipped on the day of collection unfrozen (on ice packs) to Marshfield Clinical Research Institute for testing. On a daily basis, the Marshfield Clinical Research Institute performs a CDC-specified RT-PCR assay to ascertain infection with SARS-CoV-2. Study staff at all sites inform participants of their test results when they are positive for SARS-CoV-2, noting that results are not meant to replace recommended clinical tests. Some study sites also notify participants of negative test results. Each study site complies with the reporting requirements of their state and local public health departments. Remaining aliquots of all study specimens are sent to a CDC-designated facility for additional virus characterization (including but not limited to genetic sequencing and novel severity markers), banking, and storage.

Laboratory Methods: Serum and Blood Specimens

All participants contribute 20 mL of whole blood at least 4 times per year, including at enrollment and approximately every 3 months thereafter. Participants who experience an immune-modifying event, including SARS-CoV-2 infection indicated by a confirmed positive RT-PCR test or vaccination, have blood drawn approximately 28 days after infection and 14 to 28 days after each vaccine dose. The next blood collection occurs 3 months after any event-related blood draw to keep the burden on the participant to a minimum. All participant blood collections occur in-person at the study sites and are performed by trained study staff or affiliated phlebotomists.

Whole blood is collected and processed by the study site laboratory using CDC guidelines for serum collection. The serum specimen is divided into aliquots. All specimens are stored in a −20°C or colder freezer and shipped to the central study CDC laboratory for SARS-CoV-2–specific antibody detection and characterization. A serum aliquot from the first or second serum collection is stored for analysis of PFAS. Additional specimens from later in the study will be kept for potential future analysis of longitudinal changes in PFAS concentrations.

Ethical Approval and Ethical Considerations

The study protocol and procedures were reviewed and approved by the following 5 IRBs: Baylor Scott and White Research Institute IRB; Kaiser Permanente Northwest IRB (IRB of record for the CDC and Abt Associates); St. Luke's Hospital Duluth IRB; University of Miami Human Subjects Research Office (IRB of record for University of Arizona); and University of Utah IRB. All participants have completed informed consent. Small gifts or stipends are given to participants at study milestones on a site-specific basis. Each study site follows local policies for employer notification of positive SARS-CoV-2 test results and reporting to state or local health departments.

Sample Size

The RECOVER study has enrolled approximately 500 participants at each of the 6 sites for a total of 3000 participants. The required sample size to achieve incidence and vaccine effectiveness objectives accounts for the expected cumulative incidence of symptomatic and asymptomatic SARS-CoV-2 infections in the essential worker population, vaccine effectiveness, and study attrition. Early reports of the SARS-CoV-2 incidence and seroprevalence in essential workers ranged from 4% to 18%; thus, we assume a 10% cumulative incidence of infection among those with no documented RT-PCR infection before enrollment and 10% attrition [24-26]. We expect the cumulative incidence of reinfection to be 1% among those with a documented RT-PCR–positive SARS-CoV-2 infection before enrollment. Using these assumptions, we have determined that the sample size would have at least 80% power to detect a true percentage of 4% symptomatic infection and 8% asymptomatic infection.

Vaccines for COVID-19 were not available at the start of the study, but started to become available at each site in mid-December 2020. To account for vaccination status as a time-varying exposure, we used a Monte Carlo simulation to estimate the statistical power to detect a vaccine effectiveness of interest. Given the vaccine coverage, SARS-CoV-2 incidence, and underlying effect size, expected person-time of participants while unvaccinated and vaccinated and time to infection events were generated from the equation proposed by Austin, and a frailty/marginal model was fitted to estimate vaccine effectiveness [27]. We considered vaccine uptake to be 50% to

80% by occupation, accounting for the highest uptake and prioritization for HCP and first responders, and the lowest uptake and prioritization for EFWs. Assuming a monthly attack rate of 1% to 2% and a conservative vaccine effectiveness of 60% to 75%, sufficient statistical power will be reached with 6 months of participant time contributed.

Data Analysis

The primary outcome of SARS-CoV-2 infection incidence will be estimated overall and according to asymptomatic and symptomatic presentation using individual participant contributions of person-time from the time of study entry. To control for the contribution of age, sex, and occupation to the risk of infection, incidence will be estimated using negative binomial models with a person-time offset. The association of individual, occupational, and environmental predictors with SARS-CoV-2 infection will be assessed using a mixed-effects Cox proportional hazards model, incorporating study site as a random effect.

Vaccine effectiveness against SARS-CoV-2 infection and COVID-19 illness will be calculated using the Andersen-Gill extension of the Cox proportional hazards model, which allows vaccination status to be time varying. Unadjusted vaccine effectiveness is calculated as 100% × (1−hazard ratio). The effect of the following covariates on vaccine effectiveness estimates will be considered for all outcomes: study site, sociodemographic characteristics, occupation, self-reported occupational SARS-CoV-2 exposure and PPE utilization, and underlying health status. We will calculate stabilized weights to create a pseudopopulation where measured covariates are independent of vaccination. In this way, we can properly measure the causal association between vaccine and infection. Depending on sample size, vaccine effectiveness may be calculated by age group, full versus partial vaccination, and vaccine type, if multiple products are in use.

Cell-Mediated Immunity Substudy

The Baylor Scott and White Health and Kaiser Permanente Northwest sites are conducting a substudy to compare cell-mediated immune response to SARS-CoV-2 infection and vaccination, and metabolome and microbiome diversity among participants with symptomatic and asymptomatic SARS-CoV-2 infections or vaccination. To achieve these objectives, 3 subgroups are invited to participate, and are independently screened for eligibility, consented, and enrolled. These 3 subgroups include those with symptomatic or asymptomatic SARS-CoV-2 infection, COVID-19 vaccine recipients, and uninfected and unvaccinated controls. SARS-CoV-2–infected individuals are invited to participate upon diagnosis, and controls are time-matched with a 1:1 case-control ratio. Participants provide a self-collected dry mid-turbinate nasal swab for metagenomic characterization of the microbiome or virome, and whole blood for serum and peripheral blood mononuclear cell (PBMC) extraction. Serum and plasma aliquots will be used to supplement existing antibody testing time points with Ig-Seq to determine antibody clonotypes, metabolome, and VirScan multipathogen assays. The PBMCs will be used for human B- and T-cell repertoire analysis, phenotypic characterization of innate lymphoid cells with multiparametric flowcytometry, and single-cell transcriptomics. The substudy protocol and procedures have been reviewed and approved by the Baylor Scott and White Research Institute IRB and the Kaiser Permanente Northwest IRB (IRB of record for the CDC and Abt Associates).

Serial Serology Substudy

The St. Luke's Hospital site is conducting a substudy to determine time to seroconversion from a positive nasal swab and define the duration of seropositivity in those who seroconvert. All participants are invited to join the substudy, and those enrolled provide 7 mL of whole blood every 4 weeks, the serum of which is divided into 3 aliquots and frozen for serologic testing. The frequency of blood draws is increased to every 2 weeks for individuals with known SARS-CoV-2 infection by RT-PCR prior to enrollment in the RECOVER study or at any time after enrolling in the study. Serum aliquots will be tested for antibodies to SARS-CoV-2 to determine the kinetics of the immune response. The substudy protocol and procedures have been reviewed and approved by the St. Luke's Hospital Duluth IRB and the Kaiser Permanente Northwest IRB (IRB of record for the CDC and Abt Associates).

Results

The study observation period began in August 2020 and is expected to continue through spring 2022. There are 2623 actively enrolled RECOVER participants, including 280 participants who have tested positive for SARS-CoV-2 by RT-PCR through the study. Enrollment is ongoing at 3 of the 6 study sites (3 study sites have completed enrollment). In June 2021, the RECOVER network published estimates of vaccine effectiveness [28].

Discussion

The RECOVER cohort continues to enroll participants in a unique research opportunity to estimate the incidence of asymptomatic and symptomatic SARS-CoV-2 infections in essential workers. It also provides early estimates of COVID-19 vaccine effectiveness against both infection and transmission of SARS-CoV-2 to household members of the RECOVER cohort. Here, we describe the recruitment, data gathering, active surveillance, laboratory testing, and planned data analysis procedures for this prospective longitudinal cohort study of essential workers representative of working-age adults in these professions. Through weekly collection and testing of respiratory specimens from all participants, regardless of the presence of CLI symptoms, we are able to examine the occurrence of asymptomatic and presymptomatic SARS-CoV-2 infection, which has been shown to represent the highest risk of transmission [29]. The longitudinal study design and collection of both periodic and weekly information about behaviors and risk factors will inform measurement of primary outcomes, including incidence and vaccine effectiveness estimations. Further, our study includes blood specimens from all participants, which affords the opportunity to identify infections that may not be captured by RT-PCR–based testing or that may have occurred before the participant joined the cohort. We are

also able to assess the kinetics of the immune response, both postinfection and postvaccination.

In addition to the longitudinal design and weekly specimen testing, the RECOVER study has geographic variability and a stratified recruitment design. The study is recruiting participants from geographically diverse areas of the United States, which will allow us to evaluate trends in SARS-CoV-2 infection in areas with varying prevalence levels, policies around social distancing and large gatherings, and rates of COVID-19 vaccine uptake. The geographic diversity may also help to identify SARS-CoV-2 variants and help inform how vaccine effectiveness is affected by these variants. The study utilizes a stratified recruitment approach to ensure there is sufficient variability in sex, age, and occupational categories within the cohort. This approach intentionally creates an opportunity to examine risks associated with heterogeneity in sociodemographic characteristics and improves the ability to compare and collapse data across study sites if necessary. This systematic approach is also intended to minimize convenience sampling, which can introduce known and unknown biases.

Our study will face challenges and have limitations. First, ensuring consistent adherence to study procedures over a long period of time is challenging. To overcome this obstacle, site staff will strive to develop a relationship with participants and provide feedback regarding strategies the study may implement to help participants adhere to study methods. Second, while the diversity of the occupational categories will enhance the overall representativeness of the RECOVER study population, it may increase the complexity of specimen collection by including individuals who may not work near clinical facilities. To facilitate submission of respiratory specimens, participants may choose to ship their specimens overnight, drop them off at a study facility, or have them picked up from home by a medical courier. Third, we are relying on self-collected mid-turbinate nasal swabs, which have ranged in sensitivity from 75% to 90% in studies comparing SARS-CoV-2 detection in swabs collected by nonclinical subjects with that in swabs collected by HCP [30,31]. This limitation will be minimized by the volume of participants who are HCP and are familiar with swab collection; regardless, all participants are trained by study staff in proper sample collection [31]. Finally, unforeseen shipping interruptions may delay specimens and impact viral detection. Studies have demonstrated nasal swab specimen stability at ambient temperatures for up to 9 days, and specimens are shipped with ice packs as a precaution [32].

The RECOVER cohort is designed to answer critical questions regarding SARS-CoV-2 incidence and COVID-19 vaccine effectiveness among essential workers. Data collected through the cohort are expected to inform public health decisions related to PPE use, exposure risk factors, assessment of humoral and cellular responses to infection and vaccination, evaluation of COVID-19 vaccine effectiveness, and policies for returning to work after infection. Furthermore, the RECOVER cohort will have the capacity to examine variant strains of SARS-CoV-2 and their impacts on vaccine effectiveness.

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Conflicts of Interest

ALN reports funding from Pfizer for a meningococcal B vaccine study unrelated to the submitted work. KTH serves at the Editor of the American College of Occupational and Environmental Medicine evidence-based practice guidelines. MST reports grants and personal fees from Reed Group and the American College of Occupational and Environmental Medicine, outside the submitted work. The other authors report no conflicts of interest.

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Abbreviations

CDC: US Centers for Disease Control and Prevention
CLI: COVID-19–like illness
EFW: essential and frontline worker
EMR: electronic medical record
HCP: health care personnel
IRB: institutional review board
PBMC: peripheral blood mononuclear cell
PFAS: per- and polyfluoroalkyl substances
PPE: personal protective equipment
RECOVER: Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel
REDCap: Research Electronic Data Capture
RT-PCR: reverse transcription polymerase chain reaction
VTM: viral transport medium

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Protocol

Increasing Participation Rates in Germany's Skin Cancer Screening Program (HELIOS): Protocol for a Mixed Methods Study

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Abstract

Background: In 2008, a nationwide skin cancer screening (SCS) program was implemented in Germany. However, participation rates remain low.

Objective: The overall objective of the HELIOS study is to identify subgroup-specific invitation and communication strategies to increase informed SCS participation in Germany.

Methods: Focus group discussions will be performed in Erlangen, Germany, to explore potential invitation and communication strategies as well as possible barriers and motivating factors to participate in SCS. Male and female patients of different age groups who have already been diagnosed with skin cancer, as well as participants without a prior diagnosis of skin cancer, will be invited. Based on these results, an online questionnaire will be developed to identify subgroup-specific invitation strategies. A random sample of 2500 persons from the general population aged >35 years from the Munich area will be contacted to complete the questionnaire. Besides descriptive analysis, multinomial logistic regression will be performed. Additionally, a cluster analysis will be conducted to discover patterns or similarities among the participants.

Results: Recruitment for the focus group studies started in February 2021 and is ongoing. As of August 2021, we have enrolled 39 participants. We expect to end enrollment in the qualitative study in September 2021 and to finish the analysis in December 2021. The second part of the study will then start in January 2022.

Conclusions: The results of this project will enable us to derive improved and more efficient invitation and communication strategies for SCS. These may be implemented in the future to facilitate increased SCS uptake and early skin cancer detection.

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KEYWORDS

skin cancer; melanoma; squamous cell carcinoma; basal cell carcinoma; screening; early detection; focus group; mixed methods; cross-sectional study; prevention

Introduction

Skin cancer is one of the most frequently diagnosed cancer entities in Germany. The incidence of melanoma and nonmelanoma skin cancer has steadily increased in recent years [1]. Besides reducing exposure to ultraviolet radiation by means of sun protection measures, early detection of suspicious skin lesions represents a key secondary prevention strategy [2,3]. Aiming to reduce skin cancer–associated mortality and morbidity, a national skin cancer screening (SCS) program was

introduced in Germany in July 2008. It involves a voluntary, standardized full-body examination by dermatologists or general practitioners who have been specifically trained for this purpose. As a part of this examination, risk factors for skin cancer as well as prevention measures are addressed. The costs are reimbursed by all German statutory health insurance companies biannually for members who are >35 years, while some health insurance companies also cover SCS costs for younger members [4]. The decision to implement SCS at the population level was based on the results of the pilot SCREEN (Skin Cancer Research to Provide Evidence for Effectiveness in Northern Germany) project [5]. Following this study, there was both a significant decrease in melanoma mortality [6] and a shift in the T-stage distribution in favor of thin melanomas [7]. These differences in comparison to neighboring regions without SCS suggested that they were attributable to SCS, but this has been subject to debate [6,8].

Since its introduction, more than 13 million patients have participated in the SCS program, and estimated participation rates have ranged between 24% and 39% [4,9-11]. However, this highlights that about 60% to 75% of eligible residents in Germany have never taken advantage of the SCS program. Nevertheless, most people appreciate the option to participate in the SCS program and, additionally, informed persons use SCS more frequently than uninformed persons [9]. Moreover, women undergo SCS more frequently than men [12]. However, unlike the organized invitation programs for mammography, cervical cancer, and colorectal cancer screening, there are currently no campaigns or target group–specific invitation strategies aimed at increasing people's decision to participate in SCS in Germany.

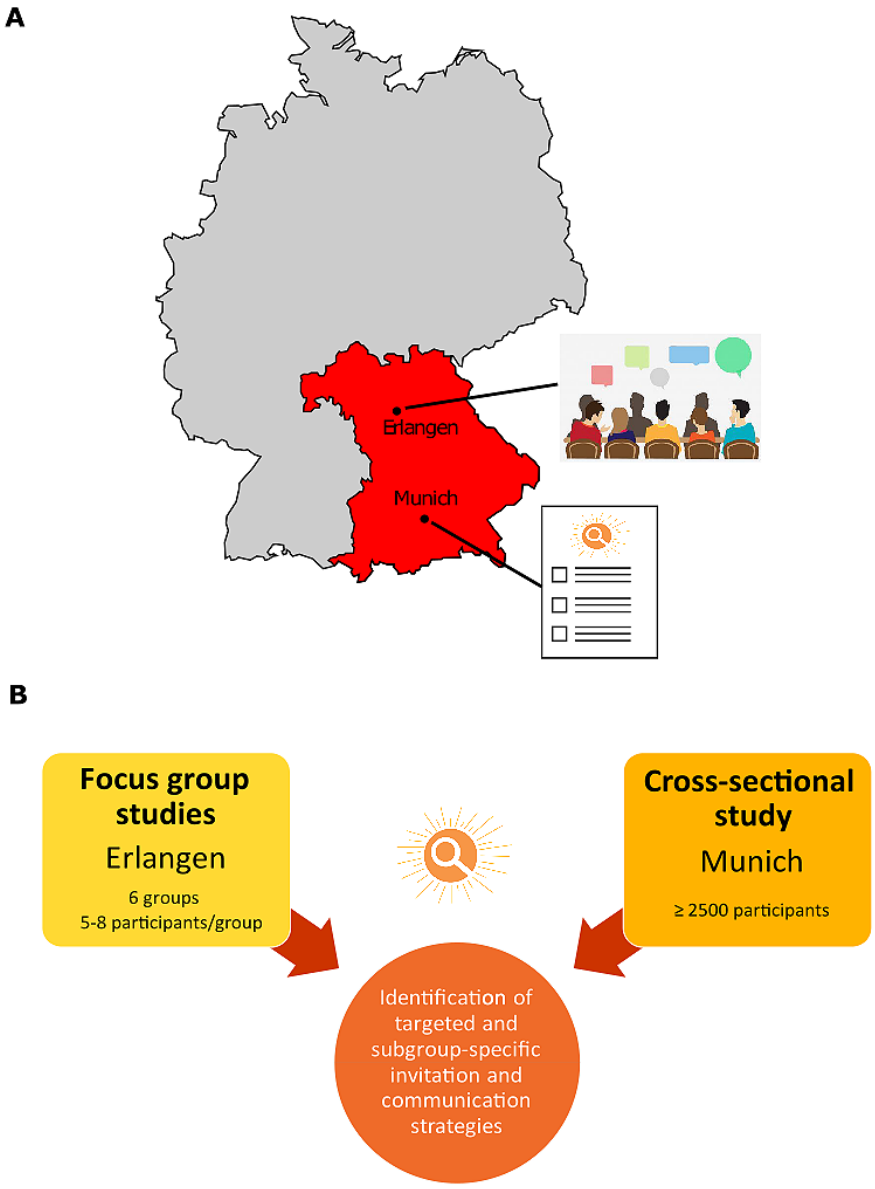
In order to develop target group–specific invitation strategies to ultimately increase the SCS participation rate in Germany, we initiated the HELIOS study (German acronym for *Hautkrebsspezifische Einladungsverfahren zur informierten Screeningteilnahme*, or in English, Skin Cancer–Specific Invitation Strategies to Participate in the Skin Cancer Screening Program). Here, we describe the study design and summarize the study protocol. The results of our project will contribute to increase participation rates in SCS and thus lead to earlier detection of skin cancer.

