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Usability and Effectiveness of Immersive Virtual Grocery Shopping for Assessing Cognitive Fatigue in Healthy Controls: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cognitive fatigue (CF) is a human response to stimulation and stress and is a common comorbidity in many medical conditions that can result in serious consequences; however, studying CF under controlled conditions is difficult. Immersive virtual reality provides an experimental environment that enables the precise measurement of the response of an individual to complex stimuli in a controlled environment.

Objective: We aim to examine the development of an immersive virtual shopping experience to measure subjective and objective indicators of CF induced by instrumental activities of daily living.

Methods: We will recruit 84 healthy participants (aged 18-75 years) for a 2-phase study. Phase 1 is a user experience study for testing the software functionality, user interface, and realism of the virtual shopping environment. Phase 2 uses a 3-arm randomized controlled trial to determine the effect that the immersive environment has on fatigue. Participants will be randomized into 1 of 3 conditions exploring fatigue response during a typical human activity (grocery shopping). The level of cognitive and emotional challenges will change during each activity. The primary outcome of phase 1 is the experience of user interface difficulties. The primary outcome of phase 2 is self-reported CF. The core secondary phase 2 outcomes include subjective cognitive load, change in task performance behavior, and eye tracking. Phase 2 uses within-subject repeated measures analysis of variance to compare pre- and postfatigue measures under 3 conditions (control, cognitive challenge, and emotional challenge).

Results: This study was approved by the scientific review committee of the National Institute of Nursing Research and was identified as an exempt study by the institutional review board of the National Institutes of Health. Data collection will begin in spring 2021.

Conclusions: Immersive virtual reality may be a useful research platform for simulating the induction of CF associated with the cognitive and emotional challenges of instrumental activities of daily living.

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KEYWORDS

cognitive fatigue; immersive VR; user experience; virtual grocery shopping; instrumental activity of daily living

Introduction

Background

The application of digital technologies to improve the monitoring and treatment of chronic clinical conditions is an emerging field in medical research and practice. At the most basic level, the maintenance of and nearly instantaneous access to medical records facilitates tracking and coordination of care among providers is an example of how digital technologies have directly influenced the practice of medicine. The steady increase in apps and digital devices developed to track health-related behaviors and monitor physiological data is a testament to the interest and potential powerful role that technology will play in the future of medicine. These tools may become most useful for aiding health care in the gaps between formal treatment (eg, hospital, clinic, and doctor visit) and day-to-day living in extended or chronic conditions. For example, individuals with chronic medical conditions often experience significant symptoms of cognitive fatigue (CF); however, it is a challenge for clinicians to evaluate the impact of this symptom on daily activities. Technological solutions potentially provide greater insight into the impact of symptomatology on the quality of life. Researchers and clinicians alike have a profound interest in technology and its current and future role in health care delivery.

Immersive Virtual Reality

Immersive virtual reality (VR) technology has been increasingly used by researchers in many fields as a tool to observe and measure the responses of individuals to complex stimuli in a controlled environment [1-3]. Auditory and visual stimuli induce the sense that they are in a space different from where their physical body is located. Usual tasks (locomotion, pointing, and grasping) are accomplished in a modified manner using ancillary equipment (eg, hand controllers and sensor gloves). Immersive VR environments enable researchers to study psychological phenomena that are more closely connected to the subjective experience of an individual (eg, a tall building to elicit fear) to recreate situations that elicit symptoms (eg, anxiety) or measure specific skills (eg, a kitchen to evaluate home safety). VR environments have been used to evaluate human and environmental factors associated with performing important instrumental activities of daily living (IADLs) such as driving [4], navigating public transportation [5], cooking [6], social relatedness [7], and grocery shopping [8]. The relative advantage of virtual environments over physical spaces is the ability to safely expose individuals to situations that may pose a risk in real life (eg, driving while distracted) and the ability to create controlled environments that would be extremely difficult to duplicate in a consistent, standardized fashion in real-life simulations.

Implications of CF

CF is a common human experience that can result in serious negative consequences, such as mistakes [9,10] and accidents [11-13]. Although most healthy people experience some degree of CF at varying times, CF can become a debilitating and life-altering experience for individuals diagnosed with chronic medical conditions [14-16]. Debilitating levels of CF occur as a frequent comorbid symptom in a range of medical [17], neurological [18], and acquired conditions [19], particularly those affecting the integrity of neuronal processes [20,21]. The serious consequences of CF at work, during daily activities, and as a potential cause of disability across a broad spectrum of clinical conditions make the study of objective and subjective fatigue in healthy and clinical populations a priority across multiple disciplines.

CF Induction

The most well-established model for inducing CF under experimental conditions is prolonged cognitive performance. Specifically, participants perform a cognitive task for an extended period (eg, 15-120 minutes) and assessments of fatigue level occur before, during, and after the fatiguing task. Various cognitive tasks reliably induce subjective feelings of fatigue, including continuously performed attention [22,23], inhibition [20,24,25], working memory [26-28], and complex cognitive activities [29-31]. Tasks requiring continuous visual monitoring for *critical events* produce a highly replicable phenomenon called the *vigilance decrement* [32], which has a moderate effect size [33]. Factors affecting the onset of vigilance decrement include image quality [34], response frequency [35], rest breaks and secondary task interruption [36], and multitasking [37]. Moderately complex cognitive functions such as working memory [27,38-41] and inhibitory control [24,42-48] tasks produce subjective feelings of fatigue but inconsistently produce performance decrements. Simple and complex vigilance tasks produce CF; however, these laboratory tasks may not best represent how CF occurs in daily life as boredom and task disengagement may account for observed vigilance decrement effects [38]. A better approach to understand CF for clinical purposes may require the evaluation and assessment of fatigue in typical daily living activities.

Work Task and Environment Characteristics and CF

Work fatigue studies target tasks and environmental characteristics that produce CF in everyday activities. Close visual work involving inspection, comparison, or identification of details on visual images [49-53] and high rates of decision-making are sources of work fatigue [54-56]. Work interruptions interfering with workflow increase feelings of frustration [57], stress [58], and feelings of emotional exhaustion [59]. Work interruptions cause a loss of focus [60] and increase cognitive workload [61], mental effort, annoyance, frustration, and sense of time pressure [62,63]. Random, uncontrollable, interruptions in the middle of a task [61,62] that require immediate attention induce the most stress [62-64]. Individual differences in personality impact the level of perceived stress and fatigue associated with work-related tasks [63]. Work requiring intensive visual inspection or high rates of decision-making induce fatigue, and environmental factors such as distractions and interruptions significantly increase perceived frustration, workload, and fatigue.

Daily Living and CF

Managing complex activities, such as shopping, cooking, using transportation, driving, and finances is referred to as an IADL [65]. Extensive research has focused on the relationship between driving and CF. Fatigue and cognitive workload increase with

driving [66,67]. Time to fatigue while driving is hastened by extra cognitive demands, stress, distractions, multitasking, and environmental factors [66-68], although time on task and monotony are most impactful [69,70]. Personal characteristics associated with driving fatigue include fatigue proneness, dislike of driving, and coping style [66]. Surprisingly, few studies have evaluated the relationship between IADLs and CF; however, such assessments offer tremendous potential for discerning points for clinical intervention. There is some evidence that apathy, depression, and impaired cognitive functioning are risk factors for difficulties in performing IADLs [71,72]. A public transit study demonstrated that a common IADL induces cognitive workload in real life, task experience moderates perceived workload, and immersive VR provides a close approximation of the cognitive effects observed in real life [5]. The extended performance of a daily activity may induce CF, and the effects are moderated by individual and environmental factors. Grocery shopping provides an apt task for assessing CF.

Immersive VR and Grocery Shopping

Virtual shopping environments have been used to evaluate how cognitive functions might operate in real-life situations [73-75] and may prove effective for the study of CF. Grocery shopping requires a combination of low and high levels of cognitive processes [8,73-75]. Looking for a specific product requires visual inspection, scanning, and focused attention. Traversing a shopping store requires visual attention (eg, looking for signs), spatial mapping, working memory, memory, and executive functioning [8,73-77]. Virtual shopping environments have been used successfully among individuals with significant cognitive impairment [8,78-81], and virtual shopping tasks correlate with real-life shopping activities [81,82].

We identified immersive VR grocery shopping as a suitable model to study fatigue associated with an IADL because it provides familiar but complex visual stimuli, affords the opportunity to search and choose, and presents the participant with well-known but complex cognitive challenges, such as comparisons, discernment, and decision-making. A potential disadvantage of using immersive VR to study CF is the risk of physical distress and eye strain in VR, which may confound the experience of CF or its measurement [83-85]. The risk of eye strain and other physical symptoms is reduced when high-quality head-mounted display (HMD) devices are used, motion is performed using physical walking or teleporting, the field of view is large, and each eye receives high-quality images [84]. In some cases, the realism of the environment must be sacrificed to reduce side effects.

We propose a 2-phase evaluation of the CF induction in VR. In phase 1, we will explore the feasibility of using immersive VR as a platform for studying CF using a user experience (UX) research methodology. We will use a combination of qualitative and quantitative approaches to identify components of the VR interface or environment that may contribute to feelings of eye strain or distress or make the shopping task difficult to perform. Phase 2 explores cognitive, environmental, and individual characteristics associated with VR-based grocery shopping–induced CF.

Objectives

Despite extensive research on CF, questions remain regarding the individual and environmental characteristics that relate to CF, particularly in daily living activities. Prior studies evaluating CF in daily activities have primarily focused on driving [5,70] or very specific job-related activities [49,53,86]. We will use immersive VR to control environmental and task characteristics to identify factors that affect the onset of fatigue. Grocery shopping is used as a fatigue-induced activity because it requires multiple simple and complex cognitive functions, has been identified as a significant cause of CF in susceptible individuals [87], and is susceptible to disruption by disability [88]. On the basis of previous research, engaging healthy participants using virtual shopping environments indicates the feasibility and acceptability of VR and therefore provides the best chance of detecting the CF response [5,86,89].

In the experiment, we will replicate numerous cognitive aspects of shopping, including simultaneous and successive engagement of multiple cognitive processes including working memory, spatial planning, inhibitory control, visual search, inspection, and comparison, reading and applying information from nutritional labels, and decision-making. We can manipulate the mental workload through specific task requirements. In addition, we can test the relative effect of environmental factors, such as the effect of sound and visual cues on CF and workload, by introducing the presence of interruptions, distractions, and goal interference. In a controlled shopping environment, where interruptions can be planned carefully, as the participant executes goal-directed behaviors, real-life frustrations such as poor shelf organization and item placement, crowded conditions, noise, and other disruptions can be implemented. In future studies, the virtual shopping environment will allow us to test hypotheses related to the relationship of task difficulty, perceived task difficulty, environmental disruptions, and feelings of frustration with CF. Initial trials will use healthy controls, and subsequent studies will evaluate CF in clinical populations.

The aim of phase 1 is to evaluate the design elements of the virtual shopping environment to identify any factors that may hinder the ability of participants to effectively perform tasks in the virtual environment, identify the risk of physical distress, and obtain user feedback about realism and functionality. The primary hypothesis for the UX study is that the VR environment will be acceptable; however, some users will exhibit minor difficulties using the controllers and interacting with the environment. The primary outcome measures will be observational ratings assessing user difficulties with controller use, interacting with objects, and moving in the environment. The secondary hypotheses include that participants will report only minimal feelings of distress, will report that the virtual grocery store appears realistic and immersive, and will provide a general positive response to the experience with additional helpful ideas about how the experience could be improved.

The primary aim of phase 2 is to evaluate individual and environmental characteristics associated with susceptibility to experiencing CF in the context of performing an IADL, specifically shopping. Our primary hypothesis in phase 2 is that individuals performing structured grocery tasks will report more

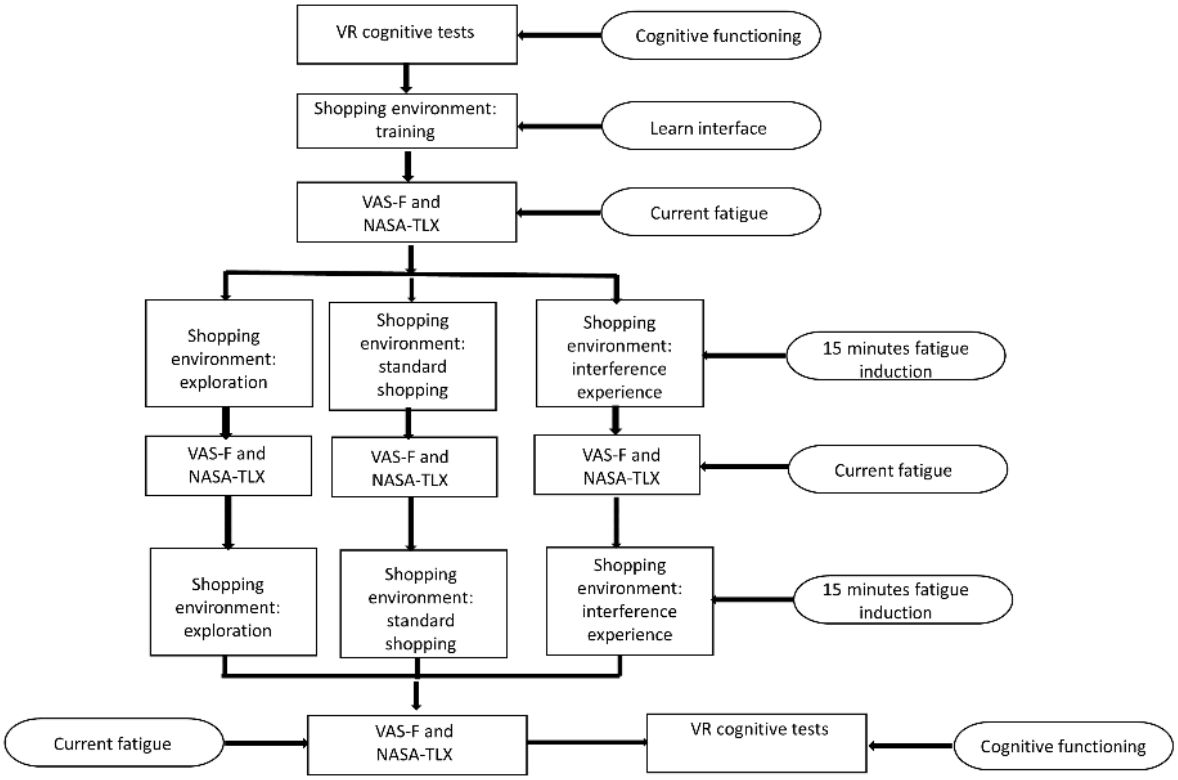
CF than simple exploratory behavior in the grocery store and that individuals experiencing distractions and interruptions will report more fatigue than those who do not experience interruptions. The primary outcome measure in phase 2 is the self-reported change by participants in CF by shopping experience. The secondary aims of phase 2 are to identify performance and eye-tracking measures that objectively identify fatigue, cognitive abilities, personality characteristics, shopping experience, or transient mood states that affect susceptibility to fatigue during shopping. Specific secondary exploratory hypotheses include that perceived workload increases with time on task for structured tasks and disruptive environments, percent eye closure and gaze shift increase with time on task and are associated with self-reported fatigue, and shopping accuracy declines with time on task.

Methods

Study Design

This will be a 2-phase development (UX) and implementation (eg, randomized controlled trial) research protocol. The two phases share the same general immersive VR environment, as shown in Figure 1. The two phases diverged in the non–VR-related procedures used in each protocol. The VR sequence in each phase will follow the standard model commonly used in CF induction studies, that is, baseline cognitive assessment, baseline subjective fatigue and workload assessment, fatigue induction with a midpoint (eg, at 15 minutes) subjective assessment of fatigue, finishing with a postassessment of fatigue, and cognitive assessment. Each of these elements is shown in Figure 1.

Figure 1. Virtual reality content in sequence. NASA-TLX: National Aeronautics and Space Administration–task load index; VAS-F: Visual Analog Scale Fatigue; VR: virtual reality.



Randomization will be used in each study to assign participants to 1 of the 3 grocery shopping experiences: shopping exploration, standard shopping, and shopping interference. In each study phase, participants completed a brief self-reported medical history to rule out conditions associated with chronic fatigue, cognitive impairment, or susceptibility to seizures. Participants in both studies completed the Virtual Reality Symptom Questionnaire (VRSQ) [90] before VR immersion and immediately after VR immersion. These procedures will help differentiate the impact of VR immersion from the fatigue induced by the shopping task.

The phase 1 study will evaluate the participants' capacity to learn to interact with objects in the virtual environment, navigate within the grocery store environment, read and respond to information and questionnaires, and identify any early adverse effects of VR exposure. The data collected from this study will be used to improve the VR interface and modify the participant interactions or the length of exposure. The study staff will observe the engagement of the participant in the immersive task by viewing the person as well as by viewing their exact point of view on a separate computer screen. Participants will complete rating scales including feelings of presence [91] in the shopping environment, self-reported simulator sickness symptoms [90], and shopping values or experience [92]. All participants completed a standardized UX interview. The phase 2 study protocol, detailed in Figure 2, will incorporate additional self-report and performance measures (see Table 1 for lists of measures in each phase). Additional measures include state and trait measures of fatigue [93,94], current emotional state (ie, anxiety and depression) [94], personality traits [95], and cognitive functioning [96]. These measures will be completed

before the VR portion of the study with a 1-hour break between completing additional study measures and VR immersion. Similar to phase 1, participants will complete measures of presence [91] and shopping values or experience [92] to assess the impact of realism, shopping as a pleasant versus utilitarian task, and frequency of grocery shopping in real life on fatigue and performance. A brief post-VR interview will be completed to obtain additional insight about the environment and to debrief participants about the purpose of the study.

Figure 2. Detailed procedure of the cognitive fatigue study. BFI: Big Five Inventory; HMD: head-mounted display; NASA-TLX: National Aeronautics and Space Administration–task load index; NIHTB-CB: National Institutes of Health toolbox–cognition battery; PFS: Pittsburgh Fatigability Scale; PROMIS: Patient-Reported Outcomes Measurement Information System; SDH: social determinants of health; VAS-F: Visual Analog Scale Fatigue; VR: virtual reality.

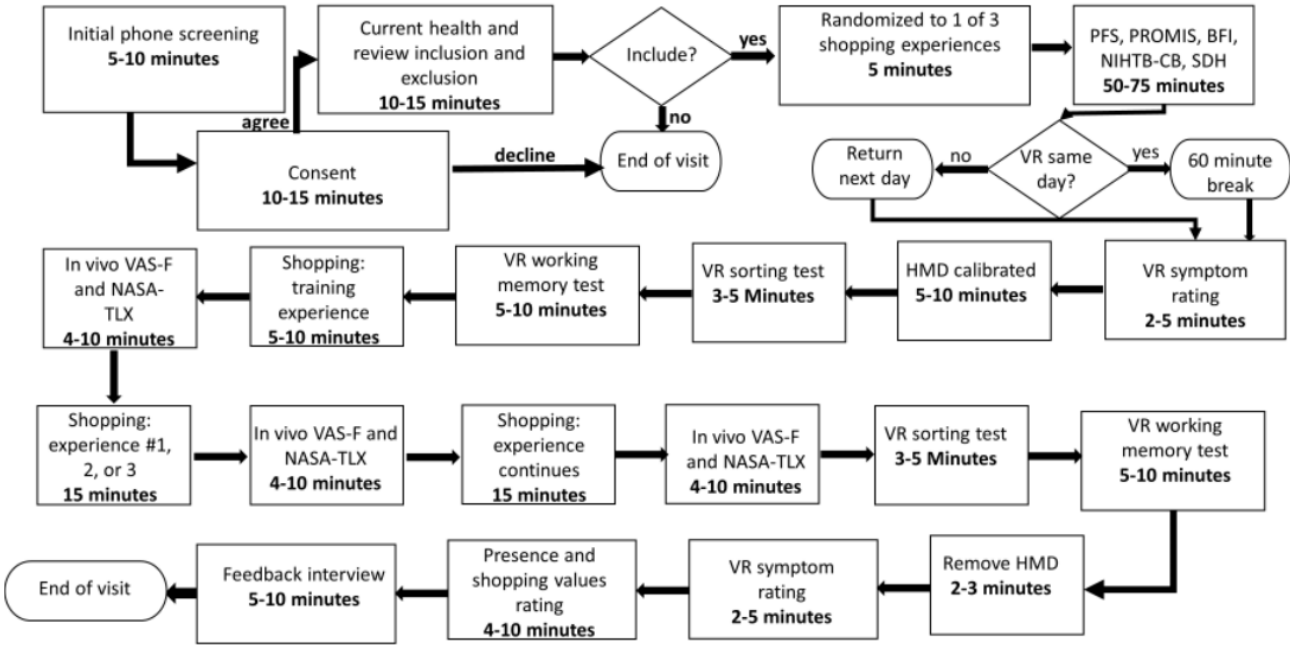


Table 1. Assessments by phase.

Assessments	Phase 1	Phase 2
Virtual Reality Symptom Questionnaire	✓[a]	✓
Immersive VR[b] cognitive tests	✓	✓
Immersive VR Visual Analog Scale–Fatigue	✓	✓
Immersive VR NASA-TLX[c]	✓	✓
Presence Questionnaire	✓	✓
Shopping Values Questionnaire	✓	✓
Social Determinants of Health	✓	✓
User Experience Interview	✓	
PROMIS[d] Depression		✓
PROMIS Anxiety		✓
PROMIS Fatigue		✓
Pittsburgh Fatigability Scale		✓
Big Five Inventory		✓
National Institutes of Health Toolbox–Cognition Battery		✓

[a]Assessment is present.

[b]VR: virtual reality.

[c]NASA-TLX: National Aeronautics and Space Administration–task load index.

[d]PROMIS: Patient-Reported Outcomes Measurement Information System.

Kitchen Tasks

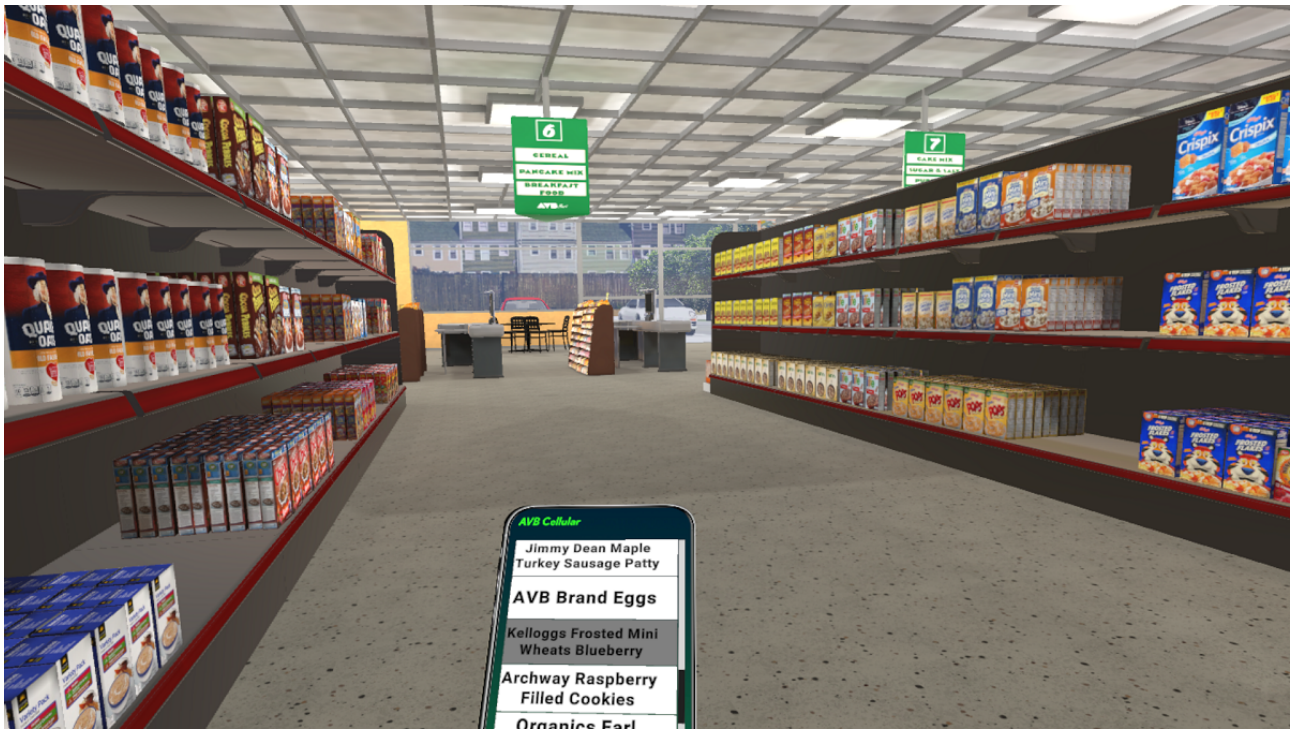
The participants will be seated while performing the tasks in the kitchen environment. The participant will appear to be seated in a kitchen table with a pillbox and pill bottles in front of them. In the first task, the participant will be instructed to correctly select the pillbox compartment (labeled with the days of the week) where each pill belongs. A calendar on the table shows an image of each pill and the pillbox location (eg, Sunday or Monday); when a pill appears in front of the examinee, they will select the correct pillbox location by using a scroll and trigger pull sequence. An animation sequence will show the pill entering the selected location. Another pill will appear with a sound alert until 120 seconds have passed or 120 pills have been sorted.

In the working memory task, the participant will be shown a series of pills by day and time of day associations. Using the same calendar concept, the participant will see where 2 pills are to be placed in the pillbox (eg, red pill in the morning on Monday and blue pill in the evening on Friday) for 10 seconds. They were instructed to remember the location of each pill. The key will be taken out of view and the pills will appear one at a time. Each participant will select the location where each pill belongs using a scroll and trigger sequence. The task will increase in difficulty with 3, 4, 5, and 6, the number of pill locations to recall. The task will end when the participant obtains four consecutive scores of zero.

Shopping Tasks and Experiences

Participants will remain seated during all VR shopping experiences. Product labels are legible for brands and specific products without selecting the object. Product selection enables the viewing of all product details. Products will be selected off a shelf using a wand controller acting as a pointing device (eg, laser beam), followed by a point, highlight, and trigger pull selection sequence. Selected product labels will appear on a virtual cell phone in front of the participant with a menu of options (eg, buy product, return product, and review shopping list). Participants traverse the store using a restricted teleport feature. Movement will be restricted to a more realistic experience and to avoid long-distance movements that might result in disorientation and difficulties in learning the store layout. Figure 3 presents a screenshot of the grocery store and shows the cell phone, products, and aisle.

Figure 3. Grocery store screenshot.



Shopping Training

The participant will appear in a small version of the grocery store. They will be instructed on how to use the virtual cell phone to check their shopping list, review items in their cart, and answer text messages with the left-hand controller. They will be instructed on how to teleport and select items off the shelf with the right-hand controller. In the shopping training task, the participant must follow specific directions and must correctly put four items in their cart from the shopping list, one of which must be returned to the shelf, and they must answer a text to complete the shopping training. To complete the shopping portion of the task, the participant will need to teleport successfully to multiple shelves and aisles.

Shopping Experience Number 1

Experience number 1 will be a control experience that will allow the participant to explore the grocery store with no specific task to complete. The shopping environment includes a few avatars and some low music in the background to simulate a realistic shopping environment during off-hours. All shopping actions will be enabled, and the participant may select items and place them in the shopping cart. The only requirement will be that they remain in the environment for 30 minutes. The control

experience will evaluate whether the VR environment itself induces significant fatigue that may confound the interpretation of task-specific fatigue induction.

Shopping Experience Number 2

Experience number 2 is a standard shopping experience designed to mimic a realistic shopping experience during a typical day. Participants will be provided with a shopping scenario. They will be told that they are shopping for sick friends. The participant will try to obtain as many items as possible from the cell phone shopping list. Participants will traverse the grocery store to find objects on the list and place them in the shopping cart. Avatars are present in the store but do not hinder progress or create any specific distractions. The background sound includes typical background noise, music, and overhead announcements. This condition assesses the cognitive load and fatigue related to the mental activity of shopping.

Shopping Experience Number 3

Experience number 3 will be the standard shopping experience with frustrating and interrupting events. Participants will be provided the same shopping scenario as experience number 2; however, this shopping experience will be designed to mimic very high traffic, a holiday shopping experience, store crowding, misplaced items, and loud distractions. In addition to environmental stressors, the cell phone will receive *texts* from the friend requesting changes to the grocery list after items have already been selected. Text alerts will be short, repetitive, high-pitched sounds that continue until the text is answered. The progress of the participants will be impeded by an avatar standing in front of a needed item, an aisle blocked for a spill, or a palette blocking access to a specific shelf area. The sounds of a baby crying, people talking, coughing, laughing, and sneezing are present. The music and announcements are played at a slightly higher volume than in the standard shopping condition. This condition will assess the cognitive load and fatigue related to the mental activity of shopping in the presence of distractions and frustrating events.

Fatigue Assessment

Fatigue induction studies evaluate real-time changes in fatigue symptoms by self-reporting, performance, and eye tracking. An adapted version of the Visual Analog Scale–Fatigue (VAS-F) [97] will be used as a state fatigue measure given its history of use in fatigue induction research. [27,98,99] A closely linked concept to CF is cognitive workload. Cognitive workload applies an ergonomic and human factors model (eg, elements of a job or task that create a feeling of mental work) to understand fatigue as it relates to sustained work performance [100-104]. The NASA-TLX is a commonly used measure of workload [105,106]. In addition to subjective measures, there are two approaches to use performance data to objectively measure fatigue: change in performance on the induction task or using a pre- versus postintervention cognitive assessment [26,29,107,108]. Tests of reaction time [42], working memory [23], and inhibitory control [32] are used to assess fatigue effects.

Psychophysiological measures identify objective brain or autonomic nervous system indicators of fatigue using EEG (electroencephalogram) [22,23,30,109], ERP (event related potential) [28,31,86,110], functional brain imaging [27,40,107,108], and ECG (electrocardiogram) [29,30] to measure changes in brain or cardiovascular activity associated with fatigue. Of the various physiological indicators, eye tracking has emerged as a promising, noninvasive tool for identifying objective measures of CF. Eye tracking studies show changes in blink rate, percent eye closure, gaze fixation (eg, length and location), and gaze shift rate are associated with CF [30,49-51,111-114]. Changes in gaze shift rate may indicate use of less efficient lower-level cognitive processing [49] and a centralized fixation can indicate a loss of full attention to the task [115]. Several sources, using different task demands, show changes in visual activity as the time on task increases.

Engineering and Technology

The virtual environment was created using Unity 3D (Unity Technologies). Products will be created by the graphics design team using digital image files obtained from the product manufacturer, labels scanned from acquired grocery items, or modified from items purchased through the Unity Asset Store. All labels are converted into 3D objects using a variety of programs and techniques. The design team will develop a cohesive store branding and coordinated color scheme for store assets. Within the environment, near objects will be displayed with a high degree of visual detail, whereas distant objects will have reduced detail. General product labeling will be legible without selecting the object; however, specific product information (eg, reduced sodium or nutritional values) will only be legible after product selection.

The VIVE Pro Eye (HTC Corporation) will be the HMD device used in each study. This device has a 2880 × 1600-pixel display resolution and includes eye tracking and high-resolution surround sound and allows for the use of glasses and adjustable optics that are designed to minimize eye fatigue and cybersickness. Participants will interact with the virtual environment and objects within the environment by using a wand. The VR program is delivered to the HMD via a display port from a Dell Precision workstation 7920. The technical features of the 7290 include Intel Xeon Gold 5122 3.6 GHz, 3.7 GHz Turbo, 4C, 10.4 2UPI, 16.5 MB Cache, NVIDIA Quadro P5000, 16 GB, 4 DP, and 32 GB 2 × 16 GB DDR4 2666 MHz RDIMM ECC (error correction code) memory. This equipment will have adequate processing power, graphical speed and resolution, and memory to provide a vivid, smooth immersive experience. Eye-tracking data will be collected from individual participants using the integrated eye-tracking system contained within the HTC Vive Pro HMD. The data sampled by the HMD eye tracker include data output (eye information): timestamp (device and system), gaze origin, gaze direction, pupil position, pupil size, and eye openness, which are captured every 200 ms.

Participants

The participants will be recruited from a local metro region. We anticipate that participant background characteristics (eg, education, ethnicity, sex, and age) will be representative of the metro area in background characteristics (eg, education, ethnicity, sex, and age). Recruitment will be managed by the

National Institutes of Health (NIH) Office of Patient Recruitment, using local flyers; Office of Patient Recruitment website; and posts on social media, including Facebook and Twitter. Participants will be remunerated to participate in the study. All protocol activities will take place in a local NIH facility in Bethesda, Maryland.

For each phase of the study, participants will be healthy individuals aged 18-75 years. Recruitment for phase 1 will target an older (≥55 years) and younger group (18-54 years) with 50% targeted for each group, stratified by sex. Recruiting a broad age range will ensure usability among older individuals, as future apps will likely involve older adult clinical populations. The sample will be stratified by sex, as some research suggests that women may experience immersive VR differently from men [116,117]. The phase 1 sample size will be 24, with 8 participants completing each of the three shopping conditions. Evaluating participants from a variety of backgrounds is important in UX research to identify any systematic issues in the interface, content, or instructions. The phase 2 study recruited 60 healthy individuals aged 18-75 years. For this study, there will be no targeted recruitment of older adults, as any design issues specifically associated with subject age will be addressed before phase 2. The sample size was determined based on the calculated effect sizes of fatigue induction studies that used the VAS-F (Cohen *d*=0.65; SD 0.25) and vigilance decrement studies [34]. The inclusion and exclusion criteria are included in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Participants aged 18-75 years
- Willingness to complete the study procedure
- Willing to provide feedback on virtual reality experience
- Able to provide consent

Exclusion criteria

- Self-reported
  - Any impairment in visual functioning (eg, 3D depth perception, color blindness, visual acuity, and oculomotor control) not corrected with lenses
  - Eye pain or iritis
    - Susceptibility to photosensitive seizures or diagnosis of seizure disorder
  - Inability to use hands
    - Diagnosis of neurological conditions
  - Diagnosis of sleep disorders
  - Current treatment for chronic physical pain, migraines, any diagnosis of a clinical condition associated with cognitive or physical fatigue (eg, multiple sclerosis and chronic fatigue syndrome)
  - History of acquired brain injuries
    - Current cold or flu symptoms
- National Institute of Nursing Research employees and staff or subordinates, relatives, and coworkers of National Institute of Nursing Research employees and staff or a study investigator
- Not fluent in English
- For phase 2, participation in phase 1

Analysis

Overview

This statistical analysis plan was reviewed by the National Institute of Nursing Research (NINR) statistician. All data will be processed, cleaned, and analyzed using the SAS 9.4 (SAS Institute). The data analysis approach for phase 1 focuses on descriptive and nonparametric tests. The primary goal of the phase 1 study is to evaluate the measures and identify any interface issues that cause participants to have problems interacting with the environment or producing unexpected physical symptoms. The phase 2 study will test specific hypotheses using inferential statistics.

Phase 1

The data analysis for phase 1 will inform decisions related to programming, data outputs, adequacy of obtained score distributions, evaluation of the psychometric quality of the cognitive tests, and identification of any potential confounds (eg, length of VR exposure) that could impact future studies. We will examine the initial evidence for the fatigue induction effects of the three shopping conditions. We will use frequency

and nonparametric procedures to evaluate the rates of observed difficulties using controllers, interacting with the environment, and following instructions generally, by age groups and by sex. We will compare self-reported feelings of distress before entering the VR environment to the self-reported symptoms after exiting the VR environment. For this analysis, the Wilcoxon signed-rank test will be used. Secondary analyses evaluate distributions of key dependent measures including self-reported CF and workload, eye-tracking data (eg, blink rate, percent eye closure, gaze fixation length, and gaze shifts), and performance data for shopping and cognitive tasks (eg, correct response and response speed), as having a score distribution of several SDs will be important when the measures are applied in hypothesis testing. Following a structured interview, responses will be analyzed for common interface or immersive content issues (eg, difficulty teleporting, difficulty reading text, and problems accessing grocery list).

For example, in phase 1, we will compare the participants' self-reported physical symptoms and eye-related symptoms from the VRSQ before versus after completing the VR shopping experience. We will use the Wilcoxon signed-rank test, given the high probability of a nonnormal distribution in the dependent measure. This comparison will provide evidence to determine whether the VR environment produces physical distress or eyestrain. We computed the total scores for each of the observation scales. These totals inform about the number of times the participant had difficulties with the interface. We will compare the frequencies of interface problems in older and younger and male and female subjects using the chi-square test. These are structured statistical analyses planned as part of the formal UX results. Exploratory procedures are used to identify the relationship between user behavior (eg, number of items reviewed, distance traveled in the environment, and accuracy of shopping behaviors with measures of shopping enjoyment, shopping experience, and sense of immersion in the environment). For these analyses, we used Spearman rank-order correlations.

Phase 2

We will use the repeated measures analysis of variance (ANOVA) with the VAS-F and NASA-TLX as repeated dependent variables by shopping experience (fixed) to test the hypothesis that grocery shopping creates fatigue and workload, particularly when the person experiences interruptions and distractions. Secondary analyses will evaluate whether objective indicators of fatigue, such as eye tracking, shopping performance, and cognitive functioning (eg, pre- and postshopping processing speed and working memory) significantly differ by shopping experience using repeated measures ANOVA. A third series of analyses evaluated the relationship among individual characteristics, perceived CF, and workload. We will primarily use correlation to evaluate the relationship among pre-existing symptoms of fatigue, anxiety depression, personality traits, and fatigue susceptibility. Cognitive measures from the NIH toolbox will be correlated with perceived fatigue and workload to identify whether cognitive abilities influence the perception of cognitive workload and fatigue.

For example, we will use the repeated measures ANOVA to test the primary hypothesis that the cognitive activity of shopping for specific items will create a greater perception of mental workload and fatigue compared with just exploring the environment unless the distribution of dependent measures does not allow for using this specific statistical procedure. Similarly, we will use an appropriate correlation procedure to compare the level of activity measures such as distance traversed in the store, number of items selected and reviewed, and efficiency and accuracy of shopping activity with perceptions of fatigue and workload. Correlation procedures will be used to assess the relationships between constructs, such as personality style, cognitive ability, fatigue susceptibility with self-reported mental workload, and fatigue to identify individual differences in fatigue susceptibility. Eye tracking such as percent eye closure will be explored as a possible objective indicator of fatigue by serving as a dependent measure in the repeated measures ANOVA by shopping experience and in correlational analysis with self-reported fatigue and workload. The actual analysis considers the appropriateness for each specific variable distribution.

Results

This study was approved by the scientific review committee of the NINR and identified as an exempt study by the institutional review board of the NIH. Data collection will begin in spring 2021.

Discussion

Overview

The development of a complex, immersive VR environment requires close collaboration between individuals from multiple disciplines. The iterative design of the grocery store involves simulation of activities (eg, selecting objects using various techniques), legibility assessment of various product creation strategies, user testing by team members to identify potential sources of physical discomfort (eg, effect of antialiasing on visual acuity and developing headache), comparison of movement modalities (eg, walking vs sitting), ambient environmental factors (eg, store sounds and signage), and sizing of store elements (eg, shelf height, length, and store size). In addition, the research team will implement several simulations to evaluate the software performance and integrity of the data outputs. For each activity, the team of engineers, graphic designers, clinical experts, and researchers evaluated the relative impact of design on study requirements, UX, and software functionality. This process requires a high degree of communication and knowledge sharing.

The digital development process is fraught with potential pitfalls, particularly if team communication breaks down, and a collaborative spirit is diminished. For example, the design of the user interface can have a significant effect on the cognitive demands of using the software. If not created collaboratively, the resulting user interface may create a confound in the interpretation of the cognitive processes required for performing an IADL, as unintended skills may be introduced into the process. When communication is effective, multiple options for

the experience are evaluated, such as comparing the use of different processes to remove an individual item from a shelf. Some of these options produce unintended consequences associated with product legibility and the potential for users to develop headaches from the experience. However, a seemingly less natural object selection process (eg, point and trigger pull) alleviates these issues with only a slight reduction in the sense of realism. Similarly, creating intricately detailed products had a negative effect on software functionality (eg, lower flicker fusion rate), which produces an unpleasant experience for the user. By reducing the object vectors and polygons, it is possible to maintain a high degree of realism without interfering with the software functionality. Researchers wishing to deploy complex, immersive VR experiences must anticipate the myriad of factors that potentially introduce confounding variance that reduces the fidelity of an intervention or the measurement of key constructs. In our experience, team communication of design requirements, relying on an interdisciplinary set of skills and knowledge, continuous informal UX testing, and applying an iterative design approach are necessary for effectively using VR as a research platform.

Strengths and Limitations of This Study

CF is a complex phenomenon influenced by task, environment, personal experience, and individual differences. Our experimental conditions included a familiar task performed in a realistic immersive VR environment that allows for the precise control of stimuli. The ability to control stimuli and timing of events will enable us to determine the relative contribution of distraction, boredom, task complexity, and person characteristics on the development of CF. The strength of the immersive VR experience is the capacity to create a cognitive experience that closely aligns with real-life demands. Our ability to control the presence and timing of interfering factors enables us to assess environmental influences that would be almost impossible to standardize using an actual grocery store.

The immersive VR environment allows us to seamlessly use multiple measures of CF. We will use subjective indicators of CF and workload to better understand how perceived fatigue (eg, physical fatigue: *tiredness* and *sleepiness;* cognitive fatigue: *efficiency* and *difficulty in concentrating*) and workload (eg, mental demand, effort, and frustration) relate to the effects of tasks, environments, and other factors. Potential objective measures of CF, such as changes in behavior (eg, performance efficiency, shopping list rechecking, rate, and the efficiency of movement) and changes in eye movement, can be measured unobtrusively. The use of a randomized controlled design is a strength of this study. Participants will be randomly assigned to 1 of the 3 shopping conditions to control for any confounding effects of person-level background characteristics (eg, age) that may affect fatigue or reactions to the VR experience.

The primary weakness of the study is the potential for the immersive VR environment itself to create feelings of eye strain and fatigue. This visual effect of the VR environment may have a stronger impact compared with the fatigue effects of the cognitive task, reducing the observed differences between experiences. We are mitigating the potential of VR-induced fatigue by using high-resolution HMDs. In addition, we will measure symptoms of physical distress pre- and postimmersion to identify any signs of physical distress that could affect the levels of self-reported fatigue. We are limiting the potential for motion sickness by using the teleport function for movement and other changes to the visual presentation to minimize any potential for headaches. The UX study is performed to specifically address questions of usability, including identifying any factors that might produce physical discomfort.

Conclusions

Our initial informal user testing indicated a high sense of immersion and realism in the virtual shopping experience. We will continue to modify the shopping experience to meet the research goals of evaluating the effect of cognitive and emotional factors that influence fatigue onset. The store size will be 18,000 square feet, consistent with the dimensions of a small grocery store in the United States with hundreds of unique items created. Additional products are being created to give the store correct proportionality, typicality in selection options, and a visual experience that is consistent with a grocery shopping experience in the United States. The software will be ready for formal UX testing as outlined in this paper in the spring of 2021. We anticipate that the virtual shopping experience will provide a wealth of data related to the experience of CF while performing routine activities.

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Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
CF: cognitive fatigue
ECC: error correction code
HMD: head-mounted display
IADL: instrumental activity of daily living
NIH: National Institutes of Health
NINR: National Institute of Nursing Research
UX: user experience
VAS-F: Visual Analog Scale–Fatigue
VR: virtual reality
VRSQ: Virtual Reality Symptom Questionnaire

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Protocol

Efficacy of the Self-management Support System DialBetesPlus for Diabetic Kidney Disease: Protocol for a Randomized Controlled Trial

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Abstract

Background: Diabetic kidney disease (DKD) is one of the main complications of type 2 diabetes mellitus (T2DM). DKD is a known risk factor for end-stage renal disease, cardiovascular disease, and all-cause death. Effective intervention for early-stage DKD is vital to slowing down the progression of kidney disease and improve prognoses. Mobile health (mHealth) is reportedly effective in supporting patients' self-care and improving glycemic control, but the impact of mHealth on DKD has yet to be shown.

Objective: The purpose of this study is to evaluate the efficacy of standard therapy with the addition of a self-management support system, DialBetesPlus, in patients with DKD and microalbuminuria.

Methods: This study is a prospective, randomized, open-label, multicenter clinical trial. The target population consists of 160 patients diagnosed with T2DM accompanied by microalbuminuria. We randomly assigned the patients to 2 groups—the intervention group using DialBetesPlus in addition to conventional therapy and the control group using conventional therapy alone. DialBetesPlus is a smartphone application that supports patients' self-management of T2DM. The study period was 12 months, with a follow-up survey at 18 months. The primary outcome was a change in albuminuria levels at 12 months. Secondary outcomes included changes in physical parameters, blood test results (glycemic control, renal function, and lipid metabolism), lifestyle habits, self-management scores, medication therapy, and quality of life.

Results: The study was approved in April 2018. We began recruiting patients in July 2018 and completed recruiting in August 2019. The final 18-month follow-up was conducted in March 2021. We recruited 159 patients and randomly allocated 70 into the intervention group and 61 into the control group, with 28 exclusions due to withdrawal of consent, refusal to continue, or ineligibility. The first results are expected to be available in 2021.

Conclusions: This is the first randomized controlled trial assessing the efficacy of mHealth on early-stage DKD. We expect that albuminuria levels will decrease significantly in the intervention group due to improved glycemic control with ameliorated self-care behaviors.

Trial Registration: UMIN-CTR UMIN000033261; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000037924

International Registered Report Identifier (IRRID): DERR1-10.2196/31061

(JMIR Res Protoc 2021;10(8):e31061) doi:10.2196/31061

KEYWORDS

diabetic kidney disease; microalbuminuria; albuminuria; diabetes mellitus; self-management support system; mHealth; randomized controlled trial; diabetes; kidney; chronic disease; support; self-management; efficacy; protocol; therapy; intervention; self-care; behavior

Introduction

The increase in type 2 diabetes mellitus (T2DM) worldwide is the primary cause of the increasing prevalence of end-stage renal disease (ESRD) [1]. The number of ESRD patients under renal replacement therapy is estimated to be more than 3 million worldwide and is projected to increase to more than 5 million people by 2030 [2]. Therefore, effective management of diabetic kidney disease (DKD) is essential, especially in the early stages. It has been demonstrated that albuminuria is one of the earliest detectible clinical manifestations of kidney disease and is a potent risk factor for ESRD and all-cause death [3,4]. Renin-angiotensin blockades are approved as a strategy to reduce urinary albumin excretion and are in widespread use [5,6]. Recently, glucagon-like peptide-1 analogs and sodium-glucose cotransporter-2 inhibitors have also been shown to slow the progression of DKD potentially [7,8]. Despite all these pharmacological interventions, the overall prevalence of DKD did not change significantly among US adults with diabetes from 1988 to 2014 [9]. Moreover, with 415 million patients with diabetes reported worldwide in 2015, the number is still increasing and is predicted to rise to 642 million by 2040 [10]. There is an increasingly urgent need for a more effective methodology to prevent the progression of DKD.

Modification of dietary and exercise habits is still one of the most fundamental therapeutic strategies. However, a sufficient support system for patients' self-care has not been established. Whereas mobile health (mHealth) interventions supporting patients' self-management have shown effectiveness in glycemic control of T2DM [11-14], the effects of mHealth on DKD have yet to be evaluated.

In 2015, over half of the people with diabetes worldwide lived in Southeast Asia or the Western Pacific Region. In Asia, it is estimated that the number of patients with diabetes will increase 1.8 times by 2040, and ESRD prevalence will rise sharply relative to other regions [2,10]. However, a population-based approach is also reported to decrease diabetes-related ESRD successfully [15,16]. mHealth might be a promising population-based approach, providing basic treatment and reliable information with easy accessibility at low cost.

We previously reported that the self-management support system DialBetics significantly improved glycemic control in T2DM patients, possibly due to improvement in diet and exercise [17,18]. We have since developed an updated system, DialBetesPlus, to investigate the effect of mHealth on DKD. In this study, we investigate the impact of DialBetesPlus on patients with DKD and microalbuminuria.