Methods

HELIOS Project

The HELIOS project comprises two discrete, yet complementary, subprojects. The first part consists of a qualitative approach comprising several focus group sessions with different subgroups in Erlangen, Germany, to exploratively collect possible communication strategies for SCS. The second part is based on the results of the focus group sessions and involves a cross-sectional study among a random sample of residents in Munich, Germany, aimed at identifying suitable, targeted communication strategies for different subgroups (Figure 1).

Figure 1. (A) Map of Germany showing the location of the 2 subprojects within the federal state of Bavaria. (B) Overview of the study flowchart of the subprojects within the HELIOS project.



Part 1: Focus Group Study

Objective and Study Design

In order to exploratively collect possible invitation procedures and communication approaches for different subgroups, a qualitative and explorative design will be used through focus group discussions. As a part of these discussions, the already existing information brochure *Detecting Skin Cancer*, of the German Cancer Aid, will be additionally evaluated in order to obtain target group–specific suggestions for improvement [13].

Qualitative approaches facilitate an in-depth picture of patients' preferences and needs [14,15]. In addition, the interactive component of the focus groups enables participants to ponder, reflect, and listen to the experiences and opinions of others [16]. The interview will be structured according to published guidelines for focus groups [16]. A manual with questions for the focus groups will be developed by the investigators of this study and will be based on an assessment of the literature and dermato-oncologic experience.

The focus group interviews will assess the following aspects:

1. Willingness to participate in the SCS program with reasons for or against participation;
2. Interest in invitation procedures and preferred communication strategy;
3. Information required for an informed decision for or against participation in the SCS program;
4. Evaluation of the German Cancer Aid's information brochure Detecting Skin Cancer [13] to obtain patient-specific suggestions for improvement.

Follow-up and probing questions will be used for clarification and elaboration. This subproject is particularly important as it takes into account the perspective and view of both participants

who have not been diagnosed with skin cancer and patients with skin cancer. The semistructured interview guide is available in Multimedia Appendix 1.

Sampling, Recruitment, and Data Collection

Participants will be recruited via German patient support groups (eg, Hautkrebs-Netzwerk Deutschland, Melanom Info Deutschland), local Facebook groups, as well as through in-hospital flyers and direct contact by attending physicians in the Oncological Outpatient Department of the university hospital (Friedrich-Alexander-Universität Erlangen-Nürnberg). Patients who have already been diagnosed with skin cancer, as well as healthy or previously unaffected participants, will be eligible to participate in the discussions. A total of 6 focus groups of 5 to 8 participants, each with a duration of 45 to 90 minutes, are planned (a total of 30 patient or participant representatives) in Erlangen. The respective groups will differ in terms of gender composition (male/female) and age (35-50 years, 51-65 years, and >65 years). The participants will receive a financial incentive for successful participation. The interviews will be audiorecorded and moderated by an experienced interviewer and assistant. Demographic data such as age or gender will be obtained in advance from the participants using an anonymized questionnaire.

Data Analysis

All sessions will be transcribed verbatim and analyzed by 2 investigators independently, presumably via a qualitative content analysis according to Mayring [16] with the aid of the software MAXQDA (VERBI Software). The transcribed data will not be linked to any patient-identifying information to assure anonymity. Sociodemographic data will be presented descriptively as frequencies (%); age will be presented as mean or median and range. Prior to the focus groups, we will collect informed consent from each participant. We will closely adhere to the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist [17].

Part 2: Cross-sectional Study

Objective and Study Design

The aim of the second subproject is the identification of target group–specific invitation procedures for the SCS program by means of an anonymized, questionnaire-based cross-sectional study in which the previously identified relevant invitation procedures from the focus group discussions (eg, postal invitation, invitation via email) will be further investigated. The invitation procedures will be correlated with the respective sociodemographic profile of the participants to create a prediction model from which the preferred invitation procedure can be derived. The following questions will therefore be answered:

1. Which subgroups prefer which invitation procedure?
2. Have different personal factors such as age, gender, social status, or family background influence or impact the preferred invitation procedure and willingness to participate in the SCS program?

Inclusion Criteria

Adult residents with a primary residence in the city of Munich aged >35 years will be included. Furthermore, participants need to have sufficient German-language skills to understand the general information provided about the project and to complete the online questionnaire.

Survey Dissemination

A random sample of the general population aged >35 years from the Munich area will be drawn from the local population registration office. The selected population will receive invitation letters with personalized 6-digit passwords (consisting of letters and numbers), which allow access to the online questionnaire. Additionally, the invitation letter will include a scannable QR code directly leading to the online questionnaire. Before answering the questionnaire, participants will have to confirm that they have read the general information provided online, including information about data protection. After this step, informed consent will be obtained online. Those who do not respond to the invitation will not be contacted again. The recruitment period is estimated to take 4 months. The questionnaire will be made available to the participants through a web-based survey tool, such as SurveyMonkey (Momentive Inc) or LimeSurvey (Carsten Schmitz and LimeSurvey Team). Each participant contacted may only take part in the survey once. The questionnaires will be numbered consecutively for data entry but will not be linked to participant-identifying information to ensure irreversible anonymity. We chose Munich as it is the capital city of Bavaria and has a larger number of available residents. In addition, we believe that the project will benefit from an intercity design as views from a medium-sized city (Erlangen) and one of the largest cities in Germany (Munich) will be included. No incentive will be offered for completion of the survey.

Questionnaire Development

Since there are currently no validated survey instruments tailored to the aim of our study, the questionnaire will be developed de novo based on the results from the focus group discussions as well as an assessment of the literature and dermato-oncological expertise. The questionnaire will consist of a multiple-choice format and will address sociodemographic data as well as previous participation in the SCS program. Further questions will elaborate the participants' preferred invitation and communication procedure. Before final dissemination, the questionnaire will be pretested and validated for clarity and comprehension by independent researchers who will not be involved in the design of the original questionnaire and volunteering patients from University Hospital Erlangen. Unclear items will be thoroughly discussed and rephrased until a consensus on clarity is reached. Based on this feedback, the questionnaire will be revised to its final version. The first draft of the questionnaire can be obtained from Multimedia Appendix 2.

Data Analysis and Sample Size Calculation

The sample size calculation is based on a significance level of α=.05 with a minimum effect size of 30% and a response rate of 20% in Munich. At least 500 questionnaires are needed to

detect an actual significant effect; therefore, at least 2500 participants should be contacted since we expect a low response rate of 20%. Descriptive analysis and multinomial logistic regression models will be performed to identify relevant correlations. The preferred invitation procedure will be used as the dependent variable, while age, willingness to participate, and other risk factors will serve as independent variables. Furthermore, chi-square tests or exact Fisher tests will be performed to investigate correlations between the sociodemographic variables and the individual questions. To counteract the problem of multiple testing, the Bonferroni correction method will be applied. A cluster analysis will be performed to discover patterns or similarities within the participants. Categorical variables will be expressed as frequencies and percentages, and continuous variables as median and range. A P value <.05 will be considered as statistically significant. The statistical analyses will be performed with SAS (SAS Institute). This subproject will be guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [18].

Results

The study was approved by the institutional review board of University Hospital Erlangen (August 2020). The manual for the focus group discussions has been created. Recruitment for the focus group sessions started in February 2021 and is ongoing. We expect to end enrollment in the qualitative study in September 2021 and to finish the analysis in December 2021. The second part of the study will then start in January 2022. This study is expected to conclude in the summer of 2022.

Discussion

The HELIOS project aims to determine target group–specific invitation strategies to ultimately facilitate an increase in SCS participation rates in Germany, and thus lead to an earlier detection of skin cancer. Based on the results, suitable and motivating invitation and communication procedures can be implemented in the future. Therefore, our study will contribute to the realization of the goals of the National Cancer Plan in the field of dermato-oncology. In addition, the HELIOS project should contribute to the realization of the goals of the SCS such as the reduction of mortality and morbidity in Germany. Importantly, this project consists of 2 distinct subprojects in order to include the views of both patients with skin cancer and unaffected individuals.

While SCS was implemented more than 10 years ago based on the evidence derived from the results of the SCREEN study, SCS acceptance at the population level remains highly controversial [19,20]. SCS itself is noninvasive and does not cause any relevant damage. However, unnecessary biopsies as a result of false-positive examinations and overdiagnosis need to be kept in mind. A further point of criticism is that no reduction in melanoma mortality has been observed thus far after the implementation of the nationwide SCS, which contrasts with the results of the pilot project [21]. The reasons for this discrepancy remain unclear. One possible reason is that the performance of the 2 screening programs differ in some aspects [22]. Whereas in the national SCS only dermatologists and general practitioners conduct the screening, in the SCREEN project general practitioners, gynecologists, urologists, and surgeons were also involved. Furthermore, the initiators of the SCREEN study concluded that the preceding public promotion prior to the implementation of the SCREEN project may have contributed to the success of the project [6].

In Germany, mammography screening is currently performed as an organized screening program. It was established between 2005 and 2009 and is based on an invitation system. All women between the ages of 50 and 69 years are invited to get screened with a mammography every 2 years and are informed about the screening offer by means of a leaflet. The overall participation rate among 5,528,937 invited women in 2015 was 51.5%. Depending on the federal state, the participation rates ranged between 43% and 63% [23]. In a cross-sectional study with 13,144 women in 2014-2015, an even higher participation rate with 74.2% was described. Of these, 80.7% cited the invitation letter to account for participation [24]. Since July 2019, colorectal cancer screening has been implemented as a nationwide, risk group–adapted, organized program in Germany [25]. Following the promising participation rates of mammography in Germany as well as the decision to implement colorectal cancer screening and cervical cancer screening as an organized screening program, it is necessary to also investigate and derive communication strategies for SCS to increase participation rates.

A potential barrier to carrying out the focus group discussion in the first subproject is participant recruitment. If an insufficient number of people agree to participate, the recruitment period will have to be extended. In a next step, we will have to adjust the subgroup distribution and broaden, for example, the age restrictions. If participant numbers still remain low, we will have to critically discuss within our project coordination team whether we will perform focus group discussions with less than 5 persons or whether we will perform individual interviews. Due to the current COVID-19 pandemic and the subsequent social-distancing regulations, we are unsure whether focus group discussions are feasible. Nevertheless, we are confident that we can assemble a desirable number of participants for the discussions since we will use various recruitment strategies, such as patient support groups (including a Facebook group with more than 2000 active members), active contact through physicians, and flyers. Besides this, participants will receive an incentive, which will also be a motivation to engage in the discussions. Additionally, recruitment for the second subproject bears the risk of a low response rate since residents in the Munich area are often skeptical of surveys [26,27]. To counteract a small sample size and the consequent underpowering of our results, we will contact at least 2500 participants in order to obtain at least 500 data sets. Further, we will provide a scannable QR code that directly leads to the online questionnaire in order to facilitate accessibility.

Overall, the results of the HELIOS study will enable us to derive suitable evidence-based invitation and communication strategies for SCS. These may be implemented in the future to facilitate increased SCS uptake and early skin cancer detection.

Acknowledgments

The authors thank all the patients for their willingness to participate.

CB is a member of the German Dermatologic Society (Deutsche Dermatologische Gesellschaft), a board member of the Dermatologic Cooperative Oncology Group (Arbeitsgemeinschaft Dermatologische Onkologie) of the German Cancer Society (Deutsche Krebsgesellschaft), a board member of the Nationale Versorgungskonferenz Hautkrebs, and a member of the UV-Schutz-Bündnis.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group guide for part 1 of the project.
[DOCX File , 18 KB - resprot_v10i12e31860_app1.docx]

Multimedia Appendix 2
Draft of the questionnaire for part 2 of the project.
[DOCX File , 48 KB - resprot_v10i12e31860_app2.docx]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
HELIOS: Hautkrebsspezifische Einladungsverfahren zur informierten Screeningteilnahme (Skin Cancer–Specific Invitation Strategies to Participate in the Skin Cancer Screening Program)
SCREEN: Skin Cancer Research to Provide Evidence for Effectiveness in Northern Germany
SCS: skin cancer screening
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Multiplex Droplet Digital Polymerase Chain Reaction Assay for Rapid Molecular Detection of Pathogens in Patients With Sepsis: Protocol for an Assay Development Study

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Abstract

Background: Blood cultures are the cornerstone of diagnosis for detecting the presence of bacteria or fungi in the blood, with an average detection time of 48 hours and failure to detect a pathogen occurring in approximately 50% of patients with sepsis. Rapid diagnosis would facilitate earlier treatment and/or an earlier switch to narrow-spectrum antibiotics.

Objective: The aim of this study is to develop and implement a multiplex droplet digital polymerase chain reaction (ddPCR) assay as a routine diagnostic tool in the detection and identification of pathogens from whole blood and/or blood culture after 3 hours of incubation.

Methods: The study consists of three phases: (1) design of primer-probe pairs for accurate and reliable quantification of the most common sepsis-causing microorganisms using a multiplex reaction, (2) determination of the analytical sensitivity and specificity of the multiplex ddPCR assay, and (3) a clinical study in patients with sepsis using the assay. The QX200 Droplet Digital PCR System will be used for the detection of the following species-specific genes in blood from patients with sepsis: *coa* (staphylocoagulase) in *Staphylococcus aureus*, *cpsA* (capsular polysaccharide) in *Streptococcus pneumoniae*, *uidA* (beta-D-glucuronidase) in *Escherichia coli*, *oprL* (peptidoglycan-associated lipoprotein) in *Pseudomonas aeruginosa*, and the highly conserved regions of the 16S rRNA gene for Gram-positive and Gram-negative bacteria. All data will be analyzed using QuantaSoft Analysis Pro Software.

Results: In phase 1, to determine the optimal annealing temperature for the designed primer-probe pairs, results from a gradient temperature experiment will be collected and the limit of detection (LOD) of the assay will be determined. In phase 2, results for the analytical sensitivity and specificity of the assay will be obtained after an optimization of the extraction and purification method in spiked blood. In phase 3, clinical sensitivity and specificity as compared to the standard blood culture technique will be determined using 301 clinical samples.

Conclusions: Successful design of primer-probe pairs in the first phase and subsequent optimization and determination of the LOD will allow progression to phase 3 to compare the novel method with existing blood culture methods.

International Registered Report Identifier (IRRID): PRR1-10.2196/33746

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KEYWORDS

sepsis; ddPCR; clinical microbiology; molecular diagnostics; infectious diseases

Introduction

Sepsis, a dysregulated host response to infection leading to life-threatening organ dysfunction [1], often caused by bloodstream infection (BSI), is a major public health concern worldwide. Sepsis affects more than 48 million people annually, including an estimated 3 million newborns, leading to more than 11 million deaths annually, mainly in a hospital setting [2,3]. This makes it one of the leading causes of death worldwide [4]. In Denmark, the incidence rate is estimated to be 56,145 cases per year with a mortality of 8085, potentially accounting for 15% of all deaths [5,6].

Most sepsis survivors experience additional morbidities, resulting in reduced physical and mental quality of life after diagnosis [7,8]. Up to 32% of patients with sepsis have a rehospitalization episode within 30 days and 60% are readmitted at least once within one year [8]. According to a Danish study by Perner et al [9], more than 50% of sepsis survivors die in the first year following diagnosis. The significant burden of morbidity and mortality from sepsis has a profound impact on patients and their families, and it is a substantial economic burden on health care systems and society [10].

Sepsis is a profound inflammatory response to infections caused by bacterial, viral, fungal, or parasitic pathogens [11]. One of the primary reasons for the high morbidity and mortality rate of sepsis is delay in diagnosis and initiation of antimicrobial therapy—every hour of delay in appropriate antimicrobial treatment increases mortality by 7.6% [12,13]. As many as 80% of sepsis deaths could be prevented with rapid diagnosis and treatment [14]. During BSI, the bacterial load is estimated to be 1-10 CFU/mL [15] or 10^3 to 10^4 copies of bacterial DNA/mL [16]. Blood cultures are the cornerstone of microbiological diagnosis of sepsis. Key limitations are low sensitivity and long detection time (24-72 hours), with failure to detect a pathogen occurring in approximately 50% of patients with sepsis [15,17,18]. Gupta et al [19] have shown that sepsis-associated mortality was significantly higher in patients with a negative blood culture (34.6%) compared to patients with a positive blood culture (22.7%). Infection with fastidious microorganisms, antimicrobial treatment prior to blood collection, and low bacterial load all contribute to the occurrence of false-negative blood culture [15,20].

Multiplex real-time quantitative polymerase chain reaction (qPCR) has been increasingly employed in combination with positive blood culture to increase diagnostic sensitivity in patients with sepsis [21]. Multiplex qPCR also facilitates more rapid diagnosis [21-23], as demonstrated for the commercially available Septifast (Roche Diagnostics) [24] and FilmArray Blood Culture ID Panel (BCID; BioFire Diagnostics) [25]. The use of multiplex qPCR demonstrated high concordance with the blood culture technique, with up to 100% specificity and a limit of detection (LOD) ranging from 1 to 10 CFU/reaction [22,24]. It has been reported in some studies that multiplex qPCR detected the presence of a pathogen in 10%-40% of cases that were negative by conventional blood culture [26-28]. However, other studies have shown a reduced sensitivity, ranging from 28%-66%, in comparison with conventional blood cultures [28-30]. It is apparent that there is still a need for techniques to improve the diagnostic yield and reduce the time to diagnosis from blood culture specimens. The combination of nanoliter-sized droplet technology paired with digital polymerase chain reaction (PCR), known as droplet digital PCR (ddPCR), is a novel diagnostic tool that partitions the reaction into up to 20,000 droplets before amplification [31]. This method provides absolute quantification of target sequences and has demonstrated greater sensitivity, reproducibility, precision, and accuracy compared to qPCR [32-34]. For instance, the sensitivity of ddPCR was 6.4 copies/20 µL reaction for plasmid DNA and 5 CFUs/20 µL reaction for bacterial cells as compared to 12 copies/20 µL reaction and 36 CFUs/20 µL reaction using qPCR, respectively [35]. Furthermore, a study by Dong-Ku et al [36] demonstrated that, by using droplet digital detection technology, they were able to detect bacteria at the single-cell level in unprocessed diluted blood.

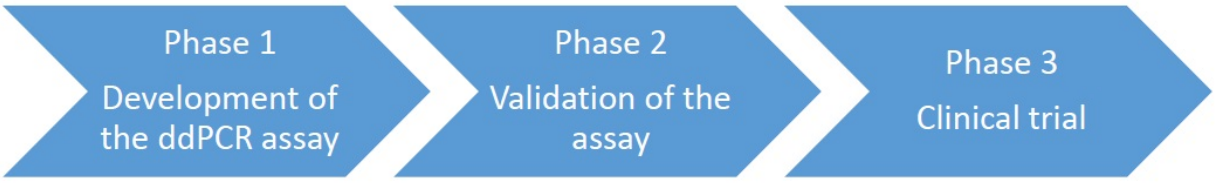
Recently, ddPCR has been investigated as a novel technique for the detection of pathogens in BSI. Wouters et al [37] demonstrated an overall sensitivity and specificity of 80% and 87%, respectively. Furthermore, they were able to detect *Escherichia coli* at a 10- to 100-fold lower concentration when compared to qPCR and with a detection limit of approximately 1-2 bacteria. Zhang et al [38] demonstrated similar results, with a detection rate up to 80%-90% of *Staphylococcus aureus* and *E coli* in blood when using ddPCR; both studies had promising results.

In this study, we will investigate ddPCR as a novel technique for sepsis diagnosis from whole blood and blood culture after 3 and 72 hours of incubation. To the best of our knowledge, this would be the first study that involves developing and implementing a multiplex ddPCR assay as a routine diagnostic tool for early detection of the most common sepsis-causing pathogens (ie, *S aureus*, *Streptococcus pneumoniae*, *E coli*, and *Pseudomonas aeruginosa*) in patients with sepsis. We believe that the technique will subsequently support clinicians to initiate early and rational antimicrobial treatment by reducing processing time and increasing the detection rate in blood cultures. Improved microbiological diagnosis of sepsis will not only help improve outcomes for sepsis, but also will contribute to improved antimicrobial stewardship and rational antibiotic prescribing.

Methods

This study will be conducted in three phases (for flowchart, see Figure 1).

Figure 1. Flowchart showing the three phases of the study, consisting of the development of the assay in phase 1, validation of the assay in phase 2, and a clinical trial using the assay in phase 3. ddPCR: droplet digital polymerase chain reaction.



Phase 1: Establishment of the Multiplex ddPCR Assay for the Detection of Quantitative Bacterial Genomic DNA and Determination of the LOD

In this phase, we will develop a novel multiplex ddPCR assay for accurate and reliable quantification of the genomic DNA of the most common sepsis-causing pathogens in our hospital region (ie, *S aureus*, *S pneumoniae*, *E coli*, and *P aeruginosa*) from cultured blood. This phase will be conducted in collaboration with the Department of Biochemistry, Hospital of Lillebaelt, Vejle, Denmark, since our laboratory facility does not currently have the QX200 Droplet Digital PCR System (Bio-Rad). This phase will include the following steps:

1. Design of primers and probes for the amplification of species-specific genes—that is, *coa* (staphylocoagulase) in *S aureus*, *cpsA* (capsular polysaccharide) in *S pneumoniae*, *uidA* (beta-D-glucuronidase) in *E coli*, *oprL* (peptidoglycan-associated lipoprotein) in *P aeruginosa*, and the highly conserved regions of the 16S rRNA gene for Gram-positive and Gram-negative bacteria.
2. Determination of the optimal thermocycling conditions for all primer pairs by varying the annealing temperature, extension time, and number of cycles.
3. Determination of the LOD of the assay by using a series of 10-fold serial dilutions of quantitative genomic DNA from a well-characterized stock (10^5 copies/µL). The serial dilutions of the stock will also be aliquoted and used as positive controls in subsequent analyses.
4. Determination of the rate at which false positives occur per run by analyzing a whole 96-well plate containing only nontemplate controls (ie, saline and uninfected cultured blood samples). Based on the evidence from this experiment, criteria for samples considered to be positive will be determined.

In this phase, primer-probe pairs for the targets of *coa*, *cpsA*, *uidA*, and *oprL* were designed using AlleleID (version 7.85; PREMIER Biosoft). The following ATCC strains were used for preliminary validation and testing of the designed primer-probe pairs: ATCC 29213 (*S aureus*), 49619 (*S pneumoniae*), 25922 (*E coli*), and 27853 (*P aeruginosa*).

Phase 2: Determination of the Analytical Sensitivity and Specificity of the Multiplex ddPCR Assay Compared to the Blood Culture Technique and BCID Assay in Spiked Blood

This phase will be divided into two parts.

Part A

In order to determine the analytical sensitivity and specificity of the multiplex ddPCR assay in cultured clinical samples, we will establish and optimize a procedure for the extraction and purification of bacterial genomic DNA from blood cultures in spiked blood. To confirm the adequacy of the purification procedure, the spiked blood will be compared to saline samples of the chosen bacteria of 1, 5, 10, and 10^2 CFU/mL from 5 healthy/noninfected donors. Certified reference materials for the spiking of blood samples will be used.

Part B

To validate the multiplex ddPCR assay, the analytical sensitivity and specificity will be compared to the blood culture technique and the BCID assay. For this study, a total of 50 blood samples (two BD BACTEC bottles corresponding to 20 mL and 1 mL of whole blood) from healthy/noninfected donors will be used. A total of 48 samples will be spiked with *S aureus*, *S pneumoniae*, *E coli*, and *P aeruginosa* (12 samples per bacteria) in triplicates of each concentration (ie, 1, 5, 10, and 10^2 CFU/mL). Two samples will be cultured with saline as nontemplate controls. All samples will be analyzed in duplicate by the multiplex ddPCR and BCID assay in parallel with blood cultures.

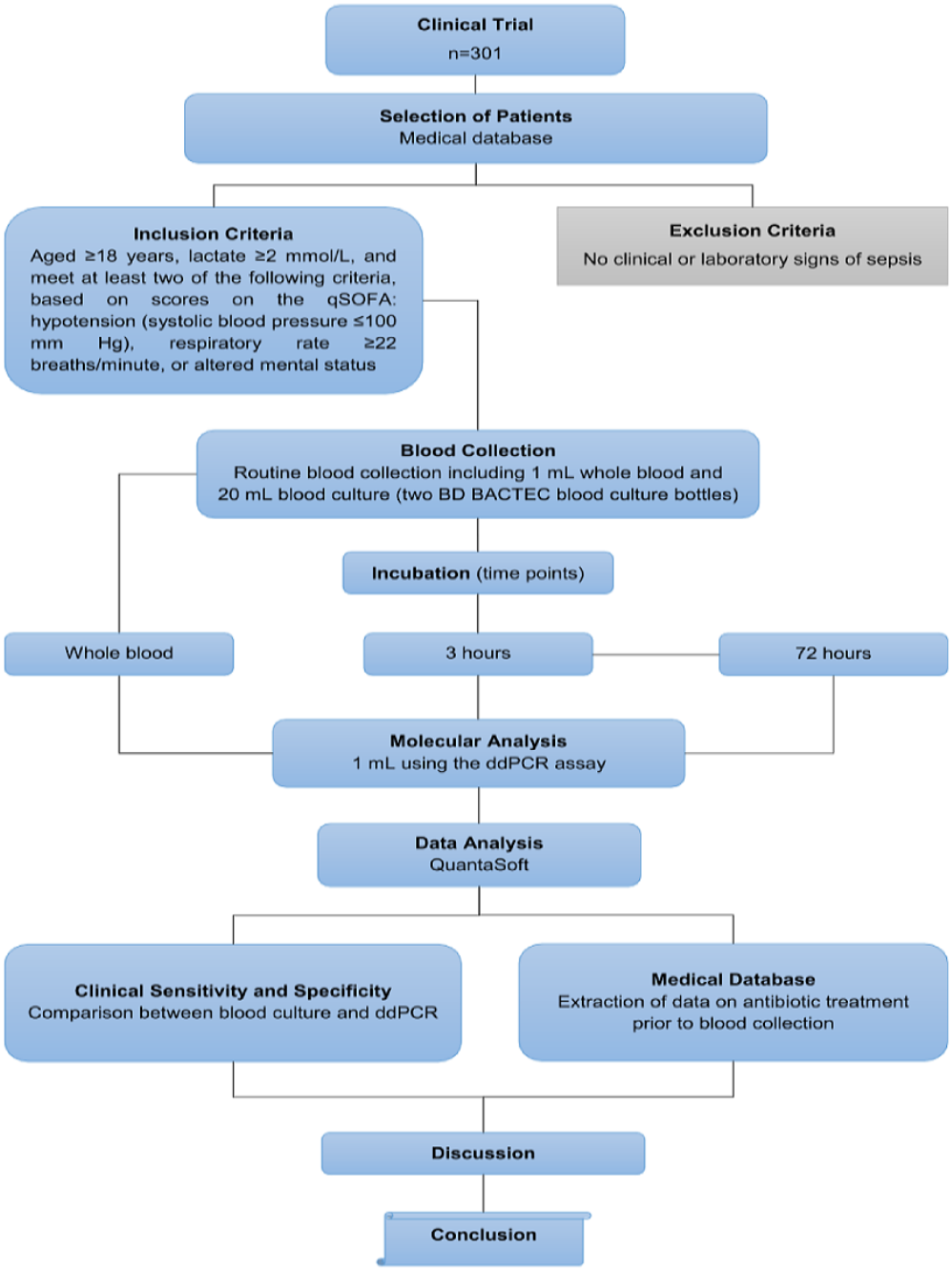
Phase 3: Multiplex ddPCR for Rapid Identification of Pathogens in Cultured Blood and Comparison of the Rate of Detection of Pathogens by Multiplex ddPCR With Conventional Blood Culture in Patients With Sepsis

Overview

This phase will investigate the use of the developed multiplex ddPCR assay for clinical samples from 301 patients with suspected sepsis. Patients will be selected for inclusion based on the following criteria: aged ≥18 years, lactate ≥2 mmol/L, and meet at least two of the following criteria, based on scores on the quick Sepsis-related Organ Failure Assessment (qSOFA): hypotension (systolic blood pressure ≤100 mm Hg), respiratory rate ≥22 breaths/minute, or altered mental status [1]. Patients will be excluded if they have no clinical or laboratory signs of sepsis.

The experiment will be blinded, and the results of the ddPCR assay will not be available to the clinical teams before the end of the study. This phase will be divided into two parts (for flowchart, see Figure 2).

Figure 2. Flowchart showing the study design of the clinical trial in phase 3, including patient selection, molecular detection divided into two parts (whole blood and incubation of blood cultures), and data analysis. ddPCR: droplet digital polymerase chain reaction; qSOFA: quick Sepsis-related Organ Failure Assessment.



Part A

The multiplex ddPCR assay will be performed directly on 1 mL of whole blood, and again after 3 hours of incubation in BD BACTEC blood culture bottles. The results of these tests will be compared with those obtained after 72 hours of incubation in conventional blood cultures to compare the rate of detection in clinical samples.

Part B

For Part B, 1 mL from conventional blood cultures that remained negative after day 3 will be analyzed retrospectively by ddPCR to confirm negative results [39]. Based on previous studies [26-28] showing that 10%-40% of negative blood cultures were found to be positive using a multiplex qPCR assay, we anticipate that at least 10% of those bottles that are negative by conventional culture will be positive using the multiplex ddPCR assay [32-35]. Data on antibiotic treatment and routine laboratory analyses will be extracted from clinical records and evaluated after collection and analysis of all blood samples. Data from the ddPCR assay will be analyzed using QuantaSoft Analysis Pro Software (Bio-Rad).

The sample size was calculated using Statulator, an online tool, with a power of 80% and a significance level of 5%. The calculation is based on the assumption that 15% and 20% of

the pairs are positive by blood culture and ddPCR, respectively, and that the correlation between paired observations is 70%.

Patient and Public Involvement

Patients and the public were not involved in the design or conduct of the study in any way, since the clinical trial will not influence patient management decisions. Therefore, the results will not be disseminated to the study participants.

Timeline

The outlined study will be conducted as a regional study within the Region of Southern Denmark. For this study, six months will be allocated to phase 1, five months to phase 2, and 16 months to phase 3. Finally, 14 months in total will be allocated for writing articles in parallel with the experiments. The study started in February 2021.

Ethics and Dissemination

Blood samples from healthy/noninfected donors will be anonymized and only used for spiking and nontemplate controls. All samples in phase 3 will be collected as part of routine diagnosis and management of patients, and the ddPCR results will not influence patient management decisions. Blood samples from patients with suspected sepsis will be pseudonymized and only used for method comparison. The Regional Committees on Health Research Ethics for Southern Denmark have notified for permission to conduct the study. Since the clinical study in phase 3 will not influence patient management decisions, no approval is required according to the Regional Committees on Health Research Ethics for Southern Denmark.

The results and findings from phases 1, 2, and 3 are expected to be published in peer-reviewed journals, preferably open access. National and at least two international conferences will be attended to present results and liaise with the scientific community. Science channels and the news will also be used to disseminate results.

Results

Phase 1: Establishment of the Multiplex ddPCR Assay for the Detection of Quantitative Bacterial Genomic DNA and Determination of the LOD

In phase 1, results from a gradient temperature experiment will be collected to determine the optimal annealing temperature for the designed primer-probe pairs. In addition, the results for the LOD of the multiplex assay will be obtained.

Phase 2: Determination of the Analytical Sensitivity and Specificity of the Multiplex ddPCR Assay Compared to the Blood Culture Technique and BCID Assay in Spiked Blood

In phase 2, results of the optimized extraction and purification method will be presented and the analytical sensitivity and specificity of the multiplex assay will be obtained using spiked blood samples.

Phase 3: Multiplex ddPCR for Rapid Identification of Pathogens in Cultured Blood and Comparison of the Rate of Detection of Pathogens by Multiplex ddPCR With Conventional Blood Culture in Patients With Sepsis

In phase 3, the clinical sensitivity and specificity of the multiplex ddPCR assay will be obtained and compared with the blood culture technique using 301 clinical samples.

This study is expected to conclude in February 2024.

Discussion

Successful design of primer-probe pairs for a multiplex reaction in the first phase—and subsequent optimization and determination of the LOD—will allow progression to phase 2 to determine the analytical sensitivity and specificity of the assay, which will allow progression to phase three to compare the method with existing blood culture methods.

Acknowledgments

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Authors' Contributions

SB wrote the protocol. All authors contributed equally to the conception and design of the protocol. The protocol was revised critically for important intellectual content by MC and JEC.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the University of Southern Denmark, Graduate School - Faculty of Health Sciences.
[PDF File (Adobe PDF File), 85 KB - resprot_v10i12e33746_app1.pdf]

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Abbreviations

BCID: Blood Culture ID Panel
BSI: bloodstream infection
ddPCR: droplet digital polymerase chain reaction

LOD: limit of detection
PCR: polymerase chain reaction
qPCR: quantitative polymerase chain reaction
qSOFA: quick Sepsis-related Organ Failure Assessment

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Protocol

Augmenting the Referral Pathway for Retinal Services Among Patients With Diabetes Mellitus at Reiyukai Eiko Masunaga Eye Hospital, Nepal: Protocol for a Nonrandomized, Pre–Post Intervention Study

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Abstract

Background: Diabetic retinopathy (DR) is an important public health issue in Nepal with a huge social and economic impact. Despite the availability of retinal services, people may not access them because of the lack of knowledge about DR and poor referral systems. Published studies on referral pathways in Nepal are scarce. Improving DR awareness among general physicians has the potential to address these challenges.

Objective: The aim of this study is to evaluate the effect of a health education intervention on health personnel, establish a referral pathway, and assess the impact of the intervention on the attendance of patients with diabetes mellitus for retinal screening at Reiyukai Eiko Masunaga Eye Hospital in Nepal.

Methods: This is a nonrandomized, pre- and postintervention study. Health education on DR will be provided to selected health personnel of the intervention hospital (Scheer Memorial) using information education and communication (IEC) materials in the form of PowerPoint presentations, posters, pamphlets, videos, and pre- and postevaluation questionnaires along with referral slip. Pre- and postevaluation will be undertaken during the study period. Data will be analyzed using MS Excel and Epi Info 7.

Results: The ethical approval for this study has been obtained from the Ethical Review Board of the Nepal Health Research Council (ERB Protocol Registration Number # 582/2020P). The study is expected to be completed in 18 months from the start of the project. The baseline data collection was from June to January 2020 for a period of 8 months. The postintervention data collection was from February to September 2021 for a period of 8 months. The last 2 months are planned for data analysis and report writing.

Conclusions: Health education intervention could be a low-cost solution to improve the awareness, access, and utilization of retinal health care services; this is an understudied topic in Nepal. Working closely with the stakeholders, this study will evaluate the role of health education interventions (which are already validated in other low-income settings) to strengthen referral and reduce the burden of DR in Nepal.