Methods

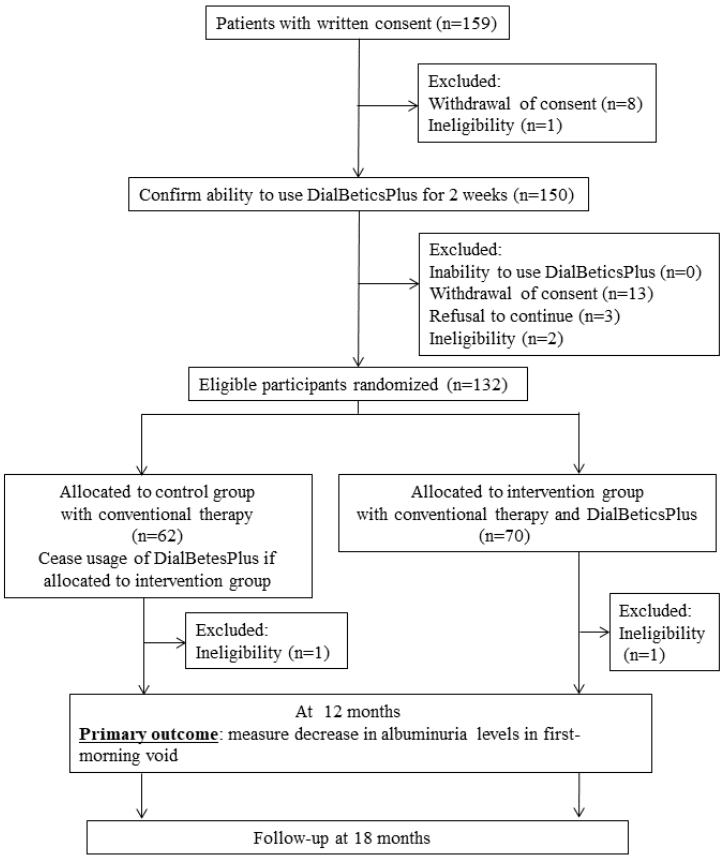
Study Design

This study is a prospective, randomized, open-label, multicenter clinical trial. The study was conducted at 8 hospitals located in Tokyo and Kanagawa, Japan (Textbox 1). We aimed to evaluate the efficacy of DialBetesPlus on microalbuminuria in T2DM patients. Figure 1 shows a flowchart of this trial. The intervention group used DialBetesPlus and conventional therapy for 12 months, while the control group was treated with conventional therapy alone. The primary outcome was a change in albuminuria levels in a first-morning void after 12 months. The final follow-up was in 18 months, 6 months after the 12-month intervention period.

Textbox 1. List of trial institutions.

- The University of Tokyo Hospital
- Yokohama City University Hospital
- Yokohama City University Medical Center
- Yokohama Rosai Hospital
- Saiseikai Yokohamashi Nanbu Hospital
- Fujisawa City Hospital
- Chigasaki Municipal Hospital
- Mitsui Memorial Hospital

Figure 1. Protocol flowchart.



Participants

We recruited patients who passed all the inclusion and exclusion criteria before randomization (Textbox 2). The criteria were designed to include T2DM patients experiencing the early stage of DKD without any restrictions on physical activity. Eligible participants had T2DM with microalbuminuria (30-299 mg/g creatinine), hemoglobin A_{1c} (HbA_{1c}) of 6.5% or more, and an estimated glomerular filtration rate (eGFR) of 45mL/min/1.73m^2 or more. We obtained written, informed consent from all the patients participating in this study. Prior to the randomization, all enrolled patients were asked to use DialBetesPlus for 2 weeks to confirm their ability to use the system and devices properly. Eligible participants were those able to use DialBetesPlus for over 7 days during the initial 2-week confirmation period. The participants were randomized into either the intervention or control group in a one-to-one fashion based on albuminuria levels, gender, and age. The research team consisted of diabetologists, nephrologists, pharmacists, dieticians, nurses, a laboratory technician, and technical support experts. While the team handled technical troubles and monitored usage of the system, the patients continued to consult their attending doctors about their general health status. If 7 days passed without any input into the system, an alert was sent to encourage the patient to resume providing input. If 3 weeks passed without a patient inputting any data, we defined the patient as a dropout. Participants with whom the study team has lost contact were also treated as dropouts. The criteria for study discontinuance were a serious adverse event, patient request for discontinuance, pregnancy, or the judgment of a lead physician.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Diagnosed with T2DM
- HbA_{1c} 6.5% or more
- Between 20 and 75 years of age
- BP lower than 180/110 mmHg
- eGFR 45mL/min/1.73m^2 or more
- Two detected instances of microalbuminuria (30-299 mg/g creatinine) in spot urine samples prior to study enrollment
- BMI of 22 kg/m^2 or more
- No history of severe hypoglycemia requiring additional medical support
- No history of the following symptoms indicating hypoglycemia within the last 3 months: palpitations, tremors, dizziness, anxiety, loss of consciousness, sweating, facial pallor, tachycardia, headache, sleepiness, blurred vision, or convulsions
- Regular patients of hospitals listed in Textbox 1
- Signatories of the informed consent form

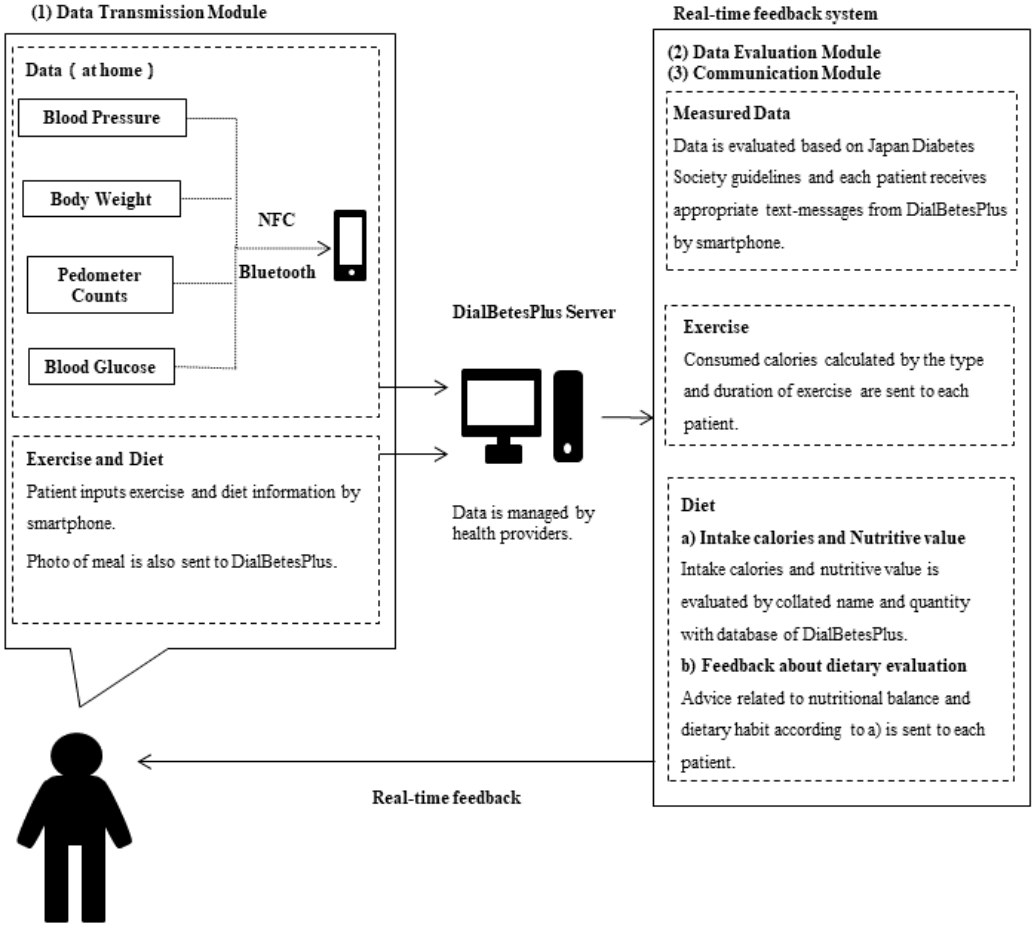
Exclusion criteria

- Use of cardiac pacemaker
- Hyperthyroidism diagnosis, under medication other than thyroid hormone supplementation in the last year
- Medical instability or exercise restriction as ordered by a physician, with autoimmune, heart, liver, digestive, neurological, or respiratory disease
- Hb less than 10 g/ dL
- Albumin 3.0 g/dL or less
- eGFR less than 45mL/min/1.73m^2
- Those with preproliferative diabetic retinopathy within one year of signing consent forms
- Inability to exercise
- Pregnancy, potential planned pregnancy, or lactating
- Participation in other clinical trials
- Under a diet that restricts protein
- Judged as ineligible by doctor's discretion for other reasons

Design of DialBetesPlus

The details of the DialBetesPlus system are shown in Figure 2. Patients measured blood glucose, blood pressure (BP), body weight, and pedometer counts at home. The data were transferred from each device to a smartphone by either Near Field Communication (NFC) or Bluetooth, and then immediately sent to a server, where they were automatically evaluated following the Japan Diabetes Society (JDS) guideline's target values [19]. Optimal values include blood glucose below 110 mg/dl before breakfast and 140 mg/dl at bedtime, BP below 125/75 mmHg, and pedometer counts above 8000 steps per day. DialBetesPlus determined if each reading satisfies the JDS guideline requirements and immediately sent the results to the patient's smartphone. Patients also entered the contents and quantity of their meals and the type and duration of exercise not counted by a pedometer. Then, their intake and consumed calories were automatically calculated and sent to the smartphone along with specific advice regarding lifestyle modifications based on JDS guidelines. Critical values with blood glucose levels above 400 mg/dl or below 70 mg/dl, systolic BP above 220 mmHg, or diastolic BP above 110mg were automatically reported to the research team, and the team informed attending doctors when necessary.

Figure 2. DialBetesPlus overview. NFC: near field communication.



The DialBetesPlus Intervention and Control

The patients allocated to the intervention group used DialBetesPlus for 12 months. Patients in the intervention group receive an NFC-enabled glucometer (MS-FR201B; Terumo), a Bluetooth-enabled BP monitor (HEM-7271T; Omron), a pedometer (MT-KT02DZ; Terumo), and a scale (HBF-255T; Omron). These devices were all paired with a single provided smartphone (Arrows F-02H; Fujitsu or Galaxy Note3 SC-01F; Samsung) that transmits readings to the DialBetesPlus server via a wireless network. In addition, as a part of standard therapy, the participants in the control group were provided with sphygmomanometers to measure BP at home.

In this study, we divided the participants into 2 models (a hospital-led model and a pharmacy-led model) depending on the location of study enrollment. In the hospital-led model (the University of Tokyo Hospital, Yokohama City University Hospital, Saiseikai Yokohamashi Nanbu Hospital, and Fujisawa City Hospital), the instructions included guidance on DialBetesPlus use provided by health care providers at the patient's hospital. In a pharmacy-led model (run by the other 4 hospitals), instructions on using DialBetesPlus were provided by pharmacists supporting the study. The pharmacists are Nihon Chouzai Co, Ltd employees, with whom we signed a business cooperation contract to conduct the pharmacy-led model portion of the study.

Sample Size

The primary outcome of this study is a change in albuminuria levels at 12 months. We estimated that baseline first-morning-void albuminuria level would be 200 plus or minus 200 mg/g creatinine and hypothesized the difference in the change in albuminuria between the intervention group and the control group at 12 months would be 100 plus or minus 200 mg/g creatinine. Based on previous reports [20,21], we calculated 63 patients were required in each group to achieve a 2-sided significance level of .05 and a statistical power of 80%. Factoring ineligibility and dropouts, we calculated a final target number of 80 patients per group.

Study Outcomes

We defined the primary outcome as a change in albuminuria levels in the first-morning void over 12 months. A first-morning void is less influenced by hydration and physical activity than a spot urine sample [22-25]. As the participants in this study are restricted to patients with microalbuminuria but without macroalbuminuria, we validated albuminuria in a first-morning void.

The secondary outcomes were changes in physical parameters (BMI and BP), blood tests, lifestyle habits, self-management, medication therapy, adherence to the diabetes medication regimen, and quality of life (QoL). Blood test parameters included renal function (eGFR), glycemic control (HbA_{1c} and fasting blood glucose), and lipid metabolism (high-density

lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL], and triglycerides [TG]). We also assessed all-cause deaths, composite cardiovascular outcomes, composite renal endpoints, safety, and the usage frequency of DialBetesPlus.

Changes in lifestyle habits were assessed via food-log diaries covering 3 days. Dietitians calculated caloric intake and nutrient balance. The Summary of Diabetes Self-Care Activities Measure (SDSCA)—which evaluates 7 aspects of the diabetes regimen: general diet, specific diet, exercise, medication taking, blood-glucose testing, foot care, and smoking—is a widely used self-reporting tool for patients with diabetes in the United States [26]. We evaluated changes in self-management using the Japanese version of the SDSCA, the J-SDSCA. Change in medication therapy was assessed by evaluating prescriptions. Diabetes medication adherence was monitored using the 8-item Morisky Adherence Scale (MMAS-8). The MMAS-8 is reliable and valid in measuring the adherence of patients with multiple chronic conditions worldwide, including T2DM [27-29]. We measured patients' QoL using the Japanese version of the Audit of Diabetes-Dependent Quality of Life (JP-ADDQoL). The ADDQoL is a diabetes-specific QoL measurement scale producing reliable and valid scores [30,31]. JP-ADDQoL also showed adequate reliability and acceptable validity [32].

Composite cardiovascular outcomes included the first occurrence and recurrence of myocardial infarction and stroke, the first occurrence of percutaneous coronary intervention and coronary artery bypass, hospitalization for unstable angina and heart failure, and cardiovascular death. The composite renal endpoint was defined as ESRD and more than a 2-fold increase in serum creatinine.

To ensure safety, we monitored the number of hypoglycemic events, other adverse events, and issues with the DialBetesPlus system throughout the study. The results of the hospital-led model and the pharmacy-led model will also be compared.

Data Collection

At registration, we collected information on patients' background, albuminuria level in a first-morning void, physical parameters, medications, blood tests, food-log diaries, J-SDSCA, MMAS-8, and JP-ADDQoL. Follow-up visits were scheduled at 2 months (plus or minus 4 weeks), 6 months (plus or minus 6 weeks), 12 months (plus or minus 6 weeks), and 18 months (plus or minus 6 weeks). We collected and recorded information according to the schedule in Table 1. Even if the interventional treatment was discontinued, we collected as much information as possible with the consent of participants.

Table 1. Assessment and follow-up schedule.

Assessments	Follow-up period				
	Registration	2 months	6 months	12 months	18 months
Patient background	●				
Albuminuria level in a first-morning void	●			●	●
Albuminuria level in a spot urine			●		
Physical parameters	●		●	●	●
Medication therapy	●	●	●	●	●
Blood test	●	●	●	●	●
Dietary intake log	●		●	●	●
J-SDSCA[a]	●		●	●	●
MMAS-8[b]	●			●	●
JP-ADDQoL[c]	●			●	
All-cause death		●	●	●	●
Composite cardiovascular outcome		●	●	●	●
Composite renal endpoint		●	●	●	●
DialBetesPlus safety questionnaire				●	
Safety		●	●	●	●
DialBetesPlus usage frequency			●	●	

[a]J-SDSCA: Japanese version of the Summary of Diabetes Self-Care Activities Measure.

[b]MMAS-8: 8-item Morisky Adherence Scale.

[c]JP-ADDQoL: Japanese version of the Audit of Diabetes-Dependent Quality of Life.

COVID-19 Related Adjustments

Due to the COVID-19 pandemic, we made some adjustments to ensure complete data collection if participants canceled their hospital visits to avoid infection risk. The Research Ethics Committee of The University of Tokyo Graduate School of Medicine and its affiliated institutions formally approved adjustments to the trial protocol. First, we adopted a self-administered blood collection kit to measure blood glucose, HbA_{1c}, eGFR, HDL-C, LDL-C, and TG levels when participants canceled in-person hospital visits. Albuminuria levels were also measured using the first-morning void mailed with the self-collected blood sample. We can conduct a blood examination by collecting 65 µl of blood from a fingertip with the self-administered blood collection kit, Ouchide-doc (Halmek Ventures, Inc). It is reported that the assay results with this blood collection method are quite comparable to the conventional methods used in hospitals [33]. Second, to minimize the face-to-face contact for data collection, we sent questionnaires to participants' homes in advance of their hospital visits.

Ethics and Dissemination

The study is being carried out in compliance with the Declaration of Helsinki. This protocol and informed consent forms were approved by the Research Ethics Committee of The University of Tokyo Graduate School of Medicine and affiliated institutions. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000033261) [34].

All participants are included after providing their signed and informed consent to participate in the trial. The participants are also informed of their right to withdraw from the study at any time. After the study concludes, data will be accessible by study groups for analysis and dissemination. All results of any analyses will be presented at major national and international scientific conferences and submitted for peer-reviewed journals of international repute and visibility.

Statistical Analysis

Data regarding patients' characteristics are presented as mean (SD) or median (IQR). We will compare changes in albuminuria levels, physical parameters, blood tests, and nutritional intake between the intervention and control groups. These will be analyzed using the 2-tailed *t* test or Mann-Whitney U test, as appropriate. Changes in J-SDSCA, MMAS-8, and JP-ADDQoL scores will also be analyzed using the Mann-Whitney U test. We will compare the proportion of hypoglycemia during the study in the intervention group to the proportion in the control group using Fisher's exact test. *P* values <.05 will be considered statistically significant. Statistical analyses will be performed using SAS (version 9.4; SAS Institute Inc).

Results

The study was approved in April 2018. We started recruiting patients in July 2018 and completed recruitment in August 2019. The final 72-week follow-up was completed in April 2021. The first results are expected to be available later in 2021.

We recruited 159 participants with written informed consent (Figure 1). We had 24 participants excluded due to withdrawal of consent (21/159, 13%) and ineligibility (3/159, 2%). No participants were excluded due to an inability to use DialBetesPlus. A participant in the control group and another in the intervention group were also excluded after randomization due to the late discovery of ineligibility. The baseline characteristics of the remaining 133 patients are shown in Multimedia Appendix 1. Data for continuous variables are expressed as mean (SD) or median (IQR).

Of the 150 participants, 3 (2%) subsequently declined to continue and were excluded, resulting in 132 randomized participants. Table 2 displays the baseline demographic characteristics of the remaining 130 participants, excluding the 2 late-discovered ineligible participants. Data for continuous variables are expressed as mean (SD) or median (IQR). *P* values for continuous variables were calculated with 2-tailed Student's *t* test or Mann-Whitney's U test. *P* values for categorical variables were calculated with Fisher's exact test.

The baseline characteristics showed no significant differences between the control group and the intervention group.

Table 2. Baseline patient characteristics.

Characteristics	Total (n=130)	Control (n=61)	Intervention (n=69)	*P* value
Age (years), mean (SD)	59.5 (9.4)	60.5 (8.7)	58.7 (10.0)	.28
Sex, n (%)				.55
Male	96 (73.8)	47 (77.0)	49 (71.0)	
Female	34 (26.2)	14 (23.0)	20 (29.0)	
Physical parameters, mean (SD)				
BMI (kg/m^2)	28.5 (4.6)	28.3 (4.0)	28.6 (5.2)	.67
Systolic BP[a] (mmHg)	133.2 (16.7)	133.8 (17.2)	132.8 (16.3)	.73
Diastolic BP (mmHg)	82.0 (10.7)	83.2 (10.2)	80.9 (11.0)	.23
Smoking status, n (%)				.79
Nonsmoker	53 (40.8)	23 (37.7)	30 (43.5)	
Current smoker	29 (22.3)	14 (23.0)	15 (21.7)	
Ex-smoker	48 (36.9)	24 (39.3)	24 (34.8)	
Duration of diabetes (years), mean (SD)	13.1 (7.2)	12.5 (6.4)	13.7 (7.9)	.35
Laboratory test, median (Q1-Q3)				
Fasting plasma glucose (mg/dL)	144.0 (124.0-174.0)	139.0 (124.0-159.0)	150.0 (123.0-185.0)	.37
HbA_{1c}[b] (%)	7.5 (7.0-8.0)	7.4 (6.9-7.9)	7.5 (7.1-8.1)	.31
LDL[c] cholesterol (mg/dL)	99.0 (78.0-117.0)	106.0 (78.0-117.0)	98.0 (83.0-112.0)	.55
HDL[d] cholesterol (mg/dL)	49.5 (42.9-60.8)	49.0 (44.0-60.8)	50.0 (42.0-60.5)	.64
Triglycerides (mg/dl)	155.5 (100.0-261.0)	149.0 (100.0-261.0)	158.0 (100.0-252.0)	.64
Creatinine (mg/dL)	0.78 (0.65-0.92)	0.82 (0.68-0.93)	0.78 (0.62-0.92)	.33
eGFR[e] ($mL/min/1.73m^2$)	72.0 (61.8-85.3)	71.0 (63.8-83.0)	76.5 (59.5-85.5)	.29
UACR[f] (mg/gCr)	36.4 (15.1-76.2)[g]	32.3 (14.8-70.6)	41.0 (15.1-78.0)	.49

[a]BP: blood pressure.

[b]HbA_{1c}: glycated hemoglobin.

[c]LDL-C: low-density lipoprotein cholesterol.

[d]HDL-C: high-density lipoprotein cholesterol.

[e]eGFR: estimated glomerular filtration rate.

[f]UACR: urine albumin-to-creatinine ratio.

[g]One case had a missing value.

Discussion

The beneficial effect of mHealth on T2DM in improving glycemic control has been widely reported [14,35,36]. However, the impact of mHealth on DKD, one of the major microvascular complications of T2DM, has not yet been shown. To our knowledge, this is the first study evaluating the efficacy of mHealth on DKD in which microalbuminuria is the primary endpoint and eGFR is one of the secondary endpoints. Furthermore, because we followed participants for 6 months after the intervention, this study enables us to assess if the novel smartphone-based self-management support system DialBetesPlus can discernibly modify self-care behaviors in T2DM patients.

DialBetesPlus is an improved version of the previously reported DialBetics [17]. The main upgrade is providing feedback on a patient's diet. The assessment is designed to provide positive feedback praising the patients' achievement, encouraging patients, and improving their self-efficacy. The system assesses a patient's diet precisely for each meal with an upgraded database. Additionally, patients can receive feedback on their daily and weekly diets to comprehensively look at their lifestyles.

While recent meta-analysis on mHealth shows that bidirectional communication between patients and health providers is indispensable for better glycemic control outcomes of T2DM patients [35,37], DialBetesPlus features a completely automated feedback system using the algorithm of DialBetics. Even though patients who used DialBetics cannot contact their health providers directly via DialBetics, a previous study showed significant reductions in HbA_{1c} (0.4% decrease), comparable

to that achieved by other systems accompanied by interactive communication [17].

We hypothesize that albuminuria levels will significantly decrease in the intervention group compared to the control group due to improved self-care behaviors and glycemic control. This study may broaden the potential of mHealth to prevent the progression of T2DM microvascular complications.

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The ADDQoL was applied in the study with the consent and license received from the author, Clare Bradley (Health Psychology Research Unit, Royal Holloway, University of London) [38]. Finally, we would like to thank the participants, physicians (see Multimedia Appendix 2), and other health care professionals at the 8 participating institutions. This research was supported by AMED (grant JP19ek0210095).

Authors' Contributions

KW, YT, KT, TY, TK, MN, NK, and KO contributed to the design and implementation of the study. YK, AS, KW, KM, AH, MM, HW, YT, SJ, NH, TY, SK, AI, SS, TM, UO, TI, and TT conceived and planned the study. YK, AS, and KW drafted the manuscript. KW is the principal investigator of the study and was responsible for conducting the study overall. All authors commented on the manuscript and approved the final version.

Conflicts of Interest

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Multimedia Appendix 1
Patient characteristics prior to randomization.
[DOCX File , 19 KB - resprot_v10i8e31061_app1.docx]

Multimedia Appendix 2
Physicians involved in participant recruitment.
[DOCX File , 19 KB - resprot_v10i8e31061_app2.docx]

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Abbreviations

BP: blood pressure
DKD: diabetic kidney disease
eGFR: estimated glomerular filtration rate
ESRD: end-stage renal disease
HbA_{1c}: hemoglobin A_{1c}
HDL-C: high-density lipoprotein cholesterol
JDS: Japan Diabetes Society
JP-ADDQoL: Japanese version of the Audit of Diabetes-Dependent Quality of Life
LDL-C: low-density lipoprotein cholesterol
mHealth: mobile health
MMAS-8: 8-item Morisky Adherence Scale
NFC: near field communication
QoL: quality of life
J-SDSCA: Japanese version of the Summary of Diabetes Self-Care Activities Measure
TG: triglycerides
T2DM: type 2 diabetes mellitus

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Protocol

Exergaming Using Postural Feedback From Wearable Sensors and Exercise Therapy to Improve Postural Balance in People With Nonspecific Low Back Pain: Protocol for a Factorial Pilot Randomized Controlled Trial

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Abstract

Background: Physical exercise is a common treatment for people with low back pain (LBP). Wearable sensors that provide feedback on body movements and posture during exercise may enhance postural balance and motor control in people with LBP.

Objective: This study aims to investigate whether physical exercising with postural feedback (EPF) improves postural balance, motor control, and patient-reported outcomes in people with LBP.

Methods: The study was an assessor-blinded 2×2 factorial trial. We planned to recruit 80 participants with nonspecific LBP who did not receive treatment for LBP. In addition, we aimed to recruit 40 patients with chronic, nonspecific LBP who were receiving exercise therapy (ET) at the University Hospital Zurich. Both ET patients and participants without treatment were randomized to receive either an additional EPF intervention or no additional intervention. This resulted in four different combinations of interventions: ET+EPF, ET, EPF, and no intervention. The participants underwent outcome assessments at inclusion (T1); 3 weeks later, at randomization (T2); after an intervention period of 3 weeks with a predefined exercise schedule for participants receiving EPF (T3); and after an additional 6 weeks, during which participants assigned to the EPF groups could exercise as much as they wished (T4). Patients receiving ET completed their regularly prescribed therapies during the study period. Balance was assessed during quiet standing on a force platform, and motor control was assessed during a lifting task and a waiter's bow task. Physical activity was recorded using an activity tracker and the participants' mobile phones during the study. The predefined EPF schedule consisted of nine sessions of 20 minutes of exercise with a tablet and inertial measurement unit sensors at home. Participants performed a series of trunk and hip movements and received feedback on their movements in a gamified environment displayed on the tablet.

Results: The first participant was recruited in May 2019. Data collection was completed in October 2020, with 3 patients and 32 eligible people without therapy who passed the eligibility check.

Conclusions: Although it will not be possible to investigate differences in patients and people without other therapies, we expect this pilot study to provide insights into the potential of EPF to improve balance in people with LBP and adherence to such interventions.

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KEYWORDS

low back pain; exercise therapy; postural balance; postural feedback; motor control; fear of movement; exergame; randomized controlled trial; physical activity; smartphone; sensors; activity tracker; mobile phone

Introduction

Background

Digitalization is transforming health care and has the potential to increase the effectiveness of interventions. Novel tools can complement traditional therapies, offer new training formats, and allow different settings for providing interventions. As the number of those affected by low back pain (LBP) exceeds 500 million people worldwide [1] and self-management is recommended [2], digital tools may have a beneficial impact in reducing the total burden. It has been suggested that changes in spinal motor control can contribute to LBP persistence [3-5]. Digital tools that quantify trunk movements and provide feedback during physical exercises may be efficient in supporting people with LBP to improve their motor control of the trunk. As studies have demonstrated that fatigue of the trunk muscles [6] and trunk stiffness [7-9] affect postural balance, we hypothesize that exercising with postural feedback (EPF) on trunk movements can improve postural balance in people with LBP. Exergaming has shown promising effects in initial applications for musculoskeletal conditions [10]. However, available studies cover different conditions and interventions, and because of this heterogeneity, the results could not be numerically integrated in a recent review [10]. It was concluded that this field should be further explored [10]. In a review, it was shown that exercise interventions supported by digital tools for people with chronic LBP were successful only when provided in conjunction with other treatments and tested against the unaccompanied other treatment but not when compared by itself against another condition [11]. Similarly, improvements in postural balance may depend on being combined with parallel rehabilitative interventions. Therefore, this study included patients who received regular prescribed therapies, including exercise therapy (ET), and a group of participants who did not receive therapy for LBP.

Objectives

The primary research objective is to investigate whether a home exercise program with feedback on trunk movements can improve postural balance and other health-related outcomes in people with LBP. Secondary research objectives refer to the adherence to EPF, subgrouping participants with LBP based on digitally acquired data, comparison of objectively monitored activity data with self-reported activity data, and the relationship between fear of movement and postural balance. To keep the protocol concise, only the primary research objective is described in detail in this paper, and additional research questions will be addressed in future publications.

The hypotheses corresponding to the first research objective and the primary outcome of postural balance are as follows: EPF improves *postural balance*, and the improvements in *postural balance* because of EPF among participants not receiving therapy are more beneficial than the improvements in postural balance in ET patients receiving ET. Secondary outcomes include indicators for *motor control*, *pain intensity*, *disability*, *quality of life*, and *fear of movement*.

The intervention group is compared with a control group that did not receive an additional intervention. Potential difficulties in recording and comparing adherence in equal quality in groups with and without a digital tool played a role in this decision.

Postural Balance in LBP

Postural balance is different in people with LBP in comparison with the postural balance of healthy participants [12-14], although balance may not be changed in the same manner across all people with LBP [14]. In studies where passive trunk stiffness was experimentally manipulated using corsets or lumbar belts, balance was reduced in different tasks, for example, when regaining balance after being released from an unstable, forward-leaning position [7] or during seated balancing on a labile surface [8]. However, in another study using a similar seated balancing task, only voluntary activation of trunk muscles led to faster sway, whereas stiffness caused by a lumbar belt did not lead to a reduction in balance [9]. In addition, a systematic review reported that trunk muscle fatigue resulted in faster sway during standing [6]. This indicates that deviating motor control of the trunk may play a significant role in the altered postural sway characteristics observed in people with LBP. Further evidence provided by a meta-analysis indicates that postural balance can be enhanced in older adults through balance exercises, although no changes were found for interventions targeting strength or comprising different training approaches [15].

For people with LBP, the effects of exercise on postural balance have been documented in several studies [16-21]. An effect on postural balance was found in some of these studies comparing different groups [18-20] but not in other studies [21]. The results of the study by Lomond et al [17] indicated that different interventions can even result in diverging changes in the same outcome. Although the included populations, tasks, postural balance parameters, and interventions vary considerably in the abovementioned studies, they show that postural balance can

potentially be modified by exercising interventions in people with LBP.

EPF for People with LBP

Some feedback is naturally available during movement, for example, as visual or proprioceptive input [22]. Additional information that needs to be obtained from external sources can be measured or reported by another person and may be used for the acquisition and correction of movement patterns [22]. For people with LBP, additional feedback on trunk movements might be effective in improving motor control of the trunk and, thus, postural balance.

Two systematic reviews reported that different types of digital feedback, for instance, from electromyography [11,23] or ultrasound data [23], on muscle activity have been investigated more frequently for their use in exercising interventions for LBP than postural feedback from digital tools. Some studies have already investigated exercise interventions on postural feedback on trunk movements in clinical settings in people with LBP [24-27]. In one study, it was concluded that the intervention increased range of motion and movement speed [25], although it is unclear from the reporting whether these results refer to a comparison between groups or a change over time. Kent et al [24] found no group differences in range of motion, and another study investigating effects on movement control impairment did not find a significant difference between groups [27]. As the number of studies seems to be limited, more research could help to better estimate the potential of such interventions on movement characteristics and postural balance in people with LBP.

Methods

Overview

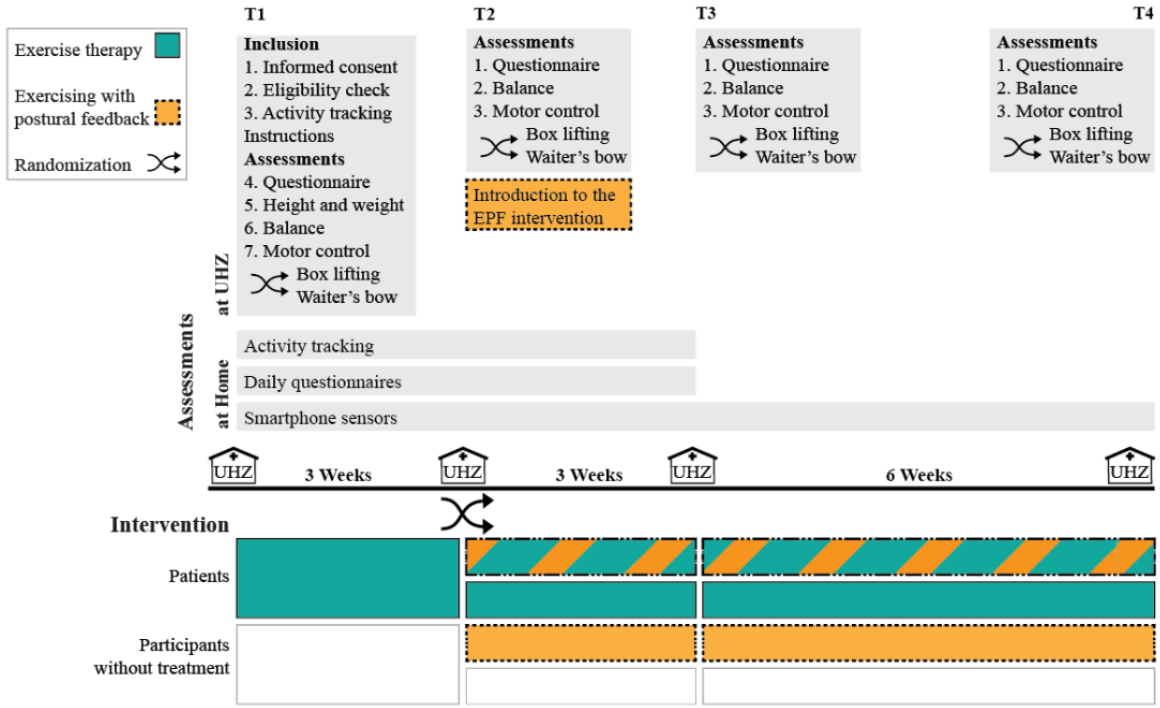
The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [28-30] for this protocol can be found in Multimedia Appendix 1.

Study Design

The study was conducted at the Physiotherapy Occupational Therapy Research Department at the University Hospital Zurich (UHZ). The Cantonal Ethics Committee Zurich (Business Administration System for Ethics Committees 2018-02132) approved this study.

The study is a 2×2 factorial randomized controlled superiority trial, and it has been summarized in Figure 1. We aimed to recruit 40 patients with chronic, nonspecific LBP receiving ET training at the UHZ and 80 additional participants currently not receiving any treatment for LBP. Patients in ET continued with their regular prescribed therapies during the study participation, whereas participants without therapy for LBP were requested not to seek treatment for LBP while participating. At the second appointment (T2) at 3 weeks from inclusion, the patients and the participants without treatment for LBP were randomized to either receive or not receive the EPF intervention. This setup resulted in 4 groups: ET+EPF, ET, EPF, and no intervention. Study participants who did not receive EPF during the study (the ET alone and no intervention groups) had the possibility for EPF for 3 weeks after the completion of their last assessment (T4). Assessments of primary and secondary outcomes at the UHZ took place at inclusion (T1), 3 weeks after randomization (T2), after completion of the 3-week intervention period (T3), and after a second intervention period of 6 weeks without a predefined exercise schedule (T4).

Figure 1. Study procedures. Procedures displayed in orange are specific for participants receiving exercising with postural feedback. Procedures in green are specific to exercise therapy patients receiving exercise therapy. EPF: exercising with postural feedback. UHZ: University Hospital Zurich.



Randomization

Participants were randomized to the EPF intervention or control condition while completing the second assessment at T2 with the outcome assessor. Stratified block randomization (1:1 assignment ratio) was used, with stratification by height and block sizes of 2 and 4. AM generated the randomization lists in R using the blockrand package (Snow, 2013, version 1.3) and randomized the participants using the randomization tool in Research Electronic Data Capture (REDCap) [31] hosted at Eidgenössische Technische Hochschule Zurich (ETH Zurich). Outcome assessors were blinded to the randomization results but other study staff members were not. The conditions under which group assignments could be revealed to outcome assessors were not specified.

Eligibility and Consent

The participants received a detailed information document that was sent via email or was printed in advance, discussed the study participation, and provided informed consent to AM. On the consent form, the participants could separately indicate whether they wished to contribute with their data to answer other research questions that were not defined. Eligibility was determined according to the criteria listed in Textbox 1 after the participants provided informed consent. If interviewing the study participants with respect to the criteria was insufficient to determine eligibility, the research scientist (AM, psychologist by training) consulted a physiotherapist team member (RP, RK, or JS). As ET is usually but not always provided in conjunction with physiotherapeutic treatments, additional treatments in combination with ET were not restricted. Participants without therapy were not allowed to undergo other treatments for LBP during the study. Leisure-time sports activities were not restricted.

Textbox 1. Eligibility criteria for patients receiving exercise therapy and participants without treatment for low back pain.

Inclusion Criteria

- Patients receiving exercise therapy
  - Patients with chronic nonspecific low back pain
  - Patients undergoing medical training therapy (exercise therapy) at the University Hospital Zurich
  - Adult male and female participants (aged ≥18 years)
  - Informed consent as documented by signature
- Participants without treatment
  - Nonspecific low back pain
  - Receiving no therapy or medical treatment for the last 6 months
  - Adult male and female participants (aged ≥18 years)
  - Informed consent as documented by signature

Exclusion Criteria

- Patients with specific causes for low back pain
- Radicular syndrome
- Unable to participate currently in the program due to pain
- Pregnancy
- Medication reducing postural balance
- Uncorrected heavy visual impairment
- Allergy to adhesive tape
- Unable to understand and communicate in German or English

ET Intervention

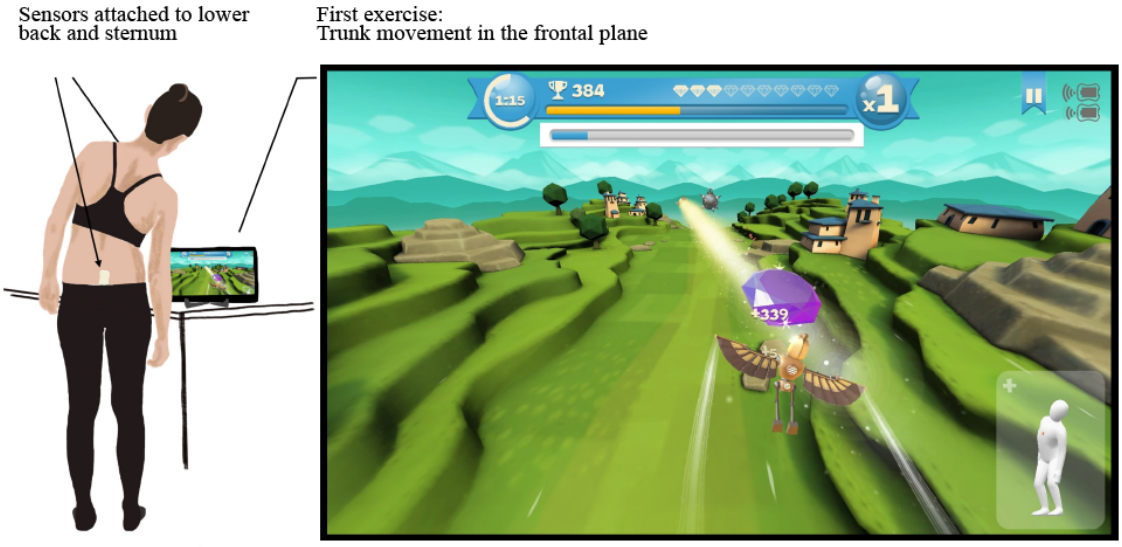
At UHZ, patients begin with ET after completing nine physiotherapy appointments. ET includes two sessions of 60 minutes per week for a period of 12 weeks. The therapy starts with an introductory session in which the physiotherapist develops an individually tailored exercise plan based on the personal needs of the patient, and the therapy ends with a debriefing session. Patients are contacted via phone when they miss an ET appointment. During the therapy sessions, patients follow their exercise plans independently but under the supervision of an experienced physiotherapist in a group setting at the UHZ. The primary goal of ET is to increase the general load-bearing capacity of the lumbar-pelvic region. ET is focused on functional exercises such as front raises or squats and includes exercising with standard fitness equipment such as ergometers and fixed and free weights at a progressive resistance.

EPF Intervention

This section summarizes the information required by the Template for Intervention Description and Replication (TIDieR) checklist [32]. Other information regarding the intervention rationale and assessment of adherence can be found in the corresponding sections. Participants who were randomized to the EPF intervention received the Valedo home system (Hocoma AG) and a tablet (MediaPad T5, Huawei) for exercising at home. The participants were asked to complete nine exercise sessions at regular intervals within the 3-week period between T2 and T3. The sessions consisted of 10 predefined exercises of 2 minutes each, resulting in a total exercise time of 180 minutes. Starting from T3 to T4, participants in the EPF groups could continue to exercise without adhering to a defined schedule and choose freely among all available exercises.

After the assessments at T2, AM introduced the EPF intervention to the participants randomized to the EPF groups. This included completing the first exemplary exercise and familiarization with the handling of the tablet and the Valedo. The participants created a user profile and were guided through an assessment of the range of motion of the trunk and hip. This information is used by the software to adapt the extent of movement required for each user [33]. Furthermore, the participants were instructed on how to exercise at home and received a document summarizing the instructions, including the list of exercises to complete (Figure 2) and the user manual of the device [33].

Figure 2. EPF Exercises given to participants to complete at home. (A) Setup of the home exercising intervention and screen view of the Valedo app (with permission from Hocoma AG). (B) Movements practiced during the exercising with postural feedback intervention.



(A) Setup during exercises with postural feedback

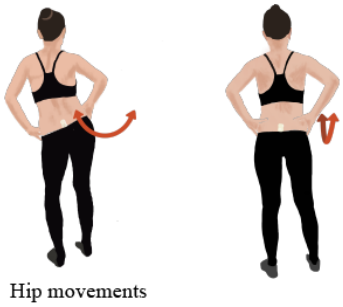
Trunk movements
Frontal plane

Sagittal plane

Transversal plane

Movements during each exercisig Session:

1. Trunk frontal plane
2. Trunk sagittal plane
3. Trunk frontal+sagittal plane
4. Trunk transversal plane
5. Trunk sagittal plane
6. Trunk transversal+sagittal plane
7. Hip frontal plane
8. Hip sagittal plane
9. Hip frontal+sagittal plane
10. Trunk frontal+sagittal plane



Hip movements
Frontal plane

Sagittal plane

(B) Movement planes

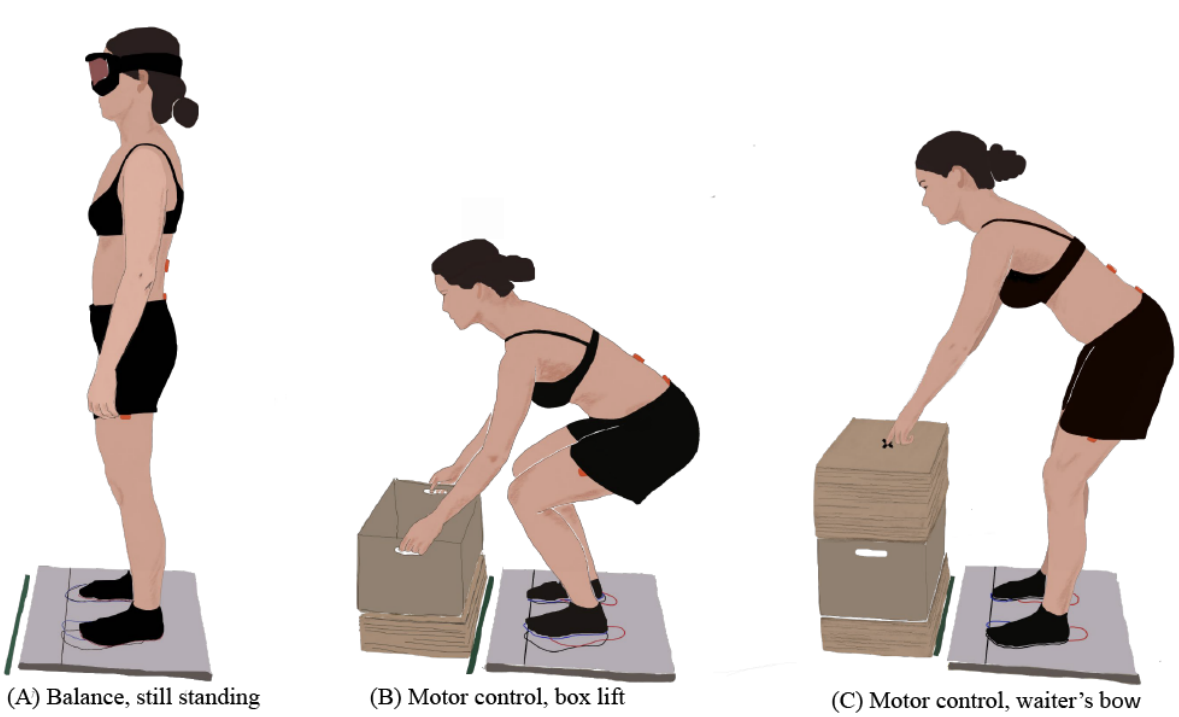
The Valedo system consists of two inertial measurement unit sensors and an accompanying app that provides different exercises within a gamified environment. For exercising, the IMUs are attached using either medical adhesive tape or belts to the lower back and the sternum (Figure 2) and they measure trunk and hip movements on different planes. The posture and position of an avatar on the screen continuously show the player's movements relative to the movement goal. This goal is either displayed as a white track the participant tries to follow or as crystals that are collected by performing the required movements as accurately as possible. In addition to this visual feedback, the player receives auditory feedback when matching the track precisely and gathering crystals. After completion of an exercise, the last exercise is shown in a ranking of the 10 best previous attempts of the player. For this study, the first nine exercises within the Valedo exercising environment were selected, whereas the third exercise was repeated once. Each exercise required a trunk or hip movement on a single plane or alternating movements on different planes. It was not specified in advance how the intervention would be adapted if this would become necessary. Adherence was analyzed after the completion of the study. The participants were instructed to contact the study coordinator in case of difficulties.

Outcomes

Postural Balance

Postural balance was assessed through center of pressure (COP) recordings during bipedal stance (Figure 3). The design of the balance assessment was based on the recommendations of Ruhe et al [34]. COP data were collected at a rate of 100 Hz using an Accusway Plus force platform (Advanced Medical Technology Inc). Each recording took 120 seconds and was repeated four times at each assessment visit. Study participants were instructed to stand on the force platform "as still as possible" [34] with their arms hanging at the side. During the recording, the participants kept their eyes closed and wore an opaque mask. To standardize the foot position across all assessment repetitions and assessment visits, the participants were asked to step on the force platform and stand in a comfortable foot position before the first COP recording. The foot position was then marked on a foil and kept for all following postural balance recordings of the participant. Differences in COP sway in the anterior-posterior direction between T3 and T2 will be analyzed as the primary outcome. In addition, other sway characteristics, such as sway in the mediolateral direction and COP velocity, will be examined.

Figure 3. Movement tasks. (A) Balance: standing still, (B) motor control: box lift, and (C) motor control: waiter's bow.



Motor Control

Assessments of lumbar spine and hip angles during a box lifting and waiter's bow task were used as indicators of motor control. The tasks, setup, and instructions of the motor control assessments were adapted from the study by Matheve et al [35], where the assessments demonstrated good reliability. Unlike Matheve et al [35], we did not adjust the lumbar spine posture to fit an ideal posture before the assessments because we assumed that this procedure could increase the task difficulty selectively for participants with a stronger deviation. Furthermore, we added an assessment of balance during the tasks, only allowed the participants to practice each task once before the assessment, and asked participants to report their pain during the practice run.