Trial Registration: ClinicalTrials.gov NCT04829084; https://clinicaltrials.gov/ct2/show/NCT04829084

International Registered Report Identifier (IRRID): DERR1-10.2196/33116

(JMIR Res Protoc 2021;10(12):e33116) doi:10.2196/33116

KEYWORDS

diabetes mellitus; diabetic retinopathy; Nepal; health education; study protocol

Introduction

Background

Diabetic retinopathy (DR) is a complication of diabetes mellitus (DM) damaging the retinal vessels. If left untreated, it can lead to blindness [1]. It is observed that more than 75% of people with DM for 20 years or more will have some form of DR and 10% will have retinopathy requiring treatment. Timely screening, early detection, and treatment can reduce the risk of blindness by more than 90% [2].

The worldwide prevalence of DR is 34.6% [3]. Globally, it is the fifth leading cause of visual impairment and the fourth leading cause of blindness. DR is responsible for 4.8% of the 37 million cases of blindness worldwide [4].

DR is an emerging cause of blindness in developing countries such as Nepal. Mishra et al [5] reported that 10% of people with DM had some form of DR in Nepal. The prevalence of nonproliferative DR, proliferative DR, and complete vision loss was 9.1%, 0.5%, and 0.3%, respectively, in Nepal [5]. Awareness about retinopathy remains very poor in Nepal and therefore, there is a need to sensitize the public about diabetic eye diseases [6]. Timely referral of patients with DM to retina care centers for screening is likely to improve early diagnosis of DR [7].

Our organization, Reiyukai Eiko Masunaga Eye Hospital (REMEH), is a nonprofitable community-based hospital in Banepa, Nepal, that provides eye care services to a population of 411,057 in the Kavrepalanchok District. In 2019, the hospital launched the retinal clinic and started retinal care services. Because the uptake of DR screening did not increase as expected, we conducted a problem tree analysis and identified that a poor referral system is one of the major reasons for the low uptake of DR screening at our hospital. Similarly, Piyasena et al [8] identified that the lack of knowledge and awareness about DR, and zero awareness of the importance of regular DR screening and follow-up, combined with poor information on referral pathways, were key elements to improve the uptake of DR in Sri Lanka [8].

Published studies on referral pathways in Nepal are scarce. We aim to see if providing health education intervention to selected health personnel and establishing a referral pathway increase the attendance of patients with DM for retinal screening at REMEH. This is a pilot study as no such study was previously conducted in Nepal.

Research Objective

The aim of this study is to increase retinal screening uptake among patients with DM and to decrease DR-associated blindness, by augmenting the referral pathway in a selected hospital in Nepal.

Hypothesis

Providing DR health education to selected health personnel and creating a referral pathway will increase the uptake of retinal services (screening and treatment) by patients with DM referred to REMEH.

Methods

Study Design, Setting, and Participants

This is a nonrandomized, pre- and postintervention study without a control group. The study was performed in REMEH. This study included selected health personnel of Scheer Memorial Hospital (the intervention hospital) who are directly involved in providing health services to patients with DM. A total of 19 health personnel of Scheer Memorial Hospital fit the inclusion criteria (4 physicians, 4 pediatricians, 8 medical officers, and 3 assistants).

Sampling Techniques

This involved complete enumerations of all health personnel managing patients with DM in the intervention hospital.

Inclusion and Exclusion Criteria

All health personnel involved in the management of patients with DM at the intervention hospital were included. Health personnel in the intervention hospital who are not directly involved in managing patients with DM were excluded.

Intervention Hospital

Scheer Memorial Hospital is the intervention hospital. The retinal physician and the optometrist/outreach coordinator of REMEH will conduct the intervention. The assistant manager of the hospital will be responsible for the logistics. There is no control group in this study.

Outcome

Primary Outcome

This includes change in the proportion of referred patients from Scheer Memorial to REMEH compared with baseline referrals before the intervention.

Secondary Outcome

This includes change in the knowledge level of the health care personnel who participated in health education sessions in Scheer Memorial.

Materials

The following information education and communication (IEC) materials developed by the Indian Institute of Public Health, Hyderabad, India, will be used for intervention after converting its content into Nepalese: PowerPoint slides, poster (Multimedia Appendix 1), pamphlet (Multimedia Appendices 2 and 3), and video. A referral slip (Multimedia Appendix 4) will also be used.

Pilot Study

We will conduct a pilot study 1 week before the intervention with a group of doctors managing patients with DM in another hospital. The pilot study will help to see if the materials are well

understood and the duration of sessions are optimal. Based on the feedback, we will make necessary changes to the IEC material and training delivery method before the intervention.

Implementation of Intervention

Ethical approval has been obtained from the Nepal Health Research Council. Written informed consent has been obtained from all participants. All selected health personnel of Scheer will visit REMEH for the health education sessions, which will be implemented once a month for 3 months, lasting an hour during the weekends. The session will begin with a preassessment test to know participants' baseline knowledge about DR. We will deliver a PowerPoint presentation explaining the burden of DM globally and in Nepal. It will include the effect of uncontrolled DM on eyes and possible damage to the retina, risk of DR, and the preventive measures for the early detection and management of DR to avoid vision loss. We will explain to the participants the contents of educational pamphlets. Lastly, we will present the educational video on DR. At the end of the first session, we will hand over the posters, pamphlets, and referral slips to the participants. We will request all 19 participants to distribute pamphlets to patients, counsel them to have fundus examination, and to use referral slips while referring patients to REMEH. We will provide posters related to DR with a request to display them in the waiting area of Scheer Memorial, and at the end of the intervention, we will conduct a quiz and postintervention assessment of the participants. The intervention plan is outlined in Table 1.

Actions expected from selected health personnel in Scheer Memorial:

- Counsel patients with DM to visit REMEH.
- Use the referral slip while referring patients to REMEH.
- Handover DR-related pamphlets to patients with DM.
- Record total cases referred to REMEH in a month.

Table 1. The intervention plan with IEC[a] materials used during each visit.

Visit	Materials	Questionnaire(s)
Pilot	All IEC materials	Pre- and postassessment questionnaires
First	PowerPoint presentations, posters, referral slips	Preassessment questionnaire
Second	Video presentation, pamphlets	—
Third	Refresher of the previous session and a small quiz	Postassessment questionnaire

[a]IEC: information education and communication.

Data Collection

Data will be collected before and after the health education at Scheer Memorial; besides, patient referral data at REMEH will be collected. All data will be entered into MS Excel every week. The data variables and tools are mentioned in Multimedia Appendices 1-5.

Data Analysis

The proportional increase of patients referred as a result of the intervention compared with baseline data will be calculated. Change in knowledge of health personnel will be assessed with pre- and postassessment questionnaires prepared using Public Health Foundation of India's "Certificate Course in Evidence Based Management of Diabetic Retinopathy assessment questionnaire" as a guide (Multimedia Appendix 5). The first 5 questions will be on DM and its complications and the remaining 5 questions will be specific to DR. The Diabetic Retinopathy Awareness Index will be calculated based on the scoring made by Datti et al [9].

Information on DR and duration of DM will be collected, visual acuity will be measured, and stage of DR will be noted to understand the clinical outcomes. Descriptive analysis for the same will be presented. Information on referred data from the intervention hospital will be extrapolated. Mean and SD will be calculated for the demographic variables. The *Z* test will be applied to determine the number of referrals. Paired *t* test will be used for the change in average knowledge score of health care professionals and a chi-square test will be used for pre–post referrals based on the education and experience of health care professions. Data will be analyzed using Epi Info 7.

Ethical Approval

The ethical approval for this study has been obtained from the Ethical Review Board of Nepal Health Research Council (ERB Protocol Registration Number # 582/2020P).

Results

The study is expected to be completed in 18 months from the start of the project. The baseline data collection was from June to January 2020 for a period of 8 months. The postintervention data collection was from February to September 2021 for a period of 8 months. The last 2 months are planned for data analysis and report writing. Descriptive analysis will be presented on the demographic variables of the health care professionals, demographic variables of patients, and clinical findings by computing means with SD. The proportion of increase in referral will be calculated by the *Z* test. The change in average knowledge score will be calculated by means and SD. *P* value will be calculated by a paired *t* test. The pre- and postintervention referrals will be determined based on the experience and education of the health care professionals by a chi-square test.

Discussion

Our study is a nonrandomized, pre- and postintervention design that focuses on health professionals as stakeholders to increase the referral of DR. The stakeholders will be provided health

education to create awareness and knowledge about DR using PowerPoint slides, posters, pamphlets, and referral slips. After the intervention, we hope to see increased referral of patients with DR from the intervention hospital (Scheer Memorial) and better knowledge among health care personnel. Different studies have shown that providing health education sessions on DR to physicians and assessing their awareness improved the uptake of screening for DR. Use of a referral slip for communication between an ophthalmologist and physicians was an effective strategy to change the behavior of referring physicians [8-17].

Health education intervention could be a low-cost solution to improve the awareness, access, utilization of retinal health care services, but this is an understudied topic in Nepal. Working closely with the stakeholders (health care professionals), this study will evaluate the role of health education interventions (which are already validated in other low-income settings) to reduce the burden of DR in Nepal.

The strength of our study is that it will be one of the first in Nepal that includes health care professionals involved in DM management and strengthens the referral for DR screening.

Because of COVID-19 restrictions, the number of selected health personnel participating in health education could reduce. We also do not have a control hospital to compare our intervention and the effect of the referral pathway between 2 hospitals, which could limit our study's generalizability. We need further studies to understand barriers faced by health personnel on the referral process and reasons for delays, if any.

Acknowledgments

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Authors' Contributions

RS, PS, PD, ST, and TB conceptualized and designed the study. RS, PS, PD, and PST were responsible for the data handling. RS, ST, and TB drafted the protocol manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Poster for Diabetic Retinopathy.
[PNG File , 1881 KB - resprot_v10i12e33116_app1.png]

Multimedia Appendix 2
Pamphlet for Diabetic Retinopathy.
[PNG File , 162 KB - resprot_v10i12e33116_app2.png]

Multimedia Appendix 3
Pamphlet for Diabetic Retinopathy.
[PNG File , 84 KB - resprot_v10i12e33116_app3.png]

Multimedia Appendix 4
Referral Slip.
[PNG File , 54 KB - resprot_v10i12e33116_app4.png]

Multimedia Appendix 5
Pre- and postquestionnaire.
[DOCX File , 44 KB - resprot_v10i12e33116_app5.docx]

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Abbreviations

DM: diabetes mellitus
DR: diabetic retinopathy
IEC: information education and communication
REMEH: Reiyukai Eiko Masunaga Eye Hospital

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Protocol

Study of Treatment and Reproductive Outcomes Among Reproductive-Age Women With HIV Infection in the Southern United States: Protocol for a Longitudinal Cohort Study

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Abstract

Background: Nearly a quarter of the 1.1 million individuals with HIV in the United States are women. Racial and ethnic minority women in the Southern United States are disproportionately impacted. Reproductive-age women with HIV are prone to poor HIV outcomes but remain underrepresented in HIV research. We will answer contemporary questions related to the health outcomes in this population by enrolling a prospective cohort of reproductive-age women with and without HIV in the Southern United States.

Objective: The Study of Treatment and Reproductive Outcomes (STAR) will enroll and retain 2000 reproductive-age women with and without HIV. The STAR will leverage the infrastructure of the US-based Multicenter AIDS Cohort Study (MACS)/Women's Interagency HIV Study (WIHS) Combined Cohort Study, comprising the WIHS (a cohort of women with and at risk for HIV, which began in 1993), and the MACS (a cohort of gay and bisexual men with and at risk for HIV, which began in 1984). Although the advancing age of the participants enrolled in the MACS/WIHS Combined Cohort Study provides an opportunity to address the questions related to HIV and aging, the research questions pertinent to the reproductive years must also be addressed. The STAR will conduct high-priority scientific research in key areas with the overall aim of addressing the unique needs of reproductive-age women with HIV.

Methods: The STAR is a prospective, observational cohort study that will be conducted at 6 sites in the United States—Atlanta, Georgia; Birmingham, Alabama; Jackson, Mississippi; Chapel Hill, North Carolina; Miami, Florida; and Washington, District of Columbia. Visits will occur semiannually for 2 years, with additional visits for up to 5 years. At each visit, the participating women will complete a structured interview for collecting key demographic, psychosocial, and clinical variables, and undergo biospecimen collection for laboratory testing and repositing (blood, urine, hair, vaginal, anal, and oral specimens). Pregnant women and infants will undergo additional study assessments. The initial scientific focus of the STAR is to understand the roles of key social determinants of health, depression, reproductive health, and oral health on HIV and pregnancy outcomes across the reproductive life span.

Results: Enrollment in the STAR commenced in February 2021 and is ongoing.

Conclusions: Through in-depth, longitudinal data and biospecimen collection, the newly initiated STAR cohort will create a platform to answer scientific questions regarding reproductive-age women with and without HIV. STAR will be uniquely positioned to enable investigators to conduct high-impact research relevant to this population. Building on the legacy of the MACS and WIHS cohorts, the STAR is designed to foster multidisciplinary collaborations to galvanize scientific discoveries to improve the health of reproductive-age women with HIV and ameliorate the effects of the HIV epidemic in this population in the United States.

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KEYWORDS

HIV; women's health; depression; oral health; longitudinal cohort study

Introduction

Background

Women of reproductive age are uniquely affected by the HIV epidemic. In the United States, nearly a quarter of the 1.1 million people living with HIV are women and most are racial or ethnic minority women in the Southern United States [1]. Reproductive-age women with HIV are highly vulnerable to poor health outcomes [2,3] and side effects of antiretroviral therapy (ART) [4,5], likely because of the structural, psychosocial, and biological factors, which manifest differently over time and across women's reproductive experiences. Young racial or ethnic minority women with HIV are more likely to report lower retention in care and ART adherence, worse long-term clinical outcomes [6], and higher mortality [7] compared with men, White women, and older women. Outcomes vary across women's reproductive lives; for example, although high levels of health care engagement and motivation for treatment adherence are documented during pregnancy [8], loss to follow-up [3,9], ART discontinuation [10], and lack of viral suppression [11] frequently occur during the postpartum period. These issues contribute to morbidity [12], mortality [13], ongoing HIV transmission risk to sexual partners [14] and future children, and lead to persistent disparities in perinatal HIV transmission [15]. Furthermore, women with HIV commonly face unplanned pregnancies [16,17] and adverse pregnancy outcomes [18].

Despite worse outcomes and unique challenges across multiple domains, the reproductive-age women with HIV in the United States remain underrepresented in HIV research [19,20]. Gaining a comprehensive understanding of the effects of HIV infection, reproductive health, and other key conditions in women of reproductive age is critical for developing future strategies to curb the HIV epidemic across populations in alignment with the US HIV National Strategic Plan [21].

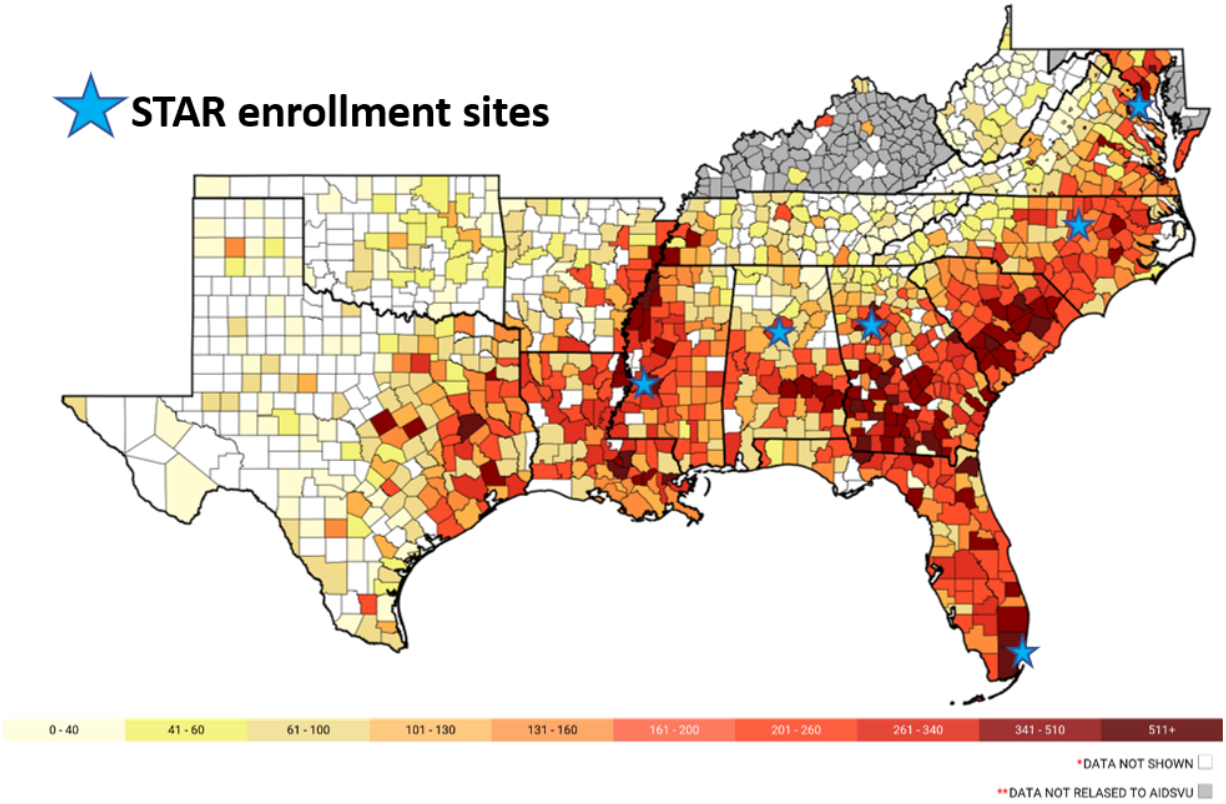
The Southern United States is now the epicenter of the nation's HIV epidemic. The 16 southern states and Washington, District of Columbia account for only 37% of the US population but 44% of all the people with HIV, and most new HIV diagnoses in the United States occur in the south: 8 of the 10 states and the 10 metropolitan statistical areas with the highest HIV rates are in the south [22]. Furthermore, 11 of the 13 states with the highest lifetime risk of HIV diagnosis are in the south [23], highlighting the urgent need to scale up the efforts to reduce the burden of the epidemic in this region. Geographic disparities observed in the HIV epidemic are particularly notable among women. Counties with the highest female-to-male HIV

prevalence ratio are concentrated in the south; these counties have a higher proportion of people living in poverty and with lower education [24]. Of most concern, people with HIV in the south have very limited access to care [25], initiate ART at later stages [6], and have worse survival outcomes than people with HIV in other US regions [26]

The Women's Interagency HIV Study (WIHS) [27], established by the National Institutes of Health (NIH) in 1993, was the largest and the longest running comprehensive prospective cohort study designed to investigate the effects of HIV infection on US women. The cohort included nearly 5000 women who completed biannual study visits with detailed structured interviews, physical, oral, and gynecologic examinations, laboratory testing, and specimen biobanking, and was managed by a robust data center. In 2019, the WIHS combined with the Multicenter AIDS Cohort Study (MACS) [28], a 30-year study of the effects of HIV infection on gay and bisexual men that enrolled over 7000 men with and without HIV, to form the MACS/WIHS Combined Cohort Study (MWCCS). The merger of MACS and WIHS sets a strong precedent for data harmonization and demonstrates the feasibility of pooling data from a cohort of reproductive-age women and the potential for important comparisons based on age and sex. Currently, women in the MWCCS are older (the median age of female participants is now 50 years) and do not adequately represent the contemporary population of women of reproductive age. The Study of Treatment and Reproductive Outcomes (STAR) will fill this gap by establishing a new cohort of reproductive-age women with and without HIV, a group that is underrepresented in HIV research, to address issues that uniquely affect this population, and to assess outcomes across women's reproductive life span. In addition to the establishment of the cohort, the STAR will address health conditions that are highly prevalent, understudied, and likely to be linked to poor health and HIV outcomes among women with HIV—mental health and oral health—as its initial scientific focus.

The 6 STAR sites, located in the Southeastern United States, provide optimal settings for the recruitment and retention of young women with and without HIV into a new longitudinal cohort study focused on reproductive-age women. The STAR sites are located in Atlanta, Georgia; Birmingham, Alabama; Jackson, Mississippi; Chapel Hill, North Carolina; Miami, Florida; and Washington, District of Columbia (Figure 1 [29]). These sites include 3 of the 5 metropolitan areas with the highest HIV rates in the United States (Miami [first], Atlanta [third], Jackson [fourth]) [1], and all have been recently prioritized in the Health and Human Services' *Ending the HIV Epidemic* initiative [29]. The STAR will recruit and follow 2000 reproductive-age women with and at risk for HIV infection to address key scientific questions in this understudied population. The STAR will open a new line of scientific investigation to address the unique health challenges of women spanning the reproductive life span. Using approaches similar to those used by the MWCCS (including its standardized assessments, clinical sites, data management approach, and strong community partnerships), the STAR will rapidly achieve its recruitment targets. In this study, we describe the research protocol for establishing this new longitudinal cohort.

Figure 1. Southern United States with county-level rates of women with HIV per 100,000 persons in 2018. Source: AIDSVu, Emory University, Rollins School of Public Health [29]. *Data not shown to protect privacy because of a small number of cases and/or a small population. **State health department, per its HIV data rerelease agreement with CDC, requested not to release data to AIDSVu. There are no county-level maps for Alaska, District of Columbia, and Puerto Rico because there are no counties in these states. STAR: Study of Treatment and Reproductive Outcomes.



Key Scientific Objectives of the STAR

The overall objectives of this study are (1) to create a platform for multi- and cross-disciplinary research by enrolling a representative cohort of women with and at risk for HIV and collecting longitudinal clinical, behavioral, and laboratory data to investigate key issues across women's reproductive lives using novel scientific approaches; (2) to understand the impact of depression on critical HIV-related, pregnancy-related, and other reproductive health outcomes across the reproductive life span; and (3) to investigate the role of key social determinants of health, HIV-related factors, and pregnancy on oral health among women. The long-term goal is to use results from the STAR to develop strategies to improve the health of women with HIV, their children, and their communities.

Depression is highly prevalent among women with HIV and the prevalence of depressive symptoms among these women is higher than that in the general population [30]. Co-occurrence of HIV infection and depression contributes to poor health outcomes, including suboptimal ART adherence [31], substance use [31-33], sexual risk behaviors [34], accelerated HIV disease progression, viral nonsuppression, HIV-related and all-cause mortality [35-39], and adverse maternal and child health outcomes [40-44]. Reproductive-age women with HIV are at higher risk for depression-related adverse outcomes and are less likely to seek mental health services than older women, owing to stigma, lack of awareness, limited resources, and competing childcare and other obligations [34,45,46]. Depression is of particular concern for pregnant women with HIV; perinatal depressive symptoms have been reported in nearly half of the women with HIV compared with 10%-20% in the general population [40]. We seek to understand the effects of depression on HIV and reproductive health outcomes, and how these relationships are modified by individual and socio-contextual factors and their interacting combinations. We hypothesize that depression, especially during and after pregnancy, is associated with poor HIV and reproductive health outcomes and its effects are modified by individual- and community-level factors.

Racial and ethnic minority women experience a higher burden of oral disease compared with their White counterparts, and these health disparities persist and are augmented in the context of HIV infection [47-49]. Common oral health conditions are gingival inflammation and periodontal disease, which are more frequent and severe among persons with HIV [49,50] and may influence pregnancy outcomes [51-56]. Previous research on women with HIV have demonstrated the associations between oral health and other nonoral health outcomes, low dental services access and use [57-59], and have shown that high rates of periodontal disease are associated with systemic inflammation among persons with HIV [49]. In this study, we will evaluate the intersecting relationships of depressive symptoms, reproductive health, oral health, and pregnancy outcomes and their mediators across the reproductive life span of women with HIV. We hypothesize that oral health indicators (such as periodontal disease and oral health-related quality of life [OHRQOL]) are influenced by HIV-related factors and social determinants of health, particularly during and after pregnancy.

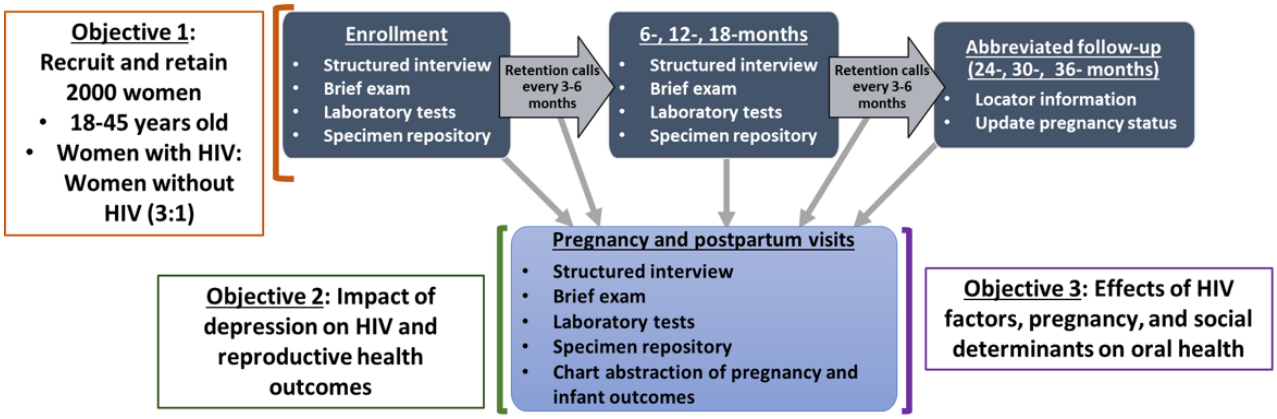
Methods

Study Overview and Design

The STAR is a longitudinal observational study that will include 2000 women aged 18-45 years at the time of enrollment who have been diagnosed with HIV infection or are HIV-seronegative but at risk for HIV infection. To evaluate the effect of HIV status on key study variables, 1500 participants with HIV and 500 participants without HIV who meet the inclusion criteria will be enrolled.

Comprehensive study visits will occur at the time of enrollment and at 6, 12, and 18 months thereafter. Semiannual brief telephone or web-based visits will continue until the end of follow-up (ie, up to 5 years) to facilitate retention and identify women who become pregnant. Women who become pregnant during follow-up will have additional pregnancy and postpartum study visits that comprise of interviewer-administered questionnaires, biological specimen collection, and medical record abstraction (Figure 2). Selected mental and oral health measures and biospecimens (including oral specimens) will be included to assess the key scientific objectives of investigating depression and oral health. Additional data and biospecimens will be available for future studies aimed at addressing key research priorities for women with HIV.

Figure 2. Overview of the Study of Treatment and Reproductive Outcomes objectives and study visits.



Consent and Institutional Review Board Approval

The study was reviewed and approved by the STAR single Institutional Review Board (sIRB) at the University of Miami (sIRB# 20190953) that provides regulatory oversight over all the participant recruitment sites. Informed consent will be obtained from all willing participants before enrollment. Any substudies that require additional questionnaires or measures will be submitted as an amendment or as a separate study protocol and additional consent will be obtained as determined by the sIRB. Consent forms and questionnaires will be administered in English or Spanish, according to each participant's preference.

Participants

All the participants must meet the following eligibility criteria: (1) aged between 18 and 45 years, (2) be female at birth, (3) able and willing to give informed consent, (4) able to complete the interview in English or Spanish, (5) able and willing to have blood drawn and stored, and (6) agree to medical record abstraction to ascertain pregnancy-related outcomes (including infant demographics and clinical characteristics). Participants with HIV must have evidence of HIV infection, as documented by any Food and Drug Administration–approved assay.

Participants without HIV must report at least one of the following high-risk exposures within 5 years before enrollment: (1) sex with ≥3 men; (2) use of crack, cocaine, opiates, methamphetamines, or any injection drug use; (3) sexually transmitted infection (STI) diagnosis; (4) sex for drugs, money, or shelter; (5) sex with a man with known HIV infection; or (6) a male sexual partner who reports one of the following within the last 5 years before enrollment: (a) use of crack, cocaine, opiates, methamphetamine, or injection drugs; (b) STI diagnosis; (c) sex with ≥3 people; (d) sex for drugs, money, or shelter; (e) sex with an individual with known HIV infection; or (f) any prior incarceration. Similar inclusion criteria were previously used to enroll HIV-seronegative women for WIHS and resulted in the enrollment of a group of HIV-seronegative women who were well-matched to women with HIV with respect to demographic, behavioral, and other risk characteristics [27]. Participants will be excluded if they are planning to move out of the area during the study follow-up period, if the study procedures are not completed at any of the study sites, or if they have any condition that would make participation in the study unsafe or interfere with achieving the study objectives.

Recruitment

The recruitment of eligible study participants will be distributed across the 6 study sites and is expected to occur over the next 3 years. The STAR sites and the data center will review and monitor the enrollment demographics. The recruitment strategy is designed to ensure recruitment of women who are (1) representative of the local epidemic with regard to race or ethnicity and other sociodemographic factors, (2) committed to participate in all the study-related activities, and (3) willing to commit to long-term follow-up. Participants will be recruited from (1) clinical sites (adult or women's, obstetric, adolescent, and pediatric HIV clinics), (2) current MWCCS participants, (3) other existing local research studies, and (4) community locations (ie, community-based organizations and clinics). All the participating study sites have forged deep relationships with

clinical sites and community advocacy groups to facilitate clinic- and community-based recruitment of diverse populations of women with and without HIV. We will iteratively review our procedures in collaboration with our community partners during the enrollment period to optimize and maintain effective recruitment strategies to meet the recruitment targets.

Incentives

All the participants will be offered appropriate compensation for their time and effort. Compensation will vary according to the study procedures completed at the respective visit and may include reimbursement for travel to and from the location of the study clinic.

Study Procedures

Screening and enrollment may be conducted in 1 visit. Data collection and procedures will include participants' demographics and residential addresses for geocoding, a series of interviewer-administered questionnaires (including medical, reproductive health, sexual risk behavior, medication adherence, psychosocial variables, oral health, and mental health), limited physical examination (blood pressure, pulse, height, and weight), and biological specimen collection (including blood, urine, hair, and oral, anal, and vaginal specimens). Mucosal swabs (oral, anal, and vaginal) will be self-collected but may be clinician-collected (if self-collection is not feasible or based on the participant's preference). Participants will be asked to attend semiannual study visits for at least 18 months and will be contacted every 3-6 months thereafter to facilitate study retention for the duration of the study period. Women may be asked to attend additional visits during pregnancy or for substudies, and medical record abstraction will be used to collect pregnancy, birth, and infant outcomes data. To evaluate the intersecting relationships between oral disease and other health outcomes in reproductive-age women with and without HIV, an additional dental plaque specimen will be collected from a subset of pregnant women as part of an oral substudy.

All the sites in this multicenter study use a common protocol, consisting of the same questionnaires; specimen collection, processing, storing, and shipping protocols that meet federal standards for all specimen types; and centralized data management, hosted at Johns Hopkins University. The study personnel will be trained to perform all assessments. All the specimen collection, handling, processing, and storage will be conducted according to written standard operating procedures. All the study laboratories will maintain the required certifications and adhere to best practices. The sites will have site-specific standard operating procedures for the notification of clinically relevant laboratory results and referral for appropriate clinical follow-up (if required). All the specimens will be tracked using the laboratory information management system to manage the collection of biological specimens. Tracking will be centralized using unique STAR study ID and specimen identification numbers assigned by the data center.

Description of Study Assessments

Data collection will include a structured interview and limited physical assessments (Table 1). Specific to the key scientific objectives of the STAR, depressive symptoms will be measured using the widely used Center for Epidemiologic Studies Depression scale for all the participants and with the Edinburgh Postpartum Depression Scale administered to the participants who are pregnant or within 12 months of delivery, as continuous scores and categorized by key cutoffs [27,40,60,61]. We will also obtain supplemental mental health histories and the related medication use through questionnaires. Oral health histories will be collected using validated questionnaires previously used in WIHS [57-59] and OHRQOL information will be collected using the Oral Health Impact Profile [62-64]. Clinical outcomes will be abstracted from the medical records, and biological specimens described above will be collected for laboratory testing and repository storage (Table 1). The following biological specimens will be stored in the local biospecimen repository of each study site using standardized methods and will be shipped at 3-month intervals to an NIH-sponsored central repository for long-term storage: blood (plasma, serum, and peripheral blood mononuclear cells), saliva, urine, mucosal specimens (vaginal, oral, and anal), and hair. If the interview components or biospecimens cannot be completed or collected, respectively, at the designated visit, then a participant may return or be contacted to complete the visit elements within 90 days of the visit initiation.

Table 1. Study of Treatment and Reproductive Outcomes schedule of assessments.

Visit	Baseline	Baseline+6 months	Baseline+12 months	Baseline+18 months	Baseline+24, 30, 36 months
Interview					
Sociodemographics	X[a]	X	X	X	P[b]
Medical or health history, including HIV history and treatment, pregnancy history, and mental health history	X	X	X	X	P
Obstetric, gynecologic, and reproductive health history (includes pregnancy intentions)	X	X	X	X	P
Contraception access	X	X	X	X	P
Use of Health care	X	X	X	X	P
Oral health questionnaire[c]	X	—[d]	X	—	—
Behavior form[e]	X	X	X	X	P
Pregnancy or postpartum form[f]	P	P	P	P	P
Drug Abuse Screening Test-10 [65,66]	—	X	*[g]	*	*
Lifetime discrimination [67] and stigma [68]	—	X	*	*	*
History of abuse [69]	—	X	*	*	*
COVID-19 questionnaire	X	—	X	—	—
Abbreviated interval health (medication changes, pregnancy, contraception)	—	M[h]	M	M	X
Outcomes ascertainment					
Outcomes ascertainment form[i]	X	X	X	X	X
Pregnancy ascertainment form	P	P	P	P	P
Infant ascertainment form	P	P	P	P	P
Physical examination					
Height, weight, blood pressure	X	* or P	X	* or P	—
Brief oral exam with dental photograph review	X	P	P	P	P
Laboratory assessments					
CBC[j], differential	X	*	—	—	—
CD4/CD8 panel (women with HIV only)	X	*	X	* or P	—
HIV RNA (women with HIV only)	X	*	X	* or P	—
HIV antibody or antigen test (HIV only)	X (if last test >3 weeks)	*	X	* or P	—
Comprehensive metabolic panel	X	*	—	—	—
HgA_{1c}[k] and lipids	X	*	—	—	—
STI[l] (chlamydia, gonorrhea, trichomonas)	X	*	X	—	—
Syphilis test	X	*	X	—	—
HPV[m]	X	*	X	—	—
Urine pregnancy screen	X	* or P	X	* or P	—
Biospecimens for repository					

Visit	Baseline	Baseline+6 months	Baseline+12 months	Baseline+18 months	Baseline+24, 30, 36 months
Serum, plasma and cells (PBMC[n])	X	* or P	X	* or P	P
Urine supernatant	X	* or P	X	* or P	P
Vaginal, oral, rectal self-swab	X	* or P	X	* or P	P
Unstimulated saliva	X	* or P	X	* or P	P
Hair (women with HIV only)	X	* or P	X	* or P	P
Dental plaque	P	P	P	P	P

[a]X: Form completed at the visit.

[b]P: Additional forms to be completed if the participant meets criteria for a *pregnancy visit* or a *postpartum visit.*

[c]Includes Oral Health Impact Profile [62-64], dental neglect [70], and oral health-related quality of life [71-74].

[d]Assessment not performed at this visit.

[e]Includes the following topics: sexual behavior, alcohol use, substance use, tobacco use, Center for Epidemiologic Studies Depression [60], loneliness [75], social support [76], perceived stress [77], quality of life [78], attitudes toward aging [79], resilience [80], sense of community [81], safety [82], and perceptions on *undetectable=untransmittable.*

[f]Includes Edinburgh Postnatal Depression Scale [61] (pregnancy and postpartum) and intimate partner violence (postpartum)[69].

[g]If not completed at the preceding visit in which assessment was scheduled as noted by "X".

[h]M: Additional forms to be completed if the participant is unable to come in for an in-person visit.

[i]Includes HIV history and treatment, cervical health (Papanicolaou test and human papillomavirus testing and vaccination, dysplasia, and cancer), sexually transmitted infection history, cancer, and death.

[j]CBC: Complete blood count.

[k]HgA_{1c}: hemoglobin A_{1c}.

[l]STI: sexually transmitted infection.

[m]HPV: Human papillomavirus.