Lumbar spine and hip angles were derived from measurements using the Valedo Pro assessment tool (Hocoma AG). Three IMUs were attached to the skin with medical adhesive tape at the S1 and L1 spinous processes and at the left thigh, 20 cm on top of the lateral femoral condyle, analogous to the study by Matheve et al [35]. For positioning the IMUs correctly, the

outcome assessors palpated the back and knee of the participant. The orientation of the sensors was sampled at a rate of 50 Hz, and the data were transmitted via Bluetooth to a laptop. During the motor control assessments, additional data on postural balance were collected using the force platform. The outcome assessor randomized the order of the motor control tasks before each assessment visit by flipping a coin. The participants repeated each motor control task five times. The outcome assessor demonstrated correct and false task performance before the participants practiced each task once at each assessment visit. The participants then reported their pain during the practice movement as a safety outcome. Before the performance on each task was recorded for the first time, the outcome assessor instructed the participants to stand on the force platform with their feet parallel, with their toes on a marked line, and at a width that the participants perceived as comfortable for the task. The outcome assessor recorded the foot position on the foil to standardize the position across all task repetitions and assessment visits for each participant.

To perform the box lifting task (Figure 3), the participants started in an upright standing position, with the feet parallel and the toes touching the marked line on the force platform. The participants lifted the box, held it in a standing position, and put the box back down. The participants were instructed to maintain the same neutral position of the lumbar spine during the task. The box was 40 cm wide, 30 cm deep, 24 cm high, and 3.5 kg heavy, and the position was individually adjusted for each participant (upper front edge at a level of 10 cm below the apex of the kneecaps and 15 cm in front of the toes).

For the waiter's bow task (Figure 3), the participants stood with their feet parallel and toes on the line on the force platform. The outcome assessor asked the participants to bend forward using their hips and touch a marking in front with the tip of the index fingers and return to the starting position. The participants were instructed to keep their lower back in a neutral alignment and not to bend the knees during the task. The placement of the marking was adapted to each participant (10 cm above the base of the kneecap and 30 cm in front of the toes). Outcome assessors were trained on the assessment protocol and tools before performing any assessments.

Questionnaires

The participants completed a series of questionnaires at each assessment visit (Table 1) before the balance and motor control assessments. The questionnaires were administered on a laptop in English or German via REDCap surveys [31]. Pain intensity, physical functioning, and health-related quality of life were assessed as secondary outcomes, as these constructs have been proposed for general use in clinical trials on nonspecific LBP to enhance comparability among different studies [36]. Pain intensity was reported on an 11-point numeric rating scale (NRS; 0=no pain and 10=worst imaginable pain) referring to average pain during the previous week [37]. In a recent review, the results regarding the measurement characteristics of the NRS were found to be mostly mixed, and the measurement error was rated as too high [38]. Nevertheless, the NRS was selected based on the recommendation for widespread inclusion of the NRS in clinical trials on LBP [37].

Table 1. Overview of the questionnaires used in the study.

Outcome	At assessment visits				Daily	
	T1[a]	T2[b]	T3[c]	T4[d]	Morning	Evening
Demographic data	✓					
History of LBP[e]	✓					
Pain intensity: NRS[f]	✓	✓	✓	✓		
Disability: RMDQ[g]	✓	✓	✓	✓		
Quality of life: WHOQOL-BREF[h]	✓	✓	✓	✓		
Fear of movement: TSK-11[i]	✓	✓	✓	✓		
Movement-specific fear ratings	✓	✓	✓	✓		
Depression: PHQ-9[j]	✓	✓	✓			
Self-efficacy chronic disease: SES6[k]	✓	✓	✓	✓		
General self-efficacy: GSES[l]	✓					
Personality dimensions: BFI-10[m]	✓					
Amount of sleep					✓	
Sleepiness: KSS[n]					✓	
Physical activity: adapted from IPAQ[o]						✓
Pain intensity						✓

[a]T1: Assessment Time 1.
[b]T2: Assessment Time 2.
[c]T3: Assessment Time 3.
[d]T4: Assessment Time 4.
[e]LBP: low back pain.
[f]NRS: numeric rating scale.
[g]RMDQ: Roland Morris Disability Questionnaire.
[h]WHOQOL-BREF: World Health Organization Quality of Life-short version.
[i]TSK-11: Tampa Scale of Kinesiophobia-11.
[j]PHQ-9: Patient Health Questionnaire-9.
[k]SES6: Self-Efficacy for Managing Chronic Disease 6-Item Scale.
[l]GSES: General Self-Efficacy Scale.
[m]BFI-10: Big Five Inventory-10.
[n]KSS: Karolinska Sleepiness Scale.
[o]IPAQ: International Physical Activity Questionnaire.

Physical functioning was assessed using the Roland Morris Disability Questionnaire, which consists of 24 items [39,40]. Participants check all items that apply to their situation on the day of assessment [39,40]. The Roland Morris Disability Questionnaire is comparable with other established questionnaires [41], is reliable [39,40] and valid [39], and is suggested as one of the standard questionnaires to be used in clinical trials investigating LBP [37]. Quality of life was assessed using the short version of the World Health Organization Quality of Life Questionnaire, which consists of four subscales formed by 26 items [42]. A large study including data from different language versions and nations indicates that the World Health Organization Quality of Life Questionnaire-short version is a reliable tool for assessing quality of life [43]. Fear of movement was assessed using an 11-item version of the Tampa Scale of Kinesiophobia [44,45]. The adequacy of the psychometric characteristics of the Tampa Scale of Kinesiophobia with 11 items was confirmed for the English version [44,46] and a German translation [45]. These results were obtained from participants with LBP [44,45] and from a study that included participants with diverse pain conditions [46]. In addition, participants were asked to rate six movements (flexion, extension, sideways bending, rotation, lifting, and stretching) on slider scales (0=totally disagree and 100=totally agree) with respect to the harmfulness of the movement, pain, and how carefully participants would execute each movement. The movements were visualized using small icons. These questions were inspired by the format of the photograph series of daily activities-short electronic version

[47] and the suggestion by Pincus et al [48] to consider painfulness and avoidance in addition to fear.

Instruments not listed as outcomes under the primary research question were the Patient Health Questionnaire-9 for assessing depression [49,50], Self-Efficacy for Managing Chronic Disease 6-Item Scale [51,52], the General Self-Efficacy Scale [53-55], and the Big Five Inventory-10 [56].

Activity Assessments

During the first 6 weeks of the study, the participants wore an activity tracker [57] and completed a short questionnaire on their mobile phone every morning and evening. The activity tracker was worn on the wrist of the nondominant arm or on the ankle in cases where the profession of the participant did not allow this. The tracker recorded activity counts at a sampling rate of 1 Hz. The participants were instructed to wear the tracker continuously, night and day, except when taking a shower or swimming. The questionnaire in the morning contained questions on estimates of bedtime, wakeup time, actual sleep duration, and quality of sleep. Sleepiness was assessed using the Karolinska Sleepiness Scale [58]. The questions in the evening were adapted from the International Physical Activity Questionnaire [59,60] and referred to the time spent in walking, sitting, and high and moderate amount of physical activity on that day. Furthermore, the participants were asked to rate the pain intensity during the day on a slider scale.

For the entire study duration, sensor data of the phone were collected from participants who agreed to the collection of these data and had a mobile phone with an Android operating system. The data collection was dependent on the availability of sensors in the phone and included acceleration and speed readings of the GPS location. In addition, data on the use of the app that provided the questionnaires were recorded.

Baseline Data and Adherence

General demographic data such as age, gender, education, occupation, and data on the participants' history of back pain were collected using the questionnaire at T1. Participants' height and weight were measured using a personal scale and a bar before the first balance assessment. Completed exercises including timestamps were exported from the Valedo app and will be used to quantify adherence to the intervention. For patients in ET, data routinely assessed by physiotherapists at initiation of treatment, such as information on the diagnosis and dates of ET and physiotherapy appointments, were recorded.

Data Management

Electronic case report forms and questionnaire data and exercise adherence data were stored in REDCap [31]. Postural balance, motor control, and activity tracker data were stored on a protected network drive at ETH Zurich. Data from the activity tracking app were stored on a secured server (geographic location: CH, EU, or DE). Only staff members involved in the study had access to the study data and had to keep the data confidential. Data were saved with ID numbers and not with participant names. Electronic case report forms were double-checked for completeness by the principal investigator (JS). No data monitoring committee was established, but an external monitor reviewed the conduction and completeness of the study data. Parts of the data were reviewed while the trial was in progress, but intervention effects were not analyzed before the end of the study was determined. After trial completion, all data will be available to study team members from the UHZ and ETH Zurich. The results of the trial will be presented in a peer-reviewed journal.

Harms

The study was deemed low risk, as the Valedo home is a certified medical device and exercising is well established as a treatment for LBP. At the assessment visits, the participants were asked how they felt, and adverse events were documented on REDCap [31].

Recruitment

ET patients were recruited at UHZ. Potentially eligible patients were contacted in person by the study personnel or physiotherapists, or they responded to flyers. The study personnel approached the patients at the initial appointments to keep the amount of therapy the patients had already received when entering the study similar. Participants without therapy for LBP were recruited by advertising on digital channels, word of mouth, and flyers. Participants received initial information on the study before the first assessment visit on the phone, either via email or in person. Reasons for dropping out were documented when specified by participants, and dropouts were not replaced. Email reminders were sent before assessment visits.

Sample Size

Power was estimated using Gpower [61] using the *Linear multiple regression: Fixed model, single regression coefficient* menu. As this is a pilot study and we did not have data available to estimate the effect, we planned with an effect size of f^2=0.063 and three predictors in the model to account for both factors and the interaction effect. The primary hypotheses refer to the effect of the EPF assignment on postural balance and the interaction effect of EPF with treatment status (patients in ET or no treatment); therefore, α was set to .025. To detect this effect at a power of 0.6, it would be necessary to include 80 participants. The number of patients receiving ET training at the UHZ is limited, whereas recruitment of more participants with LBP but not in therapy seemed feasible. Owing to these limitations, we planned to include 40 patients and 80 participants without therapy to account for dropouts.

Statistical Methods

We will test the primary hypotheses using multiple regression models (with the two factors patient or participant and EPF or no EPF and their interaction term as predictors, and T3−T2 differences as outcome) or nonparametric equivalent tests where required. We will use intention-to-treat analysis to examine intervention effects and replace missing values at T3 if less than 10% (12/120) of the data are missing. The method of replacing missing data has not been defined in advance. We will explore other assessment visits between T1 and T4 using multilevel models. Analyses related to other questions not described in this manuscript are not listed.

Amendment

This paper refers to protocol version 3, August 31, 2019. Few major changes have been made since the beginning of the study. To facilitate recruitment, the period participants had to be without treatment before inclusion was reduced from 1 year to 6 months and participants randomized to the control condition received the EPF program after study completion. In addition, the research questions referring to fear of movement and movement-specific fear questions were added. The described changes were approved by the Cantonal Ethics Committee Zurich in September 2019 and were implemented accordingly.

Results

The first participant was recruited in May 2019. Owing to the COVID-19 pandemic, the trial was paused from March to May 2020. In October 2020, data collection was concluded, with 38 participants providing informed consent. Of those participants, 3 patients and 32 participants passed the formal eligibility check and completed T1. The trial ended with the time that had been allocated for the study conduction, not based on interim analyses. Data analysis is ongoing.

Discussion

Principal Findings

This study will provide information on how a digital intervention with feedback from IMUs on trunk movements affects postural balance and other outcomes in people with LBP. Daily questionnaires and continuous activity tracking will enable us to explore the development of pain intensity and other physical activities of each participant during the study in detail. The second intervention period without a predefined exercise schedule will give hints to the transferability of the results to a less controlled setting.

Within the allotted time, fewer participants could be recruited than initially planned, and only a few patients in ET could be recruited. Therefore, it will not be possible to compare the effects of the intervention between patients in ET and people with LBP who are not in treatment. Furthermore, when interpreting the results, it should be considered that no sham intervention was provided to the participants without therapy. Thus, general treatment-related factors are different among these groups.

The use of movement feedback from wearable sensors in exercise interventions is a promising approach to improve interventions. The detailed properties of the feedback given are likely to have an impact on the success of an intervention [22,23]. Continuous feedback received during a task performance is generally seen as disadvantageous for learning [22,23]. Conversely, feedback that shifts the focus outside of the body, for example, to a consequence or external visual representation of the movement, as used in this study, presumably enhances learning, even when provided very frequently [22]. However, it is not yet clear how interventions with feedback should best be designed for people with LBP [23].

In people with LBP, deficits in proprioception are suspected to contribute to consolidating changes in motor control in the long run [5] and to the reduction in postural balance [12,13]. Feedback can help overcome limitations in motor learning caused by these deficits in people with LBP [23]. Nevertheless, in a recent study investigating different feedback conditions, no differences between people with chronic LBP and people without LBP were found in learning to keep the spine in a constant position during motor control tasks [62]. In this study, practice with graphical displays of data from wearable sensors resulted in superior performance compared with practice without any feedback or practice in front of a mirror [62].

Conclusions

We expect to gain insights into the effect of EPF from wearable sensors on postural balance, motor control, and patient-reported outcomes in people with LBP. In addition, we will estimate the extent to which people with LBP adhere to such exercising interventions when they are free to choose exercise time and frequency.

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Authors' Contributions

All authors contributed to the conceptualization of the study. JS was the principal investigator and WK (email: walter.karlen@ieee.org) was the study sponsor. AM coordinated the study. RP, RK, and JS were consulted when a physiotherapist's opinion was needed. AM drafted the protocol. All authors were involved in reviewing and editing the manuscript and approved the final version. The sponsor participated in all activities related to the publication of the study results. The funding agency,

Swiss National Science Foundation, was not involved in any research activity. Authorship is defined in accordance with ETH Zurich regulations [63].

Conflicts of Interest

WK coauthored the grant proposal with Lars Lünenburger from Hocoma AG.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 119 KB - resprot_v10i8e26982_app1.pdf]

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Abbreviations

COP: center of pressure
EPF: exercising with postural feedback
ET: exercise therapy
ETH Zurich: Eidgenössische Technische Hochschule Zurich
LBP: low back pain
NRS: numeric rating scale
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication
UHZ: University Hospital Zurich

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Protocol

Psychoeducational Interventions for Caregivers of Persons With Multiple Sclerosis: Protocol for a Randomized Trial

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Abstract

Background: Of the approximately 1 million people living with multiple sclerosis in the United States, more than half receive informal, unpaid care or support from family or friends (caregivers). These caregivers report high levels of stress, anxiety, and negative emotions. Few researchers have conducted psychoeducational interventions for these caregivers.

Objective: This paper presents a protocol for a randomized clinical trial that aims to test the efficacy of two interventions for improving stress, anxiety, depression, and negative emotions for caregivers of persons with multiple sclerosis.

Methods: Participants included any self-identified family or friend caregiver of a person with multiple sclerosis. Data collection began in April 2021 and is expected to continue until November 2021. Participants will be randomized to receive either a website-only or a website-coaching intervention delivered for 6 weeks. Data will be collected at baseline, 6 weeks after baseline (after delivery of intervention), and 6 weeks later.

Results: The protocol was approved by the institutional review board of the Case Western Reserve University on January 21, 2021 (protocol 20201484). As of May 2021, 66 participants were enrolled.

Conclusions: Our findings will have implications for identifying the efficacy of two types of interventions developed for caregivers of persons with multiple sclerosis to reduce negative psychological outcomes associated with caregiving.

Trial Registration: ClinicalTrials.gov NCT04662008; http://clinicaltrials.gov/ct2/show/NCT04662008

International Registered Report Identifier (IRRID): DERR1-10.2196/30617

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KEYWORDS

multiple sclerosis; caregivers; distress; anxiety; depression; psycho-education; website; coaching; mobile phone

Introduction

Background

Currently, there are approximately 1 million people with multiple sclerosis in the United States [1], with an estimated 46%-58% of them receiving informal, unpaid care from family or friends in the course of their illness [2,3]. These caregivers are critical in maintaining high-quality care and support for persons with multiple sclerosis and often provide care not routinely provided through the established health care system [4].

These informal caregivers, such as those of persons with other chronic illnesses (eg, Alzheimer disease and cancer), provide a variety of care and support that often vary according to the

needs of the person with multiple sclerosis [5,6]. They are often frustrated by a lack of information regarding how to accommodate the changing needs of the person with multiple sclerosis, deal with the uncertainty of the course of the illness, and find support for their own emotional and physical needs [5,7-9]. Research has found that these caregivers experience negative physical and psychological outcomes that tend to increase as the disease progresses and care needs increase [10-13]. For example, these caregivers have a lower health-related quality of life [14,15], elevated levels of fatigue [16], and significantly higher levels of anxiety (68%), depression (44%), and distress (51%) [5,17-19]. In addition, these caregivers have reported that their increased anxiety, distress, and burden not only worsened their health but also had a negative impact on their employment. Approximately 24% of caregivers reported that they had to reduce or stop working because of the demands of caring for a person with multiple sclerosis [3], thus placing an additional source of stress on this caregiver group. In addition, these caregivers report concerns about the possibility of relapse or progression of the disease—concerns that lead to anticipatory grief for the future [6,20]. Thus, they must not only deal with the current care and emotional needs of the person with multiple sclerosis but also often deal with their own grief about the losses that potentially lie ahead.

Research examining the needs of caregivers of persons with multiple sclerosis has highlighted the need to reduce caregiver distress and sense of burden [5,17,21,22] (which often precede caregiver anxiety and depression), provide information relevant to caring for a person with multiple sclerosis [5,23], and provide information and skills to facilitate communication [24,25]. Strategies that include psychoeducational programs providing information and support have shown promise [5,9,20]. Interventions supporting caregivers of persons with other chronic illnesses (eg, cancer) have shown that the use of tailored strategies to increase caregiver self-efficacy and provide emotional support has effectively reduced distress, anxiety, and depression [26-31].

Although caregivers of persons with multiple sclerosis report poor emotional and physical outcomes, to date, few researchers have tested interventions for these caregivers. Interventions delivered to both persons with multiple sclerosis and their caregivers [24,25,32] and interventions delivered solely to caregivers [23,33-35] have been published. Of the interventions focused solely on caregivers, the types of interventions varied, including a group psychoeducational intervention [23], a psychoeducational intervention for empowerment [33], a cognitive behavioral web-based mindfulness intervention [34], and a behavioral intervention providing information and skills related to patient mobility problems [35]. Outcomes have focused on caregiver burden, empowerment, anxiety, and depression—factors shown to relate to ongoing emotional and physical dysfunction [9,23-36]. Only one of the caregiver-focused intervention used an individualized psychoeducational intervention—despite the success of this type of intervention in other caregiver populations [36-39].

Psychoeducational interventions, as conceptualized for this study, encompass a broad range of activities that combine education and supportive activities (eg, counseling and support to adopt self-management strategies). These interventions are tailored to individuals and can be delivered individually or in groups [39,40]. Some psychoeducational studies have reported effectiveness in improving psychological outcomes [31,37,41,42] and self-efficacy for care tasks [43]. In addition, some studies using coaching reported that this approach is effective in providing individualized information and emotional support [44]. The strategy of providing individualized coaching sessions for this study was based on research indicating that psychoeducational interventions, which are multidimensional, individualized, and flexible, are most effective [37].

The use of websites and other technologies (eg, videoconference) to deliver interventions has been well established, feasible, and acceptable to patients and caregivers [40,45-49]. In addition, previous research has noted the benefits of eHealth interventions for anxiety and depression, support for self-management activities, and improvement of family functioning in a variety of populations [41,43,46,48]. The use of videoconference and telephone to deliver coaching sessions to caregivers in our previous study [31,49] was well-received by caregivers.

The conceptual model underlying this study intervention is the Stress Appraisal Model, which identifies caregiving as a dynamic process involving caregivers and care receivers. The key to this model is the idea that stress influences the appraisal of caregiving, which, in turn, influences the caregiver's psychological response [50]. Thus, stress is a proximal outcome of perceived burden and poor psychological outcomes. Testing the model using path analysis has demonstrated that delivering emotional support and information (as in a psychoeducational intervention) enhances the caregiver's sense of self-efficacy and reduces the appraisal of caregiving, which improves psychological outcomes [50].

Objectives

To date, caregivers of persons with multiple sclerosis remain an understudied group of caregivers who demonstrate poor psychological outcomes throughout the trajectory of their loved ones' illness. These negative psychosocial outcomes can have significant impacts on caregivers' physical health and their abilities to support and provide quality care to their loved ones (the patient) [19,51]. A tailored psychoeducational intervention can alleviate some of this stress [40] by providing web-based information—available 24 hours per day, 7 days per week to address questions and concerns of caregivers of persons with multiple sclerosis. In addition, individualized coaching from trained professionals familiar with the needs of this caregiver group may enhance their sense of self-efficacy as a caregiver and decrease distress, anxiety, depression, and negative emotions [5,21,44,52,53].

This randomized clinical pilot trial aims to compare the effectiveness of a tailored website-coaching intervention (delivered via videoconference or telephone) with a website-only intervention on caregivers' negative emotional state, distress, anxiety, and depression. Changes in outcomes between the intervention groups will be compared over time (baseline, 6 weeks, and 12 weeks). We hypothesize that the

website-coaching intervention will yield a greater reduction in negative emotions, distress, anxiety, and depression over time compared with the website-only group.

Methods

Setting

This study takes place virtually using a website designed for the study (delivered to both groups) and coaching via videoconference or telephone (website-coaching group only) to adult caregivers of persons with multiple sclerosis who have responded to recruitment outreach throughout the United States. Trained research assistants will obtain informed consent and collect data remotely using REDCap (Research Electronic Data Capture). REDCap is a secure web application for building and managing web-based surveys and databases for research studies [54].

Participants

We used two convenience sampling strategies to recruit the study participants. One strategy uses targeted recruitment using a list of persons with multiple sclerosis, as indicated in a previous study (Patient-Centered Outcomes Research Institute [PCORI] grant Multiple Sclerosis-1610-37015) who are willing to participate in future research. Research assistants refer to persons with multiple sclerosis from previous studies and ask if they have a caregiver who might be interested in the study. If the person with multiple sclerosis says "yes," then the research assistant asks for telephone contact information for the caregiver and permission to contact the caregiver. After contacting the caregiver, the research assistant screens for eligibility, explains the study (if eligible), and, if the caregiver agrees to participate, sends the electronic consent via REDCap for web-based signature.

Participants may also enter the study by responding to an email sent by the National Multiple Sclerosis Society to all caregivers in their database or by responding to a Facebook advertisement that describes the study. The email and Facebook advertisement approaches include a flier developed by the Case Western University Marketing Department and approved by the institutional review board. In both the email and Facebook approaches, potential caregiver participants use a link from the posted flier that leads them to a REDCap survey form where they provide contact information and verify that they are interested in participating in the study. The research assistants then follow the same screening and consent procedures used in the first recruitment approach.

This study aims to enroll 150 caregivers of persons with multiple sclerosis. A caregiver is defined as someone (family or friend) who provides any type of support (eg, physical, emotional, or administrative support, such as paying bills) to the person with multiple sclerosis, who is not a professional caregiver, and is not paid for their efforts [31,55]. Inclusion criteria for caregivers were (1) self-identifying as an adult (18 years or older) caregiver for a person with multiple sclerosis; (2) being capable of providing informed consent; (3) identifying English as their primary language; and (4) being able to access the internet. Exclusion criteria were (1) being younger than 18 years; (2) receiving payment for caregiving responsibilities; (3) being unable to provide informed consent; (4) not identifying English as their primary language; and (5) not having access to the internet.

Study Procedures

Caregivers received an email that included a link to the baseline REDCap survey with all study tools after providing signed consent. Caregivers were randomly assigned to one of the two study arms after completing the baseline survey. A minimization stratified randomization technique (MinimRan) was used to balance preidentified stratifying covariates across treatment assignments [56,57]. In this study, the stratification variable was gender. The project director, who is blind to other characteristics, performs randomization and uses a computer-generated list of random numbers. This list is stored in a separate document that is unavailable to the research assistants who enroll participants.

After randomization, the project director emails or calls the caregiver with their group assignment, website link, unique password to the study designed website, and instructions regarding the name of the interventionist who will be contacting them to set up the first coaching session (for those randomized to the website-coaching group). The project director asks participants to be randomized to the website-coaching group if they will be charged minutes if they use their cell phones. To date, no one has indicated that using the telephone (should they choose) for coaching sessions will result in charges. A study cellphone will be mailed to any individual who states that they will incur individual charges for the use of their cell phone to participate in the study. All research assistants were blinded to group assignment, and all contact information for potential and enrolled participants were housed within REDCap to protect confidentiality before, during, and after the study.

The intervention began immediately after randomization and continued for 6 weeks. research assistants send emails to all participants at the end of the intervention (using REDCap) and 12 weeks after randomization to obtain all study measures. Plans to promote participant retention and complete follow-up involve providing all participants with a US $20 gift card after completion of each data collection time point. research assistants send an email to participants who do not complete their web data surveys within a week of receiving the REDCap link with a reminder message to complete the survey as soon as possible. This procedure has been successful in other longitudinal studies involving REDCap data collection [31].

Interventions

The website was developed for this study by a website team at Dalhousie University. It is hosted on a secure server housed in Canada. The website meets all privacy requirements outlined in both the US Health Insurance Portability and Accountability Act (HIPAA) and the Canadian Personal Information Protection and Electronic Document Act [58,59]. IP addresses are collected to increase security; however, they are immediately scrambled, and neither the web team nor the research team has access to IP addresses.

No personal information is collected or stored on the website. A secure, individual password to access the website is provided by the project director to the participants when they are enrolled. The key to the list of passwords is saved in a password-protected file accessed by the project director. Participants do not interact or communicate with the research or website teams at Dalhousie.

The development of the website followed strategies used by other psychoeducational websites [40,51,53,60]. The website content and delivery was informed by (1) a systematic review of psychoeducational interventions for caregivers of persons with multiple sclerosis [M Plow, personal communication, June 16, 2021]; (2) findings from tested web-based psychoeducational interventions [31,41,43]; (3) findings from interviews and focus groups conducted with caregivers of persons with multiple sclerosis, professionals with experience working (and conducting research) with persons with multiple sclerosis and their caregivers; (4) discussions with experts in the development of educational websites (Dalhousie) and caregiver experts; and (5) use of best practices for written patient education materials (eg, avoiding jargon, defining new or complicated terms, using active voice as much as possible, breaking information into chunks, and using short sentences) [61,62].

Caregivers of persons with multiple sclerosis and persons with multiple sclerosis both provided input into the development of the website through two web-based meetings hosted by one of the study investigators (MP). Both groups provided input into the research design, the utility of intervention comparisons, recruitment strategies, and the selection of meaningful outcomes. They confirmed the overall need for the research and the importance of supporting caregivers (called *care partners* in study materials per the request of the caregivers).

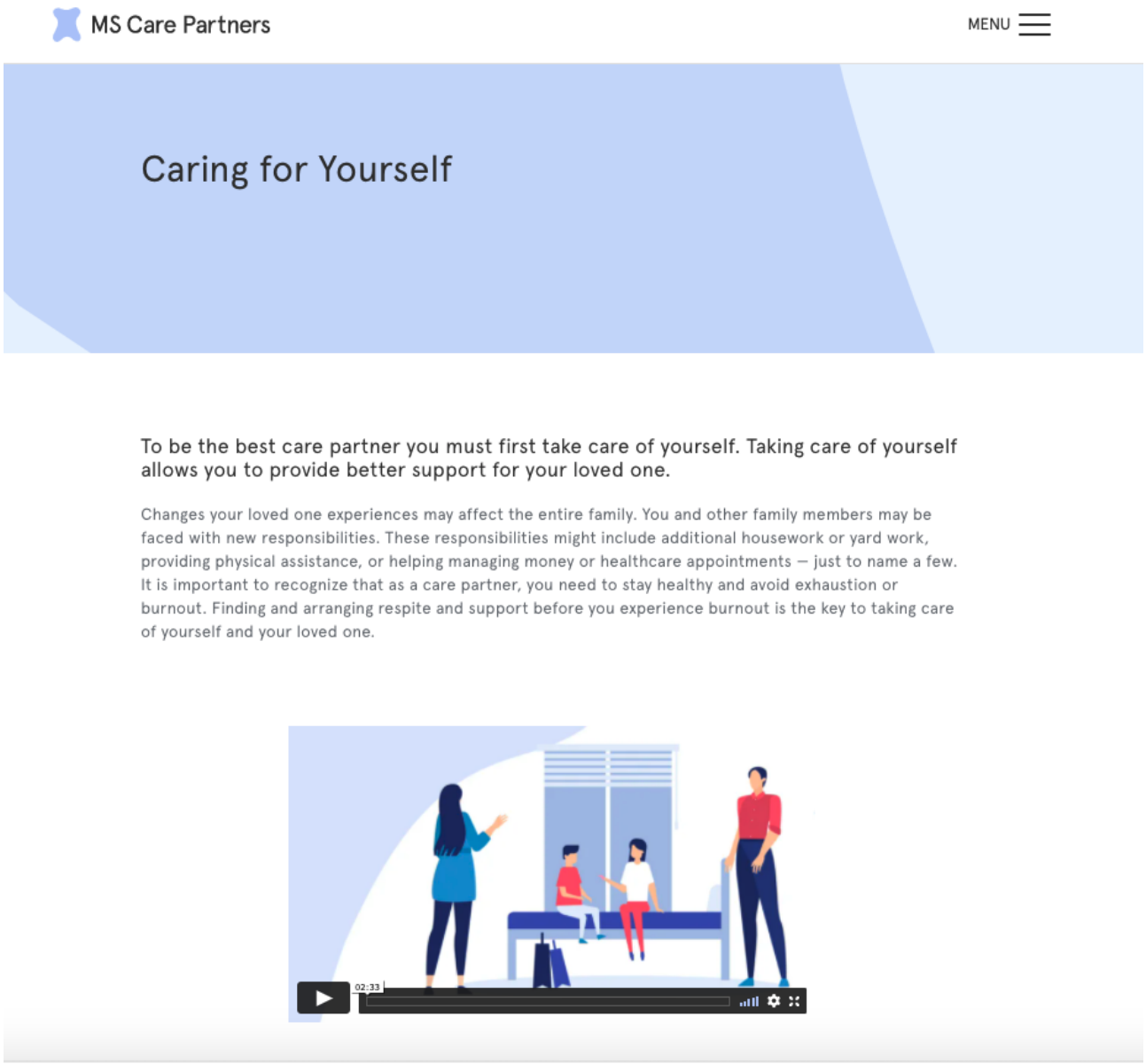
The website materials consist of text information, weblinks, and video scenarios designed specifically for caregivers of persons with multiple sclerosis in the following areas: (1) information about multiple sclerosis, (2) obtaining reliable information about multiple sclerosis on the web, (3) caring for your loved one with multiple sclerosis, (4) COVID-19 and multiple sclerosis, (5) caring for yourself, and (6) planning and decision-making. The main landing pages for the website were based on findings from previous psychoeducational websites and descriptions of key informational topics provided in web-based psychoeducational interventions [41,42,63]. Investigators for the project who had expertise in the areas of caregiving (SLD and ARL), multiple sclerosis (MP, TP, and MJL), and website interventions (TP and MJL) developed the content for the project. The development of the video vignettes was based on previous research that identified the unique needs of caregivers of persons with multiple sclerosis [5,7-10,21,22], general caregiving research [26-31], and answers to a series of questions emailed to caregivers of persons with multiple sclerosis. The website developers oversaw the development and testing of the video vignettes and the overall website.

Videos were designed to support behavior change through peer modeling and social persuasion, which are two key mechanisms to support behavioral change [64,65]. They showcase caregivers discussing and modeling topics that may be of importance to caregivers in general. Videos were designed using input from caregiver members of two group meetings held with caregivers and persons with multiple sclerosis. At that meeting, caregivers responded to questions focused on each of the intervention coaching sessions. Their responses were used to construct videos reflecting their concerns and responses to concerns. Quotes from persons with multiple sclerosis (present at the meeting) were also included to provide descriptions of lived experiences. Each video vignette scenario includes a caregiver speaking to either another caregiver or friend about issues and decisions. Storyboards and scripts for video animation and voiceovers were created and refined by the research team. Once voiceovers and storyboards were complete, the videos were animated.

COVID-19 information was included in the content of the interventions (and analyses) to describe the concerns that caregivers of persons with multiple sclerosis and persons with multiple sclerosis have regarding COVID-19. Persons with multiple sclerosis are at increased risk for severe illness from COVID-19 and their caregivers want to ensure that they are doing what is right when providing care. Rather than ignoring issues around providing care that will inevitably emerge as the pandemic evolves, we have decided to directly address it to ensure that interventionists are consistent in their responses to questions and in providing information and resources. Finally, the psychological toll of the pandemic has been described for both patients and caregivers, and it is important to examine its influence on our primary outcomes of mental health [66].

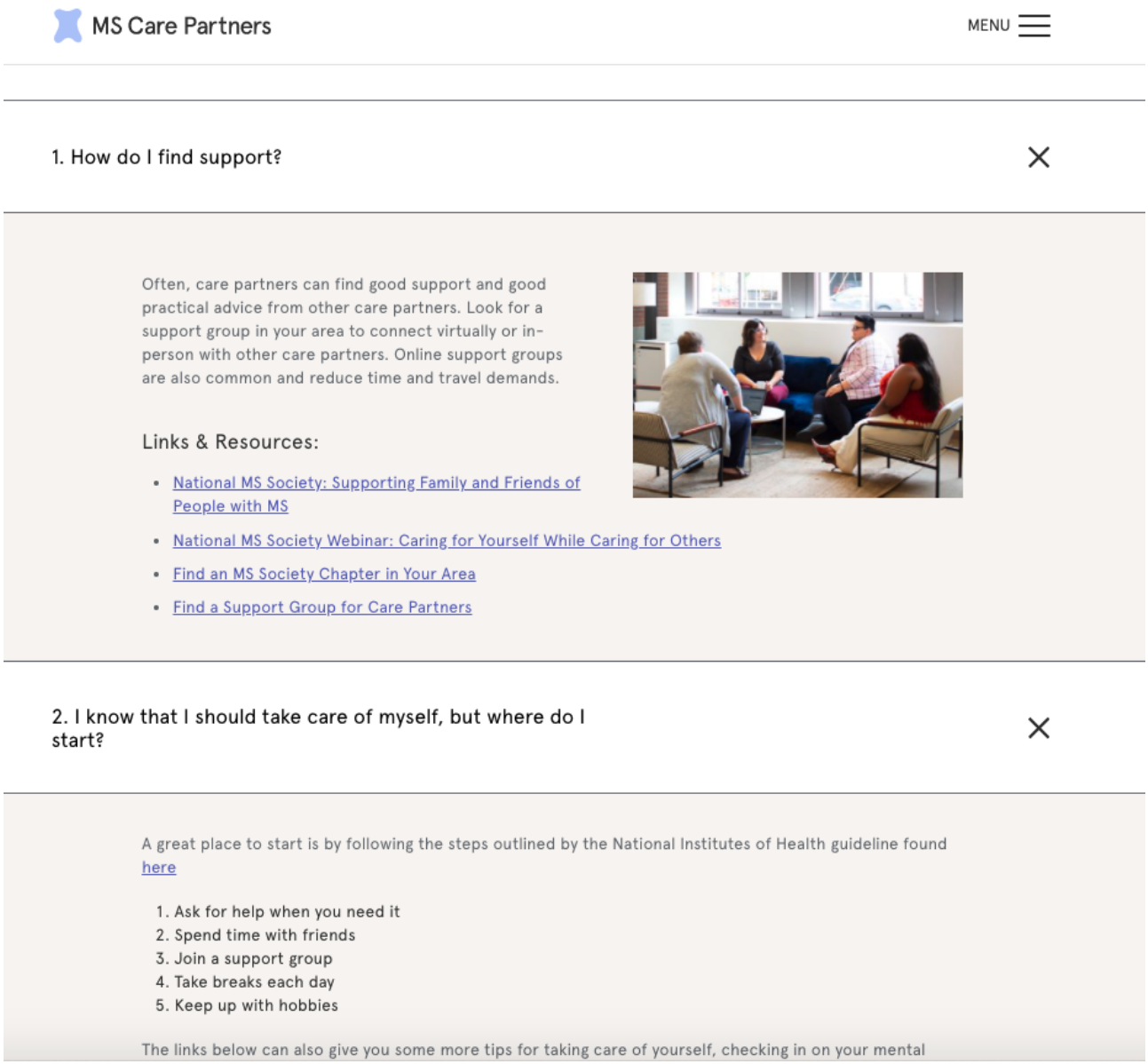
Each key area (eg, *caring for yourself* and *COVID-19 and multiple sclerosis*) follows the same format. A brief summary providing an overview of the key area is found on the landing page (Figure 1). Participants then chose to watch a short video or find answers and external links to a series of commonly asked questions.

Figure 1. Homepage for the "caring for yourself" module from the study website.



Each video vignette (2 to 3 minutes in length) depicts a conversation between a caregiver of a person with multiple sclerosis and another individual (eg, friend, caregiver, or person with multiple sclerosis) discussing an issue identified as relevant during the caregiver engagement process before developing the website. For example, on the website page *caring for yourself*, a caregiver talks to a friend about problems finding time for himself; the other caregiver suggests strategies for dealing with this problem. The list of commonly asked questions provides the selected resources and links related to each question (Figure 2). Each participant in the study can access the website as many or as few times as they wish. At the completion of the 6-week intervention period, researchers at Dalhousie will track the frequency of website use and the most frequently visited components of the website to provide aggregate descriptive information about website use.

Figure 2. Frequently asked questions for the "caring for yourself" module from the study website.



Participants randomized to the website-coaching group receive (in addition to access to the website) a dose of four personalized coaching sessions (for 6 weeks) from a trained interventionist (licensed independent social worker) who conducts the sessions via videoconference or telephone per each participant's preference. Completion of these four coaching sessions constitutes a full *dose* of coaching [37]. The four key components of the coaching sessions are (1) session 1—identifying caregivers' needs for information and support; (2) session 2—strategies for caring for a loved one with multiple sclerosis; (3) session 3—caring for yourself; and (4) session 4—planning and decision-making for the future. The key topics associated with each session are listed in Textbox 1.

Textbox 1. Key components of each coaching session.

Components of the Session

- Session 1
  - Assess caregivers' emotional and physical distress, key needs, and needs for information and support.
  - Work with caregivers to develop strategies (plan) for their most immediate need.
  - Review the study website and focus on information and sources of support that are most relevant to the caregivers' immediate needs.
  - Establish goals for caregivers to focus on for next session.
- Session 2
  - Review previous issues of concern and assess their status; determine if there are new needs or concerns (performed at the beginning of each session).
  - Assess caregivers' need in information or support regarding how to assist persons with multiple sclerosis with their physical needs and symptoms. Provide information, support, and resources as needed.
  - Assess caregivers' needs related to assisting person with multiple sclerosis with emotional needs or emotional symptoms. Provide information, support, and resources as needed.
  - Assess caregivers' needs related to communication with person with multiple sclerosis and family. Work with caregiver to develop strategies to assist identified communication issues.
  - Provide information regarding COVID-19 and multiple sclerosis (testing, multiple sclerosis society and Centers for Disease Control and Prevention recommendations, and vaccinations).
  - Discuss goals and plans for next session.
- Session 3
  - Review previous issues (session 2 point 1).
  - Assess caregivers' needs related to emotional support. Provide information, support, and resources as needed.
  - Assess caregiver involvement in self-care activities (eg, stress management and respite care). Provide information, support and resources as needed. Develop specific strategies to enhance identified issues regarding self-care activities.
  - Discuss goals and plans for next session.
- Session 4
  - Review previous issues (session 2 point 1).
  - Discuss strategies for preparing for future health care provider visits (eg, questions to ask, how to get concerns addressed, and how to be an advocate for the person with multiple sclerosis).
  - Discuss strategies to start planning for changing care needs of the person with multiple sclerosis (eg, evaluating whether home care services are needed and how to find assistive devices).
  - Provide information and discuss strategies for making decisions and plans for advanced stages of multiple sclerosis.
  - Assess, provide information on, and discuss advance care planning and palliative care.

Interventionists were trained by the project director (a social worker). First, all content and website links found in the coaching manual were reviewed. Next, the project director demonstrated a coaching session with an *actor* caregiver with interventionists then practicing each coaching session. Throughout the practice sessions, the project director provided feedback, and retraining occurred when components of the coaching needed clarity or additional practice as deemed by the project director. Finally, the project director listened to the initial coaching sessions provided to caregivers of persons with multiple sclerosis to establish baseline fidelity and consistency of the coaching delivery.

At the beginning of session 1, the interventionist conducted a brief assessment interview that focused on the caregiver's assessment of their distress related to illness and care of the person with multiple sclerosis, their emotional and physical health, and their level of satisfaction with communication (persons with multiple sclerosis, family regarding the care of the person with multiple sclerosis, and multiple sclerosis health care providers). Finally, the interventionist asked the caregiver to identify one or two specific issues of concern regarding their role in assisting the person with multiple sclerosis. The development of this assessment was based on a review of previous psychoeducational coaching interventions [44,63] and findings from previous work providing coaching sessions to caregivers of persons with a chronic illness (cancer) [31]. The purpose of this assessment was to ensure that the intervention targeted key problems and concerns identified by the caregiver.

Each session uses standardized content but is tailored to focus on issues of relevance to the caregiver. Interventionists follow

detailed outlines in the intervention manuals (with links to additional information) in providing skill-building exercises (communication, stress reduction), information, and other topics (evaluating content on the web for accuracy). Outlines were modified as needed by the interventionists based on the caregivers' assessments. For example, a caregiver who has experience with stress reduction techniques and does not identify high distress will not receive as much depth and detail regarding stress reduction as a caregiver who has little experience with these techniques. Each session takes approximately 35 to 40 minutes based on data from current coaching sessions. The total dose for all four sessions will be 120 to 160 minutes—a dose that reduced caregiver distress and anxiety in previous work [31].

Each participant determined whether their coaching sessions were delivered via telephone or videoconference. For those selecting videoconferences, Zoom (Zoom Technologies, Inc) is the app used for their sessions. We chose this app based on the recommendation of the Case Western Reserve University's Information Technology department because it provides end-to-end encryption, and we can prohibit invitees from recording videoconference sessions [67]. Caregivers can join Zoom coaching sessions on smartphones, tablets, laptops, or desktop computers.

Outcomes

The primary outcome was caregiver distress, and the secondary outcomes were anxiety, depression, and negative emotions. Distress is the primary outcome, as distress contributes to the development of anxiety and other negative emotions [68]. All outcome measures were caregiver-reported outcomes assessed using psychometrically sound tools and were analyzed using the metric of change from baseline.

Sample Size

The sample size needed to address the major aim of the study (N=150) was calculated using the Hedeker formula [69] for a repeated measures mixed effects model and included the following assumptions: a power of 0.80, correlation among 3 repeated measures of 0.5, a small Cohen *d* effect size of 0.35, and an attrition rate of 20%. These assumptions are consistent with previous studies on unpaid caregiver interventions reporting clinically meaningful changes in mental health outcomes [31,37,41,42,70].

Given that this is a pilot study, the analyses are considered exploratory in nature. Given the absence of studies testing interventions for caregivers of persons with multiple sclerosis, we will identify potential moderators a priori before testing them in the full analyses and will not test them simultaneously. As a result, we will have adequate power to detect medium to large effects using a structural equation modeling approach for our full analyses.

Study Instruments

All tools were selected based on psychometric properties, clinical applicability, and low participant burden. When possible, tools from the National Institute of Health Toolkit were used.

The *overall negative emotional state* was measured using the Depression Anxiety Stress Scale-42 [71]. This instrument consists of 42 statements representing negative emotional states of depression, anxiety, or stress (eg, "I found it hard to wind down" and "I felt sad and depressed") during a 7-day recall period. The Depression Anxiety Stress Scale-42 uses a 4-point Likert scale ranging from 0 to 3, with higher scores representing a greater amount of time experiencing each statement of negative emotion (eg, 3=applied to me most of the time). Three subscale scores (depression, anxiety, and stress) were computed, and all items were summed to compute a total composite negative emotion state score. The total composite score will be used for analytic purposes, with higher scores representing a greater amount of time associated with overall negative emotions. The tool has excellent reliability and validity, with Cronbach α ranging from .88 to .94 [71], indicating that the items are homogeneous and measure a single construct.

Anxiety and *depression* were measured using the short-version Patient-Reported Outcomes Measurement Information System (PROMIS) instruments PROMIS-Anxiety and PROMIS-Depression, each of which has excellent psychometric properties [72]. The instruments consist of four items, use a 7-day recall period, and use a 5-point Likert scale ranging from 1 to 5, with higher scores representing more of the domain (anxiety or depression). Raw scores are converted to standardized T-scores for analysis following the PROMIS guidelines (mean 50, SD 10). Higher scores indicate greater levels of either anxiety or depression. Cutoff scores that classify scores as normal, mild, moderate, or severe are validated [70,73].

Distress was measured using the National Comprehensive Cancer Network distress thermometer tool. This tool is a single-item, self-report measure of psychological distress and has excellent psychometric properties for caregivers [74]. Participants rated their distress in the past 7 days using an 11-point visual analog scale ranging from 0 (no distress) to 10 (extreme distress), with higher scores indicating higher levels of distress. Scores ≥4 represent clinically elevated levels of distress for caregivers [75,76]. The use of the distress thermometer will allow us to examine its applicability within the caregiver of persons with multiple sclerosis population and compare our caregiver sample and other caregiver groups.

Data Collection

At study enrollment, a web-based survey within REDCap was used to obtain demographic information and baseline outcome measures (negative emotions, anxiety, depression, and distress). The same measures and procedures are used 6 weeks later (the end of the intervention period) and once more 6 weeks later (to assess ongoing effects). Caregivers in both study arms answered the same survey questions. We found that participants completed the measures in approximately 8 to 10 minutes.

For participants receiving coaching sessions, our interventionists tracked the time spent in coaching visits with each caregiver so that we could describe the time required for delivery of that component of the intervention. Website use is tracked via participants' unique password log-ins to describe the frequency of use, commonly used portions of the website, and patterns of

use for participants in both arms of the intervention. The data are presented in the aggregate.

Fidelity of the Intervention

Throughout the study period, we will randomly select 15 participants randomized to receive coaching sessions. All coaching sessions are observed by an independent expert (with permission from the caregiver). The expert evaluates whether the core topics for each session are presented by the interventionists as outlined in the intervention manual using a checklist (Multimedia Appendix 1). Afterward, the project director analyzes the consistency between the expert and interventionists' notes (housed in REDCap) using checklists for each session and following a protocol established in previous work [31]. This procedure ensures the robustness and reproducibility of the intervention. Retraining will occur if the agreement between the interventionist and the independent expert falls below 80% (12/15) of the comparisons—to date, our cumulative agreement rate is 100% (5/5). We have successfully used this approach in other caregiver intervention studies [31,77].

Safety Monitoring and Adverse Events

A data and safety monitoring plan was established for the study. On a quarterly basis during the enrollment and data collection period, our research team will review data regarding recruitment, refusals, attrition, differential (study group) attrition, morbidity, and mortality.

Owing to the potential clinical significance of the anxiety and depression data, we will monitor potential anxiety and depression through an evaluation of participants' T-scores on both the PROMIS-Depression short form 4a and PROMIS-Anxiety short form 4a tools. If a participant has a depression score ≥75.7 (depression) or an anxiety score ≥77.9 (these scores represent the upper 10% in a range of scores), the research assistant will contact the participant via telephone within 48 hours of receiving the score. The research assistant will recommend the participant contact their primary care provider for further evaluation and, in addition, will provide links to the American Psychological Association and State Psychology Associate Therapist databases where they can find names of mental health professionals in their geographic location. This reaction management protocol has been used previously in a large randomized controlled trial that tested this intervention in a cancer caregiver population [31]. All adverse events, concerns, or problems identified by the research team will be reported to the institutional review board and then to the funding agency.

Data Management

All data will be collected via REDCap and downloaded for use with SPSS and SAS statistical packages. Data management and cleaning involve frequencies for range checks for data values for all variables. Missing data will be examined and imputed as outlined in the PROMIS scoring manual for PROMIS measures. The distress thermometer uses a single item; therefore, cases with missing data for this item will not be included in analyses involving distress. Missing data for other tools will be imputed using mean imputation at the tool level.

Statistical Methods

Data will be analyzed using SPSS and SAS, and all investigators, along with the statistician and data manager, will have access to the final data set. Before conducting multivariate analyses to examine group differences, we will use descriptive techniques to examine univariate characteristics and bivariate relationships among variables, covariates, and outcomes. These techniques will be based on proportions, medians, and means. We will also describe (for each variable) frequencies and measures of central tendency for all variables and assess data for violations of assumptions for all planned statistical tests. Data transformations will be used to remedy issues concerning nonlinearity or high skewness.

To address the primary outcome (distress), a linear mixed effects model will be used to test whether there is a significant difference between intervention groups in time on the caregiver outcome of distress. The linear mixed effects model will include the variables of group assignment, time, and the interaction of time by group, along with the participant-specific random intercept and slope. Intention-to-treat and per-protocol analyses will be conducted. The linear mixed effects model should be sufficient in most cases to account for missing data in the intention-to-treat analysis. Participants who provide complete data and attend three or more coaching sessions will be included in the per-protocol analysis. We will also explore the influence of COVID-19 anxiety and website usage as covariates and test for moderation by multiple sclerosis disability, race, ethnicity, rural versus urban location of the caregiver, caregiver COVID-19 positive or negative status, whether the caregiver is local or distant from the person with multiple sclerosis, and socioeconomic status. The analytic approach for the secondary outcomes (anxiety, depression, and negative emotions) will be identical to that used for examining the primary outcome of the study.

The study results will be communicated to the participants via email and publication in patient-focused venues, such as the National Multiple Sclerosis Society's website [78]. In addition, the results will be reported to the sponsor in the final report and via publications and presentations to health care providers in appropriate journals (eg, the *Multiple Sclerosis Journal* and the *Journal of Neurological Sciences*) and conferences.

Results

This study was funded in November 2020 by the PCORI. The research protocol was approved by the institutional review board committees of the Case Western Reserve University (January 21, 2021, protocol 20201484) and Dalhousie University (March 23, 2021, protocol 20215484). The study was registered with ClinicalTrials.gov (NCT04662008). Data collection began on April 1, 2021, and as of May 2021, we enrolled 66 participants.

Discussion

Principal Findings

There are two main areas of innovation related to this study that add to science. First, caregivers of persons with multiple sclerosis have been the sole focus in only four intervention

studies (one was a pilot study), despite the documentation of significant and ongoing needs for strategies to reduce their poor psychological outcomes [5]. This is the first study to examine the effects of a tailored psychoeducational intervention on this vulnerable group of caregivers and will add to the science of caregiving and the evolving science of caregiving of the person with multiple sclerosis.

In addition, this study will test two types of interventions for caregivers of persons with multiple sclerosis. The website-only group intervention represents the delivery of information and support that is self-directed as the person chooses what information is of interest and relevance. However, the website-coaching group enables information and emotional support to be tailored to the caregiver's needs and allows for professional guidance for skill-building, understanding information, and receipt of emotional support. In addition, although our sample size is not large enough to incorporate many covariates, we will be able to examine the impact of a few caregiver variables (eg, gender, race, and hours of caregiving provided) on the efficacy of the two interventions. This information will guide the refinement of interventions for future testing in a larger study of caregivers of persons with multiple sclerosis.

By examining patterns of use of the website, we will also be able to add to the understanding of the issues and concerns that are of most interest to caregivers of persons with multiple sclerosis. Although previous research has provided some descriptive data [6,8,10], these studies have primarily focused on describing poor psychological outcomes [4,5,14,15], coping strategies [7,9,13], or stressors [6,18,20], identified by caregivers of persons with multiple sclerosis. We will be able to identify topics of most interest (eg, self-care activities) and questions of greatest concern (eg, "How is multiple sclerosis treated?") elicited directly from website usage of caregivers of persons with multiple sclerosis. This will provide new information and guide recommendations for refining both interventions in preparation for large-scale testing. Similarly, by evaluating aggregated comments from interventionists' coaching sessions, we will be able to assess issues of greatest concern and topics of greatest interest for caregivers at different points in the trajectory of the illness.

Conclusions

There remains a lack of data regarding strategies to assist caregivers of persons with multiple sclerosis at different points along the course of illness. Results from this pilot study will determine whether either or both of these interventions provide clinically meaningful improvements in caregivers who are providing care at different points along the caregiving trajectory. Data from this study will provide insights regarding issues of concern for this group of caregivers and guide the refinement and large-scale testing of interventions for this group of vulnerable caregivers.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Fidelity checklist example.
[PDF File (Adobe PDF File), 94 KB - resprot_v10i8e30617_app1.pdf]

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Abbreviations

HIPAA: Health Insurance Portability and Accountability Act
PCORI: Patient-Centered Outcomes Research Institute
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture

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Protocol

Implementing Exercise in Standard Cancer Care (Bizi Orain Hybrid Exercise Program): Protocol for a Randomized Controlled Trial

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Abstract

Background: Despite the established benefits of regular exercise for patients with cancer to counteract the deleterious effects of the disease itself and treatment-related adverse effects, most of them do not engage in sufficient levels of physical activity and there is a paucity of data on the integration of efficacious exercise programs that are accessible and generalizable to a large proportion of patients with cancer into routine cancer care.

Objective: We intend to examine the effects attributable to the implementation of a community-based exercise program on cardiorespiratory functional capacity and quality of life for patients with cancer.

Methods: This will be a hybrid study. In the first experimental phase, patients diagnosed with any type of cancer will be randomized into two parallel groups. One group immediately performs Bizi Orain, a 3-month supervised exercise program (3 times a week), in addition to behavioral counseling in a primary health care setting; the other is a reference group that starts the exercise program 3 months later (delayed treatment). In the second observational phase, the entire cohort of participants will be followed-up for 5 years. Any person diagnosed with cancer in the previous 2 years is eligible for the program. The program evaluation involves the uptake, safety, adherence, and effectiveness assessed after completion of the program and with follow-ups at 3, 6, 12, 24, 36, 48, and 60 months. The primary outcomes of the experimental study, to be compared between groups, are improved physical function and quality of life, whereas overall survival is the main objective of the prospective study. To analyze the association between changes in physical activity levels and overall survival, longitudinal mixed-effects models will be used for repeated follow-up measures.

Results: A total of 265 patients have been enrolled into the study since January 2019, with 42 patients from the hematology service and 223 from the oncology service.

Conclusions: Bizi Orain is the first population-based exercise program in Spain that will offer more insight into the implementation of feasible, generalizable, and sustainable supportive care services involving structured exercise to extend survival of patients with cancer, improve their physical function and quality of life, and reverse the adverse effects of their disease and related treatments, thereby reducing the clinical burden.

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KEYWORDS

patients with cancer; physical activity; primary care; behavioral change; randomized controlled trial; overall survival

Introduction

Cancer is one of the diseases that causes major public health problems worldwide. The lifetime probability of developing any type of cancer in Spain is 49.9% in men and 32.2% in women [1]. Currently, increasing incidence rates and decreasing mortality rates due to advances in early detection and treatment have translated to a larger number of people living with cancer. This leads to increased costs of cancer care and a growing burden on health care systems in terms of medical management, cancer surveillance, and supportive care [2].

The disease itself and the treatments used lead to increases in psychosocial distress and depression, impaired cognitive function, increased levels of pain and fatigue, and a significant reduction in cardiorespiratory fitness and strength, as well as muscle (accelerated sarcopenia and cachexia processes) and bone mass losses, alongside increases in body fat. Consequently, patients with cancer have a poor quality of life and a greater risk of developing comorbidities [3].

It has been estimated that 30%-50% of cancer cases are preventable by reducing exposure to modifiable risk factors such as a sedentary lifestyle, poor diet, and excess body fat, and hence, these risk factors have become the target of the global strategy for cancer prevention [4,5]. A growing body of evidence has demonstrated that patients with cancer who achieve the minimum of 150 min·wk^{-1} of moderate or 75 min·wk^{-1} of vigorous physical activity (PA) levels recommended by the American College of Sports Medicine [6] and Australian Association for Exercise and Sport Science [7] experience ~27%-35% lower rates of cancer-related death and recurrence [8]. Current evidence from experimental studies indicates that exercise reduces tumor growth and cancer-specific mortality in a dose-dependent manner [6]. To target tumor intrinsic factors, moderate-to-high intensity endurance exercise is better than light exercise [9]. During exercise, the release of several systemic factors (ie, catecholamines and myokines), sympathetic activation, increased blood flow, shear stress, and increased temperature exert immediate stress on tumor metabolism and homeostasis. Following long-term training, such acute effects lead to reductions in systemic inflammation and oxidative stress, hormone-receptor binding, and adaptations in the modulation of circulating factors (ie, insulin, growth factors, and sex-steroid hormones); they also lead to intratumoral adaptations allowing improved blood perfusion, enhanced immunogenicity, and changes in gene expression and metabolism, which contribute to slower tumor progression and may reduce the ability of cancer cells to form tumors in distant tissues [9,10].

Further, resistance training is particularly important for patients with cancer experiencing loss of muscle mass (ie, sarcopenia or cachexia) during and following treatment [11,12]. This type of training is associated with a 33% lower risk of all-cause death after adjusting for potential confounders, including PA [13].

Despite the established benefits of exercise for patients with cancer and calls to include it as an integral part of cancer treatment, the chances of this information reaching patients are considerably reduced by the self-reported lack of knowledge among oncologists concerning how to properly promote and prescribe exercise [14,15] and paucity of translation strategies for integrating efficacious exercise programs into routine cancer care [16]. Unfortunately, only ~13% of patients with cancer meet international PA guidelines objectively measured with accelerometers [17].

Nonetheless, in recent years, community-based oncological exercise programs have been gaining prominence. LIVESTRONG at the Young Men's Christian Association (YMCA) [18,19] is a community-based exercise program that has shown sustainable benefits in terms of physical function and self-perceived health. Our previous findings from the "Eficancer" study also indicate that exercising thrice a week during a 12-week individually tailored exercise program conducted at local health centers can improve quality of life and physical function, and these improvements are sustained over time [20].

Exercise program accessibility remains a challenge in implementing the international PA guidelines, but this challenge could be mitigated with strategies and pathways that connect patients with exercise-related resources and a well-designed behavioral intervention program to counteract the common barriers to exercise faced by patients with cancer during and after first-line treatments [21]. Further, the long-term effects on the PA levels, physical function, survival, and cost-effectiveness of large-scale community-based programs that are accessible and generalizable to a large proportion of patients with cancer (ie, administered in a standard supportive care setting) are unknown.

The main objectives of this study are as follows:

- to examine the effects attributable to an exercise program on physical function, and quality of life, and adverse effects compared to health habit prescriptions, and to explore whether these effects vary by cancer type, stage and treatments, age, or sex
- to analyze the association between the actual exercise dose (ie, number of sessions and exercise intensity, objectively measured PA level with accelerometers) and measured outcomes
- to assess the cost-effectiveness of the program

Methods

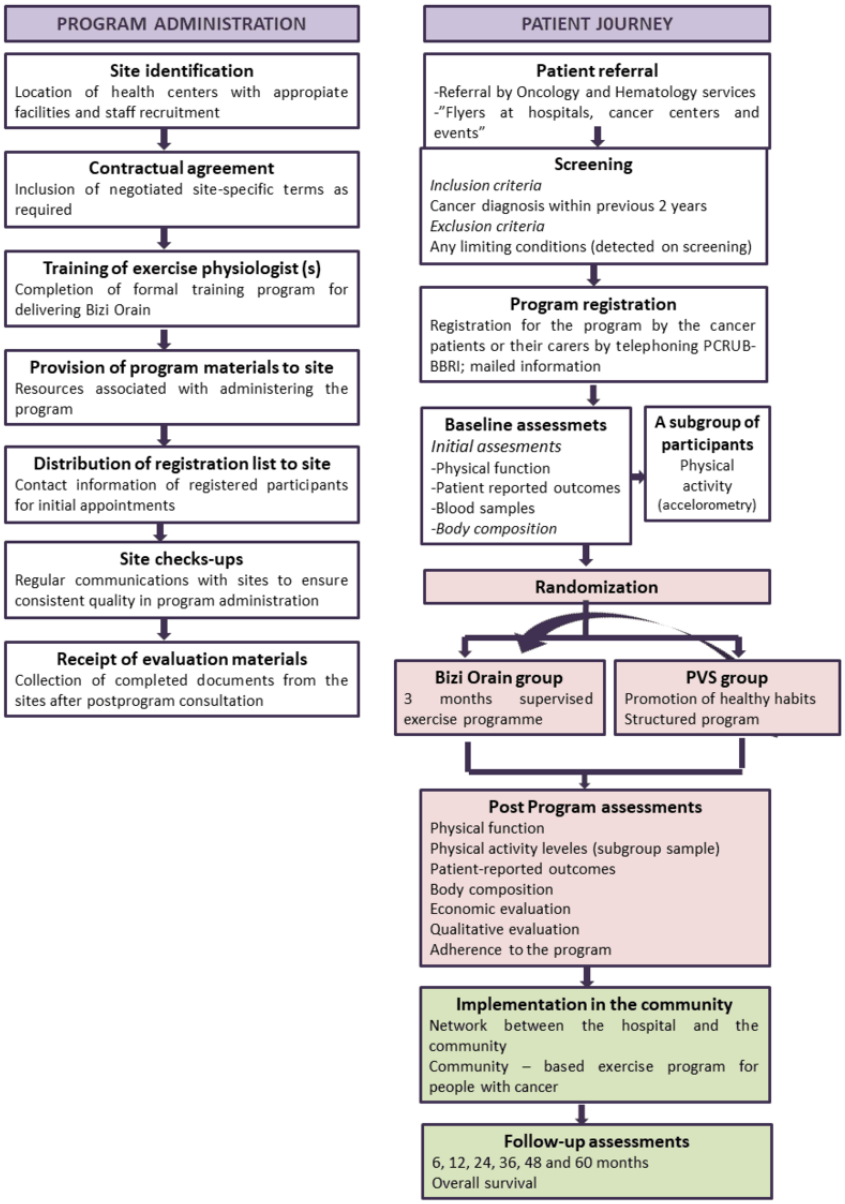
Bizi Orain, which means "live now" in Basque language, is an evidence-based exercise program that adheres to the American College of Sports Medicine guidelines for cancer survivors [6] and is based on the "Life Now" exercise program for people with cancer delivered in Australia [22]. The program is administered by the Primary Care Research Unit of Bizkaia-Biocruces Bizkaia Research Institute (PCRUB-BBRI) and Deusto University and is delivered at a network of health centers equipped with Bizi Orain exercise laboratories integrated into the public health system of the Basque Country (Osakidetza).

Program Design

Bizi Orain is a hybrid two-stage study. During the first 3 months, the study has a parallel-group randomized controlled clinical

trial design, where study participants are randomly allocated (1:1) to either the Bizi Orain exercise program in addition to a previously reported behavioral intervention [23,24] for the promotion of healthy habits, or to the Prescribe Vida Saludable (PVS) group (In Spanish, "Prescribe Vida Saludable" means "prescription of healthy habits") alone. After the postprogram assessments, participants allocated to the PVS group will initiate the Bizi Orain exercise program. Thereafter, a 5-year prospective observational cohort study will be conducted with follow-ups at 3, 6, 12, 24, 36, 48, and 60 months (Figure 1) to (1) examine the long-term clinical effects of PA exposure on overall survival, physical function, and patient-reported outcomes and (2) evaluate the feasibility of Bizi Orain, identifying potential barriers and facilitators for a generalized and sustainable exercise program within standard health care settings. To address this point, a qualitative research study will be conducted involving clinical, research, administrative, and community staff, and patients with cancer.

Figure 1. Schematic overview of the process for program implementation and evaluation.



Participants

Participant recruitment will last for 2 years starting from January 2019. People with any diagnosis of cancer currently receiving treatment or diagnosed less than 2 years earlier are eligible to participate and they are referred by their hospital oncologist, hematologist, or primary care general practitioner. To minimize the risk of hazards associated with program participation, patients will be excluded if they meet any of the following criteria: (1) neutropenia: absolute neutrophil count<500 mm^3; (2) severe anemia: hemoglobin concentration<0.8g/dL; (3) platelet count<50000 µL; or (4) any musculoskeletal, cardiovascular, or neurological disorder that could place the participant at risk of injury or illness resulting from the exercise program (as determined by the patient's clinician).

Numerous approaches are to be adopted to raise awareness about the program including the following: (1) training for oncology clinicians and support staff to facilitate direct referral of patients;

(2) distribution of program flyers at hospitals, cancer centers, and community-based organizations as well as events for health professionals and patients; 3) sending information (by email and post) to people who have contacted the regional cancer association and expressed interest in exercise; 4) advertisements and coverage in local media; and 5) posts on the regional cancer association website and social media accounts. Specifically, the hospital's Department of Oncology has established a system for identifying eligible patients. The oncologists, hematologists, or primary care general practitioners who have identified eligible patients inform them about the study, invite them to participate, and give them a written informed consent form. Once a patient agrees to participate, the clinicians inform the program administrators, and in the case of the hospital specialists, the patient's general practitioner. Potential participants are able to self-enroll in Bizi Orain by telephoning the program administrators and by direct referral from their clinician. Eligible patients who agree to participate are invited to the baseline assessments. Participants are included in the study once they have signed the informed consent form and baseline data have been collected.

Randomization

Patients will be centrally randomized by PCRUB-BBRI in a 1:1 ratio into the two study groups. A researcher who is independent of the organization responsible for managing the study will randomly allocate patients to groups using a computer-based random number generator.

Evaluation

Evaluation of the Bizi Orain exercise program involves measuring the uptake, safety, adherence, and effectiveness of the program. These analyses incorporate elements of the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework [25]. Evaluation of the effectiveness of the program involves comparisons among the preprogram, postprogram, and follow-up assessments. The evaluation will be undertaken yearly from the beginning of the recruitment (2019) and will proceed until the target sample size is achieved.

Uptake

The proportion of people participating in the Bizi Orain exercise program out of all people with cancer in the province of Bizkaia (Basque Country) who are eligible will be reported as the participation rate. People with cancer who register for the program but do not commence their participation will also be reported. The representativeness of the participants will be determined by comparing their demographic and clinical characteristics to those of the people diagnosed with cancer in Bizkaia. Information about cancer diagnoses will be derived from the Basque Health System Registry (Osabide).

Safety

The incidence and severity of any adverse events (ie, falls, muscle strains) that occur during the health center–based sessions will be monitored and reported by the supervising exercise physiologist/nurse using program-specific documentation. Additionally, participants will be asked to self-report the incidence and severity of any adverse events they experience during health center–based sessions or home-based exercise using program-specific documentation.

Adherence

Attendance at health-center–based exercise sessions and the reason for any missed sessions will be tracked throughout the program. Adherence to the recommended amounts of PA for cancer survivors [26] is to be assessed by 7-day accelerometer recordings obtained from a randomly selected subset of the participants. Further, completion of assessments at preprogram and postprogram time points as well as follow-up questionnaires will be reported. Compliance with the Bizi Orain exercise program procedures by exercise physiologists/nurseries at each site will be monitored through evaluation of program documentation (ie, screening, assessment, and exercise prescription documents).

Effectiveness: Primary Study Outcomes

Physical Function (Clinical)

Physical function is assessed by 400-m walk tests in a 20-m corridor, repeated chair stand tests (5 times), and handgrip dynamometry tests [27-29]. Each participant will perform a graded submaximal cardiopulmonary exercise test (CPET) on an electric braking cycle-ergometer (ergoline GmbH, ergoselect 4) in the laboratory of the University of Deusto in a controlled environment (temperature, ±21 ºC; relative humidity, 50%-55%; barometric pressure, ±720 mm Hg). Briefly, the test protocol involves an unloaded 5-min warm-up followed by 1-min stages with 10-W workload increments from an initial workload of 20 W [30]. Participants will be asked to maintain a steady cadence between 60 to 70 rpm. Gas exchange will be recorded breath by breath using a CPET machine (Geratherm Ergostik). The test is performed until confirmation of at least one of the following criteria: (1) The second ventilatory threshold or the so-called "respiratory compensation point" (RCP) is observed from the Wasserman figures (respiratory equivalents, and O_2 and CO_2 partial pressure changes). (2) The respiration exchange ratio (RER)>=1.05 and rating of perceived effort (RPE)>8 on the 0-10–point Borg scale [31]. (3) Participants exhibit volitional exhaustion without meeting the previous criteria.

From a pragmatic viewpoint and owing to the difficulties of performing a CPET in a community-based program setting, the results obtained from the CPET will not be used for individualized prescriptions of exercise intensity during the sessions. However, these results (ventilatory threshold heart rates) will be used to evaluate the actual exercise intensity undertaken by participants when following a standard exercise prescription based on simpler cost-effective methods like RPE and estimated heart rate reserve (HRR).

The maximal strength in the upper and lower body will be measured in terms of the 5-repetition maximum (5RM) (the maximum load that can be lifted five times) in chest and leg press exercises, respectively [32]. These assessments are to be conducted by an independent exercise physiologist not involved with administering the exercise intervention.

Patient-Reported Outcomes (Clinical)

A series of questionnaires with sound psychometric properties are to be used to assess general health and cancer-specific quality of life and cancer-related fatigue. The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is used to assess general health-related quality of life status across physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health domains (higher scores indicating a greater quality of life) [33]. Cancer-specific quality of life is evaluated by the core quality of life (QLQ-C-30) questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) [34]. This questionnaire includes five functional domains (physical, role, cognitive, emotional, and social, with higher scores representing greater function/quality of life) and three symptom scales (fatigue, pain, and nausea, with lower scores indicating greater quality of life/less symptom severity). The General Health Questionnaire (GHQ-12) is administered to assess the psychological morbidity and possible psychiatric disorders [35]. Cancer-related fatigue is assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale [36]. Finally, the Spanish version of the Alcohol Use Disorders Identification Test (AUDIT) is administered to screen for harmful alcohol consumption [37].

Overall Survival (Prospective Observations)

To assess survival, patients will be followed-up for 5 years. Overall survival will be measured from the time of randomization until death. Medical records and death certificates will be reviewed every year to obtain the survival status. The cause of death will be determined by reviewing medical and death records.

Effectiveness: Secondary Study Outcomes

Anthropometry and Body Composition

The height will be measured using a wall stadiometer (Seca) and body composition with a bioimpedance analyzer (Inbody 770, In-Bldg). The participants will be seated in a quiet room for measuring the resting heart rate and blood pressure.

Blood Samples

A derivatives of reactive oxygen metabolites (d-ROMS) test will be performed to assess the levels of oxidative stress in the patients [38].

PA Levels

All patients randomly selected to have their PA assessed will be asked to wear an accelerometer (DynaPort MoveMonitor; McRoberts BV) for a full week. This will be fitted around the waist, with the sensor at the middle of the lower back, and should be worn throughout the waking hours, except during water-related activities (ie, swimming and showering). Further, patients are asked to complete a diary documenting the main PA they perform, how tired they feel, and how many hours they sleep each day. With these data, we will analyze the time spent performing moderate PA, time spent on sedentary activities, number of steps walked, and calories burned per day [39].

Health Economics

An economic evaluation will be performed in parallel with the trial to assess the health benefits, additional costs, and potential savings of including exercise therapy as a standard of care for patients with cancer. This health economics analysis will provide the relative value for money of exercise medicine compared with other health care interventions in this patient population, stratified by age, cancer type, point along the cancer continuum, and stage of the disease. Hospital resource usage and associated costs will also be assessed to compare the costs of secondary health care utilization between the intervention and reference (usual care+PVS) groups. All hospital events, including emergency department attendances and admissions, outpatient visits and procedures, and inpatient admissions for all causes will be explored to quantify and identify potential disease-related events, as well as the total health care resource use for all other purposes inclusive of comorbidities and other chronic diseases. The cost of providing the supervised exercise and PVS interventions will also be quantified. Health benefits will be measured in terms of the quality of life based on the SF-6D utility index derived from the SF-36 and converted to a health utility score to obtain quality-adjusted life years for cost-utility analysis [40].

Adverse Events

An external committee will review and compare all nonserious adverse events, whereas researchers will be obliged to report any serious adverse events to the research unit by email. A coordination committee with access to all the information it needs will undertake preliminary analyses of the data to monitor the safety of the program. This committee will be composed of individuals who are independent of the organization responsible for managing the study and members of the research team including the study coordinator; all are blind to patient allocation. In addition to serving on the committee, the coordinator will telephone the participating health centers daily to check on the progress of the study, report weekly on this progress to the principal investigator of the study, produce a monthly report with the study data, and provide recommendations to the study management team.

The trial was registered on January 18, 2019 (Clinical Trials.gov NCT03819595).The protocol has been approved by the local Clinical Research Ethics Committee (CEIC de Euskadi, PI2019016).

Effectiveness: Additional Measures

Qualitative Evaluation

Knowledge generated by qualitative evaluation is essential for designing a tailored implementation strategy to address organizational and professional barriers that may hinder the adoption of the Bizi Orain program under routine conditions. The qualitative evaluation is designed around the use of focus groups to explore the perceptions of each population involved in the study: clinicians (oncology and hematology services), exercise instructors, community agents (local authorities, managers, and instructors of fitness centers), and patients. Briefly, 14 focus groups with 5-8 members each will be conducted to acquire a global and heterogeneous perspective

of the Bizi Orain program: 1 for clinicians, 1 for exercise instructors, 6 for community agents (1 per exercise laboratory), and 6 for patients (1 per exercise laboratory). The moderation of the discussions is structured based on the Consolidated Framework for Implementation Research (CFIR) [41] and adapted to each population. This theoretical framework is a valuable instrument to detect and analyze barriers and facilitators. This framework differentiates 39 constructs, organized into 5 domains or dimensions, which influence the degree of the real implementation of a program or intervention. Specifically, the 5 domains of the CFIR are the following: "characteristics of the intervention," "external context," "internal context," "characteristics of the individuals involved," and "implementation process." Owing to the need for intervention on contextual factors—a key element in the design of any implementation strategy—and promotion of cooperation between health organizations and the community, the CFIR adapts to the analytical needs of this evaluation. In addition, the research team will adopt an inductive perspective to favor the emergence of concepts and issues not covered by this theoretical framework, which are key to understanding the mechanisms of Bizi Orain. The discourse generated in each group will be audio-recorded and transcribed verbatim. Moreover, the moderator and observer will prepare notes during the fieldwork to complete and triangulate the recorded data.

Qualitative data analysis will be structured into three stages. First, a deductive analysis will be conducted to identify the constructs of the theoretical framework that influence the implementation of the Bizi Orain program. Second, an inductive analysis based on grounded theory [42] will be conducted to identify other emergent categories that have an impact on the program. Finally, a qualitative comparative analysis will be performed to identify the necessary and sufficient variables needed to improve the implementation of the Bizi Orain program in primary care exercise laboratories. Atlas Ti software (version 5.0, ATLAS.ti Scientific Software Development GmbH) will be used to analyze the qualitative data.

Exercise Intervention

The program operates throughout the year and is a free 12-week, small-group (~8 people) exercise program supervised by specially trained instructors. Participants are required to participate in supervised exercise twice a week and to exercise independently a third time, walking in the neighborhood of the health center at a given target exercise intensity. Carers of eligible participants are invited to attend the program with the care recipients.

Individual Consultations

Before commencing the program, each participant receives a one-on-one consultation with an exercise physiologist at Deusto University. This consultation involves screening of the health status and initial assessments to tailor the exercise prescription according to the type of cancer, stage and treatment history, severity of symptoms/adverse effects, comorbidities, PA habits, and personal preferences. Each participant's exercise program is designed to provide optimal stimulus to the cardiorespiratory and neuromuscular systems while maximizing safety, compliance, and retention. Subsequently, patients return for further consultations to undergo assessments and assess their progress since initiating the program, discuss strategies to continue exercising after the program, and develop a plan to maintain long-term positive exercise behavior.

Group Exercise Sessions

Exercise sessions twice a week are conducted in groups of approximately 8 participants under the supervision of an accredited exercise physiologist or a nurse in the Bizi Orain exercise laboratories at the local health centers. The sessions last approximately 1-1¼ h and include a combination of moderate-to-high intensity aerobic and resistance exercises. The aerobic exercise component includes 30-35 min of at least moderate-intensity cardiovascular exercise using cycle ergometers and treadmills. The exercise intensity increases from moderate intensity for 8-min periods alternating with 2-min lower-intensity periods during the first month, moving toward higher-intensity 5-min intervals by the third month (Figure 2).

The exercise intensity zones are tailored to each patient by the estimated maximum heart rate using the equation 206.9 – (0.67 × age) [43] and applying specific intensity boundaries based on the HRR, defined as the difference between the resting heart rate and maximum heart rate. The %HRR has been adopted by the American College of Sports Medicine as the gold standard for indirect assessment of exercise intensity [44]. Every exercise session will be monitored with a heart rate monitor, teaching the patients to self-manage their exercise sessions with respect to the prescribed target intensities. The target intensity is between 40% and 85% of the HRR [44]. The perceived level of effort is recorded using the Borg RPE scale from 0 (rest) to 10 (maximal effort) [45], with the target intensity progressively increasing from 3 to 5-6 points (Table 1).

Figure 2. Bizi Orain exercise program. M1: Low-to-moderate intensity; M2: moderate intensity; M3: intensive moderate intensity; WUp: warm up.

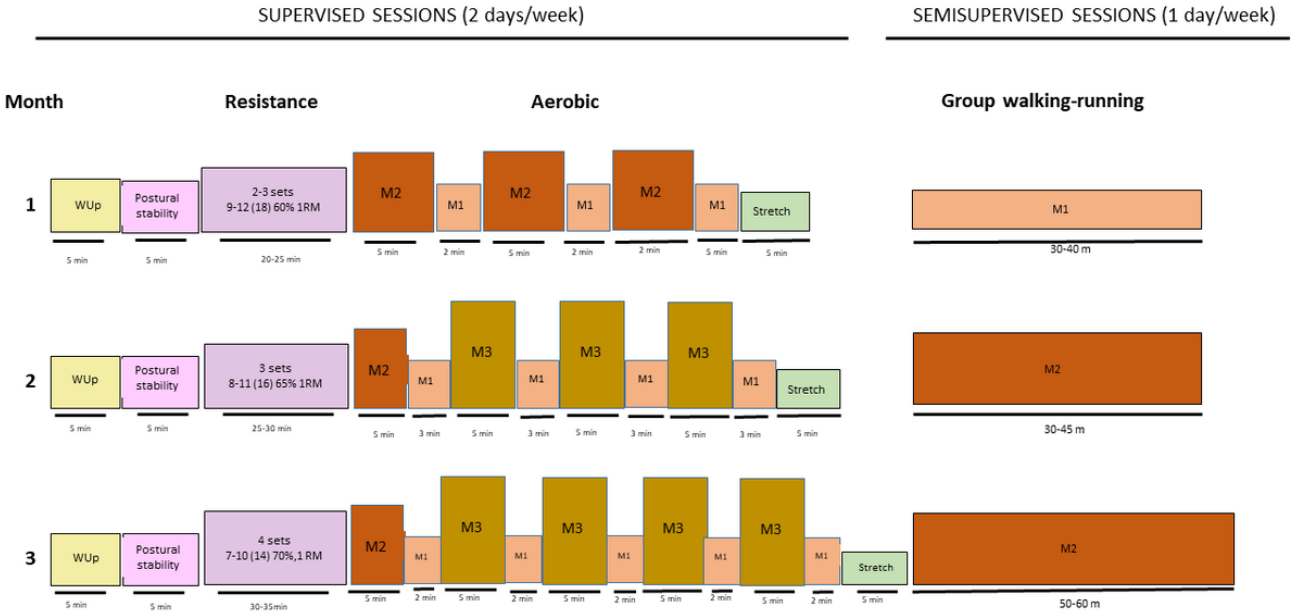


Table 1. Definitions of exercise intensity categories.

Zone[a]	%HRR[b]	RPE[c]	Training type
High-intensity training	>85	>5.5	High-intensity training. The patient nears exhaustion and is no longer in a steady state.
M3	60-84	4.5-5.5	Intensive moderate intensity. The patient has difficulties in talking and sweating increases.
M2	40-59	3-4	Moderate intensity. The patient notices an increased respiratory rate.
M1	20-39	1-2.5	Low-to-moderate intensity. The patient does not notice any increase in the respiratory rate.
Low-intensity training	<20	<1	Low intensity. This involves daily activities requiring low levels of effort.

[a]The intensity zones are based on the estimated maximum heart rate and applying specific intensity boundaries based on HRR [27]. RPE (determined using the Borg scale from 0 to 10) [28].

[b]HRR: heart rate reserve.

[c]RPE: rating of perceived effort.

The resistance component involves exercises that target six of the major upper and lower body muscle groups, as well as core exercises using exercise machines, bars, free weights, dumbbells, ankle weights, elastic bands, material for suspension training, and fitness balls. A progression from static exercises toward more dynamic exercises is encouraged, aiming to activate more muscle mass and thereby increase the cardiovascular demand. Among the main resistance exercise parameters that can be modified, the actual number of repetitions performed in a set, in relation to the maximum number that can be completed (ie, proximity to muscle failure), recently called "level of effort," will be used to individualize the resistance exercise intensity, maximize the suitability of the exercise for each patient, and optimize the induced neuromuscular fatigue [46,47]. The target intensity is adjusted from 9 to 12 repetitions out of the 18 repetitions that could be completed (written as 9-12 (18)), which is equivalent to ~60% of 1 repetition maximum (1RM) using 2-3 sets during the first 4 weeks to 7-10 (14), which is ~70% of 1RM in the last 4 weeks of the program.

Participants undertake additional group-based walking ("park walking") exercises, progressing from 30 min at low-to-moderate intensities to 40 min at moderate intensities. These walking sessions are self-managed by participants based on the perceived effort and heart rate. Patients' carers are invited to attend these sessions. These strategies (ie, leadership, independence, and carer involvement) are based on the theory of planned behavior [48] and are designed to change attitudes toward exercise, increase perceived behavioral control, and influence the subjective norms or the social factors. We believe that if patients find these sessions are enjoyable, the long-term adherence will be higher, and this will have a significant impact on the long-term study outcomes.

Behavioral Intervention (PVS)

PVS is a 5-step structured intervention delivered in routine primary care for the promotion of healthy habits [23,24]. It is based on strategies promoted by the United States National Cancer Institute and the counseling and intervention group of the United States Preventive Services Taskforce for the clinical

management of PA, diet, and alcohol [48]. These strategies are considered the minimum effective health care interventions to produce behavior changes. The participant goes through a process of change structured around the five As (assess, advice, agree, assist, and arrange) construct for clinical counseling: (1) assessment of the participant's PA, diet and smoking habits, beliefs, and attitudes, (2) provision of evidence-based advice and graphical information on the benefits and risks of these habits, as well as exploration of the participant's intention to change these habits, (3) reaching an agreement for an appointment with the clinician to discuss the changes, (4) assistance in the design of an individualized plan that overcomes the barriers reported by the participant, and (5) arrangement for continued follow-up and modification of the plan.

Statistical Analysis

Data will be analyzed on an intention-to-treat basis with the maximum likelihood imputation of missing values, comparing average change scores at 3 months of follow-up (postintervention) among participants randomly assigned to the Bizi Orain or PVS groups. These analyses will include standard descriptive statistics, Student *t* tests, and analysis of covariance models adjusted for baseline values. These models will be extended to include clinically relevant covariates. Subgroup analyses will be conducted by cancer site and treatment status. Investigations into responders and nonresponders will be conducted to explore the heterogeneity of the intervention effect. To analyze the association between changes in the PA over time and outcome variables, longitudinal mixed-effects models will be used for repeated measures throughout the 5 years of follow-ups. Cox proportional hazards models will be used for survival analysis. No imputation method will be used to handle missing data as longitudinal mixed-effect models based on maximum likelihood estimation are more appropriate to handle missing data [49] than common imputation methods such as the last observation carried forward, complete case analysis, or other possible forms of imputation.

Finally, the incremental cost-effectiveness, cost-utility ratios, and confidence intervals will be calculated through bootstrapping and sensitivity analyses. All the analyses will be performed with SAS (version 9.4, SAS Institute) and R (version 3.6, R Core Team) statistical packages.

We have a network of 6 exercise laboratories with a capacity to include at least 1013 patients during the 2 years of recruitment. Assuming a 30% rate of loss (including deaths) throughout the year of follow-up, the study has a power of 80% to detect a difference in functional capacity between comparison groups, of at least 9 s in the 400-m walk test at 3 months as significant (α=.05), assuming a standard deviation of 95 m. Regarding the quality of life, the study has a power of over 90% to detect differences of 5 points between groups as significant (α=.05).

Quality Control

To ensure the quality of the study data, maximize the validity and reliability of the program, and accurate measurement of the variables, we will undertake the following steps:

- Produce documents for the study, including operational manuals for fieldwork and forms for registering measurements and details of the intervention.
- Store all documentation (informed consent forms, documents containing results, etc) in locked cabinets or on a secure server.
- Provide training for those responsible for the standardization of the study process, including specific training for nurses involved in the study, particularly for administration of the quality-of-life questionnaires.
- Hold regular meetings.
- Establish a coordinating committee and a data monitoring committee. As mentioned above, the coordinator contacts the health centers daily, requests information regarding the study progress, and reports to the principal investigator every week.
- Produce monthly progress reports.

Ethical and Legal Aspects

This study protocol complies with the Declaration of Helsinki and its revisions, as well as with good clinical practice. The Ethics Committee of the Basque Country approved the study in the health centers ensuring it would be implemented in compliance with the established regulations. Regarding data confidentiality, only the study researchers have access to the data of individuals who agree to participate in the study, in compliance with the Organic Act 15/1999 of December 2013, on the protection of personal data and its 2011 revision.

Results

A total of 123 patients have been enrolled into the study since January 2019, with 19 patients from the hematology service and 104 from the oncology service.

Discussion

Bizi Orain seeks to substantially contribute to our knowledge concerning the effectiveness of an exercise program that is supervised and tailored for patients with cancer run in primary care centers under conditions of routine clinical practice.

Bizi Orain addresses these points through a multidisciplinary and innovative approach, applying evidence-based strategies [50] from behavioral counseling interventions [24,49,50] in primary care to promote sustained health and behavioral changes among patients and survivors of cancer. Specifically, the coordinating center at PCRUB-BBRI acts as a bridge between hospital-based and other referral pathways, and the health centers delivering the program. Patient recruitment is strengthened by providing training and progress reports for health care providers and other referral systems. The coordinating center has an extensive background in promoting and evaluating behavioral counseling interventions [24], with a multidisciplinary team of physicians, exercise physiologists, and therapists, specialized nurses, doctors in behavioral sciences, and statisticians, which provides a unique setting to assess, advise, assist, and evaluate a tailored exercise program for cancer survivors. In addition, the postprogram qualitative analysis will alert us to common concerns among the patients,

and the main barriers and facilitators for providing effective and sustained exercise programs to cancer survivors.

Despite evidence-based guidelines [6,7] and a plethora of research demonstrating the benefits of exercise for patients and survivors of cancer, most patients do not receive clear instructions to exercise. Interaction with health care practitioners is a "window of opportunity" to increase PA engagement by patients and survivors of cancer; however, the strategy of simply making recommendations for PA seems not to fully capitalize on this opportunity. Although the common barriers to promoting PA among health care providers include lack of exercise-specific expertise and lack of time for exercise-related discussions amidst other clinical activities, health care providers need to be knowledgeable about the benefits of exercise during and after treatment, ensure patient safety by pre-exercise screening, and recommend and refer patients to existing community resources. Thus, the pathway to exercise as an adjuvant cancer therapy requires consideration of the following facilitators and barriers: (1) education for health care providers (about indications, guidelines, referrals, and safety) and integration of a qualified exercise professional into the clinical team, thereby reducing the burden on the health care providers (namely oncologists and oncology nurses), (2) educational handouts for patients about the benefits of exercise during and after treatment, as well as local access to focused programs for cancer exercise rehabilitation, and (3) self-management and behavior change skill development or resources for long-term exercise [51,52].

Although cancer exercise rehabilitation in hospitals is limited by the lack of resources, the lack of awareness about the potential benefits of exercise, and the lack of expertise within oncology units, several community-based programs have been reported and are ongoing [22,53].

Bizi Orain will add to our knowledge in clinical, epidemiological, and implementation fields by administering the program as a "real-world" intervention delivered in a standard supportive care service setting. The randomized controlled trial design of the study during the first 3 months will provide data on the impact of structured exercise on clinical outcomes. The large sample size allows for subgroup analysis, which may provide insight into how people with different cancer types and treatment statuses respond to exercise. Examination of the cost-effectiveness of the program represents a unique addition to the literature and significant advance in current knowledge regarding the potential value of cancer-specific exercise interventions to the health care system. The long follow-up period has the important goal of understanding the dose–response relationship between PA and mortality. Finally, qualitative analysis will help identify and overcome potential barriers toward developing a generalizable and sustainable exercise program as part of standard health care.

The major limitation of this study is possibly the length of the exercise program. It might not be the most appropriate design to evaluate the long-term benefits of regular exercise in terms of objectively measured and patient-reported outcomes and overall survival. On the other hand, Bizi Orain is an initial exercise program delivered in a standard health care setting that addresses patients' needs during treatment or immediately after completion of the primary treatment, requiring greater supervision from qualified professionals owing to the number of adverse effects experienced at these times. Thus, delivering the program in a standard health care setting with qualified exercise physiologists, therapists, and nurses is appropriate. A second, community-based phase needs further investigation, but it could potentially contribute to maintaining higher PA levels, thereby reducing cancer-specific adverse effects and related comorbidities, resulting in a lower burden for health care systems, adding years to the lives of people with cancer, and most importantly adding quality of life to these years.

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Conflicts of Interest

None declared.

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test
CEIC: Clinical Research Ethics Committee
CFIR: Consolidated Framework for Implementation Research
CPET: cardiopulmonary exercise test
d-ROMS: derivatives of reactive oxygen metabolites
EORTC: European Organization for Research and Treatment of Cancer
GHQ-12: General Health Questionnaire
HRR: heart rate reserve
PA: physical activity
PCRUB-BBRI: Primary Care Research Unit of Bizkaia-Biocruces Bizkaia Research Institute
PVS: Prescribe Vida Saludable (It means “prescription if healthy habits” in Spanish.)
RCP: respiratory compensation point
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
RER: respiration exchange ratio
RM: repetition maximum
RPE: rating of perceived effort
SF-36: The Medical Outcomes Study 36-Item Short-Form Health Survey
YMCA: Young Men’s Christian Association

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Protocol

Effect of Community-Based Kangaroo Mother Care Package on Neonatal Mortality Among Preterm and Low Birthweight Infants in Rural Pakistan: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Neonatal mortality due to preterm birth and low birthweight remains a significant challenge in Pakistan. Kangaroo mother care (KMC) is a unique, low-cost intervention proven to reduce neonatal mortality and morbidity and increase exclusive breastfeeding rates. However, KMC has not been attempted in community settings in Pakistan. We aim to implement and evaluate the effectiveness of a community-based KMC package to reduce neonatal morbidity and mortality among preterm and low birthweight (LBW) infants, which will provide evidence for policy development and the large-scale implementation of KMC across the country.

Objective: The primary objective of this trial is to reduce neonatal mortality among preterm and LBW infants. The secondary objectives are growth (measured as weight gain), reduced incidence of possible serious bacterial infection, and increased exclusive breastfeeding and continued breastfeeding practices.

Methods: We designed a community-based cluster randomized controlled trial in one rural district of Pakistan. Stable, LBW babies (weighing 1200 grams to 2500 grams) are included in the study. The community KMC package, consisting of the KMC kit, information and counseling material, and community mobilization through KMC champions (village volunteers), was designed after preliminary research in the same geographical location and implemented in intervention clusters. The standard essential newborn care is offered in the control clusters. Infants are recruited and followed up by independent teams of data collectors. Data are collected on the duration of skin-to-skin contact, growth, breastfeeding practices, morbidities, neonatal mortality, and neurodevelopment status. Data analysis will be conducted based on the intention to treat principle. The Cox regression model will be used to assess the primary outcome of neonatal mortality. The secondary outcomes will be evaluated using linear or logistic regression.

Results: The Ethics Review Committee of Aga Khan University, Pakistan, approved the study protocol in February 2017. Data collection began in August 2019 and will be completed in December 2021. Data analyses are yet to be completed.

Conclusions: This intervention may be effective in preventing sepsis and subsequently improve survival in LBW newborns in Pakistan and other low-income and middle-income countries worldwide.

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KEYWORDS

community kangaroo mother care; low birth weight; KMC champions; neonatal mortality; RCT protocol; Pakistan

Introduction

Neonatal mortality has emerged as a unique challenge for Pakistan. Although Pakistan has made progress in reducing infant and below 5 years mortality, little progress has been made to improve neonatal mortality in the last 3 decades [1-3]. The primary causes of neonatal mortality in Pakistan are birth asphyxia, sepsis, and preterm births [1,2]. Most neonatal deaths, especially those attributed to preterm births and low birthweight (LBW), can be averted by better coverage and low-cost, evidence-based interventions [4-7]. However, despite these interventions' availability and proven effectiveness, they have not been implemented on a large scale in Pakistan [8,9].

Kangaroo mother care (KMC) is a unique and low-cost intervention that significantly impacts preterm or LBW neonatal outcomes [10]. KMC was first initiated in 1978 by Dr. Edgar Rey in Bogotá, Colombia, who developed a technologically simple method defined as “early, continuous, and prolonged mother-infant skin-to-skin contact, with (ideally) exclusive breastfeeding.” UNICEF (The United Nations International Children’s Emergency Fund) reported this practice worldwide in 1983, and it was the first time the term “kangaroo’” was used to describe this practice [11]. In 2003, the WHO (World Health Organization) developed the first guidelines on the key aspects of KMC (kangaroo position, kangaroo feeding and nutrition strategy, and early discharge and strict ambulatory follow-up of KMC) [10].

Several studies have demonstrated the benefits of KMC in reducing neonatal morbidity and mortality and improving weight gain and exclusive breastfeeding rates [12-21]. Similarly, Lassi et al. [22] documented early initiation of breastfeeding, hygienic cord care, and KMC as effective neonatal infant and child mortality reduction interventions.

Despite high rates of home births in rural areas [23,24], KMC has never been tried in Pakistan’s community settings. The noncompliance to KMC practices can be best explained by various cultural factors inherent to religious and indigenous practices [25] in the community, including but are not limited to the covering of the body for modesty [23,26]. In addition, a low facility birth rate and a short post-delivery stay among rural communities are significant obstacles to initiating and sustaining KMC in the health facilities [27-29].

Given the high burden of neonatal deaths and the paucity of evidence on locally acceptable KMC, it must be tested in the community setting to generate the evidence to scale up its implementation across the country further. We propose to test the effectiveness of community KMC (cKMC) in our sociocultural context. A preliminary study was conducted to inform the design of the cKMC package and its implementation strategies. The strategies include delivering the KMC kit to mothers; garnering support for KMC; developing a buddy system to support mothers; establishing KMC champions (volunteers) within the communities; mobilizing communities using information, education, and communication (IEC) tools, including video messages and docudramas; and training community health workers on KMC and essential newborn care.