[n]PBMC: Peripheral blood mononuclear cells.

For geocoding, the STAR staff at each site will collect the addresses from the participants who have consented to geocoding, geocode them (using ArcGIS; Esri), and assign a census block group. ArcGIS will match each participant's geocoded location to a Federal Information Processing Standard (FIPS) code that identifies geographic locations in the United States. Each site will create a limited data set that contains only the participants' FIPS codes and the study ID. This limited data set will be securely transferred to the University of North Carolina at Chapel Hill site, which will link the FIPS codes to census-linked data sets, such as the American Community Survey or Decennial Census, to create group-level variables that will describe the locations where participants live.

The participants with laboratory-confirmed pregnancies will be asked to undergo pregnancy-specific assessments either during a scheduled core visit (baseline, 6, 12, and 18 months) or at an additional visit scheduled after 20 weeks of gestation. All the pregnant participants who reach beyond 20 weeks of gestation will have a postpartum visit conducted approximately 3-6 months after delivery. For each participant who reports pregnancy that reaches beyond 20 weeks of gestation, the clinical and laboratory data related to the pregnancy will be obtained using standardized chart abstraction and will include the following obstetric outcomes: prenatal or postpartum visits attended, hypertensive disorders (including preeclampsia and eclampsia), gestational diabetes, miscarriage, preterm birth, stillbirth, and fetal growth restriction and the following infant outcomes: gestational age at birth, birth weight, length, head circumference, birth defects, newborn screen, infant prophylaxis regimen, anemia, lead levels, and Apgar scores.

Adaptations During the COVID-19 Pandemic

In light of the COVID-19 pandemic, safety measures will be taken to protect the study participants. Owing to the heterogeneity of the effects of the pandemic within the United States, each site will follow local guidance on the resumption of in-person visits using safety measures to protect the participants and the staff. To facilitate research productivity, virtual visits through phone or an Institutional Review Board–approved remote communication and signature platform will be conducted when in-person study visits are deemed unfeasible. The sites will be approved to implement remote consent procedures to limit the in-person contact time. Options to obtain consent will include (1) remote consent process using secure platforms that can handle protected health information for communication or electronic documentation (ie, Zoom, RedCap, and DocuSign) with institutional approval or (2) verbal consent process in which the script of the verbal consent is read slowly and clearly to the participant by trained study staff. If the potential participant agrees to participate in the research interview, the person obtaining the consent will sign and date the verbal consent script. The study staff will reiterate that the participant will be asked to sign the full consent documents during the first in-person visit. Verbal consent will be obtained only for administering the questionnaires. After the remote portion of the study visit is completed, the participants will have an in-person visit to complete the physical examination elements including the collection of biological specimens. As part of the

COVID-19 pandemic modifications to the protocol, the participants will be asked to self-collect unstimulated saliva in a private room. In addition, we will incorporate a brief COVID-19 questionnaire to capture data on the prevalence of COVID-19 and vaccination among the study participants.

Data Management

A confidential research record with all the source documents and data will be maintained for each study participant. Each participant will be assigned a unique study ID number at the time of enrollment that will be used in all subsequent and associated study documents and biospecimens. Any data (eg, medical records) that are acquired with identifiers will be maintained at the site and stored securely with limited access to specified site study personnel. The data collected will be entered directly during the interview by the study staff into a centralized, web-based data management system called GEMINI, which is developed and maintained by Johns Hopkins University. Each STAR site will work with the centralized data center to create and maintain data quality. The data center will provide centralized data management training, including study procedures for data collection, entry, checking for completeness and skip patterns, common mistakes, and error correction. When direct data entry is not feasible, paper forms will be used and data will be subsequently entered. The data center personnel at Johns Hopkins University will not interact with the participants and will not receive identifiable data, specimens, or the ID code link of the participants. Once all the data from a visit are entered, the data for that visit will be frozen and will undergo a rigorous central editing and quality-checking procedure to ensure the highest quality of every file that is stored. The data center will apply central editing programs at the end of each visit. Once the sites respond to edit queries through GEMINI, the data from a visit will be merged with the master longitudinal database.

Study Leadership and Investigator Procedures

The principal investigators of the STAR will lead the operations at their respective sites and contribute to the scientific research agenda based on their complementary expertise. The STAR Executive Committee (EC) will work collaboratively with the MWCCS EC, the data center, community stakeholders, and NIH representatives. The STAR EC will meet twice every month through teleconference and with the MWCCS EC during the semiannual meetings. The STAR investigators will engage the community stakeholders to provide input on study design, data interpretation, and dissemination of findings during the MWCCS semiannual meetings and as part of the local MWCCS and STAR community advisory board activities.

We have assembled a Scientific Advisory Group (SAG) of highly accomplished external investigators who are engaged in research with reproductive-age women with HIV to (1) create a collaborative framework for establishing a rigorous scientific agenda, (2) provide a venue for participation and access to the cohort to a wider group of investigators, and (3) foster systematic interaction with established investigators who complement the scientific expertise of the STAR investigators. The SAG members will participate in quarterly conference calls and an annual meeting.

In addition to the planned scientific objectives, the STAR will emphasize multidisciplinary collaborations in women's health and HIV/AIDS research among leading scientific experts across all the sites to facilitate applications for research to define and understand health outcomes over the course of women's reproductive live span. To achieve this goal, the STAR will leverage the scientific cores which already exist because of MWCCS and each STAR site will have a scientific core focused on promoting high-priority scientific research at the site led by its STAR principal investigator. The STAR SAG will also advise on establishing a research agenda that will be informed by the research priorities of the Office of AIDS Research. External investigators who wish to use the STAR data or specimens will submit a request in collaboration with the STAR investigators. Once the request is approved, the data center will coordinate the release of deidentified data and specimens.

Data Analysis

Sample Size

Owing to the anticipated size of the cohort (larger than the sample size used in a previous analysis of depressive symptoms [83]) and the high prevalence of depression among young women with HIV (over 20%), we expect more than sufficient power for the primary analyses. We anticipate that approximately 10% of the participating women will become pregnant during follow-up [84], of whom more than 40% are likely to experience postpartum depression, which will provide >80% power to detect a risk ratio of 2 for common obstetric outcomes (overall incidence>15%). The power will increase if more pregnancies are observed.

Outcomes

HIV outcomes across several planned analyses will include ART adherence (by self-report), retention in care (2 HIV care visits 90 days apart within 1 year), and durable viral suppression (HIV-1 RNA<200 copies/mL at all visits). Reproductive health outcomes will include pregnancy intentions, contraception access and use, STI acquisition, and pregnancy outcomes ascertained from medical records including adherence to prenatal care, preeclampsia, eclampsia, gestational diabetes, miscarriage, preterm birth, and fetal growth restriction.

Statistical Analysis

We will use descriptive statistics to understand the distribution of the baseline variables, exposures, and outcomes. To understand the role of depression in this cohort population, regression models will be used to examine whether individual- and community-level characteristics are associated with the incidence and prevalence of depressive symptoms, accounting for clustering by neighborhood and when appropriate, using generalized estimating equations and robust variance estimators. We will estimate the effect of depression on the outcomes and estimate how this relationship may be mediated by other individual- and community-level factors. Causal diagrams will be informed by prior literature and the Modified Social Ecological Model [85], which highlights the multilevel risks

and contexts of HIV infection and situates individual behavior within the social, structural, and policy contexts.

We will also estimate both the effects of exposures (eg, depression) and the effects of potential interventions on those exposures (eg, cognitive behavioral therapy) using both traditional regression approaches and 2 modern epidemiological analysis methods: inverse probability weighted marginal structural models [86-88] and the g-formula [89,90].

We will also use these data to investigate (1) the effects of social determinants (including dental care access or use, depression, and substance use, including opioids), psychosocial factors (depression, anxiety, medical mistrust, smoking, and substance use), and HIV factors (ART use, CD4+ T lymphocyte count, and HIV viral load) on 2 main oral health indicators—periodontal disease and OHRQOL; and (2) the associations between periodontal disease and pregnancy outcomes (preterm birth, hypertensive disorders of pregnancy, and low birth weight). We will use longitudinal mixed methods models to examine these associations with periodontal disease and OHRQOL. Among women who experience pregnancy, we will use logistic regression models, adjusting for covariates (including those associated with periodontal disease), to examine the association between periodontal disease and pregnancy outcomes.

Integration and Dissemination of Findings

Findings from all the proposed analyses will be disseminated to the STAR investigators, SAG members, community partners, and NIH representatives. The findings will also reach a broad scientific audience through presentations at national and international conferences and publication in peer-reviewed journals.

Results

Research activities for this study commenced in September 2019 and are ongoing. Participant enrollment and data collection commenced in February 2021 and are ongoing. As of July 15, 2021, 165 participants have been enrolled across the STAR sites (142/165, 86.1% non-Hispanic Black; 10/165, 6.1% non-Hispanic White; and 10/165, 6.1% Hispanic or Latina women, similar to the race and ethnicity distribution of participants previously recruited for WIHS at the same sites [27]). Data analysis is scheduled to begin next year. Owing to the scientific engagement efforts, additional scientific questions to understand genital and extragenital STI prevalence and incidence in this cohort were added as part of a substudy. Furthermore, a substudy has also been added to describe the use of the human papillomavirus vaccine and its association with human papillomavirus infection and type among the STAR participants. Scientific engagement efforts are ongoing to expand the research agenda of the STAR.

Discussion

Despite the availability of ART, reproductive-age women with HIV experience suboptimal viral suppression and engagement in HIV care, especially among racial or ethnic minority women in the Southern United States [91]. This cohort will be uniquely positioned to enable investigators to conduct high-impact research relevant to reproductive-age women with HIV, including research related to pregnancy. By leveraging strategies from the MWCCS, this cohort will be rapidly established despite the challenges posed by the COVID-19 pandemic and will obtain high-quality data using established and validated surveys, specimen collection procedures, and data management tools. When relevant, assessments will also be harmonized with those used in other US cohorts of pregnant and reproductive-age women with HIV to allow for potential future collaborations and data synergy. Adaptation of study procedures will allow remote visits and specimen collection while following pandemic procedures at the sites, enabling timely enrollment and progress. The potential impact of this cohort is evidenced by the additional supplements awarded before the start of participant enrollment to address additional scientific priorities for this population. This study will produce high-impact results with the potential to improve the health of reproductive-age women with and without HIV in the Southern United States, optimize the gains of ART, and ameliorate the effects of the epidemic in this population.

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Conflicts of Interest

DW has engaged in consulting for PRI Healthcare Solutions on behalf of Sanofi Pasteur on subjects unrelated to this work. MLA receives honorarium from the following sources (unrelated to this work): Merck Inc (educational lecture fees) and Senhwa pharmaceuticals (Data Safety Monitoring Board member). AAA has received consulting fees and funds for research to her institution from Merck and Gilead.

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Abbreviations

ART: antiretroviral therapy
EC: Executive Committee
FIPS: Federal Information Processing Standard
MACS: Multicenter AIDS Cohort Study
MWCCS: Multicenter AIDS Cohort Study/Women's Interagency HIV Study Combined Cohort Study
NIH: National Institutes of Health
OHRQOL: oral health-related quality of life
SAG: Scientific Advisory Group
sIRB: Single Institutional Review Board
STAR: Study of Treatment and Reproductive Outcomes
STI: sexually transmitted infection
WIHS: Women's Interagency HIV Study

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Protocol

Adapting Evidence-Based Early Psychosis Intervention Services for Virtual Delivery: Protocol for a Pragmatic Mixed Methods Implementation and Evaluation Study

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Abstract

Background: Timely and comprehensive treatment in the form of early psychosis intervention (EPI) has become the standard of care for youth with psychosis. While EPI services were designed to be delivered in person, the COVID-19 pandemic required many EPI programs to rapidly transition to virtual delivery, with little evidence to guide intervention adaptations or to support the effectiveness and satisfaction with virtual EPI services.

Objective: This study aims to explore the adaptations required to deliver NAVIGATE, a model of coordinated specialty care used in EPI, in a virtual format. This study will evaluate implementation of the NAVIGATE model delivered virtually by describing the nature of the adaptations to the intervention, assessing fidelity to the EPI model and the satisfaction of clients, family members, and care providers. We will investigate barriers and facilitators to virtual NAVIGATE implementation, service engagement, and health equity impacts of this work.

Methods: The Centre for Addiction and Mental Health (Toronto, Ontario, Canada) transitioned to delivering NAVIGATE virtually early in the COVID-19 pandemic. The Framework for Reporting Adaptations and Modifications for Evidence-Based Interventions will be used to describe the adaptations required to deliver NAVIGATE virtually. Fidelity to the EPI model will be measured using the First Episode Psychosis Services Fidelity Scale and fidelity to NAVIGATE will be assessed by investigating adherence to its core components. Implementation facilitators and barriers will be explored using semistructured interviews with providers informed by the Consolidated Framework for Implementation Research. Satisfaction with virtually delivered NAVIGATE will be assessed with virtual client and provider experience surveys and qualitative interviews with clients, family members, and providers. Service engagement data will be collected through review of medical records, and potential impacts of virtually delivered NAVIGATE on different population groups will be assessed with the Health Equity Impact Assessment.

Results: Virtual clinical delivery of NAVIGATE started in March 2020 with additional adaptations and data collection is ongoing. Data will be analyzed using descriptive statistics and survival analysis for quantitative data. Qualitative data will be analyzed using thematic content analysis. Integration of qualitative and quantitative data will occur at the data collection, interpretation, and reporting levels following a convergent design.

Conclusions: This study will provide information regarding the type of intervention adaptations required for virtual delivery of NAVIGATE for youth with early psychosis, ensuring access to high-quality care for this population during the pandemic and beyond by guiding future implementation in similar contexts.

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KEYWORDS

virtual care delivery; early psychosis intervention; mixed methods implementation

Introduction

Background

The COVID-19 pandemic is expected to have a disproportionate burden on people with psychosis related to anticipated adverse physical and mental health consequences, compounded by barriers to accessing quality care [1-6]. Psychosis, characterized by delusions, hallucinations, disorganization, and negative symptoms, typically occurs during adolescence or early adulthood, an age at which the pandemic may be particularly detrimental for mental health [7,8]. Early, time-limited, team-based comprehensive treatment in the form of early psychosis intervention (EPI) has become the standard of care for youth with psychosis, with demonstrated evidence of superior outcomes including reduced mortality, improved access to psychiatric care, reduced risk of relapse, fewer hospital readmissions, and increased employment rates [9-13]. There is additional evidence that a manualized package of EPI services called NAVIGATE results in improved functional outcomes relative to usual care [14]. NAVIGATE is a form of coordinated specialty care developed for early-phase psychosis that has shown greater improvement in symptoms, social functioning, and engagement in educational and vocational training compared to usual care [14-16]. EPI programs were designed to deliver care in person, emphasizing frequent contacts and community outreach. Amid the COVID-19 pandemic, EPI programs have had to transition to virtual delivery to adhere to public health physical distancing measures; however, with little prior knowledge about the effectiveness of virtual delivery of EPI care [17-20].

Virtual mental health care is generally defined as mental health care delivered via any form of information and communication technology, such as the telephone, the internet, teleconferencing, or SMS text messaging [21]. In the past, virtual care has been commonly utilized to improve access to health care, especially in underserved and remote areas [22]. There is a robust literature on the effectiveness of telehealth for mental disorders, although most of this research has focused on anxiety and mood disorders [21,23]. Regarding telehealth interventions for people with schizophrenia, a review in 2014 [24] yielded initial promising results in the limited number of studies that utilized telehealth technology at that time. A recent scoping review on videoconferencing with people with schizophrenia [20] showed that implementation was feasible and acceptance was high, but noted a lack of studies on videoconferencing interventions for individuals at clinical high risk or at the early stages of psychosis. Studies of youth with psychosis suggest that they have favorable attitudes toward videoconferencing [25] and receiving mental health information on the internet [26]. Additionally, most youth have access to smartphones or other devices with a webcam [25], suggesting that virtual care is likely to be acceptable and feasible for youth with psychosis. Barriers to implementation of virtual mental health services in general include acceptance by clinicians and clients, technology, organizational/regulatory policies, and funding to support virtual care [23]. Furthermore, digital literacy and access to technology (internet and devices), as well as the availability of private space to receive services in this manner may present barriers to specific populations and have the potential to increase health disparities [27]. Psychotic symptoms may pose further barriers to client acceptance of videoconferencing [20].

The COVID-19 pandemic compelled many mental health services to rapidly transition to virtual care [28,29]. Understanding what adaptations to the intervention are needed and how they occur over time is a vital aspect of their effective implementation because the core components of the intervention must be retained for effectiveness [30]. Adaptations that focus on improving interventions fit with the target population can lead to improved engagement and acceptability, particularly

when working with diverse populations [31-33]. However, modifications that alter or remove core components of an intervention, or fail to align with population needs may impact effectiveness and be less sustainable [30]. We propose exploring the adaptations required to deliver NAVIGATE virtually and to evaluate the implementation effectiveness of virtual delivery of NAVIGATE.

Objectives

The objectives of this study are as follows:

1. To explore the *adaptations* required to implement and deliver the NAVIGATE program virtually, including understanding how core components of the EPI model and NAVIGATE specifically are best adapted for virtual delivery.
2. To evaluate the *implementation outcomes* of virtual NAVIGATE as measured by *fidelity* to the EPI model and to the core components of the NAVIGATE intervention.
3. To explore *implementation facilitators and barriers* for virtual delivery of NAVIGATE to guide iterative development and implementation.
4. To examine *satisfaction* with virtual delivery of NAVIGATE among clients, family members, and care providers.
5. To investigate *service engagement* with NAVIGATE delivered virtually, including dropout from services and how services are used (virtually by videoconference or telephone or in person), and *health equity factors* related to virtual delivery of NAVIGATE care.

Methods

Methods Overview

We propose a pragmatic mixed methods implementation and evaluation study, with a focus on adaptations needed for the implementation of virtual NAVIGATE care and evaluation of the implementation. Virtual delivery of NAVIGATE started in March 2020 with additional adaptations and ongoing data collection. The StaRI (Standards for Reporting Implementation Studies) Statement and Checklist is used as a standard for describing the implementation strategy and intervention (Multimedia Appendix 1) [34].