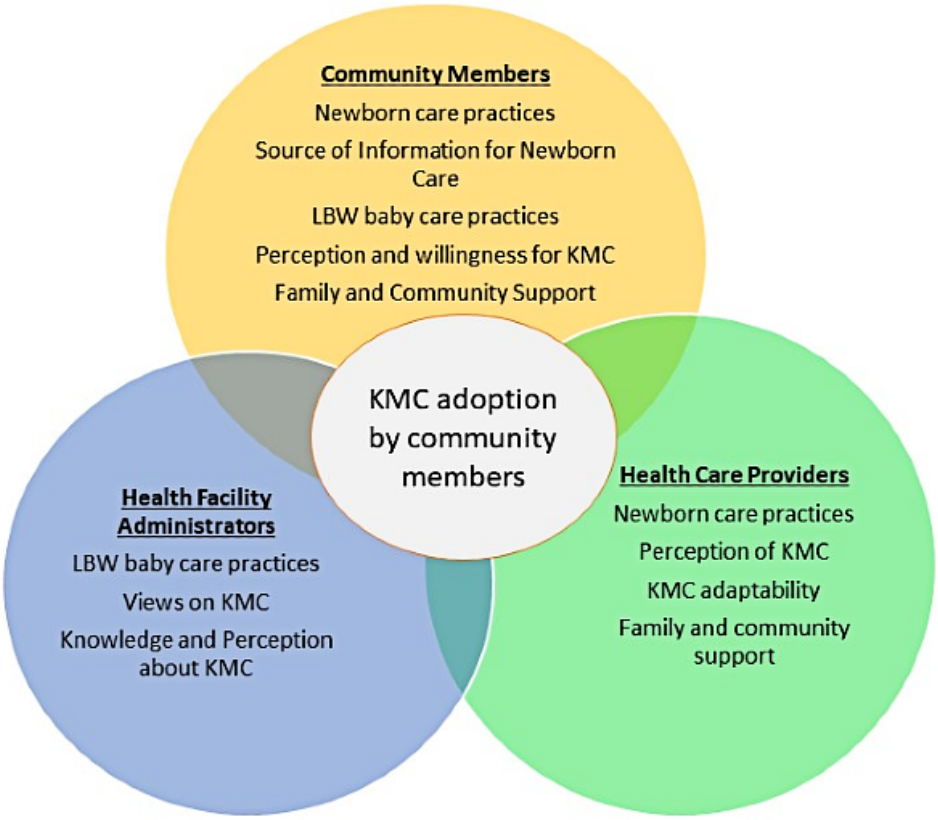
Based on these interventions, we aim to implement a cKMC package to reduce neonatal morbidity and mortality among premature and LBW infants. The primary objective of this trial study is to evaluate the effectiveness of cKMC in lowering neonatal mortality among premature and LBW infants. The secondary objectives include assessing the impact of cKMC on growth (measured as weight gain), the incidence of possible serious bacterial infection (PSBI) and referrals to the hospital, exclusive breastfeeding and continued breastfeeding practices, and neurodevelopmental assessments in a subset of recruited LBW babies at 6 and 12 months of age.

Methods

Study Design

We are conducting a cluster randomized controlled trial in one of the rural districts of Pakistan. The cKMC package has been developed based on preliminary research, involving in-depth interviews and focused group discussions with major stakeholders. A conceptual framework was developed based on the existing data to guide research themes (Figure 1).

Figure 1. Conceptual framework and major themes from formative preliminary research. KMC- kangaroo mother care; LBW- low birth weight newborn.



Study Site

The study is being conducted in 2 subdistricts (Taluka-Johi and Taluka-Khairpur Nathan Shah) of the district Dadu, which is a rural agrarian district in Sindh province of Pakistan. The overall population of the 2 talukas is about 2 million people residing in 54 union councils. The union council is the smallest administrative unit in Pakistan, with 15,000 to 25,000 people. The study area's population is largely poor, with 68% of households belonging to the lowest wealth quintiles. The study area also has an LBW prevalence of 27.7%, with an exclusive breastfeeding rate of 17.3%. Half of the women still deliver at home, and the proportion of facility births is 48.8% [30].

The public sector primarily provides the health care in the target area. There are 2 secondary care hospitals in the study area. There is a basic health unit (BHU) in each union council, and 15 to 20 lady health workers (LHW) are affiliated with each BHU, serving as frontline health care providers for a population of 1000 people in their respective areas.

Study Population

Inclusion and Exclusion Criteria

All stable LBW newborns weighing 1200 grams to 2500 grams are screened within a 72-hour window, followed by enrollment after informed consent to participate in the trial is obtained. Newborns tolerating oral feeding with no respiratory distress, the absence of any symptoms of disease, and the absence of congenital anomalies are included in the study.

Whereas newborns weighing less than 1200 grams and with symptoms of disease according to predefined criteria (ie, unable to tolerate oral feeding; severe respiratory distress, including respiratory rates of less than 20 breaths per minute or more than 60 breaths per minute; grunting–central cyanosis; severe chest in-drawing; convulsions; unconsciousness; severe hypothermia of less than 32°C; apnea; and congenital malformation) are excluded and referred to the nearest health facility for management.

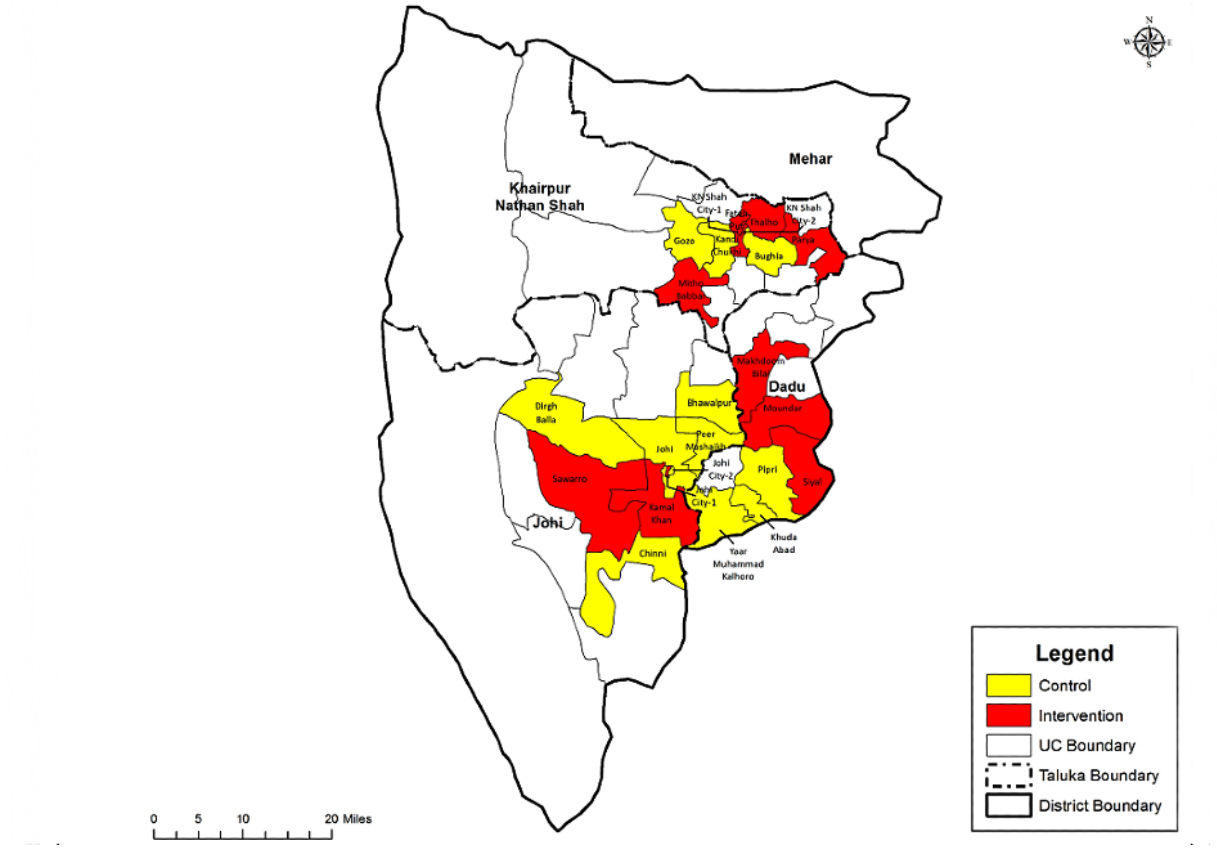
Sample Size

We considered union councils in the talukas as the clusters for our trial. The union council comprised a population of 25,000, with expected 29 births per 1000 people. We anticipated 200 LBW births per cluster, given the 27.7% prevalence of LBW in the study area [30]. Literature suggests 13.3% of the LBW infants die in the neonatal stage [31]. With an expected 30% reduction in mortality, 12 clusters (union councils) were needed per arm (a total of 24 clusters for the trial) to achieve 90% power and a 5% significance level. We estimated 200 births with a birth weight of less than 2.5 kg per cluster. A total of 4800 participants in the intervention and control groups are required to complete the study.

Randomization

The 2 targeted talukas have a total of 54 union councils. Out of these, 24 were randomly selected by an independent researcher using a computer-generated program (Figure 2).

Figure 2. Study site and selected clusters. UC: union councils.



The clusters (union councils) were randomized using a restricted randomization scheme using the following indicators: population, live birth, the prevalence of LBW, neonatal mortality, skin-to-skin contact, breastfeeding practices, and distance from the taluka hospital. We conducted a baseline survey of the study area to collect data on these indicators. Blinding is not possible because of the nature of the intervention; however, to minimize measurement bias on the effect of the intervention, the data collection team is independent of the implementation team.

Procedures

Pregnancy Surveillance and Birth Notification

Pregnancy surveillance was instituted as a continuous activity in the trial to identify and track new and existing pregnancies. A team comprising of 2 female community health workers per union councils is responsible for surveillance and birth notifications. Identified pregnancies in the intervention clusters are counseled on the KMC intervention and its benefits to mother and baby. At the same time, counseling on essential newborn care is given in the control areas.

The team also records pregnancy outcomes (ie, miscarriage, stillbirths, and live births), and all registered live births are followed up for mortality outcomes at 28 days of life. Other additional sources for birth notifications are the female health workers, village elders, and traditional birth attendants, who support the study teams and provide regular reports on births in their respective areas.

Screening, Recruitment, and Intervention Delivery

When a birth is reported, the recruitment and intervention teams will visit the household within 72 hours of the delivery. The screening and recruitment are carried out by a separate team, comprising of a male team leader and 2 community health workers. Once the eligibility criteria are fulfilled and consent from the mother or caregiver is recorded, the mother-baby dyad is recruited in the study. After recruitment, the team visits the household on days 5, 7, 10, 14, 21, and 28 in the intervention clusters to support KMC practice. They will demonstrate the steps of KMC, including KMC positioning with the support of a “chaddar” (a cloth that females use to cover their heads and body for modesty) and IEC material. The LBW babies in the control clusters will receive standard essential neonatal care as per the national guidelines. The intervention team also conducts 1-on-1 and community-based mobilization for KMC advocacy.

Data Collection

Independent data collection teams comprising of 2 community health workers in each cluster will be deployed in both intervention and control clusters. The teams collect data on KMC compliance, anthropometry (weight and length), signs of PBSI, breastfeeding practices, and mortality on scheduled follow-ups at days 7, 28, and 59. On days 120 and 365, information on mortality, breastfeeding practices, infant and young child feeding practices, and nutrition status (weight and length) will be captured. In addition, a neurodevelopmental assessment will be performed on a subset of children using the Bayley’s scale at 12 months [32].

The data collection teams examine the baby for any symptoms of disease during each household visit. If symptoms of disease are observed, a prompt referral will be made to the nearest health facility. Participant mothers willing to comply but unable to perform KMC for 1 week or more due to illness or other reasons are excluded from the study. Loss to follow-up is defined as the unavailability of a mother-baby dyad for 3 consecutive follow-ups after recruitment.

KMC Intervention Package

A cKMC package is developed to support mothers and overcome sociocultural barriers to practicing KMC. The package includes the following:

KMC Kit

The kit contains 20 diapers for the child, 10 napkins for the mother, 1 towel, a pair of socks and cap for the infant, 1 bar of soap, and an educational brochure in the local language. These items are packaged in a ziplock plastic bag. The recruitment team is responsible for providing the kit to enrolled mothers.

Education Package

We have developed a contextual IEC package for parents and families to create awareness and describe the benefits of KMC for the survival and well-being of LBW newborns. The material comprises flip charts, wall mounts, and a self-explanatory video on the steps of KMC, its benefits, and the potential implementation of a buddy system (ie, skin-to-skin contact provided by other family members).

Community Mobilization (KMC Champions)

A community mobilization team (1 male and 1 female) conducts one-on-one and group sessions concerning essential newborn care and KMC practices with newly pregnant women, mothers, and mothers-in-law. The sessions are conducted at regular intervals. The male mobilizer is responsible for the one-on-one and group sessions advocating KMC with fathers and other male members of the community.

The community mobilization team also encourages the recruitment of volunteers to function as KMC champions. The local community members serving as KMC champions serve as catalysts for mobilization. The mobilization staff also identifies and recruits cochampions (other community volunteers) to be mentored by KMC champions. This group of local community members serve to disseminate KMC practices and facilitate uptake in the community.

A simple color-coded KMC calendar depicting 24 hours was designed in the local language for families of enrolled newborns to record the number of hours that the mother or buddy practices KMC. The mother and family members are instructed on how to use the calendar and asked to mark the number of hours KMC is practiced each day on the calendar. These data are collected at the end of each week.

Outcome Ascertainment

The data are collected in a structured electronic format to ascertain outcomes. The anthropometric measurements are done per standard anthropometry guidelines [33] by the pair of measurers (weight and length). Infant weight is measured on pan scales (model 354; Seca) and length is measured by the infantometer (model 417; Seca). The details of the outcome measures are described in Textbox 1.

Textbox 1. Outcome measures and definitions. LBW: low birthweight; PSBI: possible serious bacterial infection; EBF: exclusive breastfeeding defined as the percentage of infants aged 0 to 6 months who are exclusively breastfed; KMC: kangaroo mother care.

- **Reduction in neonatal mortality:** the reduction of mortality in LBW newborns during the first 28 days of life.
- **Improvement in growth (nutrition status):** the increase in newborn weight gain from birth and at days 14, 28, 59, 120, 180, and 365; and the increase in the length of the newborn from birth and at days 180 and 365.
- **Reduction in PSBI incidence:** the reduction in PSBI incidence during the neonatal period (days 14 and 28) and 59 days of life.
- **Improved EBF:** increase in the EBF rate up to 50% at 6 months of age.
- **Improved neurodevelopment:** KMC improves neurodevelopment outcomes while impairments in physical growth and brain and central nervous system development can result in cognitive, language, motor, neurosensory impairments, and behavioral disorders. Hence assessment will be done at 12 months of age.

Training of Study Teams

The study investigators provided extensive training to the field teams regarding their assigned tasks. All staff received training on good clinical practice, and the pregnancy surveillance and birth notification teams received training on survey procedures and appropriate documentation. The implementation team received comprehensive training on the KMC package, implementation, and counseling; they were also trained on screening and recruitment procedures and referral protocols.

The data collection team was trained on interviewing techniques and data documentation using a handheld device. The training also included newborn examinations, recognizing symptoms of disease, prompt referrals, ascertaining KMC compliance, breastfeeding practices, and anthropometric measurements using the standard methodology and standardization processes [33]. The team was also trained to calibrate anthropometric instruments regularly using the standard measurement rods and weights.

The LHWs are the frontline health workers in the public sector employed by the Ministry of Health. The LHWs in the intervention clusters received orientation on the KMC intervention and standard essential newborn care. In contrast, LHWs in the control clusters were trained on standard essential newborn care only.

Data Management

A data collection application was developed to collect the data on recruitment and outcome measures during follow-ups. These applications have a built-in range and consistency checks. If there are specific queries, the data is returned to the respective teams, and the query is resolved within 48 hours of data collection. The data are transferred to the Aga Khan University (AKU) secure data servers at the data management unit daily. A trial flow was developed, detailing the number of participants through assessments of eligibility, randomization, follow-up, and analysis. Reasons for exclusions and withdrawals are appropriately explained and documented.

Data Analysis

For data analysis, we will use the intention to treat approach using STATA software (version 17; StataCorp). Data will first be analyzed using person-time as the denominator for the primary outcome (neonatal mortality between enrollment and 28 days of age). Hazard ratios and 95% CIs will then be calculated using a Cox regression model to evaluate the effect of the intervention (cKMC) on infant deaths. We will also estimate the impact of cKMC using the number of enrolled infants as the denominator to deduce risk ratios using generalized linear models of the binomial family with a log link function. The summary data for background characteristics in the intervention and control groups will be presented as means and proportions.

The effect of KMC on secondary outcomes (ie, exclusive breastfeeding, weight and length gain, the incidence of illnesses and hospitalizations, and care-seeking behavior) will be assessed using linear or logistic regression after adjusting for clustering in the case of twins or another enrolled baby subsequently born to the same mother, as well as other potential confounders.

Monitoring and Evaluation

The study investigators and technical staff from the AKU will interact with the study team through regular field site visits to review the study process and progress. The study managers will share weekly reports. All key areas will be monitored, including the enrollment rate, timing of the intervention delivery initiation, consent procedures, referrals and follow-up visits, and timely transmission of data to AKU.

Results

The Ethics Review Committee of Aga Khan University, Pakistan, approved the study protocol on February 15, 2017 (ID. 4467-Ped-ERC-16). In addition, ethical clearance was sought from the National Bioethics Committee, Pakistan. The trial is registered with clinicaltrials.gov: NCT03545204. Data collection began in August 2019 and will be completed in December 2021. Data analyses are yet to be completed. The datasets used for the article and the study is available from the corresponding author on request.

Discussion

Despite the robust evidence supporting the use of KMC for preterm and LBW survival, scaling-up of KMC has proven an elusive goal for Pakistan and other low-income and middle-income countries for the last 40 years [34]. However, with increased awareness concerning the magnitude of newborn mortality among preterm and LBW infants, our trial anticipates providing evidence on the impact of initiating cKMC in the remote areas of Pakistan, where incubator care is inaccessible. Moreover, the benefits of performing KMC in the community setting will also be emphasized, facilitating the much-needed uptake of this intervention within rural communities.

Most of the evidence that favors KMC is derived from hospital-based settings; however, a recent study concluded that cKMC substantially improves neonatal and infant survival in low-income countries. KMC in community settings for infants with LBW could substantially reduce neonatal and infant mortality [18]. Furthermore, research carried out in Haryana, India, proposed cKMC was feasible and acceptable, with high adoption rates observed in mothers of LBW babies [35]. Similarly, a study conducted in Pakistan demonstrated that a package of interventions that included essential newborn care, chlorhexidine, and KMC reduced the risk of neonatal infection and omphalitis and positively impacted weight gain [19]. Although there is some evidence in favor of cKMC in low-income countries, it is imperative to conduct robust research on the impact of cKMC in Pakistan for its large-scale implementation.

There is a need to adopt community-based KMC in Pakistan's rural areas, where most deliveries occur at home [3]. Our preliminary research showed a high acceptance rate of KMC in a community setting, with a willingness to perform KMC for at least 8 hours at home with family support. However, community mobilization was critical to resolve barriers and to achieve acceptance rates within the community. We are also focusing on pregnancy surveillance through which pregnant women are identified via door-to-door surveillance, and newborns are identified by an early birth notification system and follow-up at home. In addition, well-trained community health workers such as KMC champions carry out regular sessions in the community to develop mother and father champions and sensitize the community. Besides KMC champions, we intend to see the effectiveness of community KMC on neonatal mortality in LBW babies by engaging the LHW program through this study. The LHW program in rural Pakistan is the backbone of primary health care, including maternal and child health, and covers approximately 60% of the rural population [36].

Although there is considerable evidence on the effectiveness of KMC, previous trials were conducted in a controlled environment, where the results cannot be generalized to programs operating under field conditions. The objective of our trial is to scale up KMC practice in the remote areas of Pakistan and test this model, which can then be delivered by the health care providers employed in the public sector such as LHWs, lady health supervisors, community midwives, and lady health visitors. The findings of this study will provide enough evidence to develop policies and programs aimed at preventing neonatal mortality and improving maternal and child health and growth outcomes in poor resource settings.

cKMC intervention may be effective in preventing sepsis and subsequently improve survival in LBW newborns in Pakistan and other low-income and middle-income countries worldwide.

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Authors' Contributions

SA, AH, SS, and ZAB conceptualized the study. TA, TS, and IM developed the field instruments and data collection process. SA and AH jointly drafted the first version of the manuscript. AH, AR, MU, IA, ZM, SS, and ZAB reviewed and edited subsequent manuscript drafts. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AKU: Aga Khan University
BHU: basic health unit
cKMC: community kangaroo mother care
IEC: information, education, and communication
KMC: kangaroo mother care
LBW: low birthweight
PSBI: possible serious bacterial infection
LHW: lady health worker

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Protocol

Smartphone Delivery of Cognitive Behavioral Therapy for Postintensive Care Syndrome-Family: Protocol for a Pilot Study

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Abstract

Background: Family members of critically ill patients experience symptoms of postintensive care syndrome-family (PICS-F), including anxiety, depression, and posttraumatic stress disorder. Postintensive care syndrome-family reduces the quality of life of the families of critically ill patients and may impede the recovery of such patients. Cognitive behavioral therapy has become a first-line nonpharmacological treatment of many psychological symptoms and disorders, including anxiety, depression, and posttraumatic stress. With regard to managing mild-to-moderate symptoms, the delivery of cognitive behavioral therapy via mobile technology without input from a clinician has been found to be feasible and well accepted, and its efficacy rivals that of face-to-face therapy.

Objective: The purpose of our pilot study is to examine the efficacy of using a smartphone mobile health (mHealth) app to deliver cognitive behavioral therapy and diminish the severity and prevalence of PICS-F symptoms in family members of critically ill patients.

Methods: For our pilot study, 60 family members of critically ill patients will be recruited. A repeated-measures longitudinal study design that involves the randomization of participants to 2 groups (the control and intervention groups) will be used. The intervention group will receive cognitive behavioral therapy, which will be delivered via a smartphone mHealth app. Bandura's social cognitive theory and an emphasis on mental health self-efficacy form the theoretical framework of the study.

Results: Recruitment for the study began in August 2020. Data collection and analysis are expected to be completed by March 2022.

Conclusions: The proposed study represents a novel approach to the treatment of PICS-F symptoms and is an extension of previous work conducted by the research team. The study will be used to plan a fully powered randomized controlled trial.

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KEYWORDS

postintensive care syndrome-family; mobile health app; cognitive behavioral therapy; mobile phone

Introduction

Background

Nearly 6 million patients are admitted to the intensive care unit (ICU) each year in the United States [1]. Although the majority of patients leave the ICU after a brief stay, 20% to 39% of these patients require mechanical ventilation and a potentially prolonged stay [2]. Family members of these critically ill adult patients are at risk for developing clinically significant psychological distress. Such distress is called postintensive care syndrome-family (PICS-F), and it includes symptoms of anxiety, depression, posttraumatic stress, complicated grief, and a diminished quality of life [3-10]. The prevalence of PICS-F symptoms can be as high as 69% within the first 6 months of ICU hospitalization and has been documented up to 4 years after the development of ICU illness across transitions of care to other facilities [4-6,9,11-17]. The identification and treatment of PICS-F symptoms across the continuum of recovery has been recognized and promoted by the Society of Critical Care Medicine—the leading critical care organization in the United States. Further, many experts have emphasized the need to address the gaps between transitions of care [8,18,19]. PICS-F reduces the quality of life of critically ill patients' families and may impede the recovery of such patients [9,11,20]. Many family members of critically ill patients are called upon to provide informal caregiving during the prolonged recovery phase, which is associated with significant physical and emotional burdens [21-23]. The overall costs to society of anxiety, depression, and posttraumatic stress symptoms associated with PICS-F have not been calculated but are likely to be considerable, given the billions of dollars associated with managing the symptoms of these disorders [24-26].

A variety of strategies and interventions have been proposed to support family members during and after critical illness development, including post-ICU clinics, improved communication strategies, ICU diaries, family ICU navigators, and proactive palliative care and ethics consultation, but they have had mixed results [16,17,27,28]. A randomized controlled study of a clinician-led telephone- and web-based coping skills training program showed no improvement in psychological distress symptoms among patients and family members compared with an education program [29]. The intervention was implemented after the ICU patient and family member dyads were discharged to home, which often occurred well after the development of acute critical illness. The implementation of these clinician-led interventions requires at least moderate logistical, personnel, and financial resources and may be limited across interinstitutional transitions of care. Furthermore, family members of ICU patients are not patients themselves, and the medical services rendered to them are not currently billable. This has resulted in an inadequate medical system infrastructure for the assessment and treatment of PICS-F [10]. Therefore, effective interventions for PICS-F symptoms need to directly address the symptoms experienced by family members, be portable and longitudinal in terms of their scope for family members across transitions of care, and be made available on demand for family members while limiting the hospital resources required to implement and sustain the intervention. Strong empirical support for sustainable interventions that aim to prevent or diminish PICS-F symptoms is currently lacking.

Cognitive behavioral therapy (CBT) is a form of therapy that emphasizes cognitive and behavioral strategies for correcting unhelpful appraisals of stressful events and mitigating their influence on feelings and active coping behaviors for responding to distress [30]. CBT has become the first-line nonpharmacological treatment for the symptoms of a growing list of mental health problems, including depression, anxiety, posttraumatic stress, substance abuse, and eating disorders [31]. CBT programs delivered via mobile health (mHealth) solutions have been shown to be efficacious, cost-effective, and well accepted by individuals with mild-to-moderate symptoms of depression, anxiety, and posttraumatic stress [32-35]. Due to the development and rapid market growth of smartphone technology, mHealth apps that deliver CBT have also demonstrated significant efficacy in treating a variety of symptoms, including anxiety, depression, and posttraumatic stress [36-41]. Self-efficacy appears to be an important concept for understanding treatment gains in CBT therapy and chronic disease self-management [42-48]. Investigators have reported that the concept of self-efficacy mediates the effect between web-based and mobile CBT interventions and improvements in symptoms of stress, anxiety, and depression [49,50]. However, despite the empirical support for its effectiveness in other populations, the efficacy of delivering CBT to family members with PICS-F symptoms via mHealth technology has not been examined.

Theoretical Framework

The theoretical basis for the proposed study is Bandura's social cognitive theory, which describes human functioning as a reciprocal interplay among personal, behavioral, and environmental factors [51]. Perceived self-efficacy—an individual's belief that they can perform a behavior—is a central cognitive tenet of the theory and has been identified as an important factor for explaining treatment success in CBT, the self-management of chronic conditions, and improved psychological functioning [42-48,52]. Mental health self-efficacy (MHSE)—a person's confidence in managing his or her mental health symptoms—is a self-efficacy construct that was developed based on Bandura's guidelines for constructing self-efficacy questionnaires and was found to be a significant mediator for the beneficial treatment outcomes of a mobile phone CBT intervention for mild-to-moderate depression, anxiety, and stress [49]. Furthermore, self-efficacy is likely to be an important factor in mobile CBT interventions with minimal therapist input, given the central role of individuals in self-monitoring and problem solving.

Study Aims

The findings from our pilot study will allow for the collection of preliminary data that are needed for planning a fully powered randomized controlled study. The specific study aims are as follows: (1) determine the prevalence and severity of PICS-F symptoms (anxiety, depression, and posttraumatic stress), health-related quality of life (HRQOL), and MHSE in family decision makers of critically ill patients and their changes over time (at enrollment, 30 days after enrollment, and 60 days after

enrollment); (2) determine differences in PICS-F symptom severity, HRQOL, and MHSE between family decision makers (ie, those of critically ill patients) receiving an mHealth app intervention and family members receiving standard care and support; and (3) determine the relationship between the dose of the mHealth app (total time spent with the app and the total number of log-ins) over the course of the study (60 days) and changes in PICS-F symptom severity (anxiety, depression, and posttraumatic stress), HRQOL, and MHSE.

Methods

Design

A repeated-measures longitudinal study design that involves the randomization of participants to 2 groups (the control and intervention groups) will be used. A research assistant will randomize study participants by using computer-generated random numbers after study enrollment is completed and baseline measurements are obtained.

Previous work conducted by Petrinec and colleagues [6,7,9,11] has laid the descriptive groundwork for the proposed study. The research team has recently completed a longitudinal feasibility study at Summa Health in which they examined the implementation of the mHealth app delivery of CBT to family decision makers of critically ill patients. The data from the feasibility study was used to directly inform the methodology of the proposed pilot study. The usage of the app was encouraging, and the findings of the feasibility study have been accepted for publication [53].

Sample and Setting

The study will include family members of critically ill patients who are admitted to 1 of 2 26-bed ICUs at the Akron campus of Summa Health. A family member will be defined as a person who would be the most involved in a patient's treatment and care decisions; the person does not need to be a blood relative. A sample size of 60 family members is planned for our pilot study (intervention group: n=30; control group: n=30). The sample size was determined according to the recommendations of Whitehead et al [54] for estimating an a priori small effect size, and an attrition rate of 30% was derived from previous studies [6,9].

Inclusion Criteria

The inclusion criteria are as follows: (1) individuals aged 18 years or older; (2) individuals who self-identify as the family decision maker of the critically ill patient; (3) individuals who can read and speak English; (4) individuals who own a smartphone with an iOS or Android operating system; (5) family members of critically ill patients who have been in the ICU for more than 3 days; (6) family members of critically ill patients who are being mechanically ventilated and lack cognitive capacity; (7) family members of critically ill patients who are not expected to be transferred out of the ICU within 48 hours after the identification of their inclusion in the study; and (8) family members of critically ill patients aged 18 years or older. These inclusion criteria have been used in previous studies conducted by the principal investigator and other researchers [6,9,55].

Instruments

Demographic Form

The information obtained from the demographic form will be collected from study participants and medical records. Data about family members' characteristics will include demographic data, a history of treatment for psychiatric disorders (anxiety, depression, and posttraumatic stress disorder [PTSD]), a history of taking prescription medications for emotions or moods, and a history of previous ICU-related decision-making experience. Data about patients' characteristics will include demographic data, the length of ICU stay, the duration of mechanical ventilation, admitting ICU diagnoses, baseline medical comorbidities, the baseline severity of illness, and disposition at each study time point (T).

Hospital Anxiety and Depression Scale

Symptoms of anxiety and depression will be assessed by using the 14-item Hospital Anxiety and Depression Scale (HADS) instrument [4,17,56,57]. The HADS is a 14-item scale with 7 items that form an anxiety subscale (HADS-A) and 7 items that form a depression subscale (HADS-D). Each of the two subscales can have scores that range from 0 to 21. Higher scores indicate higher levels of anxiety or depression symptoms. A cutoff score of ≥11 is consistent with moderate-to-severe symptoms of anxiety or depression.

PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

Symptoms of posttraumatic stress will be measured by using the 20-item PTSD Checklist for the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (PCL-5) instrument [58]. The PCL-5 is a 20-item self-report measure that corresponds to the *Diagnostic and Statistical Manual of Mental Disorders,Fifth Edition* criteria for PTSD [59]. A total symptom severity score (range 0-80) can be obtained by summing all of the items' scores. Higher scores indicate a higher severity of PTSD symptoms. A cutoff score of 31 or higher is the recommended indicator for a provisional diagnosis of PTSD.

Medical Outcomes Study 12-item Short-Form General Health Survey

The Medical Outcomes Study 12-item Short-Form General Health Survey is a 12-item self-report scale for measuring HRQOL [60,61]. Each item on the scale is scored by using a Likert-type scale. Raw scores are transformed to scores that range from 0 (worst) to 100 (best). The scale provides a summary score of 0 to 100 for the physical and mental health quality of life. Higher scores represent a more positive quality of life.

MHSE Scale

The MHSE Scale is a 6-item scale for measuring MHSE [49]. Each item is measured on a 10-point Likert scale that ranges from 1 (not at all confident) to 10 (totally confident). Items are summed to obtain a total score that ranges from 6 to 60. Higher scores indicate higher levels of MHSE.

Intervention

The selection of the mHealth app was based on several criteria, as follows: (1) the app uses principles of CBT to deliver strategies for managing stress, anxiety, and depression; (2) the app is available for Android and iOS operating systems; and (3) there is a free version of the app that participants can use after the proposed study. Based on these criteria, the Sanvello (formerly known as Pacifica) app developed by Sanvello Health was chosen [62]. Sanvello has been identified as a well-designed app that is based on CBT principles, has been selected as the app of choice for other trials that have examined the implementation of the mHealth app delivery of CBT, and has been shown to be efficacious in diminishing mild-to-moderate symptoms of anxiety and depression in community samples of adults [41,63,64].

The Sanvello app is a mobile app that is marketed as a tool that provides on-demand help for managing anxiety, stress, and depression. It includes a suite of tools that are based on CBT and mindfulness principles that teach users strategies for self-managing stress, mood, anxiety, and depression. Upon initial log-in, the app asks users to select up to 3 of a possible 8 goals to work on and prompts users daily to rate their mood. Based on their mood ratings, the app suggests several activities for addressing users' moods. The app guides users through a variety of short audio lessons or branched sessions based on their moods or goals and allows users to monitor their progress. Exercises typically take 3 to 5 minutes to complete. There is an anonymous peer support community in which users may post their thoughts and struggles as well as find listings of crisis lines and resources for users in emergency situations.

Upon randomization to the intervention group, family members will be assisted with downloading the app and creating a Sanvello account. Study participants will receive an introductory training session and instructional guidebook for reviewing basic app usage and the app's components. Study participants will be instructed to start their mHealth app usage with the first "guided journey" module, which is called "feeling better." The "feeling better" module has 7 individual exercises, and participants will complete 1 exercise each day. Once the entire "feeling better" module is completed, the participants will be encouraged to continue to complete the remaining "guided journey" modules—"braving anxiety," "becoming mindful," "taking control," and "building confidence." These remaining modules are composed of 6 to 11 individual exercises. Additionally, participants will be allowed to use the components of the mHealth app in whichever way they want. This includes accessing tools that allow users to track their exercise and sleep habits; communicating with web-based coaches; and sharing experiences in a nonjudgmental, web-based, and secure forum. Participants will receive weekly text reminders that encourage them to use the mHealth app. At the conclusion of the study, app usage data (the number of log-ins, time spent with the app, etc) will be collected and provided to the research team by Sanvello via an encrypted, password-protected, and deidentified data file.

Recruitment

The research assistant will visit the ICU 3 times per week to identify newly admitted patients who are eligible for the study. The research assistant will screen for eligibility by using medical records and consulting with the health care team. If the eligibility criteria are met by a family member, they will be approached for enrollment within the first week after patient admission. The research assistant will consult with the bedside nurse to identify eligible family members while visiting patients or will contact eligible family members by phone. Family members will be randomized to the intervention group or control group after enrollment and data collection at enrollment are complete.

The longitudinal study design has 3 data collection points. Data will be collected by using the same methods as those in a previous study conducted by Petrinec and Martin [9] upon enrollment into the study (T1), 30 days after study enrollment (T2), and 60 days after study enrollment (T3). The data collection process for each time point is shown in Table 1. At 30 and 60 days after study enrollment, family members will be contacted by phone, email, or standard mail. Participants' preferences for follow-ups will be identified upon their enrollment into the study. A US $30 gift card will be offered at T1 and T2, and a US $50 gift card will be offered during follow-up data collection in T3 for a possible total of US $110.

Table 1. Data collection checklist.

Data collected	T1[a] (Enrollment)	T2[b] (30 days after enrollment)	T3[c] (60 days after enrollment)
Demographic data	✓	✓	✓
Hospital Anxiety and Depression Scale score	✓	✓	✓
PCL-5[d] score	✓	✓	✓
Mental Health Self-Efficacy Scale score	✓	✓	✓
SF-12[e]	✓		✓
Mobile health app usage			✓

[a]T1: time point 1.

[b]T2: time point 2.

[c]T3: time point 3.

[d]PCL-5: Posttraumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[e]SF-12: Medical Outcomes Study 12-item Short-Form General Health Survey.

Data Analysis and Statistical Plan

Data will be analyzed by using SPSS, version 25 (IBM Corporation), and descriptive statistics will be used to assess the frequencies and variability of the data, coding inaccuracies, outliers, and missing data. The statistical plan for each specific aim is detailed in the following subsections.

Aim 1

We will report study variables with descriptive statistics. Changes over time will be examined with a repeated-measures analysis of variance.

Aim 2

Differences between the intervention and control groups will be assessed with a two-tailed Student *t* test. Differences between groups with regard to the severity of PICS-F symptoms will be used to calculate the effect size for the intervention.

Aim 3

The relationship between total mHealth app doses and longitudinal changes in study variables will be examined with a Pearson correlation analysis.

Human Subjects and Ethical Issues

The study will undergo review and approval by the institutional review board at Summa Health. The investigators have considerable experience in conducting research on individuals with symptoms of anxiety, depression, and posttraumatic stress. The study will present no more than minimal psychological risk and harm, which largely come from the possibility that answering the questions on the anxiety, depression, and stress instruments may be distressing for participants. Psychological risk will be minimized by emphasizing that study participants can stop participating in the study at any time and are not obligated to answer any question that they find to be distressing. Family members who exhibit clinically significant symptoms will be referred to their primary care physician. Family members of patients who die during the study will be referred to local bereavement support groups.

There will be a low risk of privacy or confidentiality loss. This risk will be minimized via the following measures: (1) the only record linking participants and the research data will be the consent document; (2) consent documents will be kept in a locked cabinet in the locked office of the principal investigator; (3) data will be entered and stored by the research assistant on REDCap (Research Electronic Data Capture; Vanderbilt University)—a secure, Health Insurance Portability and Accountability Act–compliant, web-based platform; (4) all data files obtained for analysis will be stored on a password-protected laptop computer, which will be stored in a locked room; and (5) the principal investigator, coinvestigators, and research assistant are the only individuals who will have access to the data files.

Results

Recruitment for our pilot study began in August 2020. During recruitment, challenges arose due to the COVID-19 pandemic. There was a short period of time when research studies at Summa were placed on hiatus due to COVID-19–related restrictions. This was followed by challenges in recruiting family members while limitations were placed on family visitation to the hospital. Despite these challenges, data collection and analysis are expected to be completed by March 2022. The dissemination of our findings will be accomplished through conferences and publications.

Discussion

The use of a self-care mHealth app represents a novel approach to addressing the needs and untoward psychological symptoms experienced by family members of critically ill patients by leveraging technology and the growing market penetrance of smartphone ownership. The proposed study emphasizes self-care, which can function as an adjunct and complement to existing nursing efforts for supporting family members of critically ill patients without significantly increasing the need for care delivery resources. Importantly, the proposed mHealth app offers a portable, “just-in-time” benefit to users by being

available to them on demand via their smartphone across transitions of care. The findings of our study will inform the planning and implementation of a randomized controlled trial. Additionally, the findings may help to direct collaborations with app developers for modifying existing apps or creating new apps that emphasize self-care specifically for family members and caregivers of acutely and chronically ill patients.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the American Association of Critical-Care Nurses.
[PDF File (Adobe PDF File), 311 KB - resprot_v10i8e30813_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
HADS: Hospital Anxiety and Depression Scale
HRQOL: health-related quality of life
ICU: intensive care unit
mHealth: mobile health
MHSE: mental health self-efficacy
PCL-5: Posttraumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
PICS-F: postintensive care syndrome-family
PTSD: posttraumatic stress disorder
REDCap: Research Electronic Data Capture

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Protocol

A Casual Video Game With Psychological Well-being Concepts for Young Adolescents: Protocol for an Acceptability and Feasibility Study

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Abstract

Background: Many face-to-face and digital therapeutic supports are designed for adolescents experiencing high levels of psychological distress. However, promoting psychological well-being among adolescents is often neglected despite significant short-term and long-term benefits.

Objective: This research has 3 main objectives: (1) to assess the acceptability of Match Emoji, a casual video game with psychological well-being concepts among 13-15-year-old students in a New Zealand secondary school; (2) to identify the feasibility of the research process; and (3) to explore the preliminary well-being and therapeutic potential of Match Emoji.

Methods: Approximately 40 participants aged 13-15 years from a local secondary college in Wellington, New Zealand, will be invited to download and play Match Emoji 3-4 times a week for 5-15 minutes over a 2-week period. Participants will complete 4 assessments at baseline, postintervention, and 3 weeks later to assess psychological well-being and therapeutic changes. Statistical analysis will be used to synthesize data from interviews and triangulated with assessment changes and game analytics. This synthesis will help to assess the acceptability and feasibility of the Match Emoji.

Results: The key outputs from the project will include the acceptability, feasibility, and therapeutic potential of Match Emoji. It is anticipated that participants will have finished playing the recommended game play regimen by August 2021 with analysis of results completed by October 2021.

Conclusions: Data from the study are expected to inform future research on Match Emoji including a randomized controlled trial and further adjustments to the design and development of the game.

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KEYWORDS

digital mental health tools; casual video games; young people

Introduction

In New Zealand, an increasing number of young people experience elevated levels of psychological distress and low well-being [1]. Although treatments such as cognitive behavioral therapy exist and have shown promise for reducing clinical levels of psychological distress [2,3], supports for promoting psychological well-being are often underutilized despite their therapeutic potential [4-6].

Young adolescents, aged between 13 and 15 years, are particularly vulnerable to experiencing elevated levels of psychological distress and low well-being [7,8]. This is in part due to the additional external and internal demands placed on young adolescents from navigating puberty to the formation of gender norms and health and well-being attitudes [9,10]. To

compound rapid developmental changes, young adolescents enter a more complex educational environment while forging new relationships with peers and family members. As approximately half of all mental ill-health starts by age 15 years and 75% develops by age 18 years [7], it is vital to create interventions that will promote psychological well-being skills among young adolescents.

Young adolescents in New Zealand who have access to the curriculum are provided with opportunities to learn mental health and well-being skills such as stress management and resilience skills [11,12]. Although education through the curriculum is a promising preventive measure [12,13], longitudinal research suggests more targeted supports are required to promote psychological well-being among young adolescents [14].

Given the popularity of digital technologies, a plethora of digital mental health interventions (DMHIs) have been created and shown promise for alleviating psychological distress and promoting psychological well-being in trials [15-17]. This scalable and low-cost approach is promising for young people, considering the potential to bypass traditional barriers such as stigma and time [18-20]. Recent systematic reviews and meta-analyses, however, report DMHIs are yet to reach their full engagement potential, with low real-world use of many popular mental health apps [17,21].

A growing amount of research has attempted to identify ways in which to increase adherence to DMHIs among young people [17,22]. One promising approach is using microinterventions. The goal of microinterventions is to enable users to work towards a highly focused goal with support from in-the-moment elements such as reminders and nudges [23].

A popular activity among many young people that utilizes similar underlying mechanics of microinterventions are casual video games (CVGs). Globally, CVGs such as “Bejewelled” and “Angry Birds” are played by millions of people in short bursts of time [24]. According to a recent systematic review of the literature, CVGs may also hold promising therapeutic mood enhancing and brief releases from unpleasant experiences [25]. Previous research with young adolescents suggests CVGs are a popular approach among this age group who commonly play these games to distract and “calm a busy mind” [26].

Based upon a systematic review of the literature and research with young adolescents, we created Match Emoji, a CVG with psychological well-being concepts for young adolescents. Although it is important to evaluate core psychotherapeutic components of interventions to understand how specific elements guide the design of the intervention as a whole [27], it is more useful to investigate the potential for real-world usage in naturalistic settings [21,28], As such, the aim of the current protocol is: (1) to assess the acceptability of Match Emoji among 13-15-year old students in a New Zealand secondary school, (2) to identify the feasibility of the research process, and (3) to explore the preliminary well-being and therapeutic potential of Match Emoji.

Methods

Research Strategy

This study will employ a mixed methods design to assess the acceptability, feasibility, and therapeutic potential of a CVG with psychological well-being concepts among 13-15-year-old students.

Study Design

The study will involve 3 phases. First, we will recruit 13-15-year-old students from 2-4 classrooms in a local secondary school within the Wellington region of New Zealand. Once participants have returned their consent and assent forms, they will be asked to download Match Emoji onto their phone or digital device. During the second phase, participants will be encouraged to play the game 3-4 times a week for 5-15 minutes for a 2-week period. Game play time and sessions will be collected through the Unity platform to help inform the feasibility and acceptability of the recommended game play. During the third phase, researchers will follow up 2 weeks after the recommended regimen of Match Emoji and collect secondary outcomes measures (from the Child and Adolescent Mindfulness Measure [CAMM], General Help-Seeking Questionnaire [GHSQ], Flourishing Scale [FS], and Revised Children's Anxiety and Depression Scale [RCADS]), followed by short interviews with participants about their experience.

Study Population

Approximately 40 students from a local secondary school in Wellington, New Zealand, will take part in playing Match Emoji 3-4 times a week for 5-15 minutes over a 2-week period. Participants will be invited from year 9 and 10 classrooms and are typically between 13 and 15 years of age. As this is an acceptability and feasibility study, a total of 40 participants will provide a large enough sample size to show a meaningful difference in the primary and secondary outcomes between baseline, postintervention, and a 3-week follow-up.

Inclusion Criteria

Young people will be included in the study if they are between the ages of 13 and 15 years, have provided written consent from a parent or caregiver, and are able to understand and sign the assent form.

Exclusion and Safety Criteria

Young people will be excluded from participation if they do not meet the inclusion criteria. The appropriate personnel within the secondary school will be engaged if a participant self-reports a high level of mental health need. This will be determined through the 4 questionnaires. Those participants who are engaged with existing therapeutic support are able to participate in the research study if consent has been obtained from the young person.

Intervention

Match Emoji is a match-3 CVG with psychological well-being concepts designed for young adolescents. The aim of Match Emoji is to match similar colored emojis together to earn points and progress through the game. There is a total of 6 different

colored and shaped emojis that represent a unique digital expression such as an emotion, idea, or personality. When the user has successfully matched the required number of emojis with a fixed number of moves or time frame, a micromessage appears on the screen. Each micromessage consists of a short psychological well-being concept such as “notice what is going on around you” or “sometimes talking to a friend can help” and is delivered via a dynamic messaging loading system that identifies the “optimal” time to display the message. Hints are used throughout the game if players get stuck. For example, if the player waits too long before making a move, Match Emoji identifies a potential combination of similar colored emojis by moving a successful sequence of items back and forth to capture the user's attention. An example of the game can be seen in Figure 1.

Figure 1. Image of the Match Emoji game.

Outcome Measures

The primary outcomes of the study are (1) acceptability of Match Emoji (ie, is Match Emoji acceptable among young adolescents), as assessed via a short semistructured intervention with participants after the recommended regime of game play and game analytics including the number of sessions and minutes played recorded via the Unity platform, and (2) feasibility of Match Emoji (ie, is it easy to complete the study with young adolescents within a secondary school context) as measured by the number of students interested in participating in completing the 4 questionnaires, playing the recommended regimen of Match Emoji, and attending the follow-up interview.

The secondary outcome (measured at baseline before accessing Match Emoji, on completing the 2 weeks of recommended game play, and at the 3-week follow-up) is efficacy (ie, does Match Emoji promote psychological well-being skills). This will be assessed by measuring changes over time in the CAMM, GHSQ, FS, and RCADS. It is estimated to take participants approximately 10-15 minutes to complete all questionnaires.

The CAMM is a 10-item measure of mindfulness for use with children and adolescents and has been reported to have good internal consistency and significant correlations between CAMM scores and measures of psychological functioning and distress [29]. The GHSQ is a 1-page questionnaire with 2 sets of questions that examine the respondent’s likelihood of seeking help for a specific issue such as psychological distress. The GHSQ has been reported to have good reliability and validity and appears to be a flexible measure of help-seeking intentions that can be applied to different contexts and age groups including young people [30].

The 8-item FS is a valid and reliable brief summary measure of psychological well-being suited for young people [31,32]. The scale provides a single psychological well-being score derived from the 8 questions and has been used as an effective measure to access adolescents’ psychological well-being in the New Zealand secondary school context [33]. The RCADS is a youth self-report questionnaire with 6 subscales including separation anxiety disorder and low mood. The RCADS has good reliability on subscales and total scale [34], internal consistency, and good convergent validity [35]. The RCADS has been used as an appropriate and easy-to-administer assessment tool of anxiety and depressive symptoms in several populations within New Zealand [35,36].

Interviews lasting approximately 30 minutes will take place with no more than 6 participants at one time to understand experiences with playing Match Emoji. Interviews will be conducted by the first author (RP) at the local school in a setting familiar to the participants. Responses will be recorded in a paper-based format. Questions will involve (1) What parts of the game did you like? (2) What parts of the game could be improved? (3) What did you learn from playing the game? (4) Did you try and use any of the ideas from the game and if so, which ones? (5) Do you think you will continue to play Match

Emoji? Interviews will not involve more than 6 participants at a time. At the end of the interview, participants will be able to read and correct answers.

Statistical Analysis

Quantitative data from the 4 assessments and game play usage will be analyzed using Microsoft Excel, SPSS version 26, and the metrics recorded from the Unity platform including number of sessions and minutes played [37,38]. Analyses will include descriptive statistics (eg, number of sessions completed, number of minutes played, changes in assessment scores, and sociodemographic characteristics of the participants).

As this is an acceptability and feasibility study, a sample size of 40 participants will be a large enough sample to show a meaningful difference in primary and secondary outcomes between baseline and the end of the interview. Chi-square tests and *t* tests will be used to assess the statistical significance of changes in the 4 assessment scores over time. A *P* value <.05 will be used at the 95% confidence level to determine the therapeutic potential of any difference between pre- and postmeasures. NVivo will be used to store and code qualitative data from the interviews with participants. A general inductive approach will be used by researchers to identify and analyze emerging themes [39].

Ethics and Consent

This study received ethics approval from the New Zealand Health and Disability Ethics Committee (21/NTA/34) on May 28, 2021. After the college principal or senior management staff member has understood and approved the research, participants will be provided with information about the study. Students will be provided with time to ask questions before deciding to provide informed decision about their voluntary participation through an assent form. A consent form will also be required from the parent or guardian.

All the project data and materials sent for publication will be de-identified by removing statements identifying participants. Participants who disclose mental health needs that meet the threshold for a clinical diagnosis will be handled by appropriate school personnel such as a school counsellor. The data will be stored securely in a password-protected computer accessible only to the research team. The de-identifiable findings will be included in the first author's (RP) doctoral thesis as well as being disseminated through peer-reviewed academic journals, national and international conferences, and public events. If parents ask for their child's individual results such as game analytics, we will seek permission from the child first.

Results

Recruitment of participants started in June 2021, with completion anticipated to be completed by July 2021. It is anticipated that participants will have finished playing the recommended game play regimen by August 2021 with analysis of results completed by October 2021. The key outputs from the game will inform future design and iterations of the game. In addition, a larger and more robust methodological approach such as a randomized controlled trial may be created to fully understand the therapeutic effects of Match Emoji.

Discussion

Promoting psychological well-being among young adolescents may support overall health and improve disease-specific outcomes later in life [40-42]. Given the potential benefits of promoting psychological well-being coupled with a heightened risk of experiencing elevated levels of psychological distress, it is crucial to explore engaging, preventive tools for young adolescents [43]. This is particularly important in New Zealand where a growing number of young people have reported experiencing psychological distress [14].

The current acceptability and feasibility study aims to assess the acceptability of Match Emoji among 13-15-year-old students in a New Zealand secondary school, identify the feasibility of the research process, and examine the psychological well-being and therapeutic potential of the game. The primary outcomes of the study will help to shape the iterative design process of Match Emoji and understand if the game is worthy of more rigorous testing in a randomized controlled trial. The secondary outcomes will examine the psychological well-being and therapeutic potential of Match Emoji. If Match Emoji is shown in subsequent studies to be acceptable and useful for young adolescents in its final form, it is hoped that the game may be promoted and available free of charge to young people in New Zealand on Google Play and App Store.

Conflicts of Interest

TF is a co-developer of SPARX, a computerized CBT program for adolescent depression. The Intellectual Property for SPARX is owned by Uniservices at the University of Auckland and co-developers can benefit financially from licensing of SPARX outside of New Zealand.

Multimedia Appendix 1
Original peer-review report from the funding agency (Health and Disability Ethics Committees, Ministry of Health, New Zealand).
[PDF File (Adobe PDF File), 474 KB - resprot_v10i8e31588_app1.pdf]

Multimedia Appendix 2
Peer review from academic.
[PDF File (Adobe PDF File), 225 KB - resprot_v10i8e31588_app2.pdf]

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Abbreviations

CAMM: Child and Adolescent Mindfulness Measure
CVG: casual video game
DMHI: digital mental health intervention
FS: Flourishing Scale
GHSQ: General Help-Seeking Questionnaire
RCADS: Revised Children's Anxiety and Depression Scale

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Protocol

Optimizing Social-Emotional-Communication Development in Infants of Mothers With Depression: Protocol for a Randomized Controlled Trial of a Mobile Intervention Targeting Depression and Responsive Parenting

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Abstract

Background: Postpartum depression interferes with maternal engagement in interventions that are effective in improving infant social-emotional and social-communication outcomes. There is an absence of integrated interventions with demonstrated effectiveness in both reducing maternal depression and promoting parent-mediated practices that optimize infant social-emotional and social-communication competencies. Interventions targeting maternal depression are often separate from parent-mediated interventions. To address the life course needs of depressed mothers and their infants, we need brief, accessible, and integrated interventions that target both maternal depression and specific parent practices shown to improve infant social-emotional and social-communication trajectories.

Objective: The aim of this study is to evaluate the efficacy of a mobile internet intervention, Mom and Baby Net, with remote coaching to improve maternal mood and promote parent practices that optimize infant social-emotional and social-communication development.

Methods: This is a two-arm, randomized controlled intent-to-treat trial. Primary outcomes include maternal depression symptoms and observed parent and infant behaviors. Outcomes are measured via direct observational assessments and standardized questionnaires. The sample is being recruited from the urban core of a large southern city in the United States. Study enrollment was initiated in 2017 and concluded in 2020. Participants are biological mothers with elevated depression symptoms, aged 18 years or older, and who have custody of an infant less than 12 months of age. Exclusion criteria at the time of screening include maternal homelessness or shelter residence, inpatient mental health or substance abuse treatment, or maternal or infant treatment of a major mental or physical illness that would hinder meaningful study participation.

Results: The start date of this grant-funded randomized controlled trial (RCT) was September 1, 2016. Data collection is ongoing. Following the institutional review board (IRB)–approved pilot work, the RCT was approved by the IRB on November 17, 2017. Recruitment was initiated immediately following IRB approval. Between February 15, 2018, and March 11, 2021, we successfully recruited a sample of 184 women and their infants into the RCT. The sample is predominantly African American and socioeconomically disadvantaged.

Conclusions: Data collection is scheduled to be concluded in March 2022. We anticipate that relative to the attention control condition, which is focused on education around maternal depression and infant developmental milestones with matching technology and coaching structure, mothers in the Mom and Baby Net intervention will experience greater reductions in depression and gains in sensitive and responsive parent practices and that their infants will demonstrate greater gains in social-emotional and social-communication behavior.

Trial Registration: ClinicalTrials.gov NCT03464630; https://clinicaltrials.gov/ct2/show/NCT03464630
International Registered Report Identifier (IRRID): DERR1-10.2196/31072

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KEYWORDS

maternal depression; parenting; infant social-emotional and social-communication development; mobile intervention; remote coaching; trial protocol; mobile phone

Introduction

Maternal depression during the postpartum period is highly prevalent and is associated with extensive and well-documented effects on parenting behavior and infant developmental outcomes [1-3]. Depressed mothers are more irritable and less responsive to their infants, more likely to make negative attributions for infant crying, show less pleasure in response to infant social bids, and talk less to their infants relative to nondepressed mothers [4-8]. Infants of depressed mothers exhibit more negative and less positive affect, poorer emotion regulation and cognitive development, and less social engagement as well as biological markers associated with subsequent depression [9]. These developmental risks are magnified for the 1 in 6 infants living in poverty, approximately 71% of whom are children of color [10]. In the United States, mothers who are socioeconomically disadvantaged and of nondominant cultures experience depression during the postpartum period at nearly four times the rate of White economically advantaged mothers [11,12], and poverty increases infant susceptibility to the effects of early adverse parenting [13].

Programs designed to foster behavioral and biological foundations of infant and early childhood mental health focus on promoting parent sensitivity and responsiveness [14,15] and have been shown to be effective in improving both parenting behavior and infant developmental outcomes [14-16]. Of particular relevance to this study, the Play and Learning Strategies (PALS) intervention has been shown to increase maternal responsiveness and sensitivity and, thereby, improve infant social-emotional and social-communication behavior and developmental outcomes [17-19]. For infants facing early adversity, intervening early and targeting these nurturing parent behaviors has proven to be effective in promoting infant social-emotional and social-communication trajectories [20-22].

Given these strong outcomes and the associated promise of improving developmental outcomes for at-risk infants, it is of significant concern that the reach of such interventions is low [23,24]. Although home visits are the most common mechanism to support early parenting, particularly for low-income families, we know that these programs reach on average less than 4% of the population in need of such intervention and, in some cases, are prohibitively costly to bring to scale with sufficient intensity [25]. Maternal depression interferes with engagement in early intervention and is effective in improving infant social-emotional and social-communication outcomes [26,27]. Moreover, we know that relatively few depressed mothers access treatment for depression [1,26,28-30], with disparities in the receipt of treatment found for mothers of nondominant cultures and those living in socioeconomic disadvantage [31-34]. Within this context, it is notable that infant parenting interventions and treatment for depression typically operate in silos such that mothers and their infants, who are least resourced and most in need of these interventions, may be least likely to access and engage in them [34].

Although there are effective interventions for depressed mothers that include parenting components [35-38], there is a striking absence of accessible, integrated, and evidence-based interventions that target both perinatal depression and parenting practices that have been demonstrated to optimize infant social-emotional and social-communication trajectories. Moreover, remote service delivery approaches are needed to overcome access barriers that differentially affect women, minorities, and the poor [39-41]. Web-based remote coaching interventions can overcome logistical barriers that often prevent low-income mothers from participating in community-based programs, including lack of transportation and childcare as well as inflexible work schedules [42]. Increased access is particularly possible when interventions are made accessible through smartphones, which diminish or eliminate the digital divide [43].

In our previous programmatic research, we developed a highly effective, guided internet and remote coaching intervention to improve the accessibility of treatments for maternal depression (Mom-Net) [37,44] and promotion of infant and early childhood mental health (e-Play and Learning Strategies [ePALS] BabyNet) [23,45]. To address the existing silo in interventions for maternal depression and early parenting, as well as improve accessibility to these interventions, we created a mobile internet intervention (Mom and Baby Net [MBN]) [46]. MBN integrates our evidence-based guided internet intervention program targeting maternal depression [37,44] with our evidence-based, parent-mediated intervention targeting parent practices that promote infant social-emotional and social-communication competencies [45].

Methods

Study Aim and Setting

The primary aim of this study is to evaluate the impact of the MBN intervention on changes in maternal depression, parenting strategies and knowledge, as well as infant social-emotional and social-communication behavior at postintervention and 6-month follow-up. We will also examine the relationship between maternal and infant changes. The study is being conducted in the urban core of a large southern US city, which is one of the fastest growing and most segregated and economically inequitable in the country.

Clinical Trial Registration and Institutional Review Board Approval

The study is registered as a clinical trial at ClinicalTrials.gov (NCT03464630). Before human subjects' activity, the full, detailed study protocol #H18217 was approved by the Georgia State University Institutional Review Board (IRB) on November 21, 2017 (see Multimedia Appendix 1 for peer review summary statements of the grant proposal).

Trial Design, Randomization, and Recruitment

The study uses a two-arm, randomized controlled intent-to-treat trial design, with random assignment in a 1:1 allocation to one of the two parallel mobile intervention conditions. IRB approval is obtained before the involvement of human subjects. Recruitment strategies include the distribution of study information to health and social service agencies serving low-income women. Print materials were provided in agency offices, web-based posts were placed on health and social service websites, and text blasts were sent by community service providers to women on their service lists. Referral is conducted through a project web-based referral system to support mother self-referral, provider referral, and research team referral. Referred mothers are screened by phone to determine their eligibility for inclusion.

Eligibility Criteria and Participant Characteristics

The eligibility criteria include the following: biological mothers aged 18 years or older with an infant younger than 1 year, who are English speaking, and who meet the Patient Health Questionnaire (PHQ)-2 criteria for elevated depression symptoms [47]. Exclusion criteria at the time of screening include maternal homelessness or shelter residence, major physical or mental illness that would hinder meaningful participation, infant major physical illness, and not having custody of the infant. Inclusion and exclusion criteria are established to ensure that mothers were not burdened by severe stressors that might restrict their ability to participate in the study.

Sample Size Determination

Sample size determination is based on anticipated effect sizes and the minimum sample size needed to have sufficient power to detect these effects. In this study, a moderate-to-large effect size (Cohen d=0.5-1.03) is anticipated for maternal outcomes and a small-to-moderate effect size (Cohen d=0.2-0.4) is anticipated for infant outcomes based on the PALS program evidence [18,19], our Baby-Net results [23,46], and evidence of Coping with Depression Course [48] and internet-based cognitive behavioral therapy treatment success [49]. For the smallest anticipated effect sizes (ie, those for infants), to detect these effects within a 2×2 analysis based on α=.05, a sample of n=75 per condition is needed (total n=150). Within this sample size estimation, effects were viewed relative to both high (r=0.68) and low (r=0.21) repeated measures correlation. We found, with power at 0.95, we could detect an effect as low as Cohen d=0.37 (with low repeated correlation) and Cohen d=0.23 (with high repeated correlation), and with a power of 0.80, we could detect an effect size as low as Cohen d=0.29 (with low repeated correlation) and Cohen d=0.18 (with high repeated correlation). To view latent growth curve model maintenance trajectories through follow-up, the number of cases per estimated parameter needs to be sufficient, with a rough guideline of 5:1 [50,51]. Using this guideline, with an estimated sample size of 150, we will have the sample size to estimate 30 parameters, which is sufficient for modeling three time points and a condition predictor.

On the basis of a sample size of 150 needed across the three study assessment points (pre, post, and follow-up), we used anticipated attrition rates to estimate the initial sample size needed to achieve this number. We expect a pre-post attrition rate of 10% and an overall 17% rate at follow-up assessments based on traditional PALS, across a series of randomized control studies, with attrition rates ranging from 9% to 24% [52,53]. In our recent Baby-Net R01 study [45], we observed a 7% attrition from pre to postassessment and 15% at 6-month follow-up working with low-income mothers, some of whom were experiencing elevated levels of depressive symptoms. As such, we estimate that we will need an initial sample of at least 180 mothers to initiate the study, consent, and complete preassessment.

An additional consideration in this study is our need to screen for maternal depression to arrive at an initial sample of 180. The estimated range of depression within our targeted recruitment population of low-income, diverse women ranges from 30% to 50% [11,12]. Hence, at least one out of three women we screen will likely be eligible. This estimate will require us to screen 540 mothers to yield an eligible sample of at least 180 mothers. In previous studies [37,44], 4 out of 5 women who self-select to be screened and are eligible go on to consent to preassessment and intervention. Hence, it is necessary to screen a total sample of 675 to obtain a sample of 180 mothers.

Intervention and Comparisons

The study includes two parallel mobile internet remote coaching intervention programs that are identical in intervention structure. To reduce literacy demands and maximize accessibility, both programs are video- and narration-based. The structure of intervention delivery for both programs includes the following: (1) web-based administration of a 14-session intervention with video, narration, and activities to present session content and check-in questions to assess knowledge acquisition, recorded in the database for review by both parent and coach; (2) creation of a 5-minute app-collected video of mother-infant interactions for later review by coach and parent; (3) summary of topics; (4) daily activities (homework); (5) participant-rated satisfaction, ease of use, and effectiveness recorded in the database; and (6) weekly video coach calls to coview the mother-infant video. All mothers receive an iPhone with access to their assigned intervention program and unlimited mobile calls, data, and texting. Participants complete the study activities in their homes using these mobile devices.

The content of the MBN intervention sessions on mood improvement focuses on mood monitoring, behavioral activation by increasing mother pleasant activities, and cognitive coping strategies [37]. Parenting content focuses on recognition of infant signals, warm and contingent responding to infant signals,

maintaining infant attention and interest, and early language literacy promotion strategies [23,45]. Within the app, mothers receive daily reminders to rate their mood based on their preferred schedule.

As a comparison condition, the Depression and Developmental Awareness (DDAS) program [46] serves as an attention control for the time spent in intervention and remote coaching contact. In contrast to targeting maternal mood and parent practices, the content focuses on awareness of maternal depression and infant developmental milestones.

Adherence to the Study Protocol and Intervention

Project protocols for consent, assessment, and intervention are used to train all project staff before study initiation. Our consent protocol consists of staff training on a checklist to ensure ethical informed consent. Supervisors observe staff conducting mock consent administration and view their performance relative to the checklist, with a requirement that staff reach 100% accuracy on checklist coverage. For conducting assessments, detailed project protocols are used to train assessors before conducting assessments with mothers. Assessors are trained on assessment protocols focused on providing appropriate assessment instructions, helping mothers understand questions in a manner that will not influence their responses, and administering assessments to mothers verbally if desired by the mother. For interventions, coaches in both conditions are trained to conduct weekly review calls with mothers, rate maternal progress, and complete implementation fidelity checks. A total of 20% of the recorded coach calls are randomly selected for independent completion of fidelity checklists to calculate interobserver agreement of fidelity. In addition, all staff have regular supervision meetings with the principal investigator (PI) to monitor adherence to the consent, assessment, and intervention protocols.

Study Outcomes

The primary study outcomes include the following: (1) maternal depressive symptoms, (2) parent-sensitive and responsive practices, (3) parent knowledge of infant social-emotional and social-communication behaviors and their promotion, and (4) infant social-emotional and social-communication engagement.

Data Sources, Collection, and Validity

Following consent, preintervention assessment is completed face-to-face in home or via a mobile video meeting. This comprehensive, multimethod assessment includes interviews, questionnaires, and observational procedures to obtain demographic information and community service receipt and to assess the domains of maternal functioning, including depression symptoms, parenting attitudes and beliefs, parent practices, infant social-emotional and social-communication functioning, and parent-infant interaction. This comprehensive assessment protocol is repeated at postassessment. A 6-month follow-up assessment is administered electronically to assess maternal depression symptoms and parenting knowledge of infant social-emotional and social-communication behaviors and their promotion.

Maternal depressive symptoms and severity are measured using the *PHQ-9*, a 9-item self-report instrument for screening, diagnosing, monitoring, and measuring the severity of depression [54]. Question 9 screens for suicidal ideation. The PHQ-9 has an internal reliability of 0.89 in a primary care setting and 0.86 in an obstetric setting. Maternal parenting behavior, attitudes, beliefs, knowledge, and stress are assessed as follows: the *Landry Parent-Child Interaction Scale observational coding system* [55], designed to assess naturalistic parent-child interaction during play at home, is used to code video-recorded mother-infant interaction behavior. The parent scales of interest in this study relative to maternal responsiveness include ratings of maternal positive affect, warmth, flexibility, and positive verbal content. Relative to maternal negative behavior, scales of interest include ratings of maternal physical intrusiveness as well as verbal and affective negativity. The Landry Parent-Child Interaction Scale has been used in a series of federally funded longitudinal and intervention studies over the past 15 years and has yielded adequate reliability and demonstrated the predictive validity of child social-emotional outcomes [55]. Behaviors will be coded across a semistructured play activity over a 5-minute period. Coders, blinded to intervention conditions and time points, conduct coding based on observing parent-infant interaction videos of participants in both intervention conditions. To assess reliability, 20% of all interactions are scored by 2 independent coders. The *Indicator of Parent Child Interaction-2* [56] includes a brief semistructured book activity, which is video recorded, and will be used to code the following behaviors: (1) mother facilitative behaviors including conveyance of acceptance and warmth, descriptive language, following the child's lead, and maintaining the child's interest; (2) mother interrupting behaviors including intrusions, restrictions, and critical comments; (3) infant engagement behaviors, including positive social engagement, follow through, and sustained engagement; and (4) infant behaviors that interfere with engagement, such as fussiness, disruptive behaviors, and withdrawn behavior. The Indicator of Parent-Child Interaction has adequate psychometric features [57] and has been used to assess mother and infant behavior in multiple studies of high-risk infants and in population-based studies of universal interventions to promote early positive parent support behavior [58-60]. To assess reliability, 20% of all interactions are scored by 2 independent coders.

The *Knowledge of Infant Social-Emotional Behavior and Promotion* [45,61] has been used in previous intervention studies and is geared toward an understanding of the concepts of infant social-emotional behavior and its promotion by caregivers, assessing both definitional and applied concept knowledge, with items structured in multiple response formats, including open-ended, true or false, and multiple choice formats. The *Concepts of Development Questionnaire* [62] is a 20-item, Likert-type four-point scale (4=strongly agree and 1=strongly disagree) that assesses parenting beliefs. Specifically of interest in assessing our maternal responsiveness domain, the Concepts of Development Questionnaire focuses on constructs of flexibility and child centeredness, in contrast to parent centeredness. *Parenting Sense of Competence* [63] is a 17-item scale assessing parents' satisfaction and self-perceived competency in the parenting role. Adequate internal consistency,

factor structure, and construct validity have been reported [64]. *The Parenting Stress Index-Short Form* [65] is a 36-item self-report instrument that assesses stress directly associated with the parenting role using a five-point scale to indicate the degree to which that item has been stressful, with validity demonstrated for at-risk mothers [66]. The *Brief Child Abuse Potential (BCAP)* [67] is a 34-item self-report screening instrument that contains seven domains. The primary clinical scale (abuse) comprises six factor scales: distress, rigidity, unhappiness, persecution, loneliness, family conflict, and poverty. In addition, the BCAP contains three validity scales: lie, random response, and inconsistency. Overall, the 24-item BCAP abuse scale has high internal consistency (0.89); temporal stability estimates for the abuse scale are also adequate (ie, 0.91 and 0.75 for 1-day and 3-month intervals, respectively). The *Automatic Thoughts Questionnaire* [68] is a 30-item self-report instrument that measures the frequency of automatic negative thoughts related to depression. It contains four domains: personal maladjustment and desire for change, negative self-concepts and negative expectations, low self-esteem, and helplessness. The Automatic Thoughts Questionnaire has a high internal consistency (0.97). In our own work, we have demonstrated negative thoughts as a mechanistic explanation of Mom-Net intervention effects on maternal depression [69]. The *Revised Dyadic Adjustment Scale* [70] is a 14-item self-report instrument that assesses seven dimensions of relationships in three domains: consensus, satisfaction, and cohesion. Overall, the Revised Dyadic Adjustment Scale has a reliability (Cronbach α) of .90.

Infant social-emotional behavior and development change are assessed as follows: *observed infant behavior in interaction* with the mother was assessed using the Landry Parent-Child Interaction Scale, as described above [55]. Rating scales of interest in assessing infant behaviors include attention or arousal, warmth-seeking, and behavioral regulation. The *Devereux Early Childhood Assessment for Infants* [71] is a 33-item behavior rating scale that assesses child protective factors central to social and emotional health and resilience in infants aged 4 weeks up to 18 months, which displays adequate reliability and validity for use in this study [72].

Moderating Influences

The *Family Profile Report Form* [73] uses demographic and life course history data, including maternal relationship status and support, health status, psychiatric history, and other services received, to describe study participants and examine the potential moderating effects of the intervention. *Socioeconomic stress* will be assessed using Conger and Elder measure of economic hardship based on their family process model of economic hardship [74], which assesses different areas of financial stress and has been used in many studies to describe important aspects of societal disadvantage in samples [75-77]. *Intervention dosage* will be assessed by electronic recording of the mother: (1) number of sessions and homework completed, (2) time on the web, and (3) number of times the intervention was visited. System activity logs will provide descriptive statistics on (1) time of day at log on; (2) length of time in the intervention; (3) number of times logged on per week; and (4) length of time spent in the information, support, video, and assessment areas of the intervention. Program attrition will be documented, and for these subjects, we will conduct exit interviews to determine the reasons for discontinuation. Table 1 presents our project enrollment, intervention, and assessment schedule.

Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrollment, interventions, and assessments for the Mom and Baby Net randomized controlled trial.

Timepoint	Enrollment	Allocation	Postallocation				
	–T1	T0	T1 Preassessment	Intervention (6-8 months)		T2 Postassessment (7-9 months)	T3 Follow-up assessment (13-15 months)
				S1	S4		
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
Allocation		✓					
Interventions							
Mom and Baby Net				✓	✓		
Depression and Developmental Awareness				✓	✓		
Assessments							
Depression screening	✓						
Demographics			✓				
Covariates			✓				
Primary outcomes			✓			✓	✓
Secondary outcomes			✓			✓	

Data Management

All data will be deidentified by using a project-specific identification number for each participant. Links between participant names and identification codes will exist in written form only on consent forms, and these forms will be stored in a locked room and file cabinet accessible only to the Georgia State University project staff. In addition, electronic files containing participant identifiers or data will be accessible only to the approved project staff. All nonidentifiable data (ie, those labeled with codes only) will be stored in the same manner in locked file cabinets or on password-protected, secure computer networks.

The data used for progress monitoring will be obtained electronically through the iOS app. State-of-the-art security protocols are used in all data collection and monitoring activities, as used for electronic commerce, using VeriSign SSL. The program app will be established within the Oregon Research Institute network with firewall to maintain security. The program app will be accessible via an iPhone with username and password protection.

Preliminary Analysis

Overview

We will use a systematic approach to construct development to create two parent outcomes (mother positive or negative) and one infant outcome (infant social-emotional functioning). For our outcomes of maternal depression, parenting knowledge, and stress, we will examine single indicants. To view potential intervention moderating effects, we will attempt to create a maternal contextual risk indicator (eg, isolation or support, relationship status, conflict, and economic hardship); for maternal depression before intervention as a potential moderator, we will view depression onset, chronicity, and severity as well as the presence of other treatments, including medication, to examine each of these and their effect on intervention outcomes.

For factor analysis, given appropriate internal consistency and interrater reliability, we will examine questionnaire scales and observational codes using factor analytic techniques [78], retaining a 5:1 subject to parameter ratio. Scale factor loadings above 0.30 and communality estimates above 0.15 will be confirmed within the structural equation modeling methodology to produce fit indices to view how each indicant set fits into their specified domain. If satisfactory, the unit weighting of the standardized score for each indicator will be summed. If not, we will select an index variable within each domain to represent the outcome.

Random Assignment and Attention

Although mother-infant pairs will be randomly assigned to the intervention conditions, condition differences may exist due to random sampling failures or differential attrition. To address this issue, a 2×2 (group×attrition status) multivariate analysis of variance (MANOVA) will be performed using the baseline assessment for mother, infant, and contextual risk variables. The presence of a statistically significant group main effect would provide evidence that random assignment was not effective in equating groups. A second possible source of nonequivalence is differential attrition by condition. A significant interaction between group and attrition status provides evidence of differential attrition between groups. In general, analyses will proceed using an intent-to-treat approach, and all participants recruited will be included in subsequent analyses.

Missing Data Approach

Multiple imputation will be used to replace missing values following best-practice recommendations [79,80]. Missing data will be imputed using the fully conditional specification, which uses all available data to impute missing data via a sequential regression approach. Missing data points will be replaced with imputed data in 20 data sets, which will be analyzed separately. Model parameters and SEs, which incorporate within and between model variability, will be combined following Rubin methodology [81], as implemented in SPSS version 24 (IBM Corporation) [82].

Examination of Acute Intervention Effects

Our postassessment n, to examine acute intervention effects, is expected to be 150 (75 per condition). We will initially view intervention effects on our mother or infant outcomes using a 2 (pre-post)×2 (intervention group) repeated measure analysis of variance (ANOVA). We will examine the intercorrelations among outcomes and, if significant, will use a MANOVA approach to examine intervention effects. The *F* test is robust to nonnormality if such nonnormality is caused by skewness rather than outliers. We will take appropriate measures to reduce outlier influences.

To examine the relationship between maternal change (parenting and maternal depression) and infant change, one approach will be to create individual β estimates for mothers and infants using the polynomial contrast function within MANOVA to produce individual trajectory scores reflecting parent and infant change from pre to post that can then be used in external between-condition covariate analysis. The trajectory scores will be subjected to an analysis of covariance, with infant change trajectories as the dependent variable and parent change as the covariate. We will determine whether the parent change covariate is significantly related to the dependent variable (demonstrating that changes in parenting behavior and child functioning covary). We will determine the statistical significance and effect sizes of the intervention group effects (ignoring the covariate). We will then determine if entering the parent functioning covariate modifies the intervention group effect size and statistical significance. If parent change is strongly linked to infant change, then entering the covariate should result in nonsignificant intervention effects. Estimates of covariance-adjusted effect sizes will provide estimates of the proportion of the intervention group effect size, which can be explained by the parenting change variable. We will test for between-group heterogeneity of covariance to determine whether the strength of the association between change in parenting and infant functioning differs by intervention group.

Examination of Moderating Influences

To evaluate the moderating influences on parent and infant behavior, our first focus is on how maternal depression before

intervention (ie, chronicity, severity, and receipt of psychiatric treatment or medication) affects intervention dosage; second, we are interested in the moderating effect of dosage on mother and infant change. For depression experience before intervention, we will examine a 2 (high or low dosage)×2 (intervention condition) ANOVA using maternal depression indicators (eg, chronicity) as the dependent measure. A significant main effect for dosage would indicate that higher levels of maternal depression are found at different dosage levels; it is anticipated that higher depression will be evidenced in the low dosage group. A significant interaction would indicate that a higher level of maternal depression is found within a dosage by condition cell. Although we would not anticipate a significant interaction, we will examine if higher levels of depression are associated with low dosage only within the MBN intervention, which could indicate that the skills focus of MBN learning may have been too intense for highly depressed mothers.

To examine dosage as a moderating influence on mother and infant change, we will use the individual β slope estimates reflecting parent and infant change as the dependent measures in separate 2 (intervention condition)×2 (high or low dosage) ANOVA designs. We hypothesize that a significant interaction term indicating the highest positive change trajectories will be for MBN mothers with high dosage, when compared with low dosage MBN mothers and DDAS mothers, regardless of dosage level. If a significant dose-effect relationship exists within the MBN condition, we will determine if an effective dosage level can be identified that is less than the maximum number of intervention sessions offered.

For contextual risks, analysis will examine Pearson correlations between contextual risk and level of maternal depression and a biserial correlation for the relationship between contextual risk and dosage (high or low) to determine if contextual risks are related to both initial levels of depression and subsequent engagement in intervention. To further examine the contextual risk of mother and infant change, we will form a high or low risk categorical variable based on median split and use the same 2 (intervention condition)×2 (high or low risk). If the main intervention condition effect is significant, we would expect MBN mothers and infants, regardless of risk level, to show the greatest improvements when compared with DDAS mothers. If significant interaction effects occur, we would expect mothers and infants within the MBN condition with lower levels of risk to show the greatest improvement in functioning and, though not statistically significant, that MBN mothers and infants, even in the presence of high risk, would show higher positive change trajectories than those of DDAS mothers and infants.

Examination of Maintenance of Effects

Maintenance affects will be viewed by a single indicator for maternal depression and parenting knowledge administered at follow-up. To this end, we will examine maternal change trajectories using structural equation modeling methodology, perform latent growth curve model analyses, and include an intervention condition that predicts intercept and slope estimates. This analysis will supplement our aim 2 analyses, and if these follow-up variables generally reflect the acute intervention trajectories, this will provide support for our view of maternal change across time. Given the restricted nature of follow-up assessments, balancing participant burden, and the desire to maximize assessment completion across time, we will view these maintenance trajectories with caution.

Safety Considerations

Before the study activities, all staff complete human subjects training and participate in safety monitoring and safety responding training under the supervision of the PI and licensed psychologist. Training includes discussion and written responses on study safety monitoring forms, followed by completion of safety monitoring forms to fidelity based on vignette practice. Safety monitoring forms are completed at all assessment time points and upon reporting of any concern about potential harm. Mothers in both conditions receive biweekly automated texts to complete the PHQ-9 [54]. PHQ-9 results are monitored by project coaches for trends in increasing depression severity and harmful thoughts, which trigger an immediate safety response from coaches. All safety monitoring forms that include endorsement of harmful thoughts and required safety response documentation are submitted to the project PI for review. Adverse events and serious adverse events are logged and reported to the IRB and National Institutes of Health (NIH).

Results

Overview

The study was funded by the NIH to begin September 1, 2016. Recruitment efforts were initiated immediately following IRB approval on November 17, 2017. A sample of 184 mothers and their infants were recruited into the randomized controlled trial study between February 15, 2018, and March 11, 2021. Study intervention is underway, and we anticipate that follow-up assessments, which mark the end of data collection, will be completed in March 2022. Following the onset of COVID-19, we published a formative descriptive report on recruitment strategies [46] and a descriptive report of progression from referral to intervention initiation for mothers with study experience before the pandemic and mothers with study experience during the pandemic [83].

Data Availability

Deidentified study data will be made available publicly through a Georgia State University website and through a digital object identifier–linked public repository OpenTrials [84] following a 1-year embargo from the date of publication of primary study outcomes to allow for any commercialization.

Discussion

This protocol describes a randomized controlled trial to evaluate MBN, a mobile remote coaching intervention to reduce maternal depression, promote sensitive and responsive parenting, and improve infant outcomes during the first postpartum year. We have successfully enrolled a socioeconomically disadvantaged sample of primarily African-American women (N=184) into the trial. We anticipate that, relative to the comparison intervention that is focused on education about maternal

depression and infant developmental milestones and matched on technology and coaching structure, women in the MBN intervention will experience greater reductions in depression and gains in sensitive-responsive parenting and that their infants will demonstrate more optimal social-emotional and social-communication behavior.

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Authors' Contributions

KMB, BD, EGF, and LS conceptualized the study; KMB, BD, and SHL developed the methodology; EGF developed the software; BD and CL performed the formal analysis; KMB, BD, LS, and EGF conducted the investigation; KMB, BD, and EGF procured resources; KMB, BD, EAM, and KM wrote the original draft; KMB, BD, and EAM reviewed and edited the manuscript; KMB was in charge of supervision; KMB and BD were in charge of project administration; and KMB was in charge of funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

KMB, BD, SHL, and EGF are the developers of the InfantNet program, and LS is the developer of the MBN program. Each of these programs contributed to the platform for the development of the ePALS MBN program, which was developed by KMB, BD, LS, and EGF.

Multimedia Appendix 1
Peer-review report by the Center for Scientific Review Special Emphasis Panel - Member Conflict: Developmental Risk Prevention, Aging and Social Behavior (National Institutes of Health).
[PDF File (Adobe PDF File), 187 KB - resprot_v10i8e31072_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
BCAP: Brief Child Abuse Potential
DDAS: Depression and Developmental Awareness
ePALS: e-Play and Learning Strategies
IRB: institutional review board
MANOVA: multivariate analysis of variance
MBN: Mom and Baby Net
NIH: National Institutes of Health
PALS: Play and Learning Strategies
PHQ: Patient Health Questionnaire
PI: principal investigator

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Protocol

Effects of a Rehabilitation Program Using a Patient-Personalized Exergame on Fear of Falling and Risk of Falls in Vulnerable Older Adults: Protocol for a Randomized Controlled Group Study

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Abstract

Background: Older adults often experience physical, sensory, and cognitive decline. Therefore, they have a high risk of falls, which leads to severe health and psychological consequences and can induce fear of falling. Rehabilitation programs using exergames to prevent falls are being increasingly studied. Medimoov is a movement-based patient-personalized exergame for rehabilitation in older adults. A preliminary study showed that its use may influence functional ability and motivation. Most existing studies that evaluate the use of exergames do not involve an appropriate control group and do not focus on patient-personalized exergames.

Objective: This study aims to evaluate the effects of Medimoov on risk of falls and fear of falling in older adults compared with standard psychomotor rehabilitation.

Methods: This is a serial, comparative, randomized controlled group study. Both groups (n=25 in each) will receive psychomotor rehabilitation care. However, the methods of delivery will be different; one group will be exposed to the Medimoov exergame platform, and the other only to traditional means of psychomotor rehabilitation. The selection criteria will be (1) age of 65 years or older, (2) ability to answer a questionnaire, (3) ability to stand in a bipedal position for at least 1 minute, (4) score of 13 or greater on the Short Fall Efficacy Scale, and (5) stable medical condition. An evaluation will be made prior to starting the intervention, after 4 weeks of intervention, and at the end of the intervention (after 8 weeks), and it will focus on (1) risk of falls, (2) fear of falling, and (3) cognitive evaluations. Physical activity outside the session will also be assessed by actimetry. The outcome assessment will be performed according to intention-to-treat analysis.

Results: The protocol (2019-11-22) has been approved by the Comité de Protection des Personnes Nord-Ouest I–Université de Rouen (2019-A00395-52), which is part of the French national ethical committee. The study received funding in February 2020. As of October 2020 (submission date), and due to the context of the COVID-19 pandemic, a total of 10 participants out of 50 had been enrolled in the study. The projected date for the end of the data collection is December 2021. Data analyses have not been started yet, and publication of the results is expected for Spring 2022.

Conclusions: The effects of psychomotor rehabilitation using the Medimoov exergame platform on the risk and fear of falls will be evaluated. This pilot study will be the basis for larger trials.

Trial Registration: ClinicalTrials.gov NCT04134988; https://clinicaltrials.gov/ct2/show/NCT04134988

International Registered Report Identifier (IRRID): DERR1-10.2196/24665

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KEYWORDS

older adult; fall; fear of falling; exergame; randomized controlled trial; psychomotor therapy; rehabilitation; fear; risk; elderly; protocol; therapy

Introduction

The ageing population has a higher risk of developing sensory, physical, mental, and cognitive disorders, which increase their risk of falls [1,2]. Physical disability is highly prevalent in older adults and encompasses mobility and balance impairment. Cognitive alterations also induce walking difficulties, leading to increased risk of falls [2,3]. Each year, 20% to 30% of older adults fall [1]. Of these, 25% to 50% will relapse within the year, which aggravates the problem by the multiplication of injuries [1]. Falls lead to numerous and serious health consequences, loss of independence, and institutionalization [1,4]. In addition, falls and balance impairment may induce fear of falling, which may lead to social isolation, anxiety, and depression as well as decreased mobility, physical disability, and falls [5,6]. Fear of falling encompasses fall-related fear, fall-related self-efficacy, and balance confidence [7]. In community-dwelling older adults (≥75 years old), 41.5% experience fear of falling. In long-term care, this prevalence is higher: 63% of institutionalized older adults express a fear of falling. A recent literature review shows that community-dwelling older adults (≥65 years old) score an average of 15 on the Short Fall Efficacy Scale–International (Short FES-I), which measures the fear of falling; this score indicates a moderate fear of falling [8].

Fall prevention programs can reduce the risk of falls if they combine different exercise categories [9,10]. The literature review of Vieira et al (2016) [3] and the quasi-experimental study of Pereira et al (2014) [10] with 506 community-dwelling older adults demonstrate that benefiting from regular physical activities is associated with an improvement in physical abilities and balance. The systematic review and meta-analysis of Tricco et al (2017) [9], which included 54 studies and 41,596 participants, confirmed these results and added that exercise combined with vision assessment and treatment as well as environmental modification are effective in fall prevention [9]. In addition, fall prevention programs should target cognitive function improvement [2]. Cerebral plasticity and cognitive functions are essential for motion and balance [2]. Among executive functions, inhibition is particularly relevant to fall prevention because poorer results of response inhibition tests are associated with future risk of falls [11]. Cognitive inhibition suppresses irrelevant information from the working memory and facilitates automatic response, which may explain its importance for preventing the risk of falls, especially during mobility tasks involving distraction (eg, walking outside) [11]. Adapting the rehabilitation to the patient's cognitive status is paramount to prevent falls [12] and to allow older adults to focus on their rehabilitation programs. Psychomotor therapists are among the professionals recommended by the Haute Autorité de Santé, the French national health agency, to safely administer physical exercise programs to older adults [13]. These therapists possess skills and expertise in intervening in the psychomotor dimensions of falls, namely, the motor, sensory, and cognitive aspects [14].

In rehabilitation, exergames are increasingly being studied, especially exergames using Kinect sensors (Microsoft Corporation) [15-18]. According to Tanaka et al [18], "exergaming platforms are designed to track body motion or body reactions and provide both fun and exercise for game players." Several exergames have been designed for the rehabilitation of older adults, and some of them were found to be effective in studies with before-and-after designs or randomized controlled trials [19,20]. Their safety was deemed good: no adverse effects related to their use were identified [21]. We did not find any studies that compared the effects of patient-personalized exergame-assisted rehabilitation with those of traditional rehabilitation programs [21]. Studies should explore not only the efficacy of an exergame-assisted rehabilitation program, but also its acceptability [21]. Adherence to and engagement in a rehabilitation program are at the heart of its effectiveness and therefore should be considered when evaluating the exercise rehabilitation program [21]. There is no consensus in the literature regarding the adherence of older individuals to rehabilitation programs with exergames compared to programs without exergames [21]. However, some experimental studies with older adults have shown better adherence in a rehabilitation group with exergames than in the control group [22,23]. Exergames are considered to be enjoyable and have the potential to increase motivation and reduce fear of falling. Therefore, they are of particular interest in engaging older people who are afraid of falls in exercise programs.

Medimoov (NaturalPad) [24] is a movement-based video game for rehabilitation of older adults that allows the therapist to choose the movements the patient will perform to interact with the game. The difficulty and the speed of the game can be defined by the therapist, allowing for a fine-tuned personalization of the sessions according to the patient's progress. A preliminary study showed that using Medimoov's personalized activities may positively influence older adults' functional ability and motivation [15]. Most existing studies evaluating the use of exergames do not involve an appropriate control group (ie, a control group following the standard rehabilitation program) [17,21] or do not involve an exergame specifically designed for rehabilitation of older adults that allows for the personalization of the sessions [21,22,25]. Thus, this study aims to evaluate the effects of Medimoov on older adults with fear of falling compared with standard psychomotor rehabilitation as prescribed by physicians. Two aspects of the rehabilitation will be explored: the preventive function (decreased risk of falls) and the therapeutic function (decrease of fear of falling and increase of motivation during rehabilitation).

The main objective is to evaluate the efficacy of exergames played on the Medimoov platform on fear of falling and risk of falls. The secondary objective is to assess the effect of the exergame intervention on the participants' executive functions during the study. Another secondary objective is to explore the perception of exergame-assisted rehabilitation by the participants of the intervention group. The hypothesis is that exergames in rehabilitation can lead to decreased fear of falling and risk of falls due to an improvement of balance, physical functions, and executive functions, including an improvement in cognitive inhibition.

Methods

Design

This study is an open, randomized controlled study in parallel groups with blind data collection for the evaluation criteria. The protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [26,27].

Participants and Recruitment

The research project will be conducted in two intermediate-care wards for older adults at the Charles Foix Hospital, a French geriatric hospital. Guidelines to calculate the sample size do not exist in the literature yet; thus, the sample size has been estimated based on previous studies evaluating fear of falling–focused interventions [28,29]. A sample size of 20 participants per group is often reported. A total of 25 participants per group will be recruited to factor in a potential 20% withdrawal or other variations. Recruitment will be conducted among hospitalized patients in intermediate-care rehabilitation hospital wards. The inclusion criteria will be as follows: (1) age of 65 years or older, (2) ability to understand and answer short and simple questions (as determined by the clinical interview), (3) ability to stand upright in a bipedal position, feet together, for longer than 1 minute with or without a technical aid, (4) a score of 13 or greater on the FES-I [30] (moderate or severe fear of falling), (5) stable medical condition, and (6) ability to give written consent. The exclusion criteria will be as follows: (1) cannot correctly distinguish the elements on the screen, (2) in palliative care, (3) under a legal protection measure, (4) obtained a score <16 on the Mini Mental State Examination (MMSE) [31], and (5) recently underwent orthopedic surgery (<2 months); the latter is an exclusion criterion because it requires specific rehabilitation programs [32]. The MMSE will be used for screening purposes only to exclude patients with severe cognitive disorders that would prevent them from participating. Participation may be interrupted at the participant's request or if the participant experiences an adverse health event (eg, stroke). All patients hospitalized in the rehabilitation ward at the beginning of the study will be screened for eligibility by their physicians, and if eligible, will be asked to participate after a detailed presentation of the protocol by a postdoctoral fellow or a research professional. The eligibility of the patients admitted to hospital after the start of the study will be verified. Participant recruitment will be ongoing until the sample number (N=50) is reached. Eligible patients will receive a letter of information. A random selection will be conducted if the number of eligible patients is higher than the number of required participants.

Randomization

After the randomization, patients will be allocated to an intervention group (rehabilitation program with the Medimoov platform) or to a control group (traditional psychomotor therapy sessions). The randomization will be conducted directly after the signature of the consent form. To ensure concealed allocation [33], each participant will be assigned a code used for the randomization. As the participants will not all be identified before the randomization, block randomization will be conducted (rather than stratification) to control the sample size of each group using the "blockrand" function of RStudio software (RStudio PBC).

Ethical Considerations

The protocol (2019-11-22) has been approved by the Comité de Protection des Personnes Nord-Ouest I–Université de Rouen (2019-A00395-52), which is part of the French national ethical committee. Written informed consent will be collected from each older adult before their participation. The study is registered on ClinicalTrials.gov under the number NCT04134988 (2019/10/22) and in the Commission Nationale de l'Informatique et des Libertés, which verifies the legality and security of computerized personal data in France.

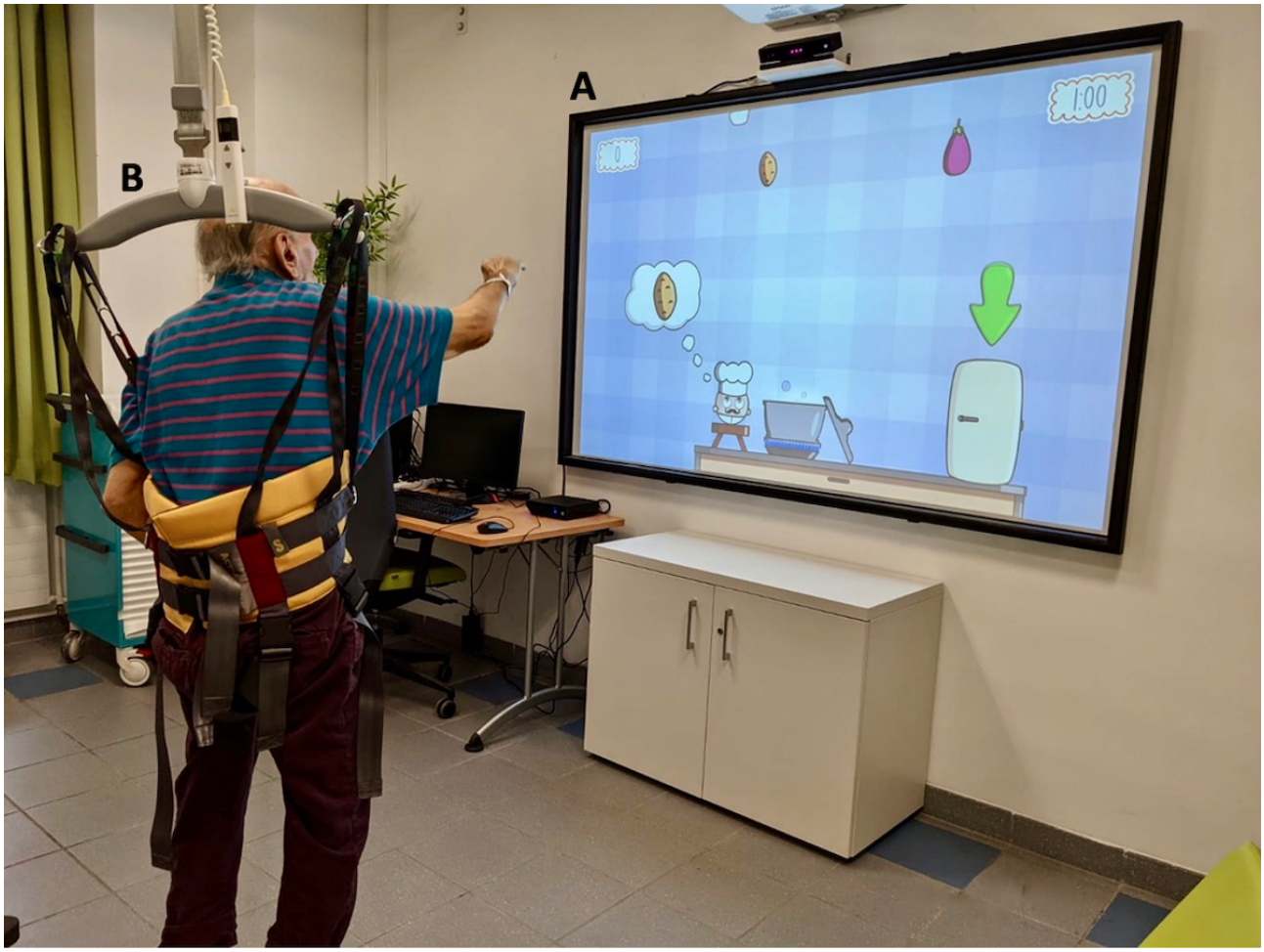
Rehabilitation Programs

Both rehabilitation programs (intervention and control) will be consistent with the prescription of the participants' physicians. For each group, the program will be guided by a psychomotor therapist and will last 8 weeks, with 35-minute individual sessions twice per week. According to professional practices in psychomotor therapy, the psychomotor therapist will ensure the progress of each group's sessions by adapting their proposals to the participant.