Study Setting and Population

The Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario, is home to the largest EPI program in Canada, providing assessment and ongoing services to people aged 16-29 years with any mental health disorder that can manifest as early psychosis (schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar I disorder, major depressive disorder with psychotic features, substance-induced psychotic disorder, or unspecified psychotic disorder) [35]. Located in downtown Toronto, the EPI program is staffed by approximately 40 clinicians and assesses over 600 new clients annually. The CAMH EPI program implemented NAVIGATE in late 2017 and is currently the coordinating center for a multisite implementation effectiveness study of NAVIGATE in diverse EPI programs across the province of Ontario (Early Psychosis Intervention-Spreading Evidence-based Treatment or "EPI-SET," trial registration number: NCT03919760) [36].

Of importance, CAMH has a dedicated Virtual Mental Health and Outreach Team. Previously, this service primarily supported telepsychiatry to clients in remote and rural areas; however, during the COVID-19 pandemic, they have supported other CAMH programs to deliver care virtually, including the EPI service. Throughout the pandemic, the bulk of EPI care has transitioned to virtual delivery, although a small number of clients have continued to access some CAMH EPI services in person; these are mainly clients who are receiving intramuscular injections, have increased symptoms, or are in a crisis and may require a hospital admission, who are at risk of disengaging, who do not have access to the technology needed for virtual care, or for whom adequate assessment is not feasible remotely. Staff have been rotating onsite approximately 1-2 days per week to ensure a small continuous onsite presence and otherwise working remotely from home.

Intervention and Implementation Approach

NAVIGATE is a highly structured model of coordinated specialty care with clearly defined roles for staff. The original model is described with four core services: individual resiliency training (IRT), supported employment and education (SEE), family education program, and individualized medication management [16]. For our context, we distilled additional core components that are fundamental to the NAVIGATE program, including the following: a team leader who facilitates monitoring, practice feedback and training, and caseloads small enough to allow for the intensity and frequency of required contact. In addition to these core components of NAVIGATE, CAMH's EPI program also incorporates peer support. Manualized protocols are used to operationalize current EPI standards, and all clients are systematically offered all treatment components, with regular team reviews to assess client progress, fidelity, and need for adjustments. The core components of NAVIGATE are described in Figure 1.

In March 2020, clinicians at CAMH rapidly transitioned to delivering NAVIGATE virtually using videoconferencing and telephone calls. Over time, clinicians have supplemented NAVIGATE delivery with group videoconferencing, interactive worksheets, and web-based videos prepared collaboratively with CAMH Education Services. This conversion to primarily virtual care delivery has been supported by policies and processes established by CAMH Virtual Mental Health, including client tools, training videos, podcasts, and a Digital Mental Health Certificate Program [37,38]. These early NAVIGATE adaptations are described in Table 1.

Figure 1. NAVIGATE core components. CAMH: Centre for Addiction and Mental Health.

Table 1. Adaptations to support virtual delivery of NAVIGATE.

	Technology to support virtual care	Policies and procedures of virtual care	Clinical Practice
Early hospital-wide	• Devices (hospital laptops and cellphones) made available to many clinicians • Limited number of cellphones and SIM cards donated to the hospital and made available for clients who lacked access to a working cellphone. • Registration and limited training for clinicians on a hospital-approved videoconference platform that integrates with email/calendar, permits screen-sharing • Registration and limited training for clinicians on specialized software to support timely access to office telephone calls while working from home • Registration and limited training for clinicians on additional software applications to support virtual care; for example, faxing, scanning, and secure document transfer	• Privacy, safety, and confidentiality standards disseminated with expectations for documenting consent to virtual care • Suggestions for virtual crisis management sent, including procedures for involuntary detainment and completion of other legal forms • Remuneration for psychiatrists to provide care over the phone or videoconference (province-wide)	• Videos created and posted on the Centre for Addiction and Mental Health Virtual Mental Health website to train on best practices in virtual care • Introduction of fillable PDF forms to document client consent (eg, to participate in virtual care)
Early NAVIGATE-specific	• NAVIGATE handouts available in fillable PDFs and Word (Microsoft Inc)	• Criteria for considering in-person appointments disseminated	• Higher level of structure/organization for group sessions • Clinician cellphones enable SMS text messaging with clients • Additional briefer appointments are encouraged to maintain attention and engagement • Connect with other clinicians during team meetings on clinical practice in virtual delivery of NAVIGATE including tips to reduce barriers or boundary-setting • Increased collaborative client meetings involving multiple NAVIGATE roles together (ie, individual resiliency training, supported education and employment, and family clinician)

The implementation evaluation plan for this study is described in Table 2. By engaging youth and family members with lived experience in accordance with current best practices [39-41], as well as frontline clinicians, administrators, and a policy maker, we aim to continue to adapt and refine the virtual delivery of NAVIGATE in a facilitated, stepwise process and to describe the nature of these adaptations using the Framework for Reporting Adaptations and Modifications for Evidence-Based Interventions (FRAME) [42]. We will explore to what extent virtual delivery of NAVIGATE retains its core components and describe adaptations in how the core components are delivered. We will also consider whether additional core components are warranted to specifically support virtual delivery of this model. We will explore implementation barriers and facilitators to virtual delivery using the Consolidated Framework for Implementation Research (CFIR) [43,44]. This approach will allow us to adjust our implementation approach in accordance with feedback and clinical outcomes [45,46].

Table 2. Virtual NAVIGATE: adaptation and implementation evaluation plan.

Objective	Project aim	Tools/Framework	Data sources	Timing
Objective 1				
Adaptations	To explore the adaptations required for delivery of the NAVIGATE model and its implementation, including understanding how aspects of the EPI model and NAVIGATE specifically are best suited to virtual delivery	• NAVIGATE Practice Profile: map adaptations to the delivery of NAVIGATE care among the different roles • Framework for Reporting Adaptations and Modifications for Evidence-Based Interventions (FRAME): when/how modification was made, whether planned or unplanned, who determined, what is modified, level of delivery, nature of context/content modifications, fidelity-consistency, reasons including intent and contextual factors	Study team, clinicians, and administrators	• Months 1-4 • Revise implementation as needed following interim analysis month 12
Objective 2				
Outcomes	Proctor's taxonomy of implementation outcomes			
Fidelity to the early psychosis intervention (EPI) model	To evaluate fidelity to the EPI model	First Episode Psychosis Services Fidelity Scale (FEPS-FS). A retrospective fidelity review will be conducted to assess practice prior to the onset of the COVID-19 pandemic (March 2020) and following the transition to virtual care, after initial adaptations have been made	Electronic health record and clinicians	• Pre–COVID-19 fidelity review based on the assessment of medical records in months 8-9 • Virtual NAVIGATE review month 10 • Integration with other analyses months 13-21
Fidelity to the NAVIGATE program	To evaluate fidelity to the core components of NAVIGATE	Measure clinician adherence to their NAVIGATE role through review of medical records and calculate the proportion of clients who receive IRT, SEE, family support or individualized medication management at least monthly or greater	Electronic health record and clinicians	• Virtual NAVIGATE review month 10 • Integration with other analyses months 13-21
Objective 3				
Facilitators and barriers	To explore implementation facilitators and barriers	Interviews based on the Consolidated Framework for Implementation Research (CFIR)	Clinicians	• Interviews and iterative analysis months 9-11 • Integration with other analyses months 13-21
Objective 4				
Satisfaction and experience	To evaluate satisfaction and experience with virtual NAVIGATE among clients, family members, and clinicians	• Virtual Client Experience Survey (VCES) • Virtual Provider Experience Survey (VPES) • Qualitative interviews	• Clients • Clinicians • Clients, family members, and clinicians	• VCES/VPES month 5-9 • Interim analyses months 8-9 • Integration with other analyses months 13-21
Objective 5				
Service engagement	To investigate service engagement in virtual NAVIGATE	Time to, rate, and correlates of premature dropout, proportions, and correlates of how services are used (virtually by videoconference or phone or in person)	Electronic health record	• Data extraction starts month 8 • Preliminary analysis months 12-13 • Integration with other analyses months 13-21

Objective	Project aim	Tools/Framework	Data sources	Timing
Health equity	To explore health equity factors that may impact service engagement in virtual NAVIGATE	• Qualitative interviews • Health Equity Impact Assessment	• Clients and family members • Clinicians, administrators, youth, and family members with lived experience	• Interviews and iterative analysis months 9-11 • Integration with other analyses months 13-21

Implementation Evaluation

Fidelity to the EPI Model

We will assess the fidelity of virtual delivery of NAVIGATE to the EPI model using the FEPS-FS [47]. The FEPS-FS is a validated assessment of fidelity of EPI service delivery to standards of EPI care [47]. Scale development was based on a review of evidence combined with an expert consensus process and is not associated with any specific model of care delivery. In total, 33 items will be rated on a 5-point scale from "not implemented" to "fully implemented." A rating of 4 is considered satisfactory adherence. Trained assessors will review data abstracted from health records and conduct interviews with staff to complete the FEPS-FS. The fidelity assessment can be performed remotely with excellent reliability [48,49]. The fidelity assessment of virtual NAVIGATE will be compared to previous fidelity assessments of traditional, in-person, NAVIGATE at CAMH and at other sites across Ontario [36].

Fidelity to NAVIGATE Core Components

Fidelity to the core components of NAVIGATE will be explored by tracking the delivery of core components against the NAVIGATE practice profile over a specific timeframe, and comparing adherence for virtual and in-person NAVIGATE delivery [50]. A practice profile is a tool that identifies the core, nonnegotiable elements of an intervention or service; the NAVIGATE practice profile that was developed for the EPI-SET study will serve as a basis for mapping adaptations and describing any changes to the core components (Figure 1) [14,15,51,52].

Implementation Facilitators and Barriers

A CFIR informed interview protocol [43,44] will be used to systematically assess contextual factors that are associated with effective implementation in relation to 5 major domains: intervention characteristics (eg, complexity and relative advantage), outer setting (eg, external policy and client needs), inner setting (eg, compatability and readiness), staff characteristics (eg, knowledge and beliefs), and implementation process (eg, planning and facilitation). Since CAMH clinicians had previously implemented NAVIGATE, the interview will focus specifically on the implementation of virtual delivery. A semistructured interview will guide data collection with 8 clinicians (IRT, SEE, family work, prescriber, and team lead) [43,53].

Satisfaction

Client satisfaction with virtual NAVIGATE will be measured using the Virtual Client Experience Survey (VCES), a 23-item survey developed to measure client satisfaction of virtual care quality that is being used in outpatient programs at the hospital. Family members receiving services are also invited to complete the same survey and identify themselves as caregivers in their responses. The VCES was adapted from a validated survey that was developed within the TeleMental Health program at CAMH [52] and contains items from the Ontario Perception of Care Tool for Mental Health and Addictions [54]. Validation of the VCES is underway. Additionally, a Virtual Provider Experience Survey (VPES) has been distributed to clinicians hospital-wide, and will gather data on the satisfaction of providers with virtual delivery of NAVIGATE; the VPES is still undergoing validation. Satisfaction will also be assessed through qualitative interviews with clients and family members. We will start by conducting 8 semistructured interviews with clients and family members (purposefully selected to represent varying durations of care and service engagement) and continue participant recruitment until thematic saturation is reached. The interviews will explore their satisfaction with virtual services and the impact on service engagement. Based on our related study, we anticipate that this sample size will allow us to achieve saturation of themes [36].

Service Engagement and Health Equity Factors

To evaluate service engagement and health equity related barriers to the adoption of virtual NAVIGATE, we will use reviews of medical records to extract information from the electronic health records, including health equity factors routinely collected at CAMH, other demographic and clinical factors, mode of service delivery (videoconference, telephone, or in person), and indicators of service engagement. Outcomes will include timing and rates of premature dropout from services, the Service Engagement Scale [55] (which is routinely completed by clinicians in the program), and frequency of appointments. Consideration of health equity is critical to support an effective implementation approach and avoid increasing health disparities [27,56]. The Health Equity Impact Assessment (HEIA) [57] will be completed by staff and administrators, together with youth and family members with lived experience, to assess how the virtual delivery of NAVIGATE may impact populations differentially, both to mitigate potential negative impacts, as well as to enhance positive impacts. Service engagement and health equity factors will also be explored in the qualitative interviews with youth and family members.

Analysis

Adaptations

We will describe the adaptations made for virtual delivery of care in accordance with the core components articulated in the

NAVIGATE practice profile. The FRAME will be used to describe when and how adaptations were made, as decided by whom, the nature of the adaptation, level of delivery, nature of context/content modifications, fidelity-consistency, and the reasons underpinning the adaptation, including intent and contextual factors.

Fidelity to EPI

We will compare FEPS-FS fidelity ratings between virtual NAVIGATE and previous fidelity assessments conducted at CAMH and other Ontario sites and calculate descriptive statistics. We will compare single items, the percentage of the items rated as 4 or 5 (satisfactory or exemplary) and the mean fidelity score.

Fidelity to NAVIGATE

For fidelity to the core components of the NAVIGATE model, we will examine adherence to the core components through review of medical records of a representative subset of the study population. The previously described practice profile incorporates predefined criteria to evaluate how the core components are delivered [50]. For example, for IRT core components we will capture the proportion of clients who had an IRT visit in the last 3 months, completed the first 2 modules (Orientation and Assessment) within 3 months and, if applicable, completed the 7 standard modules within 12 months and had at least 2 treatment reviews within 12 months. The SEE clinician, family clinician, and prescriber roles will be tracked similarly in the health record. We will interview the program director to explore fidelity to the core components of team leadership, training and practice feedback, caseload size (eg, number of team meetings with all roles per month). We will verify the initial training for new staff, practice meetings, and attendance to learning community activities.

Implementation Facilitators and Barriers

The CFIR provides the organizing framework for qualitative deductive coding and analysis of the clinician interviews. CFIR interviews will be administered and coded using a variation of the Rapid Analysis (RA) method, an alternative to in-depth analysis of interview data to allow for faster analysis and dissemination of implementation findings while using fewer resources [58,59]. In combination with the fidelity results, we will seek patterns of implementation facilitators and barriers, coded deductively to the CFIR domains and factors, as well as direction and strength of the association (valence) between factors and implementation success. The first analytic step of the RA method involves developing a templated summary table that analysts will populate with data extracted from interview transcripts in real time, during the interview. The templated summary table is based on the CFIR-based interview guide (domain and factors). Valence rating captures the factors' positive or negative influence on implementation (–2, –1, 0, mixed, +1, and +2). Strength of the association is then rated (1or 2) and is determined by a number of factors, including the level of agreement among participants, strength of language, and use of concrete examples.

Satisfaction

We will calculate descriptive statistics for the VCES and VPES to evaluate satisfaction of virtual NAVIGATE among clients and staff. We will compare VCES scores by demographic factors captured in the same questionnaire, including gender, age, racial or ethnic group, and geographical location, using *t* tests and linear regression models. The interviews with clients and family members will be audio recorded and transcribed verbatim. Using NVivo software, a mixed thematic analysis approach will be applied. A deductive coding scheme will be developed on the basis of domains of the VCES, as determined through confirmatory factor analysis. The research team will review all transcripts to identify and categorize components as reflected in the conceptual model, as well as to identify emergent themes. Transcripts will be double-coded and then coding will be discussed and adjusted accordingly.

Service Engagement and Health Equity Factors

We will compare data extracted from the charts on disengagement from services following implementation of virtual NAVIGATE with disengagement rates among clients receiving in-person NAVIGATE in previous years. Disengagement is defined as no appointments with the treatment team for 3 months or explicit refusal to engage with NAVIGATE care despite clinical need. Additionally, total scores on the Service Engagement Scale will be gathered from charts.

During both in-person delivery of NAVIGATE and virtual NAVIGATE periods, we will measure frequency and modality of appointments (videoconference vs telephone vs in-person) using descriptive statistics. Survival data analysis tools will be applied to associate time to disengagement with baseline factors and mode of delivery. Candidate methods, including Cox proportional hazards and parametric regression models, will be selected on the basis of the fitness of model assumptions. For this exploratory analysis, we anticipate having a sample of approximately 500 clients who have received virtual NAVIGATE at some point in their care, including a sample of 225 clients who completed 9 months of NAVIGATE prior to the onset of the pandemic and transition to virtual care, and approximately 125 clients newly enrolled and followed in virtual NAVIGATE for at least 9 months. In a supplementary analysis, we will examine these groups as well as clients who started the NAVIGATE program in person and then transitioned to virtual delivery of NAVIGATE during the pandemic. We will treat the pandemic indicator variable as a time-varying predictor with a potential change point on survival analysis. We anticipate a disengagement rate of 15%-20% by 9 months, based on prior data from our own program as well as another Canadian EPI program [60]. This will provide pilot data for future tests of noninferiority of virtual delivery of NAVIGATE compared to in-person NAVIGATE.

The HEIA catalogues determinants of health for a number of prespecified populations, for consideration in relation to a proposed intervention, and guides a consideration of potential impacts of the program, mitigation strategies, monitoring, and a dissemination plan to share results to address equity [27,61]. The HEIA will be completed at the outset and will be revisited during the implementation and sustainability phase [61].

The qualitative interviews with youth and family members will be reviewed on factors linked to service engagement and health equity factors.

Data Integration

Integration of qualitative and quantitative data will occur at the data collection, interpretation, and reporting level with a convergent design [62]. Qualitative and quantitative data collection occurs iteratively, with recurrent linking at multiple points for each of the evaluation objectives. For example, the fidelity assessment integrates findings from both reviews of medical records and individual interviews. Additionally, early quantitative results from the VCES on satisfaction with virtually delivered NAVIGATE will be used to guide adaptations of the client and family qualitative interviews, probing emergent quantitative findings. Similarly, findings from the qualitative interviews on service engagement may highlight the need for additional variables to be extracted in the reviews of medical records. Data sources will be woven together at the interpretation and reporting level through narrative integration and joint display methods [62]. We will explore coherence of the quantitative and qualitative findings by reporting on "fit" of data integration [62].