Intervention Group: Medimoov Sessions

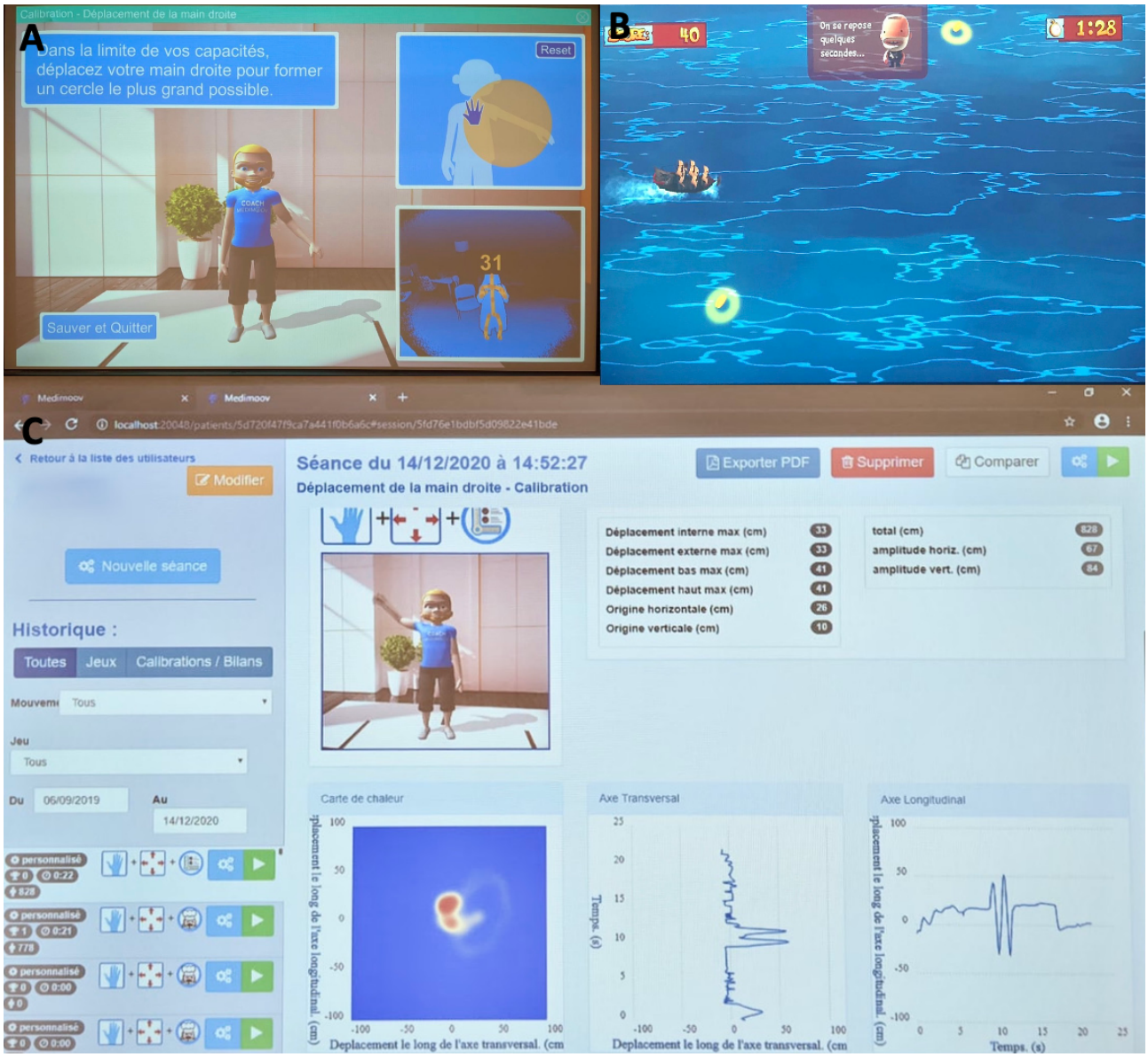
The Medimoov gaming platform [15] is a physio-gaming medical device that works using functional and postural rehabilitation software. The therapy requires a computer equipped with Medimoov, a Kinect camera, a projection screen, and an immersive sound system (Figure 1). Each participant has their own profile in which their age, gender, and physical capacities (eg, their amplitude of movement) are stored (Figure 2). Each game's required movements are adjusted to the participant's capacities with personalized calibration. Medimoov offers 14 exercises (eg, upper limb work, sit-to-stand exercises) within 6 different games that can be configured according to specific conditions (eg, spatial neglect) and different cognitive statuses (eg, simplified decor to avoid distraction for people with limited attention capacities). The length of each game can also be configured according to the participant's stamina.

Figure 1. (A) The large screen displays an exergame. The Kinect camera is positioned above the screen to capture the movements of the participant; the computer with the Medimoov platform is on the left of the screen. (B) The harness protects the participants from injury if they fall during the session.



The program will last 8 weeks, with biweekly individual sessions of 35 minutes for a total of 16 sessions. The personal calibration and the creation of the participant's profile will be performed during the first session. The psychomotor therapist will systematically offer the use of a harness before the beginning of the session. This harness, which is hung from a rail system, secures the person while they are standing and during motor activity. The psychomotor therapist will adapt their proposals to the participant according to his/her professional practice. The sessions will be conducted in the following order: (1) sessions 1 to 4, work on the cervical spine and upper limbs while seated; (2) sessions 5 to 8, in a sitting position, work on limb movement amplitude and precision and movement of the spine as a whole; (3) sessions 9 to 12, work on the spine as a whole with a special focus on the cervical spine with static and dynamic balance in the standing position; and (4) sessions 13 to 16, work on the movement amplitude and precision with static and dynamic balance in the standing position.

Figure 2. (A) Medimoov allows calibration of its games according to the participant's abilities. The instructions for the movements to be performed are displayed on the screen. The orange circle indicates the participant's maximum range of motion, and a feedback image reconstructing the movements captured by the Kinect is presented at the bottom of the screen. (B) Several games can be played. For one of the games, the participant leads a pirate ship to recover gold coins while avoiding rocks and enemy fire. (C) Each participant has a personal profile in which the psychomotor therapist can access the participant's session and performance history.



Control Group: Traditional Psychomotor Therapy Sessions

Parallel to the intervention group, the program will last 8 weeks, with biweekly sessions of 35 minutes for a total of 16 sessions. This traditional psychomotor therapy rehabilitation program will be the one that is usually conducted in the ward. As in the intervention group, the psychomotor therapist will ensure the progress of the sessions by adapting their proposals to the participant according to their professional practice. The individual sessions will be based on the following progression. (1) Sessions 1 to 4, body waking exercises, soft gymnastics with cervical spine and upper limb mobilizations in a seated position; (2) sessions 5 to 8, upper and lower limb movement coordination exercises in a seated position and movement of the spine as a whole; (3) sessions 9 to 12, static and dynamic balance exercises with work on the spine as a whole with a special focus on the cervical spine in a standing position; (4) sessions 13 to 16, in the standing position, psychomotor trails (movement amplitude and precision).

Study Outcome and Measures

Sociodemographic data will be collected from the participants' medical records and will include the following: age, gender, highest education level, living conditions (eg, alone or with relatives, at home or in long-term care), reason for hospitalization, the presence of visual or hearing impairment, and the number of falls during the past 12 months. Clinical evaluations will focus on the following: (1) balance and risk of falls (Score Physical Performance Battery [SPPB] test, One-Leg Stand test, Timed Up and Go [TUAG]), (2) fear of falling (Short FES-I) and (3) cognitive evaluations (Stroop test, Trail Making Test Parts A and B). Wrist actimetry will be used to assess all older adults' spontaneous motor activity outside rehabilitation

sessions (eg, engaging in their activities of daily living, walking indoors in their room and the common areas of the ward, or walking outdoors in the hospital garden). The study procedure and assessment schedule are presented in Table 1.

Table 1. The study procedure is presented following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) template.

Phase and time point (week)	Enrollment	Allocation	Postallocation		End
		Week 0	Week 1	Week 4	Week 8
Enrollment					
Eligibility screening	✓				
Informed consent	✓				
Allocation		✓			
Interventions					
Medimoov or standard psychomotor therapy					
Assessments					
Timed Up and Go			✓	✓	✓
One-Leg Stand			✓	✓	✓
Short Fall Efficacy Scale			✓	✓	✓
Stroop			✓	✓	✓
Trail Making Test Parts A and B			✓	✓	✓
Score Physical Performance Battery			✓	✓	✓
Actimetry			✓	✓	✓
Satisfaction questionnaire[a]					✓

[a]This assessment is specific to the intervention group.

Assessments

The FES-I

This 5-minute questionnaire [34] is composed of 7 questions on daily activities and focuses on fear of falling. Each question can be scored between 1 (“Not at all concerned”) to 4 points (“Very concerned”). Compared to the Activities-Specific Balance Confidence Scale and the Geriatric Fear of Falling Measurement, the FES-I had the best internal consistency [35]. The 4-week test-retest fidelity, measured by an intraclass correlation coefficient (*r*), is 0.83 [30]. Although the FES-I lacks responsiveness among nonfrail older adults, it has been chosen here because hospital inpatients are often frail [35]. As this scale is often used in other experimental studies, using it will allow the results of this study to be compared with those of previous studies [36-39].

The TUAG test

This test [40] consists of standing up from a chair with armrests, walking 3 meters, turning around, and coming back to sit. The test lasts less than 5 minutes. A shorter time of execution of the test indicates a better balance and stability and a lower risk of falls; the time of execution is thus analyzed as a quantitative value indicating the risk of falls. Risk of falls is identified if the duration of the test is longer than 20 seconds. The 2-week test-retest fidelity, measured by an intraclass correlation coefficient (*r*), ranges between 0.93 and 0.99 [40]. Compared to other assessment tools for risk of falls, such as the One-Leg Stand test, the Functional Reach test, and the Tinetti test, the TUAG has demonstrated better discriminant validity for fall prediction [40]. When compared to the Berg Balance Scale and the Tinetti test, the TUAG test has demonstrated the best sensitivity to change (93%) [41]. It has also demonstrated a higher participation rate than the One-Leg Stand test and the Functional Reach test [40]. For these reasons, it has been chosen as the primary outcome for this study.

The SPPB Test

This 5-minute test [42] focuses on static balance, walking, lower-limb strength and risk of falls. This functional assessment has a predictive value for the evolution of the patient's health and autonomy in daily activities after hospital discharge [43]. It provides information on the patient’s balance, quality of walking, and risk of falling. The score varies between 0 and 12; a score <6 indicates low performance and a high risk of falling. The 5-day test-retest fidelity is r=0.89 [44]. The test has been chosen for its good responsiveness to change [45].

The One-Leg Stand Test

This test [40] consists of standing on one leg for as long as possible on each side. A longer time on one leg indicates a better balance ability. As with the TUAG, the time can be analyzed as a quantitative indicator of risk of falling and quality of walking. For healthy older adults aged between 70 and 79 years, the mean duration is 15.0 seconds (SD 13.9); for healthy older adults aged between 80 and 99 years, the mean duration is 6.2 seconds (SD 9.3). The 2-week test-retest fidelity, measured by an intraclass correlation coefficient (*r*), ranges between 0.93 and 0.99 [40]. Measured by effect size, the One-Leg Stand test

has demonstrated a lower sensitivity to change than the TUAG test; thus, it will not be a primary endpoint for this study [40].

Actimetry

The participants' motor activity will be measured continuously for 3 consecutive days by actimetry using a watch that contains accelerometers (Vivago Ltd) worn on the nondominant wrist. Acceleration of movements will be recorded and stored in the watch as arbitrary units per second. For analysis purposes, activity units will be grouped in 3-hour periods during the day (midnight to 2:59 AM, 3 to 5:59 AM, 6 to 8:59 AM, 9 to 11:59 AM, noon to 2:59 PM, 3 to 5:59 PM, 6 to 8:59 PM, and 9 to 11:59 PM). For each participant, the average activity during the 3 days will be calculated based on these 3-hour periods. This innovative exploratory method will not be considered as an endpoint of the study. The aim is to explore how rehabilitation can influence spontaneous mobility in each group and to explore whether it is associated with a decrease in the fear of falling.

The Stroop Test

This test [46] is a 5-minute test to evaluate response inhibition capacities. It will be scored by calculating interference indicators and the *z* score, which adjusts the time required to complete the test to the expected performance, taking into account the age and education level of the participant [47]. The *z* score indicates a deficit in response inhibition (score inferior to –1.65), a limitation in response inhibition (score between –1.64 and –0.9), medium inhibition capacities (score between –0.9 and 0.9), superior response inhibition capacities (between 0.9 and 1.64), and highly superior response inhibition capacity (>1.65) [47]. The test-retest fidelity, measured by the intraclass correlation coefficient (*r*), ranges between 0.84 and 0.91 [48], and the meta-analyses of Demakis et al (2004) [49] demonstrated that the Stroop test is sensitive to change.

The Trail Making Test Parts A and B

This evaluation [50] focuses on executive functions, including number and letter recognition, cognitive flexibility, visual scan, and motor functions. This evaluation lasts 10 minutes. The score represents the amount of time required to complete parts A and B of the test [50]. Scores are then compared to standards that take into account age and educational level [50]. The test-retest fidelity, measured by the intraclass correlation coefficient (*r*), ranges between 0.76 and 0.94 [51]. In their literature review, Pointrenaud et al (1997) [52] demonstrated that the Trail Making Test is sensitive to change.

Documentation of Falls

Adverse events and falls during hospitalization will be documented with their date and severity.

Satisfaction Questionnaire

Within the intervention group, participants will answer a satisfaction questionnaire focusing on Medimoov and the exergaming aspect of their rehabilitation. Their answers will be useful to better interpret the results of this pilot study. The satisfaction questionnaire is composed of 10 5-level Likert-type questions; its aim is to evaluate the participants' experience and their self-confidence after the exergame-based rehabilitation program. The questionnaire takes approximately 2 minutes to complete.

Study Procedures

Three assessments will be performed by a psychomotor therapist (who is not one of the therapists involved in the rehabilitation program) focusing on physical and cognitive capacities. The first assessment will be performed during the first week, before the start of the rehabilitation program; the second will occur during week 4; and the third will occur during week 8, at the end of the rehabilitation program. Assessments will be blinded; the assessors will not know the assigned group of each participant. To preserve neutrality, assessments will be performed in a different room than the sessions.

Endpoints

The primary clinical endpoint is the comparison of the changes in FES-I scores between the two groups. The main secondary endpoint is the comparison of changes in TUAG scores between the groups. Other secondary endpoints are a significantly greater improvement in the One-Leg Stand test, the SPPB test, the Trail Making Test Parts A and B, and the Stroop test in the intervention group and a high level of satisfaction in the intervention group.

Statistical Analysis

Sociodemographic data will be descriptively analyzed (mean, standard deviation, percentage, range). Normality will be tested for all quantitative variables. The characteristics of participants of both groups will be compared via a *t* test or a Mann-Whitney test for nonnormally distributed variables. An intention-to-treat analysis will be adopted; data from all included patients will be analyzed even if they withdraw. Independent sample *t* tests for group differences (or Mann-Whitney U tests for nonparametric data) will be used to evaluated differences in endpoints between pre- and postintervention data. Analysis will be carried out using multiple imputation if some participants have withdrawn from the study before the eighth week. Analyses will be performed using RStudio software.

Results

The study received funding in February 2020. As of October 2020 (submission date), and due to the context of the COVID-19 pandemic, a total of 10 participants out of 50 have been enrolled in the study. The projected date for the end of the data collection is December 2021. Data analyses have not started yet, and publication of the results is expected for Spring 2022.

Discussion

Principal Considerations

This study will allow us to evaluate the effect of psychomotor rehabilitation using the Medimoov interactive gaming platform on fear of falling and risk of falls. Most exergames do not allow for the personalization of the games according to the patient's abilities, which is essential in rehabilitation [53]. An original aspect of Medimoov is that it provides multiple options to personalize each game and follows the progression of the

participants; evaluating the effectiveness of this platform will thus provide new rehabilitation perspectives. Moreover, the study by Lister et al (2014) [16] shows that gamification in health often does not follow professional guidelines and recommendations, which leads to mixed results on fear of falling and risks of falls across studies [17,21]. The design of the present study takes into consideration the recommendation of Lister et al (2014), and we will rigorously compare two rehabilitation programs (the program with the Medimoov platform and the traditional psychomotor therapy sessions) that follow the French national guidelines on fall prevention [13]. Thus, this study will address gaps in the literature and will provide knowledge on patient-personalized exergame effectiveness, which has strong potential for practice and policy changes.

Exergames are often considered to facilitate older adults' motivation to participate in rehabilitation programs [19-21,54]. This study will allow us to explore this assumption and compare participant adherence across groups. The results of this study will, therefore, offer new perspectives on fall prevention programs with effects on both fear of falling and risks of falls, with increased motivation and adherence from the older adult. In addition, links between actimetry and clinical data for this specific population will be explored. The study by Pereira et al (2014) [10] demonstrated that being active (at least 1125 metabolic expenditure minutes per week) was correlated with a decreased risk of falls [10]. The measurement of actimetry has been shown to be an accurate representation of older adults' motor activity [55]. However, the use of actimetry to measure physical activity has limitations; certain activities may not be measured properly depending on where the device is worn on the body (eg, wrist, waist) [55]. Moreover, the removal of the device can sometimes be interpreted as a period of inactivity [55]. This latter limitation will be mitigated through the collaboration of the hospital's care staff, who will notify the research team in the event of any removal of the device. Measuring the evolution of the older adults' actimetry during and after their rehabilitation program will help develop further knowledge on rehabilitation programs, which has the potential to provide older adults with more adapted rehabilitation programs and decrease the incidence of falls [5].

Strengths and Limitations

One of the strengths of the study is that it follows the SPIRIT guidelines [26,27] and the PEDro recommendations [33]. It ensures internal and external validity and provides the necessary information to interpret the results of this study. Another strength is the comparison to the standard in rehabilitation for fall prevention in the context of French geriatric hospitals. Regarding outcome measurement, standardized measures have been chosen based on their sensitivity to change [40] to highlight the effect of the intervention. Moreover, results regarding the intervention effectiveness are assessed with standardized scales and with accelerometers, ensuring data triangulation.

This protocol also presents some limitations. Due to the nature of the intervention, double blinding is not possible. However, measures of the outcomes will be blinded and performed by trained assessors to minimize bias. Moreover, stratification on age, gender, fear of falling, and risk of falls will not be possible for the randomization, as the participants will not all be identified at the beginning of the study. However, possible differences between groups at baseline will be tested to consider them in data interpretation. Desirability bias can occur with participants trying to please the assessor. This bias will be the same in both groups. To minimize this bias, primary and secondary outcomes will be assessed by an independent assessor (different from the psychomotor therapist administrating the intervention). This is an exploratory study with significant limitations in terms of sample size, power, and hence, depth of the statistical analysis that can be conducted. However, in the context of a future larger trial (if warranted), an appropriate sample size and power calculation will be undertaken, which would also allow for a more detailed and robust statistical analysis of the data with enhanced validity and integrity of the results.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Ethics approval and funding proof.
[PDF File (Adobe PDF File), 711 KB - resprot_v10i8e24665_app1.pdf]

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Abbreviations

FES-I: Fall Efficacy Scale–International
MMSE: Mini Mental State Examination
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPPB: Score Physical Performance Battery
TUAG: Timed Up and Go

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Protocol

Web- and Mindfulness-Based Intervention to Prevent Chronic Pain After Cardiac Surgery: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Cardiac surgery is a frequently performed procedure. However, pain after cardiac surgery may become chronic (lasting >3 months) in adults. Once discharged from the hospital, patients are at greater risk of developing chronic postsurgical pain (CPSP) and of prolonged opioid use, as they need to self-manage their pain. Psychological risk and protective factors such as pain-related catastrophic thoughts and pain acceptance determine their ability to cope and their use of opioids, which is crucial for self-management of pain. Studies on mindfulness-based cognitive therapy (MBCT) have multiplied their potential effects on pain acceptance and catastrophic thoughts. However, web-based MBCT for the prevention of CPSP has not yet been examined.

Objective: The aim of this study is to pilot test a 4-week-long web-based MBCT intervention for adults following discharge from the hospital by assessing the acceptability or feasibility of the intervention and examining preliminary effects on pain intensity, pain interference with activities and opioid use, and pain acceptance and catastrophic thoughts in the 6 months following surgery.

Methods: A double-blinded pilot randomized controlled trial will be used to assess a web-based MBCT intervention. Patients will be selected according to the following criteria: age ≥18 years; first-time elective cardiac surgery via a median sternotomy; worst pain in the past week score ≥4/10; ability to understand and complete questionnaires in English; and ability to use an electronic device such as a smartphone, computer, or tablet. After baseline measures, 32 participants will be randomized into two groups: one receiving both the brief, 4-week-long web-based MBCT intervention and usual care (experimental group) and the other receiving only one standardized, web-based educational session with weekly reminders and usual care (attention control group). Peer-reviewed competitive funding was received from Florida State University's Council on Research & Creativity in January 2021, as well as research ethics approval from Florida State University's institutional review board.

Results: Recruitment began in June 2021. Unfortunately, because of the current COVID-19 pandemic, recruitment is not progressing as expected. Recruitment strategies are constantly monitored and updated according to latest data and restrictions surrounding the pandemic.

Conclusions: This research is significant because it targets the trajectory of CPSP, a leading cause of disability and opioid misuse. This is the first study to assess MBCT for the prevention of CPSP after cardiac surgery in the recovery phase. This approach is innovative because it promotes self-management of pain through the modulation of individual factors. If successful, the intervention could be expanded to numerous populations at risk of chronic pain.

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KEYWORDS

postoperative pain; cardiac surgery; chronic pain; web-based; mindfulness; mobile phone

Introduction

Background

Cardiac surgery is a common life-saving procedure [1] that can lead to several complications during recovery. One of them is persistent postoperative pain (ie, pain developing after surgery and lasting at least 3 months with other causes of pain excluded [2]), and its incidence seems to have increased [3]. Estimates suggest that up to 37% of patients undergoing cardiac surgery have persistent pain and will potentially develop chronic postsurgical pain (CPSP; ie, pain lasting for more than 3 months following surgery), with 50% of them reporting moderate to severe postoperative pain [3] that compromises their recovery and daily functioning [3-6]. Furthermore, 10% of the patients will develop new prolonged opioid use (ie, opioid use for more than 3 months) [7], which portends addiction and overdose death [8]. Both chronic pain and chronic opioid use can exacerbate heart disease [9-14]. Compounding this human cost, CPSP is expensive, incurring annual direct and indirect costs of US $41,000 per patient in the United States [15].

Various biopsychosocial factors have been found to increase a cardiac surgery patient's risk of transitioning from acute pain to CPSP [3,5,16,17]. Modifiable psychosocial factors such as pain catastrophizing (ie, an exaggerated negative mental set brought to bear during actual or anticipated painful experience [18]) and pain acceptance (ie, a person's engagement to take valuable actions despite the pain [19]) have gained much attention from researchers. Indeed, greater levels of catastrophic thinking are associated with higher perceived pain intensity, and greater levels of pain acceptance are associated with better functioning [20,21]. A behavioral intervention targeting known risk factors during the sensitive, subacute recovery period may prevent CPSP development [16,22,23]. With reduced hospital length of stay after cardiac surgery [24,25], patients are at risk for CPSP and prolonged opioid use [26,27] as they become more isolated with relatively elevated levels of pain after discharge [3,28,29]. Moreover, rarely aware of the risk of CPSP [30], patients may seek pain management support only after their pain has become chronic and disability has already surfaced [31]. Teaching patients undergoing cardiac surgery effective, psychological pain self-management strategies that address common CPSP risk (eg, pain catastrophizing) and protective (eg, pain acceptance) factors is likely to improve their pain coping and decrease their opioid use [26,32-34]. Indeed, pain acceptance and catastrophizing have been shown to be theoretically related and mediate the relationship between pain and clinical outcomes [20,35,36]. The subacute phase following discharge from the hospital may be an optimal time for such an intervention, but there is limited research examining the efficacy of psychological interventions for pain self-management in the subacute phase [34,37]. The evidence comes from rather demanding interventions (eg, 60-minute weekly group sessions for a minimum of 8 weeks with additional homework), whose efficacy may be decreased because of limited patient adherence [34]. Therefore, it is critical to translate knowledge on pain-related psychological risk factors into timely interventions promoting pain self-management in this decisive phase of the postsurgical pain trajectory [23,38-41].

Traditionally, interventions based on cognitive behavioral therapy have been used to treat chronic pain, as considerable evidence suggests that they have a modest effect on pain and may also decrease pain-related disability and depression [42,43]. However, more recently, the number of studies on mindfulness-based interventions (MBIs) for chronic pain has increased tremendously [44-46]. MBIs train patients to engage in self-regulation of attention by increasing their awareness and acceptance of present moment thoughts, feelings, and physical sensations [47]. Some research suggests that MBIs induce adaptive neurobiological changes and that people who practice mindfulness have better pain tolerance (ie, "the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation" [48]) than those who do not [49]. The first wave of MBIs for chronic pain, such as mindfulness-based stress reduction, mindfulness-based cognitive therapy (MBCT), or mindfulness-oriented recovery enhancement, largely consist of eight weekly, 2-hour group therapy sessions [21]. However, more recent MBIs for acute and chronic pain have adopted briefer formats, and preliminary evidence suggests that they may be efficacious as well [50,51]. Although more research is needed regarding their feasibility and efficacy across different settings, brief MBIs have already been shown to (1) decrease hospitalized patients' pain intensity, pain unpleasantness, and anxiety [52]; (2) decrease surgical patients' preoperative pain intensity, pain unpleasantness, pain medication desire, and anxiety, as well as improve their physical functioning 6 weeks after surgery [53]; and (3) decrease pain intensity, pain unpleasantness, and opioid use in the first month after surgery [54]. In addition, the benefits of MBIs appear to extend beyond pain. MBIs have also been found to improve stress, depressed mood, and sleep quality [55-57], which are all intertwined with chronic pain. Moreover, MBIs are emerging as promising approaches for mitigating heart disease and promoting cardiac rehabilitation [58-60]. Specifically, MBCT—which combines mindfulness strategies and cognitive

therapy—is one of the most widely researched MBIs and may be uniquely suited for pain management given its potential effect on pain-related psychological factors such as catastrophic thinking and pain acceptance [21,61-65].

Our preliminary work with a web- and cognitive behavioral therapy–based intervention in the acute or hospitalization phase after cardiac surgery showed that (1) a brief targeted intervention may be able to modulate modifiable psychological risk factors and reduce postoperative pain interference with activities [66,67], (2) patients express the need for additional pain management support after hospital discharge [39], and (3) clinicians recommend interventions that enhance patients' engagement in their recovery [38]. However, offering additional support and engaging patients in their care can be challenging in terms of time and resources for clinicians and in terms of accessibility for patients. Nevertheless, eHealth approaches seem promising and have the potential to increase active involvement in one's health [68]. Moreover, they seem to lead to similar or improved perioperative clinical outcomes compared with face-to-face interventions [69]. To our knowledge [70], our intervention is the only web-based intervention designed to prevent CPSP in patients undergoing cardiac surgery. Furthermore, brief web-based MBCT for pain management or prevention of CPSP has not been examined.

Objectives

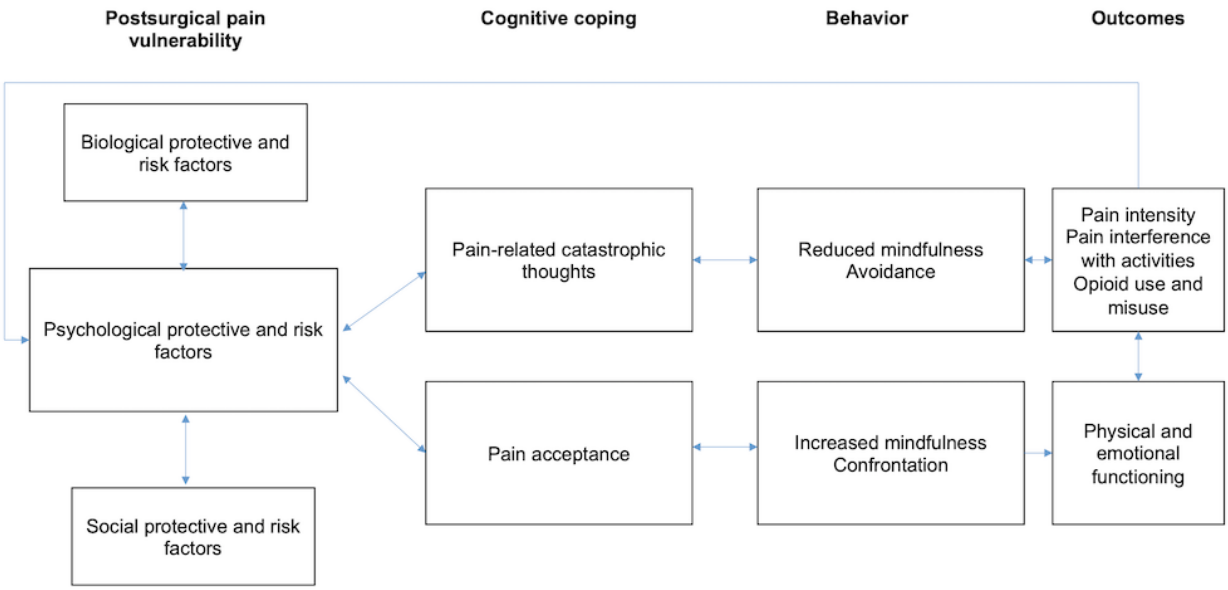
In this study, we will pilot test and evaluate a brief 4-week web-based MBCT intervention designed to promote postoperative pain self-management in patients undergoing cardiac surgery during the subacute phase. Guided by a biopsychosocial framework of pain, our team will accomplish two aims using a pilot randomized controlled trial (RCT) in this stage 1 study [71]: (1) to assess the acceptability and feasibility of the brief web-based MBCT intervention for pain self-management in the subacute phase and (2) to examine the preliminary effects of brief web-based MBCT intervention on pain intensity, pain-related interference with physical and emotional function and opioid use (ie, clinical outcomes), and pain-related catastrophic thinking and pain acceptance (ie, therapeutic mechanisms).

Methods

Theoretical Framework

The biopsychosocial model of chronic pain is the framework of this intervention and study, as it is the most comprehensive foundation for understanding, preventing, and treating chronic pain [72,73]. Psychological risk and protective factors are the cornerstone of this model [72,74-76], as they are relatively modifiable factors involved in pain processes and determine individualized pain reactions, including pain self-management behaviors [77]. Among these factors, pain acceptance and pain-related catastrophic thoughts have been recognized for their contribution to CPSP [34] and have been identified as potential contributing factors to the therapeutic mechanism of MBCT [21,61,62]. For these reasons, these two variables are the targets of the intervention (Figure 1).

Figure 1. Conceptual model based on the biopsychosocial model of chronic pain.



Study Design

A double-blinded pilot RCT will be used to assess the brief web-based MBCT intervention in the 6 months following cardiac surgery (coronary artery bypass grafting and valve replacement). This study received ethical approval from the institutional review board of Florida State University in January 2021. An experienced research assistant (RA) will be responsible for participants' recruitment and informed consent procedures at the time of follow-up with the surgeon (usually 2-4 weeks after surgery). The study will be advertised in the surgeon's offices and surgical units with posters and flyers. Social media platforms and newspapers will also be used. If interested, potential participants will contact the RA via telephone or email, and the inclusion criteria will be assessed. After baseline measures have been collected, participants will be randomized

into two groups by the principal investigator (PI): one receiving both the brief 4-week web-based MBCT intervention and the usual care procedure (experimental group [EG]); the second group receiving only one standardized educational web-based session in the first week along with weekly reminders for 3 weeks and the usual care procedure (attention control group [ACG]). At the end of the intervention, participants will be asked if they received the intervention to evaluate their blinding. Participants from the ACG will be given the opportunity to receive the entire intervention once the study is complete.

Computer software will generate the randomization schedule: permuted block randomization with block sizes of 4 and an allocation ratio of 1:1. The randomization list and opaque sealed envelopes numbered sequentially will be prepared by the PI's colleague who will not be involved in this study. The RA who will be responsible for the entire data collection will be blinded to the patient group assignment. Participants in both groups will receive gift cards of US $25 at each of the four data collection time points (baseline, after intervention, 3 months after surgery, and 6 months after surgery) for a total of US $100.

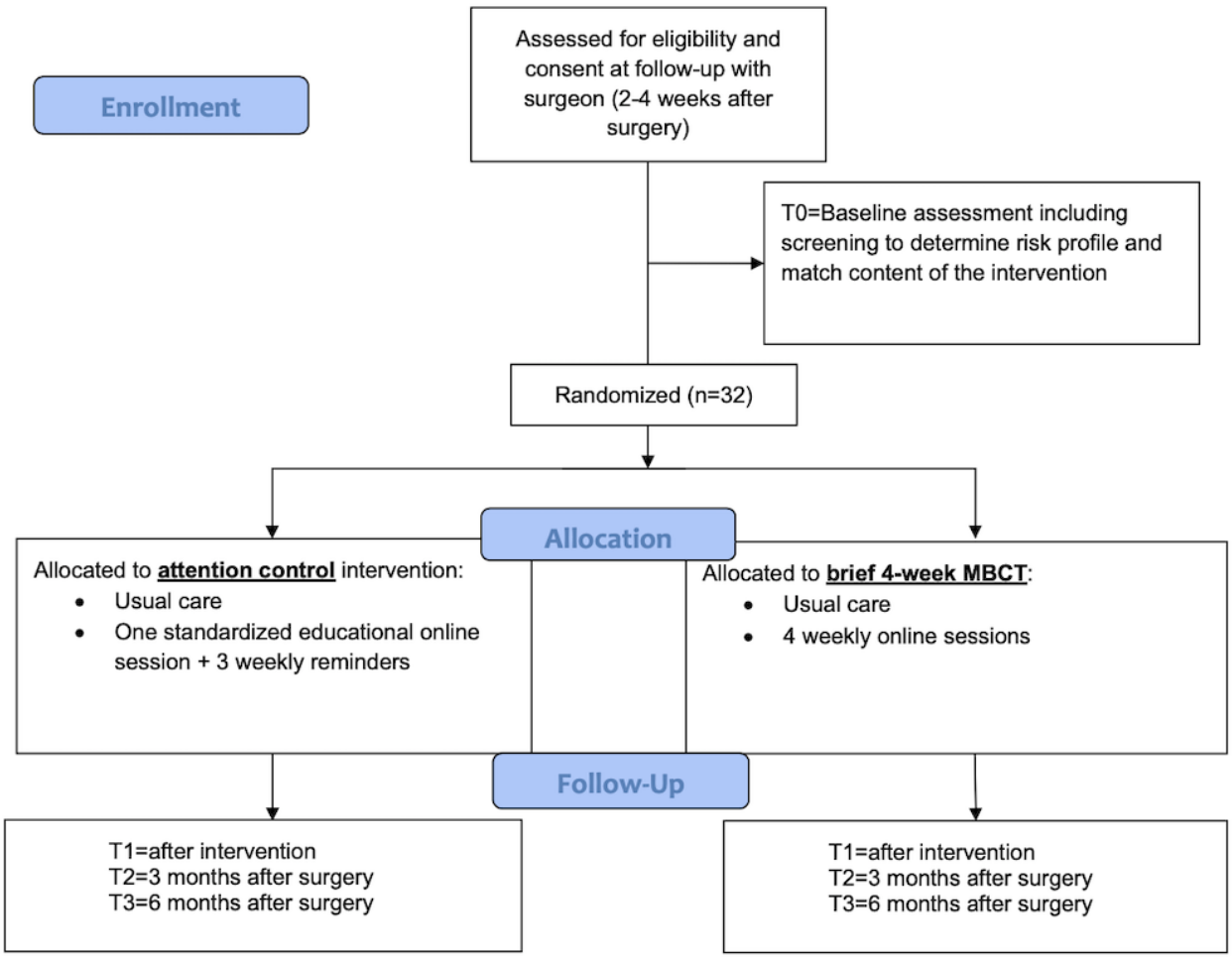
Settings and Participants

To be able to provide precise estimates of mean and variance that will aid in the planning of a larger and sufficiently powered efficacy trial, a reasonable rule of thumb for continuous variables (eg, pain intensity) is a sample size of 12 per group [78]. Based on previous experience with this population and intervention, we could expect an attrition rate of 20%. However, an attrition rate of 30% could be anticipated in the long term at the 6-month follow-up [43]. Hence, we will recruit 32 participants—16 (50%) per group. Patients will be selected according to the following criteria: (1) age ≥18 years, (2) first-time elective coronary artery bypass grafting and valve replacement via a median sternotomy, (3) worst pain in the past week score ≥4/10 [79], (4) ability to understand and complete questionnaires in English, and (5) ability to use an electronic device such as a smartphone, computer, or tablet. Patients will not be eligible for the study if they (1) had undergone a previous thoracotomy or mastectomy and (2) were unable to consent because of physical or cognitive incapacity.

Procedures

All participants will complete baseline measures via a telephone interview (with responses entered in a Qualtrics survey) at the time of enrollment (T0). Figure 2 depicts participant flow during the study protocol.

Figure 2. Participant flow diagram. MBCT: mindfulness-based cognitive therapy.



Choice of Comparators

Most MBI studies include the usual care control groups. A meta-analysis conducted by the Agency for Health Care Research and Quality including 18,753 articles found that only 47 (3%) trials included an active control treatment [80]. This approach only contributes to showing the absolute benefit of an MBI and fails to demonstrate if that MBI has more value than clinical attention alone. Based on our previous findings, accounting for therapeutic contact with clinicians is important in this phase [38]. Moreover, guidance from clinicians embedded in web-based interventions has an impact on outcomes [81]. Hence, attention control is relevant in highlighting the benefits of MBI. Moreover, ACGs may help mitigate the lack of oversight on usual care by standardizing the information received by people in the control groups [82]. Finally, although it is admitted that double blinding is complex to implement in studies with psychosocial interventions, ACGs may contribute to blinding to a certain extent [82]. Thus, an attention control approach is used in this study. Although the web-based standardized session needs to be credible and includes a video recording from a clinician, it was carefully developed so that it does not include any active ingredient [82,83].

Treatment Conditions

Usual care includes a booklet with brief instructions on postoperative care and surveillance of complications provided during hospitalization, and a general assessment and some instructions regarding medication intake and safe return to activities as needed at the time of the follow-up appointment. In addition to usual follow-up care, in the first week of enrollment, the ACG will have access to a 15-minute standardized educational web-based session on persistent postsurgical pain, how pain and stress may interact, and their potential impact on recovery. Brief instructions on self-care (eg, selecting activities that bring a sense of pleasure or mastery) and helpful self-statements (eg, “I will overcome this pain” and “this pain will not last”) will also be provided. In addition, three weekly reminders will be sent to encourage participants to review the web-based session.

Patients assigned to the EG will receive a brief web-based MBCT intervention adapted from the brief four-session clinical manual on MBCT for chronic pain by day [84]. Four 15- to 30-minute sessions are planned (Textbox 1). Each session is structured as follows: an introductory video of the clinician, mindfulness exercise audio recording, wrap-up and weekly homework, or maintenance instructions from the clinician.

Textbox 1. Outline of the four brief mindfulness-based cognitive therapy sessions.

Sessions’ Main Themes and Mindfulness Strategies

Session 1: persistent postoperative pain

- Body scan (20 minutes)

Session 2: stepping out of automatic thoughts

- Mindful breathing (10 minutes)
- 3-minute breathing space

Session 3: acceptance and self-care activities

- Mindful breathing (10 minutes)

Session 4: wrap-up and maintenance plan

- 3-minute breathing space
- Body scan (20 minutes)

The first session will first focus on providing feedback regarding persistent postsurgical pain, the role played by the brain in pain perception, and the relationships between thoughts, feelings, and behaviors. It will end with teaching one mindfulness strategy, that is, body scan, or bringing detailed awareness to each body part and bodily sensation, which is considered an accessible introductory exercise to mindfulness meditation [47]. The second session will focus on pain-related automatic thoughts and teaching the second mindfulness strategy, that is, mindful breathing or focusing attention on breathing—the inhale and the exhale. Moreover, a brief portable 3-minute breathing space strategy will also be presented. The third session will focus on acceptance and self-care strategies and practicing mindful breathing. The fourth session consists of providing feedback and reminders about cognitive reactions to pain and suggesting a maintenance plan along with an opportunity to practice the strategies. The participants will be asked to practice guided meditation (audio recording) 5 days a week for a total of 4 weeks: beginning with body scan in week 1, mindful breathing and the 3-minute breathing space in week 2, and participants may choose either practice for weeks 3 and 4. Participants will also receive a booklet with information about persistent postsurgical pain, an overview of the 4-week program, and a description of the strategies. Participants in the EG will receive reminders as needed, that is, if they do not view the weekly session at all.

The intervention will start upon follow-up with the cardiac surgeon (usually approximately 2-4 weeks after surgery). This time frame will allow participants to recover from surgery, return to their routine at home, and experience the challenges

of managing persistent pain in their home and daily activities. The intervention will end approximately 6-8 weeks after surgery but before pain is considered chronic (ie, 3 months postsurgery). At the time of enrollment, participants will receive education via telephone and email on how to access and implement the brief web-based MBCT intervention or the attention control intervention. Participants will be informed that weblinks (Qualtrics) for each weekly session will be sent via SMS text messaging or email. The link will redirect participants to a Qualtrics page where video and audio recordings are posted. Qualtrics allows viewing videos from any type of device, for example, a computer, tablet, or smartphone. Participants' progress and adherence will be monitored on web using Qualtrics.

Data Collection

As mentioned, measures will be taken via a telephone interview using Qualtrics for data entry. Given the pilot nature of this study and the timeline of the CPSP trajectory [85], all measures, except for acceptability and feasibility of the intervention, will be taken before the intervention (T0), after the intervention (T1), 3 months after surgery (T2), and 6 months after surgery (T3) for both groups [85]. Usual sociodemographic variables (ie, age, sex, civil status, living conditions, education level, and employment status) will be assessed. Relevant medico-surgical information during hospitalization will be collected: type of surgery, presence of postoperative complications, length of hospital stay, and current involvement in a rehabilitation program. The presence of chronic pain before surgery will also be documented. Considering established relations between pain, anxiety, and depression [86-88], measures of anxiety and depression will be taken with the Patient Health Questionnaire-4 for depression and anxiety [89] at all time points. The validity and reliability of the Patient Health Questionnaire-4 has been well established [89-91].

Intervention Acceptability and Feasibility

An assessment of the acceptability of the intervention will be conducted at the end of the intervention (T1) using a questionnaire. Furthermore, 30-minute semistructured individual interviews (telephone or videoconference) will then be conducted by the RA. The intervention components will be rated in terms of four attributes: (1) appropriateness in helping patients manage pain, (2) effectiveness in promoting pain self-management, (3) suitability, and (4) willingness to adhere with the use of the treatment acceptability and preference measure [92,93]. The ratings refer to a 5-point scale ranging from 0 (not at all) to 4 (very much). A total scale score between 0 and 4 was obtained as the mean of the four items to reflect perceived intervention acceptability. The four items demonstrated internal consistency reliability (α>.80) [93] and were validated in this population when used to assess the first module of the intervention [39]. The patients' rating of each component will be used to solicit feedback on the acceptability of the intervention and on the need for further modifications during interviews. The interviews will be digitally recorded and transcribed by a trained RA. Regarding feasibility, in addition to refusal, dropout, and withdrawal rates, field notes will be taken during testing regarding various criteria: fidelity in terms of planned mode, dose, timing, and activities, but material resources and context [92]. Percentages of participants completing the sessions according to the planned schedule and the number of times the sessions were accessed by participants will be assessed through Qualtrics monitoring.

Pain

Pain intensity is a global indicator of pain. It will be assessed using a numerical rating scale (0-10), with the anchors being *no pain at all* (score=0) and *worst possible pain* (score=10). This type of scale is recognized for its reliability, validity, and sensitivity in various clienteles and settings, including patients undergoing cardiac surgery [79,94,95]. Four different measures of pain intensity will be taken: (1) average pain upon movement in the past 7 days, (2) worst pain upon movement in the past 7 days, (3) present pain upon movement, and (4) present pain at rest.

Pain Interference With Daily Activities

As suggested by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials group with regard to pain core domains in clinical trials [79,96], the impact of pain on various aspects of daily living will be assessed with interference items of the Brief Pain Inventory [97]. The Brief Pain Inventory has been successfully validated in patients undergoing cardiac surgery in the context of both acute and chronic pain and intervention research [66,98,99]. It includes 7 items and evaluates the impact of pain on general activity, mood, walking, work, relationships, sleep, and enjoyment of life. Some items were added in earlier studies to measure postoperative pain-related interference with appetite, concentration, and breathing or coughing [66,99]. Each item represents a subscale and can be scored (range: 0-10) and analyzed individually, with the anchors being *does not interfere* (score=0) and *completely interferes* (score=10). The total interference score can also be calculated by considering the sum of all items.

Opioid Use and Misuse

Analgesic medication intake will be documented at all time points. If some participants report that they currently take opioids, they will complete the Opioid Compliance Checklist [100] on opioid misuse. This instrument is a brief self-report measure comprising eight items with a yes or no answer. A greater number of positive answers reflects an increased risk of current and future opioid misuse. Its validity and reliability in detecting drug-related behaviors have been well established [101].

Mindfulness, Chronic Pain Acceptance, and Pain-Related Catastrophic Thoughts

Given that the intervention is meant to increase mindfulness and the associations between mindfulness measures, pain acceptance, and pain-related catastrophic thoughts [21,61,62], mindfulness will be assessed. The Cognitive and Affective Mindfulness Scale-Revised [102] will be used to assess mindfulness. This 12-item scale captures the broad concept of mindfulness according to four domains (attention, present focus, awareness, and acceptance or nonjudgement) without being specific to any type of meditation or strategy. Each item is rated on a 4-point scale with the end points *rarely or not at all*

(score=1) and *almost always* (score=4). The total score is calculated by taking the sum of the items. The Cognitive and Affective Mindfulness Scale-Revised has demonstrated good consistency for the overall score [102] and has been validated with MBI in patients with persistent pain [50]. The Chronic Pain Acceptance Questionnaire-8 [103] is an 8-item questionnaire measuring chronic pain acceptance. This scale comprises two subscales: the degree to which patients engage in daily living activities regardless of pain (4 items) and willingness to experience pain (4 items). It has demonstrated good consistency, and its sensitivity to therapeutic changes has been validated [104]. The Pain Catastrophizing Scale [105] will be used to assess patients' pain-related catastrophic thoughts. It includes 13 items divided into three subscales: rumination (4 items), magnification (3 items), and helplessness (6 items). Each item is rated on a 5-point scale with the end points *not at all* (score=0) and *all the time* (score=4). The total score and scores for each subscale can be calculated by taking the sum of the items. The Pain Catastrophizing Scale has demonstrated an excellent internal consistency [105], and its sensitivity to psychosocial interventions for chronic pain has been established [106,107].

Statistical Analysis

With regard to the first aim, the intervention acceptability scores will be summarized using descriptive statistics. Qualitative data obtained from individual interviews will be analyzed [108] using NVivo software. A preliminary generation of codes or categories based on acceptability attributes from the treatment acceptability and preference measure (ie, appropriateness, effectiveness, suitability, and willingness to adhere) will be used. Double coding will be conducted by the PI and RA. The results will be compared and discussed until a consensus is reached. Frequency counts will also be used to confirm the emergence of themes. Triangulation of both qualitative and quantitative data will be used to develop a more comprehensive understanding of the acceptability of the intervention.

Regarding the preliminary effects of the intervention, the protocol will favor an intention-to-treat approach for the analysis of results, thus involving all patients who were randomly assigned. Participants' flow will be reported according to the Consolidated Standards of Reporting Trials guidelines for psychological interventions [109]. The statistical analysis will be mostly descriptive (mean and SD for continuous outcomes and frequency and proportion for categorical outcomes) with 95% CIs when appropriate. Pain intensity, pain interference, opioid use, mindfulness, pain acceptance, pain-related catastrophic thoughts, and depression or anxiety scores will be summarized using descriptive statistics presented per group at each time point. Furthermore, treatment effects will be estimated and presented with 95% CIs at each time point. Between-group differences will be assessed by fitting linear mixed models for each outcome: pain intensity, pain interference, opioid use, mindfulness, pain acceptance, pain-related catastrophic thoughts, and anxiety or depression. Outcome variables will be regressed on the intervention group (EG vs ACG) and time (preintervention, postintervention, and 3 and 6 months after surgery) after covarying baseline values to perform statistical matching on prerandomized values, thus ensuring that comparisons by treatment group are independent of baseline differences [110]. Of primary interest is the impact of the intervention on the prevalence and severity of CPSP (ie, pain intensity, pain interference, and opioid use) at 3 and 6 months. However, these analyses will be undertaken primarily for illustrative purposes, as the study is not powered to show statistical significance. An α level of significance of .05 will be used for all analyses.