Results

The organic nature of the rapid initial transition to virtual care has facilitated more explicit and intentional adaptation and implementation of virtual NAVIGATE delivery at CAMH. This study was funded in September 2020, and as of this writing, we have begun to explore adaptations made by clinicians delivering the service (Table 1) and to augment these with additional supports. The results of the fidelity assessments, satisfaction surveys, qualitative interviews, and service engagement outcomes are expected to shed light on how best to deliver the core components of virtual NAVIGATE with quality and fidelity, and for whom this is most suitable.

Discussion

Expected Findings

The onset of the COVID-19 pandemic has led to rapid transition of mental health services to virtual delivery, with little evidence to guide the transition from in-person mental health care to delivery via virtual care for young people with psychosis. Adaptations to the delivery of NAVIGATE core components have occurred organically and iteratively, requiring evaluation of how NAVIGATE may best be delivered to provide an effective intervention in a virtual setting. This study will identify how NAVIGATE core components are best delivered and provide essential knowledge on the fidelity, facilitators and barriers, and satisfaction with virtual NAVIGATE. Results will guide future program implementation in other EPI sites to better customize virtual NAVIGATE delivery to meet the needs and preferences of clients, family members, and care providers. Data on service engagement will improve early identification of youth likely to benefit from a virtual approach and those who may require an in-person component, either owing to digital equity issues, personal preference, or other factors. Insights into the barriers and facilitators to virtual NAVIGATE will guide further adaptations, future scale up, and identify health disparities that require further attention.

In addition to supporting the delivery of high-quality care to youth with psychosis in the near future, the virtual delivery of EPI care may also be more accessible to youth and adaptable to low-resource and geographically remote settings well beyond the COVID-19 pandemic [63].

Individuals in rural communities tend to experience poorer health, greater disability, and higher mortality related to poor access to health care and limited availability of specialized health providers [64]; Ontario has a population of approximately 14 million people spread across 1 million km^2 with mental health services concentrated in urban settings. If implementation of virtual NAVIGATE at CAMH results in high fidelity to the EPI model and demonstrates acceptability and feasibility, spread would first be coordinated across additional programs in Ontario through our existing collaboration with the EPI-SET study network of providers [36]. These programs have similarly transitioned to virtual delivery; however, without the support of a dedicated virtual care program or evaluation tools to guide iterative adaptations. The EPI-SET study sites cover a large geographical region of Ontario and suburban, rural, and Northern regions. Because of their geographic spread, these sites have even more to gain from establishing effective ways to deliver high-quality EPI services virtually.

We will also disseminate our results by preparing a manual on what is required to transition from in-person to virtual delivery of NAVIGATE. Additionally, we will engage in traditional knowledge translation activities by publishing manuscripts in open access journals and presenting our findings at conferences.

Limitations

The initial adaptations to NAVIGATE virtual delivery were organic, unplanned, and reactive, having been prompted by public health guidance for the COVID-19 pandemic. Emergent needs are being addressed iteratively and some additional tools, including provider satisfaction surveys, are still being validated as of this writing. Exposure to the intervention is dynamic over time not only because the intervention has evolved with additional supports but also because clients have received their care in different modalities, in part reflective of the changes in public health recommendations. It will be challenging to distinguish the impacts of the transition to virtual delivery on outcomes, including service engagement, from the impacts of the pandemic itself.

Conclusions

Out of necessity, mental health care has rapidly transitioned to virtual delivery in the absence of intentional and explicit guidance and evidence of quality outcomes. This study leverages existing clinical evidence and implementation science in the context of an emergent global pandemic to evaluate how best to adapt and deliver NAVIGATE virtually toward lasting improvements to quality and accessibility of services for youth with psychosis.

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Authors' Contributions

WT, MB, AC, AV, DA, JA, JD, AK, PK, AP, SS, and NK drafted and revised sections of the protocol and approved the final version. TA, CB, SB, GF, CF, LF, SJ, KP, AS, VV, and WW made critical revisions on the protocol and approved the final version. MB developed the implementation evaluation. AC consulted on virtual health care delivery. AV consulted on the development of the project. DA consulted on the fidelity assessment plan. TA, KP, and VV consulted on evaluation of engagement of people with lived experience. JD developed the fidelity assessment plan. AP consulted on qualitative interviews. WW conducted statistical analysis and power calculations. NK was the principal investigator.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STaRI checklist.
[PDF File (Adobe PDF File), 236 KB - resprot_v10i12e34591_app1.pdf]

Multimedia Appendix 2
CIHR review reports.
[PDF File (Adobe PDF File), 251 KB - resprot_v10i12e34591_app2.pdf]

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Abbreviations

CAMH: Centre for Addiction and Mental Health
CFIR: Consolidated Framework for Implementation Research
EPI: Early Psychosis Intervention
EPI-SET: Early Psychosis Intervention-Spreading Evidence-based Treatment
FEPS-FS: First Episode Psychosis Services Fidelity Scale
FRAME: Framework for Reporting Adaptations and Modifications for Evidence-Based Interventions
HEIA: Health Equity Impact Assessment
IRT: Individual Resiliency Training
RA: Rapid Analysis
SEE: Supported Education and Employment
StaRI: Standards for Reporting Implementation Studies
VCES: Virtual Client Experience Survey
VPES: Virtual Provider Experience Survey

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Protocol

Identification and Description of Balance, Mobility, and Gait Assessments Conducted via Telerehabilitation for Individuals With Neurological Conditions: Protocol for a Scoping Review

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Abstract

Background: The COVID-19 global pandemic pushed many rehabilitation practitioners to pivot their in-person practice to adopt telerehabilitation as their main method of delivery. In addition to documenting information on interventions used with clients, it is best practice for therapists to use reliable and validated outcome measures to inform their interventions.

Objective: Through this scoping review, we aim to identify (1) which outcomes are being used remotely to assess balance, mobility, and gait in patients with neurological conditions, and (2) what psychometric data (validity, reliability, etc.) for remotely administered outcomes are available.

Methods: Three main concepts will be included in our search: (1) neurological conditions; (2) administration by telerehabilitation; and (3) outcome measures for balance, mobility, and gait. Studies reporting remote assessment of neurological conditions published since 1990 will be included. The database search will be completed in MEDLINE (Ovid), CINAHL, PubMed, PsycINFO, EMBASE, and Cochrane. Gray literature including dissertations, conference papers, and protocol papers will also be sourced. Two reviewers will independently screen each title and abstract using pre-established inclusion and exclusion criteria. Manuscripts that appear to meet the criteria will be subject to further review, and full-text extraction using a pre-piloted extraction sheet if all criteria are met. The data will be categorized by assessment types describing impairments (such as balance, strength, and mobility) or activity limitations or participation restriction (such as functional mobility, ambulatory functions, and activities of daily living).

Results: This scoping review will document outcome measures currently used in the remote assessment of neurological conditions. To date, 235 titles and abstracts were screened. We are in the process of finalizing the full text screening for the inclusion of articles. We expect the full screening to be completed in November 2021 and data analysis in January 2022. Our results are expected to be published in early 2022.

Conclusions: The optimal use of telerehabilitation as a mode to deliver rehabilitation intervention should be coupled with the completion of validated outcome measures. Therefore, it is crucial to further our knowledge on remote outcome measures and therapeutic assessments.

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KEYWORDS

telerehabilitation; remote assessment; outcome measures; neurology; rehabilitation

Introduction

Telerehabilitation, teletherapy, and virtual rehabilitation are terms describing the use of information and communication technologies including phone or videoconferencing to provide rehabilitation services to people remotely, in their home or other environment [1]. In 2017, Peretti et al [2] reported that the field of telerehabilitation was considerably new but the use had rapidly grown in high-income countries. The COVID-19 global pandemic has only further driven the adoption of this rehabilitation delivery method. Data from the Ontario Telemedicine Network (OTN) [3] documented a 36% growth in virtual visits in their annual 2018-2019 report, totaling over 1 million telemedicine visits. Originally used to reduce travel time and costs for patients and health care providers, as well as to improve access to specialists for rural communities [4], the COVID-19 global pandemic has pushed health care practitioners to adopt telemedicine as their main method of delivery. Similar rapid uptake of telerehabilitation enabled rehabilitation clinicians to continue addressing patient health needs while following public health guidelines.

Remote rehabilitation interventions for a variety of neurological conditions highlight the benefits of telerehabilitation and the need for further research [5-7]. Reviews have systematically demonstrated a positive impact on outcomes including gait, mobility, strength, and daily function in people living with deficits after stroke [8,9], traumatic brain injury [10,11], Parkinson disease [12], and multiple sclerosis [13,14]. By contrast, a scoping review by O'Neil et al [15] reported that there were limited guidelines on the implementation parameters of interventions delivered remotely.

An outcome measure is defined as a clinical tool to objectively measure changes in function of a patient as a result of an intervention [16]. It is best practice for therapists to complete assessments using reliable and validated outcome measures to inform their interventions. Choosing valid and reliable outcome measures is critical in assessing intervention efficacy and meaningful clinical change [16]. While clinicians use outcome measures to guide their interventions, insurance companies require clinicians to objectively document the progress of patients using validated outcome measures to provide credible and reliable justification for treatment. Consequently, not using objective, reliable, valid, and responsive outcome measures could have financial impacts on patients and health care providers alike. More importantly, without use of appropriate outcome measures, clinicians cannot effectively measure the impact of their proposed intervention on targeted impairments, therefore not identifying whether interventions are working for each patient.

Potential barriers such as limited space in the patient's home, equipment availability, or safety issues may compromise the validity or reliability of the remote outcome measures used by the therapist. Depending on the method used for telerehabilitation, additional restrictions could also impact the choice of outcome measure. For example, when assessing balance, poor visibility via videoconference or the use of phone calls could lead to choosing measures that are less objective, such as patient-reported questionnaires instead of specific clinical outcome measures targeting balance. Ultimately, the use of outcome measures that have not been appropriately tested for reliability and validity will not be able to guide intervention planning and may adversely affect the patient's recovery.

The use of valid outcome measures regardless of whether a clinician is using in-person or tele-platforms methods is necessary. Previously, a hybrid model of service delivery with outcomes assessments performed before, after, or during telerehabilitation interventions was typically completed in-person; however, due to COVID-19, in-person visits are now curtailed or cancelled. Although there are a wide range of reliable and valid in-person rehabilitation assessments [17], there is a need to systematically review outcome measures performed via telerehabilitation, to recommend the most valid, reliable, acceptable, and safe measures to be administered remotely.

Validity, the ability for a tool to assess what it is intended to assess, and reliability, the ability for the test to be reproduced with similar results, are key features of evidence-based assessments [18]. Mani et al [19] studied assessment techniques using telerehabilitation in a population with musculoskeletal deficits including back pain, ankle and elbow joint disorders, and total knee replacement. Authors from this study concluded that there was good validity and reliability for a variety of remote outcome measures including function (eg, Oswestry Disability Index), range of motion (eg, goniometry), strength (eg, self-resistance), and balance (eg, Tinetti Balance and Gait Assessment). While there are a limited number of validated remote outcome measures for use with the musculoskeletal population, a gap remains regarding telerehabilitation assessments for individuals with neurological conditions. Remote assessments of people living with neurological conditions are limited but have been studied in both the pediatric and adult population. For example, the feasibility and concurrent validity of using the Movement Assessment Battery for Children has been established by Nicola et al in 2018 [20]. The use of smartphone apps, accelerometers, and activity tracking devices to assess activity level and gait parameters in people living with impairments after stroke, brain injury, and multiple sclerosis also has been reported as remote assessment methods in recent reviews [21,22].

This study aims to review the literature to identify and describe (1) outcome measures that are being used remotely to assess balance, mobility, and gait in patients with neurological conditions, and report (2) the available psychometric data (eg, validity, reliability, consistency, equivalence) for these outcome measures when used remotely.

Methods

Systematic Search

This scoping review will follow the methodological steps outlined by Arksey and O'Malley [23], and expanded by Colquhoun et al [24]. First, a search strategy will be identified using specific inclusion criteria around the following main concepts: (1) neurological conditions (eg, acquired brain injury,

neurodegenerative disorders); (2) administration by telerehabilitation; and (3) clinical outcome measures (eg, postural balance, functional mobility, activity of daily living, gait assessments, motor assessments). Supported by an institutional research librarian, an initial systematic database search was conducted between December 13, 2020, and January 5, 2021, in MEDLINE (Ovid), CINAHL, PubMed, PsycINFO, EMBASE, and Cochrane. The search strategy included MeSH terms and Boolean strategies to clarify the search and identify studies published from 1990 to January 2021. Gray literature including dissertations, conference papers, and references from protocol papers will also be searched using Google Scholar and reference lists of included papers will be hand searched (Multimedia Appendix 1).

Study Screening and Selection

Two reviewers (KB and EMD) will independently screen each title and abstract using pre-established inclusion and exclusion criteria (Textbox 1). Using the Covidence software (Covidence AS), abstracts meeting all inclusion and exclusion criteria will be selected for full manuscript review. Full texts from selected articles will be screened independently by the same 2 reviewers (KB and EMD) to confirm eligibility before proceeding to data extraction. This screening step will be piloted with 5 selected studies and reviewed by a third reviewer to increase interrater reliability prior to screening all articles. Following each screening step, conflicts will be resolved by a third rater (JO or LS) when necessary. Interrater reliability between the independent reviewers for the full-text review will be documented by reporting the Cohen κ agreement for the included studies. The reference list from each included scoping or systematic review will be manually searched for additional articles.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

Population with neurological conditions

- Acquired brain injury (ie, traumatic brain injury, stroke, brain tumors)
- Neurodegenerative disorders (ie, multiple sclerosis, Parkinson disease, amyotrophic lateral sclerosis, motor neuron disease)

Assessment

- Tele-platform
- Telerehabilitation (eg, telerehabilitation, virtual rehabilitation, remote rehabilitation)
- Telemedicine (eg, telehealth, eHealth, mHealth, app, text messaging, sensor based)
- Virtual reality (eg, augmented reality, computer simulation)
- Remote consultation (eg, teleconsultation, consultation, remote)
- Telemonitoring (eg, remote monitoring, remote assessment)

Health professional

- Allied health occupations, allied health personnel, and rehabilitation therapist (ie, physiotherapist, physical therapist, occupational therapist, speech language pathologist, communication therapist, kinesiologist, athletic therapist, nurse, rehabilitation therapist, psychologist, neuropsychologist, social worker)
- Physiatrist, physicians, physical medicine

Outcome measures

- Postural balance assessment (eg, balance, postural, postural control)
- Functional mobility limitation/assessment (eg, functional mobility, transfers, wheelchair mobility). See “Exclusion Criteria”
- Daily function (eg, upper extremity function, fine motor skills, dressing and toileting, communication)
- Gait assessment (eg, neurologic ambulation disorders, ambulation disorders, level of independence, ambulation, gait speed, gait analysis)
- Motor function assessments (eg, strength, range of motion, stage of motor recovery)

Limits

- Language: English or French
- Period: 1990-January 2021

Exclusion criteria

Assessment

- Only in-person assessment

Outcome measures

- All other outcome measures not listed in the “Inclusion Criteria.”

Study design

- Meta-analysis and reviews (but original papers in the reference list will be searched for inclusion)

Data Extraction

Data will be extracted using a pre-established data extraction sheet (Multimedia Appendix 2). To ensure the charting process is comprehensive, cohesive, and complete, the extraction sheet will be piloted with a set of articles prior to starting data extraction.

Quality Appraisal of Included Studies

When possible, a quality appraisal will be completed using the appropriate quality reporting tool proposed by the Equator Network [25]. As such, randomized controlled trials will be assessed with CONSORT (Consolidated Standards Of Reporting Trials), case reports with CARE (CAse REports), observational studies with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology), and qualitative studies with the SRQR (Standards for Reporting Qualitative Research). Overall, the PRISMA-ScR (PRISMA Extension for Scoping Reviews) checklist will be used to ensure proper reporting of this proposed scoping review [26].

Data Analysis and Interpretation

Once data extraction is complete, the information will be collated and synthesized following a systematic approach. Guided by the International Classification of Function (ICF), data will be categorized using various ICF domains. For example, outcome measures describing impairments of body structures will include measures such as balance and strength, while outcome measures assessing activities and participation will include functional mobility, transfers, ambulation, and activities of daily living [27]. This list of remote outcome measures will also include the available psychometric data including information around validity (eg, content, construct, convergent), reliability (eg, stability [intraclass correlation coefficient], consistency [Cronbach α], equivalence [α]).

Once synthesized, data will be subcategorized by types of regulated health care professionals to facilitate clinical usefulness. The subcategories will further be classified by the type of telehealth platform used. Finally, field consultation will be completed by asking 5 allied health professionals to review the interpretation table to validate the clinical usefulness and potential gaps in the interpretation of our findings.

Results

To date, the initial systematic search has been completed and 293 studies were imported for screening. After removing 58 duplicates, 235 titles and abstracts were screened. We are in the process of finalizing the full text screening for the inclusion of articles. We expect the screening to be completed in November 2021 and data analysis in January 2022. Our results are expected to be published in early 2022.

Discussion

Telerehabilitation can not only improve access for individuals who may not benefit from traditional in-person services, but it may also have financial benefits, reducing costs for the health care system, health care provider, and patient [2]. The optimal use of telerehabilitation as a mode to deliver rehabilitation interventions should be coupled with the completion of valid outcome measures. Therefore, it is crucial to further our knowledge on remote outcome measures and therapeutic assessments. Our findings could influence clinical practice and patient care and guide clinical research in telerehabilitation. This scoping review will help determine how remote assessments are currently being conducted and provide information on the valid and reliable measures currently available. Furthermore, results from this study will allow recommendations to be made for what assessments or areas of remote assessment need to be further validated.

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Authors' Contributions

Each author has made substantial contribution to the development of the methodology or data collection and analysis or interpretation of the findings. Each author contributed to the redaction and revision of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v10i12e27186_app1.docx]

Multimedia Appendix 2
Data extraction.
[DOCX File , 22 KB - resprot_v10i12e27186_app2.docx]

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Abbreviations

CARE: CAse Reports
CONSORT: Consolidated Standards Of Reporting Trials
ICF: International Classification of Function
OTN: Ontario Telemedicine Network
PRISMA-ScR: PRISMA Extension for Scoping Reviews
SRQR: Standards for Reporting Qualitative Research
STROBE: STrengthening the Reporting of OBservational studies in Epidemiology

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