Results

Recruitment began in June 2021. Although several clinical settings expressed a great interest for the study and type of intervention, recruitment is not progressing as expected as passive recruitment strategies were used because of the current pandemic. The decrease of elective procedures such as cardiac surgeries during surge of COVID-19 cases is also a considerable barrier. The recruitment process is constantly monitored by the research team, discussed with clinical partners, and updated according to the latest data and restrictions related to COVID-19. Data collection is expected to be completed by March 2022.

Discussion

Principal Implications

Pain after cardiac surgery is the most common symptom. However, multiple challenges still exist regarding its management [111]. The impact of unrelieved pain after cardiac surgery can be long lasting and can even influence the trajectory of cardiovascular disease [10,11]. For a few years now, a multimodal approach has been the gold standard for postoperative pain management [112]. Our previous work has demonstrated the potential to influence pain management behavior and postoperative recovery in the first days after surgery with a brief intervention if content targets specific psychosocial risk factors for CPSP. Most importantly, the intervention approach targets psychological factors that play an important role in the transition from acute to chronic postoperative pain. A logical next step in this research regarding the prevention of CPSP is to explore the potential impact of such interventions on pain after discharge from the hospital when patients are more isolated and need to self-manage their pain. In addition to our preliminary work in the acute phase, an intervention tackling pain in the different phases of the perioperative continuum could be proposed. The ultimate goal is to prevent the development of chronic pain and associated disability and opioid misuse.

Significance of Intended Outcomes

Achieving these aims is significant because they directly target the trajectory of CPSP, a leading cause of disability and opioid misuse. This approach is innovative because it promotes pain self-management through the enhancement of individual protective factors and modulation of individual risk factors. Further MBI for pain is fairly recent and has not been examined for its potential role in preventing chronic pain. Of note, preventing the transition to chronic pain and reliance on opioids while promoting patient engagement and care accessibility is closely in line with the National Institute of Health's National

Pain Strategy [23] and Helping to End Addiction Long-term initiative [113]. Finally, the lack of continuity of care has emerged as a barrier to the prevention of CPSP [111]. With the proposed approach, patients can access the intervention at their convenience and according to their needs but also gain autonomy through a self-management approach. Indeed, the use of interactive technologies helps address the challenges of continuity of care between the different phases, as well as accessibility to health education and evidence-based quality pain care, which is a current national concern [23].

Conclusions

This funded pilot RCT will examine the acceptability, feasibility, and preliminary efficacy of a web-based MBI for the prevention of CPSP during the recovery period after discharge from hospital. The results of this study will inform current clinical guidelines promoting a multimodal approach to pain management and continuity of care. If successful, the intervention could be expanded to numerous surgical populations at risk of developing CPSP, such as orthopedic surgical patients and other patients at risk for chronic pain, persons with work-related injuries, or persons living with a chronic disease. After further evaluation, a brief and cost-effective intervention could be introduced to hospitals, rehabilitation programs, and other primary care settings to support clinicians and patients in their partnership for the prevention of CPSP. The high potential of integration of the intervention in established care programs, such as rehabilitation programs, is promising for its uptake and sustainability.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from Florida State University's Council on Research & Creativity.
[PDF File (Adobe PDF File), 113 KB - resprot_v10i8e30951_app1.pdf]

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Abbreviations

ACG: attention control group
CPSP: chronic postsurgical pain
EG: experimental group
MBCT: mindfulness-based cognitive therapy
MBI: mindfulness-based intervention
PI: principal investigator
RA: research assistant
RCT: randomized controlled trial

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Protocol

Repeated Transcranial Magnetic Stimulation for Improving Cognition in Alzheimer Disease: Protocol for an Interim Analysis of a Randomized Controlled Trial

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Abstract

Background: Many clinical trials investigating treatment efficacy require an interim analysis. Recently we have been running a large, multisite, randomized, placebo-controlled, double-blind clinical trial investigating the effect of repetitive transcranial magnetic stimulation (rTMS) treatment for improving or stabilizing the cognition of patients diagnosed with Alzheimer disease.

Objective: The objectives of this paper are to report on recruitment, adherence, and adverse events (AEs) to date, and to describe in detail the protocol for interim analysis of the clinical trial data. The protocol will investigate whether the trial is likely to reach its objectives if continued to the planned maximum sample size.

Methods: The specific requirements of the analytic protocol are to (1) ensure the double-blind nature of the data while doing the analysis, (2) estimate the predictive probabilities of success (PPoSs), (3) estimate the numbers needed to treat, (4) re-estimate the initial required sample size. The initial estimate of sample size was 208. The interim analysis will be based on 150 patients who will be enrolled in the study and finish at least 8 weeks of the study. Our protocol for interim analysis, at the very first stage, is to determine the response rate for each participant to the treatment (either sham or active), while ensuring the double-blind nature of the data. The blinded data will be analyzed by a statistician to investigate the treatment efficacy. We will use Bayesian PPoS to predict the success rate and determine whether the study should continue.

Results: The enrollment has been slowed significantly due to the COVID-19 pandemic and lockdown. Nevertheless, so far 133 participants have been enrolled, while 22 of these have been withdrawn or dropped out for various reasons. In general, rTMS has been found tolerable with no serious AE. Only 2 patients dropped out of the study due to their intolerability to rTMS pulses.

Conclusions: Overall, the study with the same protocol is going as expected with no serious AE or any major protocol deviation.

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KEYWORDS

interim analysis, treatment efficacy, repetitive transcranial magnetic stimulation; Alzheimer disease; double blind; treatment; placebo controlled; randomized

Introduction

Clinical trials investigating treatment efficacy often incorporate an interim analysis of outcomes. Interim analysis is conducted for a variety of different reasons, which may include detecting unbalanced patterns of adverse events (AEs) in treatment arms with the potential to indicate harm to participants, or determining on statistical grounds whether continuing data collection to the originally planned sample size is likely to provide a definitive answer to the question framed by the primary hypothesis. Recently we have been running a large, multisite, randomized, placebo-controlled, double-blind clinical trial for investigating the effect of repetitive transcranial magnetic stimulation (rTMS) treatment for improving or stabilizing cognition in patients in the mild to moderate stage of Alzheimer disease (AD). All 3 sites are located in urban centers of countries with a socialized health care system (Winnipeg, Montreal, and Melbourne). The details of the protocol are described in [1]. In brief, the study has 2 doses of treatments (either 2 or 4 weeks, 5 days/week) with either an active or a sham coil wherein 1500 pulses at 10 Hz are delivered in 1.5-second trains with 10-second intertrain intervals; the pulses are applied to dorsolateral prefrontal cortex bilaterally. The primary outcome measure is the change in the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) score from pretreatment to posttreatment. Secondary outcome measures are changes in performance on tests of frontal lobe functioning (Stroop test and verbal fluency) [2], changes in neuropsychiatric symptoms (Neuropsychiatric Inventory–Questionnaire [NPI-Q]), and changes in activities of daily living (Alzheimer Disease Co-operative Study-Activities of Daily Living Inventory [ADCS-ADL]). Tolerability of the intervention is assessed using a modification of the Treatment Satisfaction Questionnaire for Medication (TSQM) [3]. We will assess participants at baseline and 3, 5, 8, 16, and 24 weeks after the start of the intervention. The initial sample size to have a minimum of 80% power level and a significance level of .05 has been estimated as 208 considering 10% dropout.

The goal of the interim analysis is to investigate whether continuing the trial to its planned sample size of 208 is likely to achieve the goal of determining whether active rTMS treatment benefits patients with AD beyond the placebo effect. The objectives of this interim analysis are to (1) ensure the double-blind nature of the data while doing the analysis, (2) estimate the predictive probabilities of success (PPoSs), (3) estimate the numbers needed to treat, (4) re-estimate the initial required sample size.

Methods

Overview

The initial estimate of sample size was 208. The interim analysis will be based on 150 patients who will be enrolled in the study and finish at least 8 weeks of the study. Our protocol for interim analysis is explained in detail in the following steps.

Procedure to Ensure Double-Blind Nature of Data

At the very first stage, the data will be prepared for analysis by a single investigator (ZM) who is aware of group assignment but who does not contribute to the data analysis. This individual will randomly sort and relabel the study participants as P1 (patient 1), P2, P3, etc. The same individual will then randomly sort and label the 3 arms of the intervention (2-week active, 4-week active, and sham) as Group 1, Group 2, and Group 3 before forwarding the data to the statistician. The data will be analyzed by a research assistant and statisticians blind to information about participants contributing to the study, who will also remain unaware of the group (sham versus active) assignment.

Definition of the Responders

A patient is considered as a (positive) responder to rTMS treatment if s/he meets either one of the 3 criteria below. These criteria are derived based on similar literature monitoring improvement/decline in patients with Alzheimer [4-8]. The literature most commonly suggests a change in ADAS-Cog score from baseline is considered significant (either positive or negative) if the change is 3 points or more from the baseline score. The 3+ score of ADAS-Cog change from baseline (in either positive or negative direction) is considered significant based on studies such as [4]. That study investigated what range of ADAS-Cog change has clinical relevance in a population of 181 patients across 6 months.

Note that in ADAS-Cog and NPI-Q assessments, negative changes from baseline represent improvement, whereas for ADCS-ADL a positive change from baseline implies improvement. In order to avoid confusion, the criteria for responders are written using the term “improvement,” which means a change from baseline toward better cognitive or behavioral function (ie, a positive value for ADCS-ADL and a negative value for ADAS-Cog and NPI-Q).

We define the responders/nonresponders by applying the following criteria. Note that the AND is a logical AND.

- Having 3+ score improvement in the ADAS-Cog score (compared with baseline) at *either* Week 5 *or* Week 8 (*marked positive response*).
- Having a nonsignificant improvement (<3 score) in ADAS-Cog *AND* an improvement or same (ie, improvement score 0) in ADCS-ADL *or* NPI-Q at *either* Week 5 *or* Week 8 (*moderate response*). If the AND part does not hold, then it is considered as a *Small Response*.
- Having a nonsignificant worsening (<3 score) in ADAS-Cog *AND* an improvement (1) score in *both* ADCS-ADL and NPI-Q at *either* Week 5 *or* Week 8 (*small/stabilized*

response); otherwise, if the AND part does not hold, the participant is considered as *nonresponsive*.

The above definition of responders is a slightly stricter version of the definitions of responders commonly used in studies to investigate the effect of donepezil (Aricept); for a review, see [5]. It also differs from those studies on donepezil's efficacy in that the latter outcomes were analyzed at 6 or 12 months after the intervention.

Among the responder groups, we will identify patients with small, moderate, and marked responses, and then estimate the "number needed to treat (NNT)" for each type of response, as NNT is also a measure of the efficacy of the treatment [7].

Definition of Success

Because rTMS treatment has been suggested as an alternative nonmedication treatment for AD, it makes sense to define its success rate similar to the trials investigating the efficacy of a "standard" medication.

The most commonly used medication for AD is donepezil (Aricept). Several studies have shown significant differences in the number of responders to donepezil versus sham/placebo [4-8]. However, one should also note that the number of nonresponders in all those studies has been much higher than the number of responders. For example, a review of 5 clinical trials [5] of donepezil showed that the ratio of responders versus nonresponders for active treatment was 26/74, whereas the placebo effect response ratio was 14/86. An important meta-analysis [6] of 14 randomized, double-blind, placebo-controlled trials of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) used in therapeutic doses for at least 12 weeks estimated NNT for different levels of improvement. Their results showed the NNT for 1 additional patient to benefit from the treatment was 7 to achieve stabilization or better, while it was 12 for minimal improvement or better, and 42 for marked improvement. Moreover, the NNT for 1 additional patient to experience an AE was 12. All these values were estimated at the 95% confidence interval.

To guide decision making regarding whether to discontinue or continue the clinical trial until reaching the planned target sample, we will derive predictive probabilities for the study if it continues as opposed to relying only on the *P* values of the analysis at the time of interim analysis.

Based on the above literature [4-8], if the rTMS treatment (*either* dose of the treatment: 2 or 4 weeks) results in *similar or better* outcomes (on average) than those of cholinesterase inhibitor medications as reported in the literature (cited references), and the predictive probabilities are also in favor of similar or better results than those medications after reaching the planned target, then our study should continue; otherwise, the study might be terminated.

Basic Analysis Details

For the interim analysis, we will use the primary outcome measure (ADAS-Cog) and 2 secondary measures of ADCS-ADL and NPI-Q, which are the most commonly used tests to evaluate improvement or decline of a patient with Alzheimer over time in clinical trials. The changes in these measures compared with baseline will be analyzed.

As the very first step, descriptive basic statistics will be provided to compare the mean and standard deviation of values among the 3 study sites. As the ADAS-Cog, ADCS-ADL, and NPI-Q are all continuous variables, we will use an analysis of covariance (ANCOVA) model to compare the 3 treatment groups (4 and 2 weeks of active and sham).

The models of efficacy will contain covariates for baseline score, treatment effect, and center effect. The parameters for the efficacy as well as futility models are the changes from baseline of the 3 outcome measures among responders (all 3 levels) and nonresponders in each of the 2 active treatment groups versus sham. The standard assumptions on covariance will be tested before running the ANCOVA. If they fail the normality tests, we will use equivalent nonparametric tests (ie, ranked ANCOVA) [9]. The Fisher least significant difference procedure will be used to control for multiple comparisons (responders/nonresponders of each active treatment group) with sham group.

To enroll patients into the study, we use their age and Alzheimer severity measured by the Clinical Dementia Rating Scale sum of boxes score [10] for stratified randomization to the arms of the study. At the interim analysis, and also at the end of the study, demographic variables of age and sex will be investigated using analysis of variance models with factors for treatment and site. Within-group changes in the 3 outcome measures will be analyzed using paired *t* tests. Between-group differences will be investigated by ANCOVA.

We will also investigate the occurrence, if any, of serious AEs that lead to withdrawal of participants from the study in relation to the site and treatment dose.

Predictive Probabilities of Success

Conditional power is basically the power of the test, that is, the probability to not reject the null hypothesis when it is false. At interim analysis, the conditional power is estimated as the probability of rejecting the null hypothesis of no effect, given a specific alternative hypothesis. PPoSs [11] are weighted averages of the conditional powers across the current probability that each success rate is the true success rate (ie, weighted by the posterior distribution from the existing data). In other words, PPoS is the probability of achieving a successful (significant) result at a future analysis, given the current interim data that have a specific alternative hypothesis. Hence, predictive probabilities are a much more realistic value of predictive trial success than any single estimate of conditional power. The PPoS will be estimated using available statistical software for Bayesian calculation using noninformative prior probabilities. Nevertheless, the following is a series of steps that will be done for PPoS estimation as suggested in [12]:

- At an interim analysis, sample the parameter of interest θ from the current posterior given current data $X(\theta)$. The parameter θ is the responses of patients in the study.
- Complete the data set by sampling future samples X(m), observations not yet observed at the interim analysis, from the predictive distribution.

- Use the complete data set to calculate the success criteria (*P* value, posterior probability). If success criteria are met (eg, $P<.05$), the trial is likely to be a success.
- Repeat the first 3 steps for a total of B times (B is an arbitrary but reasonable number defined by the statistician); the PPoS is the proportion of simulated trials that achieve success.

Confounding Variable (Acetylcholinesterase Inhibitor Medication Effect)

In our study, the majority of patients are on a stable dose of an acetylcholinesterase inhibitor (AChEI) medication. No participant changes or starts an AChEI medication after being enrolled into the study. However, because 35% (47/133) of participants so far are not on any AChEI medication, it should be considered as a confounding variable when analyzing the results.

As the number of participants is still small given the number of independent variables, we will use permutation statistical analysis that tests whether the observations are independent and does not make any assumption about the data's distribution. If we find the intervention arms unbalanced (statistically) in terms of the number of nonmedicated patients, we will have to adjust our analysis for such a confounding variable.

The Numbers Needed to Treat (NNTs)

The NNT is another measure to summarize effects of a treatment based on the relative risks. Thus, many clinical trials do calculate the NNT at the end of study or at interim analysis. The NNT for 1 patient to be a responder (either in mild, moderate, or marked response groups) will be calculated by predictive probabilities and method presented by [7].

Sample Size Re-estimation

At interim analysis for efficacy, a trial can be stopped early by reassessing the sample size based on existing data in case the sample size was overestimated. By contrast, if the sample size initially was underestimated, at the interim analysis, the PPoS can give a better estimation of what sample size is needed for the data to support the study's hypotheses. We will reassess the sample size at the interim analysis by the method introduced in [8].

Results

Current Trial Status

As of May 1, 2021, a total of 523 patients were screened, of whom 133 were enrolled across the 3 sites of the study (62 in Manitoba, 39 in Quebec, and 32 in Australia) and randomized to different arms of the study. Of the 133 participants, 110 have completed the 6-month study period, 1 is waiting to start the treatment (still on hold due to the pandemic), and 22 have withdrawn or discontinued due to different reasons detailed below.

The percentage of the withdrawn cases so far is therefore 16.5% (22/133), which is much higher than our initial 10% estimation. However, partial data for approximately 40% (9/22) of the withdrawn patients can be used for analysis as those were discontinued/withdrawn during the follow-up period after finishing the treatment. The withdrawn cases are categorized into 5 groups. See Table 1 for details and number of withdrawn patients in each category.

Table 1. Information on withdrawn patients.

Category	Number	Reasons
Became ineligible during the pandemic	2	They were enrolled before lockdown, but their cognitive function declined rapidly during the lockdown and they became ineligible.
Principal investigator withdrawal—noncompliant	3	One changed medication during the study and 2 developed an illness and were withdrawn by the principal investigator for safety concerns.
Participant withdrawal—changed mind before treatment	7	No particular reason was given.
Participant withdrawal—too much anxiety due to treatment	2	They found the pulses too painful to tolerate.
Unrelated health and family issues	8	Two could not finish treatment due to the pandemic, 2 could not finish treatment due to unrelated health issues, and 4 could not attend all assessment sessions due to unrelated health conditions but their data up to a point can be used.

Side Effects, Adverse Events, and Tolerability

In this study, at the end of each treatment session, the treatment administrator asks patients via a checklist about any related or nonrelated symptoms and asks them to identify the level of discomfort associated with receiving TMS pulses on a scale of 0-10 as shown in Multimedia Appendix 1. Furthermore, before starting the daily treatment session, the administrator asks the patient whether they had any lingering symptoms from the previous treatment session. In addition, the administrator asks the caregiver on every treatment session if there has been any side effect due to the treatment on the day before. This information is reported to the Data Safety Monitoring Board as well as to the Ethics Board of the study.

The expected side effects of rTMS are scalp pain/sensitivity, leg jerking, toothache, jaw clenching, or eye twitches during the treatment. These symptoms should abate immediately after the end of treatment at each session. If the duration of any of the above symptoms is prolonged, then it is considered as an unexpected side effect.

Other expected side effects include lingering eye twitches, headache, feeling exhausted, or having slight dizziness after the

treatment that may last for a few hours. These symptoms are expected to diminish without requiring medication. If they are sustained more than a few hours, they should be listed as unexpected.

Other unexpected side effects that may or may not be related to rTMS treatment include nightmares, prolonged feeling of disorientation, confusion, nausea, fatigue, dizziness, agitation, eye redness, and neck stiffness. Seizure is a rare documented side effect of rTMS among at-risk individuals; for this reason, the screening process is designed to exclude such patients from participating and a protocol for management of an unexpected seizure is in place at each site.

Information about possible side effects is written on the consent forms and explained to each participant and his/her caregiver so they are knowledgeable when signing to provide their informed consent prior to enrollment into the study. AEs, whether expected or unexpected, are managed according to the protocols developed for the Ethics Board at each site. The association of serious AEs, that is, any prolonged side effects beyond a day or any side effect that needed medical intervention, with the treatment protocol is determined by the teams' physician(s) after consultation with the site PI, patient, and any caregivers involved in the study. Nonserious expected AEs are referred to the site PI for documentation. Nonserious unexpected AEs are referred to the PI, who will consult with the team's physicians as necessary to determine their association with the treatment protocol. The extensive list of side effects is reported to the Data Safety Monitoring Board of the study as well as to the Ethics Board of the University of Manitoba on a regular basis.

To date, there has been no serious AE. Nevertheless, out of the 133 participants, 89 reported minor typical AE of the rTMS treatment and 12 have reported unexpected AE. The most commonly reported AE has been mild to moderate discomfort and sensitivity to the pulses, with a pain scale of 2-7, while receiving them; however, this reported AE generally reduced over the sessions; most discomfort is reported in the first few sessions of the treatment. The second most commonly reported AE has been fatigue, headache, or both immediately after the treatment, which subsided within a couple of hours without any pain medication. There were also reports of dizziness, disorientation, and nausea after treatment but with much less frequency.

In terms of tolerability, because only 2 of 133 participants withdrew due to finding the rTMS pulses too painful and causing excessive anxiety, we may say overall the participants have tolerated the treatment protocol well.

Medication Effect on Analysis

In our clinical trial, we enroll patients who are either on a stable dose of an AChEI medication or not taking any cognition-enhancing medication; most importantly they should not change their medication or no-medication status (or dosage, if applicable) during the course of the study (6 months). Thus, we investigated whether the number of nonmedicated patients could have any effect on the interim analysis. Overall, of the 133 participants, 46 were not on cognition-enhancing medication during the time in which they were participating in the study.

Statistical analysis of the data using chi-square and permutation tests of independent variables showed that the mean number of nonmedicated patients did not differ significantly across the 3 arms of the study ($P>.1$). The results so far also showed no significant interaction between time and medication ($P=.07$); in other words, the arms of the study are also stable over the observations made at different times (4 different batches of data, ie, the first, second, third, and fourth group of 33 participants enrolled across the sites), implying that we can expect the same nonsignificant differences in the number of nonmedicated patients among the treatment arms in future. This analysis will be repeated at the interim analysis.

Discussion

Overall, the study has been going as expected. In general, participants have found the rTMS treatment tolerable and have been compliant with the study protocol; the side effects have been minor and expected in general. Most participants in the sham group have received real treatment at the end of the 6-month study period. Medication can be a confounding variable. Because of the slow enrollment rate of patients with Alzheimer with the strict inclusion/exclusion criteria as in this study, we did not stratify or otherwise control for medication status during the randomization process. To date, 35% (47/133) of patients were not taking cognitive-enhancing medication during participation in the study, and the distribution of such participants does not differ across time or across arms of the trial. Should these results change at the interim analysis, we will adjust for this variable in our statistical analysis.

Conflicts of Interest

PBF is supported by a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (1078567). PBF has received equipment for research from MagVenture A/S, Nexstim, Neuronetics and Brainsway Ltd and funding for research from Neuronetics. He is a founder of TMS Clinics Australia.

Multimedia Appendix 1
Interim analysis.
[DOCX File , 515 KB - resprot_v10i8e31183_app1.docx]

Multimedia Appendix 2
Peer review reports.

[PDF File (Adobe PDF File), 105 KB - resprot_v10i8e31183_app2.pdf]

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Abbreviations

AChEI: acetylcholinesterase Inhibitor
AD: Alzheimer disease
ADAS-Cog: Alzheimer Disease Assessment Scale-Cognitive Subscale
ADCS-ADL: Alzheimer Disease Co-operative Study-Activities of Daily Living Inventory
ANCOVA: analysis of covariance
NPI-Q: Neuropsychiatric Inventory–Questionnaire
PPoS: predictive probability of success
rTMS: repetitive transcranial magnetic stimulation
TSQM: Treatment Satisfaction Questionnaire for Medication

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Protocol

Prevalence of Early Childhood Caries in South Africa: Protocol for a Systematic Review

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Abstract

Background: Young children are at the highest risk of developing dental caries as they have a lack of autonomy over their diet and oral hygiene practices. Dental caries develops over time due to demineralization of tooth substance (enamel), which results from acid production during sugar metabolism by bacteria. Early onset of dental caries often results in asymptomatic presentation, but if left untreated, it can result in severe pain, infection, and dentoalveolar abscesses. Early childhood caries (ECC) is defined as dental caries in children aged 6 years and younger and is a significant public health problem in South Africa. According to the Global Burden of Disease study, untreated dental caries of primary teeth affects 532 million children. Untreated dental caries has many detrimental effects which can affect the physical development and reduce the quality of life of affected children. Furthermore, long-term untreated dental caries can result in school absenteeism, low BMI, and poor educational outcomes.

Objective: The purpose of this study was to determine the prevalence and severity of ECC in South Africa in children under the age of 6 years.

Methods: All cross-sectional studies documenting the prevalence and severity of dental disease (decayed, missing, and filled teeth scores) will be included. Various databases will be searched for eligible studies. Only studies conducted on South African children aged 6 years and under will be included. There will be no restriction on the time or language of publication. The quality of all eligible studies will be analyzed by a risk of bias tool developed by the Joanna Briggs Institute. The results will be presented narratively, and if possible, a meta-analysis will be conducted.

Results: The protocol is registered with PROSPERO. The literature search was initially conducted in November 2018 and was repeated in November 2020.

Conclusions: The results of this study will be used to advise stakeholders of the prevalence and severity of dental disease in children under 6 years of age in South Africa.

Trial Registration: PROSPERO CRD42018112161; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018112161

International Registered Report Identifier (IRRID): DERR1-10.2196/25795

(JMIR Res Protoc 2021;10(8):e25795) doi:10.2196/25795

KEYWORDS

dmft; prevalence; dental caries; South Africa; early childhood caries

Introduction

Early childhood caries (ECC) is a significant public health problem in children aged 6 years and under living in South Africa [1]. According to the Global Burden of Disease study, the prevalence of untreated dental caries in primary teeth is 532 million [2].

Untreated dental caries has many adverse effects that can affect physical development, including increased absenteeism from school [3], low BMI [4,5], negative educational outcomes [3], and poor oral health-related quality of life [6,7].

Children are at the highest risk of developing dental caries as they are vulnerable and depend on their caregivers for their dietary needs and oral hygiene. Dental caries develops over time and is a consequence of the demineralization of tooth enamel by acids produced during the metabolism of sugars by cariogenic bacterial sugars [8]. The early stages of the disease are often asymptomatic, but if left untreated, dental caries can result in severe pain and life-threatening infections.

Global statistics show an inconsistent prevalence of ECC between different continents and within the same country. In 2007, the prevalence of ECC in children under 5 years of age was 40% in Brazil [9], and in 2016, it varied between 41.9% and 16% in 2 separate districts in India [10,11]. Ismail and Sohn [12] conducted a systematic review in China and reported that the prevalence of ECC in the country was between 78.6% and 85.5%. A later study by Zhang et al [13] recorded prevalence rates between 0.3% and 70.7% in children aged 1-6 years in the same country.

The most recent prevalence rate of ECC in China was documented by Zeng et al [14], who recorded it to be 49.13% in preschool children between ages 3 and 5 years in a southeast Chinese province. Similar varying prevalence rates were recorded across continents (ranging from 22.9% in India to 90% in Indonesia) [15].

African countries have also shown varying prevalence of ECC: In Burkina Faso, Mazza et al [16] recorded a prevalence rate of 16.6% and in Nigeria, Folayan et al [17] reported an ECC prevalence rate of 6.6%. Higher but inconsistent prevalence rates were documented in Sudan (52.4% [18] and 71.4% [19]), whereas in Uganda, 64% of 3-5-year-old children had ECC [20].

In South Africa, the national prevalence rate of ECC is 60% among children under 6 years or age [1]. The prevalence of dental caries in children aged between 2 and 4 years in Johannesburg was 47.74% [21], whereas in the Western Cape, this varied from 71.6% [22] to 80% [23].

For the allocation of resources necessary to manage ECC effectively, it is important to understand the demographics of South Africa. The country is inhabited by 55.7 million people, among which 10.3% are under the age of 5 years [24]. Approximately 20% of children reside with either a grandparent or a caregiver [25], and 13.1% of households live in informal dwellings. Many families lack access to basic amenities including electricity, clean water, food, and a stable income [26] and more than one-quarter of the population rely on social grants, particularly in the poorest provinces [25]. Furthermore, the prevalence of HIV in the country was estimated to be 13.1% in 2018 [24]. With the high level of poverty, lack of access to infrastructure, and high HIV prevalence, the prevention of ECC has not been a priority in this country.

The purpose of this study was to determine the prevalence and severity of ECC in South Africa in children under 6 years of age. To date, this will be the first scientifically conducted systematic review on the prevalence of ECC in South Africa.

Methods

Study and Ethics Approval

This protocol will be conducted using the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols) guidelines [27]. Ethics approval was not required as this is not a primary study involving participants. The study protocol was registered with PROSPERO (CRD42018112161) on November 21, 2018.

Study Eligibility Criteria

Types of Studies

Cross-sectional and cohort studies reporting the prevalence of ECC in healthy children aged 6 years and under living in South Africa will be included in the review. This is a prevalence/incidence study, and consequently, no interventions will be assessed. The primary outcome is the prevalence/incidence and severity of ECC. The severity of ECC will be measured using the WHO guidelines in infants and children up to the age of 6 years. The WHO criteria include dmft scores (decayed, missing, and filled teeth; lower case indicates deciduous teeth) and the percentage of children that are caries free (including noncavitated caries [white spot lesions]).

Information Source and Search Strategy

Databases such as PubMed/MEDLINE, Cochrane, Scopus, Academic Search Complete, Dentistry and Oral Science, CINAHL, and ScienceDirect will be searched. Each database will be examined using tailor-made search terms or MeSH terms: (1) “early childhood caries” OR “caries” OR “decay” OR “dmft” OR “dental” OR “oral” OR PUFA; (2) “prevalence”; (3) “children” OR “peri-natal” OR “paediatric” OR “pediatric” OR neonatal OR infant; (4) South Africa. The keywords were used in the following combinations: 1 + 2 + 3 + 4.

Scientific articles published in all South African official languages will be included in the review. Non-English articles will be translated by the Department of Foreign Languages, University of the Western Cape or a reputable translation company. To authenticate the translations, we will

cross-reference the original article with the English abstract (which is usually available online) and reverse translations will be conducted to ensure its correctness.

Commentaries/letters and other gray literature will be excluded from this review.

Secondary searching (PEARLing) will be conducted (PEARLing is a search strategy where the reference lists of all the studies, whether included or excluded, are identified for possible inclusion). Manual searching will not be conducted due to the difficulty in replicating this method.

Study Selection

The articles will be uploaded into Rayyan [28] and screened in 2 stages. Two review authors (FK-D and TR) will independently assess the titles and abstracts of the studies and compare them against the inclusion criteria. The full texts of eligible papers and those that contain insufficient information will be sourced.

Other reviewers will be consulted when a disagreement pertaining to the inclusion of a publication arises. The searching process will include all prevalence studies up to November 15, 2020. All eligible studies will be included, and authors will be contacted if any clarification is needed.

After reading the full-text articles, those that do not meet the inclusion criteria will be discarded and the reasons will be recorded in the "Characteristics of excluded studies" table. The reference list of all included publications will be reviewed for additional eligible studies.

Data Extraction and Management

Two reviewers (FK-D and TR) will independently extract data onto a standardized data extraction form (initially piloted on a small sample of studies) using Microsoft Excel (2014). Upon completion of data collection, the data will be uploaded to the University of the Western Cape's data repository for safekeeping [29]. The data will be pilot tested, and the independent authors will be trained on how to extract data. The content of the form will be compared, and any differences in opinion will be resolved by discussion and consultation with the other reviewers. If any information from the studies is unclear or missing, the corresponding authors of the original papers will be contacted (where feasible). Study information will include author, title, year of publication, study design, and year in which the study was conducted. Participant-level data will include age, the province where the study was conducted, dmft score and standard deviation, number of cases and total sample size, and urban/rural setting. Pooled prevalence will be obtained by dividing the number of participants with the caries with the number of participants in the whole population, and the data will be assessed using Stata (StataCorp LLC). Pooled standard deviations will be calculated using the Cohen (1998) formula [30].

Availability of Data and Materials

All data, irrespective of the quality of publication, will be included in the review. If details on study publications cannot be obtained, a librarian will be consulted, and if the study remains non-obtainable, it will not be included in the qualitative or quantitative analysis.

Study Quality and Risk of Bias Assessment

The quality assessment of studies will be conducted using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data [31].

Analysis of Study Findings

A meta-analysis will be conducted, using Stata 17, if there are studies of similar comparisons reporting the same outcomes using a random-effects model and only if there are 4 or more studies.

Assessment of Heterogeneity

This review will include diverse modalities of interventions and will result in heterogeneity of the content of interventions, outcomes, and outcome measures. We will contemplate the feasibility of conducting a meta-analysis on a subgroup of included studies once the data have been extracted. Where feasible, we will assess the statistical heterogeneity in the meta-analysis by visually inspecting the scatter of effect estimates on the forest plots, Cochran test (using .10 level of significance), and by using the I^2 statistic [32].

Assessment of Reporting Biases

Where possible, we will use multiple sources of data, including those from unpublished trials. Should a meta-analysis be conducted, we will assess publication bias according to the recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* [32]. Reporting biases such as selective reporting, duplication, and language of publication will be investigated.

Analysis of Subgroups or Subsets

We will use a subgroup analysis to examine heterogeneity using Stata 17. This will include exploring the influence of factors such as participant age, province, and urban/rural status. If sufficient numbers of studies are included, a meta-analysis will be performed.

Results

This protocol was registered with PROSPERO in October 2018, and the electronic searches were completed by November 15, 2020. The original search yielded 2247 articles.

Discussion

Principal Results

The study aims to assess the prevalence of dental diseases and its severity in children under the age of 6. The South African government does not regularly monitor the dental disease of children or adults. The last national oral health survey was conducted in 2004 in children only and adults were excluded [33]. There are plans to determine the disease prevalence and severity in South Africa in the next few years. Until then, this review will inform the dental and medical fraternity about the prevalence of ECC in South Africa.

Conclusions

There are very few studies detailing the prevalence and severity of dental disease in young children in South Africa. It is imperative that we monitor the trends of dental disease in children to inform stakeholders of this burden. Dental disease is a noncommunicable disease, and is associated with childhood obesity and childhood diabetes. More efforts need to be made to prevent the onset of dental disease, and thus prevent the incidence of other noncommunicable diseases in the future leaders of South Africa.

Conflicts of Interest

None declared.

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Abbreviations

ECC: early childhood caries
WHO: World Health Organization

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Protocol

Examining the Mental Workload Associated With Digital Health Technologies in Health Care: Protocol for a Systematic Review Focusing on Assessment Methods

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Abstract

Background: The workload in health care is high; physicians and nurses report high stress levels due to a demanding environment where they often have to perform multiple tasks simultaneously. As a result, mental health issues among health care professionals (HCPs) are on the rise and the prevalence of errors in their daily tasks could increase. Processes of demographic change are partly responsible for even higher stress levels among HCPs. The digitization of patient care is intended to counteract these processes. However, it remains unclear whether these health information systems (HIS) and digital health technologies (DHT) support the HCPs and relieve stress, or if they represent a further burden. The mental construct that describes this burden of technologies is mental workload (MWL). Work in the clinic can be viewed as working in safety-critical environments. Particularly in this sensitive setting, the measurement methods of MWL are relevant, mainly due to their strongly differing levels of intrusiveness and sensitivity. The method of eye tracking could be a useful way to measure MWL directly in the field.

Objective: The systematic review aims to address the following questions: (1) In which manner do DHT contribute to the overall MWL of HCPs? (2) Can we observe a direct or indirect effect of DHT on MWL? (3) Which aspects or factors of DHT contribute to an increase in MWL? (4) Which methods/assessments are applied to measure MWL related to HIS/DHT? (5) What role does eye tracking/pupillometry play in the context of measuring MWL? (6) Which outcomes are being assessed via eye tracking?

Methods: Following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement, we will conduct a systematic review. Based on the research questions, we define keywords that we then combine in search terms. The review follows the following steps: literature search, article selection, data extraction, risk of bias assessment, data analysis, and data synthesis.

Results: We expect results as well as a finalization of the review in the summer of 2021.

Conclusions: This review will evaluate the impact of DHT on the MWL of HCPs. In addition, assessment methods of MWL in the context of digital technologies will be systematically analyzed.

Trial Registration: PROSPERO (International Prospective Register of Systematic Reviews) CRD42021233271; https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42021233271

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KEYWORDS

mental workload; cognitive load; assessment; healthcare workers; health information system; digital health technology; health care professionals; stress; eyetracking

Introduction

Background

The workload for health care workers has remained high for many years [1,2]. Several factors contribute to this trend and result in different effects for employees and the health care system [3]. Factors that promote a high workload include understaffing, long working hours [4], and information overload [5]. Work-related stress has become one of the main challenges in the health care sector [6] and has different impacts on employees. Nurses in particular report high levels of work-related stress that can lead to negative physical and psychological effects for them as well as for their patients [7]. Nurses describe themselves as feeling empty and report depressive symptoms [8,9]. In Germany, health care professionals (HCPs) have an above-average number of sick days compared to workers in other sectors; overall, there was a 29% increase in sick days between 2004 and 2018 [10]. In addition to musculoskeletal disease diagnoses, which account for the majority of sick leaves, absences due to mental illness are increasing significantly [11].

Partly responsible for the workload-promoting factors described above are the consequences of demographic changes that have led to an increase in the number of multimorbid older adult patients and a decline in the number of nursing staff. The transformation process of digitization in health care is a chance to counteract this change and its consequences. However, in Germany in particular, the process is proceeding very slowly; Germany is ranked 19th of 27 countries in Bertelsmann's Digital Health Index [12]. The application of digital health technology (DHT) is an important factor of this digitization process. DHT in the context of this work means technologies that are directly linked to outpatient and inpatient care and are applied by nurses or physicians. DHT includes hospital information systems (HIS), medical devices, and other digital applications that support patient care from the perspective of HCPs.

In addition to the positive effects of the use of DHT, there is also evidence to suggest that the use of DHT causes an extra load. This may be due to a lack of usability and user involvement as well as poor implementation processes [13,14].

Poor usability and other factors rooted in technologies can cause a high mental workload (MWL) [14]. High workloads can result in a more error-prone performance—even for experts—induced by difficulties in decision-making processes [15].

Working with patients can be considered a safety-critical environment. This means that many tasks, varying in complexity, occur within limited time windows.

In this context, decisions must be made all the time and are supported by different systems (eg, HIS) through the structured and standardized presentation of information. The interaction between users and systems is complex and interdependent, which makes it difficult to predict the effects of the systems on the users [16].

High workload or overload caused by several factors (including technology) can have a severe impact. Aside from the negative impact on patient care due to a potential increase in errors, overload can also have a negative impact on the health of HCPs, potentially resulting in technostress, mental health issues (eg, depression, burnout), and decreased job satisfaction. These are only a few of the potential negative effects of overload [17]. There is growing evidence that DHT are contributing to increasing mental health problems (eg, burnout) among health care workers [18,19].

In order to identify possible causes of mental health problems in physicians and nurses (eg, emerging burnout [20]), the investigation of MWL in different situations is a possible approach.

Mental Workload

MWL can be defined using different approaches and is usually influenced by different and multiple factors. It is multidimensional, multifaceted, and one of the most important variables to understand and predict human performance.

The possible definitional approaches of workload can be derived from two different perspectives: (1) MWL as an external variable referring to task requirements (ie, the amount of work and the number of tasks to be completed in a limited time [task load]) and (2) interaction between task and human resources resulting in a subjective psychological experience [21,22].

Summarizing different approaches, we can define MWL as the amount of attentional resources that are required to perform a task mediated by task demands and experience [15,23,24]. Following this definition, the state of overload is reached when the task demands are too high while the user's resources are limited. In contrast to this is the condition of underload, which occurs when the task requirements are too low while resources are sufficient. In both cases, the result is poorer performance [25]. Mental states such as a high workload or underload play a critical role in the occurrence of errors as well as preventable adverse events [26]. Regardless of how competent and/or experienced an HCP is, this type of mental state can lead to a higher frequency of errors.

Assessment of Mental Workload

MWL assessments were first developed and applied in other safety-critical environments such as aviation/aerospace and nuclear power plants. Safety-critical environments have similar conditions (already described). Due to these similar conditions, workload assessment could also be a useful approach in the clinical setting.

MWL can be assessed using different techniques. A distinction between analytical and empirical methods may be drawn. Analytical methods tend to be used in system development, while empirical methods are employed when workload is to be measured directly in the executing system or in the simulation [21].

Analytical assessment methods are simulation models, expert opinions, or task analyses. Empirical methods are distinguished into three different categories: performance measures, subjective methods, and physiological techniques [15]. Performance measures refer to the measures of the primary and secondary task.

Depending on the situation and the underlying question, one or more of these techniques are appropriate to apply. Several factors should be considered when selecting assessments, including sensitivity, diagnostic accuracy, intrusiveness, validity, reliability, simplicity of use, and user acceptance [27].

Objectives

DHT may contribute to the heavy workload in health care. MWL can best reflect the workload caused by technology. In addition to the existence of some methodological issues (eg, assessing MWL in the field), there are also some knowledge gaps concerning MWL caused by DHT.

The planned systematic review intends to identify the impact of DHT, particularly HIS, on the MWL of health care workers. In addition, the review will aim to assess what methods are currently being used in health care to measure MWL relating to DHT. In particular, the application of eye tracking or pupillometry as an assessment method will be investigated.

Research Questions

The review will seek to answer the following research questions:

- 1. In which manner do DHT contribute to the overall MWL of health care workers?
  - 1.1. Can we observe a direct or indirect effect of DHT on MWL?
  - 1.2. Which aspects or factors of DHT contribute to an increase in MWL?
- 2. Which methods/assessments are applied to measure MWL related to HIS/DHT?
  - 2.1. What role does eye tracking/pupillometry play in the context of measuring MWL?
  - 2.2. Which outcomes are being assessed via eye tracking?

Methods

Study Registration

The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021233271). This protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 guidelines [28].

Eligibility Criteria

We define the inclusion criteria for this systematic review according to the PICO framework [29] and the research questions. Inclusion criteria relate to the study population (P), intervention (I), outcome (O) of the study, and study setting (C). In addition to these criteria, we include studies by study design as detailed below.

Study Design

All types of study designs reporting original primary data as well as systematic reviews that align with our other inclusion criteria will be included. We will exclude commentaries, letters, guidelines, and narrative reviews.

Study Participants

We focus on HCPs who work with HIS or DHT and who are directly engaged in patient care. These can be nurses, physicians, radiology assistants, or other clinicians. It is essential that the participants are supported by the HIS/DHT in their daily work with patients. We exclude studies that focus on patients who use digital technologies.

Intervention

We include studies that investigate the effects that HIS/DHT have on workers' MWL. The focus lies on the evaluation of whether there is a direct or indirect effect of DHT on workers' MWL. Since the second research question concerns the extent to which eye tracking is commonly used as a measurement method, we focus on the inclusion of studies that apply eye tracking. We exclude studies that investigate related constructs such as technostress.

Study Setting

We include all studies that take place in inpatient or outpatient care. We exclude studies that focus on the measurement of MWL in other contexts (eg, aviation).

Information Sources

The following databases were systematically searched between February 28 and March 15, 2021, using defined keywords (and synonyms) like "mental workload," "health information system," "assessment," "health care professionals," and "eye tracking" that resulted in specified search strings: MEDLINE (PubMed), Web of Science, Academic Search Premier and CINAHL (both EBSCO), and PsycINFO. Additionally, we will search for relevant research in the reference sections of included studies as well as those of relevant recently published reviews. Following PRISMA-P [28], we organized the search terms by database and question in a separate document (Multimedia Appendix 1).

Search Strategy

The search strategy includes four categories, each represented by keywords and synonyms: technologies used (eg, HIS), population (eg, health care professionals), methods (eg, assessment), and MWL. In addition, eye tracking will be added for questions 2.1 and 2.2. The terms are linked by the Boolean operators AND or OR.

We restrict our search to articles published in the period between 2000 and 2021. This search time frame was chosen because it documents the development of the current generation of prehospital communication technology, such as telemedicine and electronic patient care reports [30]. The literature search is limited to articles written in English or German since both reviewers have a sufficiently high level of fluency in these languages.

Study Records

Data Management

Citavi is used for literature handling (ie, import and further screening). The Rayaan web-based screening tool is used to perform abstract screening and full-text analysis in a structured

way. In this context, the inclusion and exclusion criteria are also provided; they will be the basis for the abovementioned analysis process. The included articles will be then imported to a Microsoft Excel (Microsoft Corp) spreadsheet.

Selection Process

The selection process will be performed by two reviewers (LK and BB; if a consensus cannot be reached, ML and RR will serve as additional reviewers) according to the PRISMA guidelines and will be displayed in a flowchart. First, both reviewers will assess the studies regarding the inclusion and exclusion criteria for abstract screening. In the next step, the full texts of the resulting studies will again be assessed independently. Finally, we will search the references of the papers for further potentially eligible studies. In case of disagreements in any of the phases, a discussion between the two reviewers (LK and BB) based on the inclusion criteria will be attempted first. If the discussion is inconclusive, a third reviewer (ML or RR) will be involved.

Data Collection Process

For data extraction, an Excel spreadsheet based on the outcomes of the review will be used. To ensure uniformity across reviewers, we will conduct a pretest standardization exercise before starting the data extraction process. Each reviewer will extract the themes of interest to an Excel spreadsheet. The extracted data items are presented below.

Data Items

LL and BB will read the full texts and extract information concerning identified and relevant aspects of the studies. We will differentiate between main study characteristics, measurements and outcomes, and relevant findings and recommendations. The aspects are aggregated in Table 1, Table 2, and Table 3.

Table 1. Systematic analyses of the main study characteristics.

Theme	Indicator
Objectives	• Aims
Assessments	• Eg, questionnaires
Quality criteria of applied assessments	• Reported/not reported • Type of quality criterium (eg, internal consistency)
Outcomes	• Mental workload related to digital health technologies • Factors of digital health technologies contributing to mental workload • Assessment type • Role of eye tracking
Type of digital health technology	• Eg, apps, health information systems

Table 2. Systematic analyses of measurements and outcomes (study characteristics).

Theme	Indicator
Study identification	• Author • Reference number
Setting of target	• Eg, hospital, outpatient setting
Study design	• Cross-sectional, longitudinal • Quantitative, qualitative, mixed methods
Sample characteristics	• Sample size • Age • Sex
Population type	• Eg, physicians, nurses

Table 3. Systematic analyses of the main findings.

Theme	Indicator
Overall workload level	• Assessed/not assessed • High, medium, low
Mental workload related to digital health technologies	• High, medium, low
Factors of digital health technologies contributing to mental workload	• Eg, lack of error tolerance
Eye tracking	• Applied • Field of application • Study settings
Outcomes measured by eye tracking	• Qualitative (eg, heat map) • Quantitative (eg, fixation duration) • Mental workload assessment

In addition to the descriptive presentation of study characteristics and findings, we are aiming to extract factors or aspects of DHT that contribute to an increasing MWL. Furthermore, we would like to extract how the included studies assess workload and in which settings eye tracking is used with regard to specific outcomes. Based on the extraction, we would like to develop an overview of the methods that can be used to measure MWL caused by DHT and provide meaningful and valid data.

The methods, settings, and outcomes will be organized into logical categories that are rated by the reviewers. The typical categories of methods referring to MWL assessments are analytical or empirical techniques. Typical categories for settings are laboratory or field. Categories referring to assessed outcomes have to be defined during the reviewing process. In each category, we will extract how often an indicator for a category was applied (category percentage, ie, method applied/n studies) and how often combinations of specific indicators were used (total percentage, eg, method A with setting B and outcome C; combination applied/N studies). A typical indicator for the category empirical technique would be a questionnaire. If an indicator was identified, the reviewers fill the row with a 1; if no indicator was identified (eg, if the method was not applied), the table is filled with a 0. An example is displayed in Figure 1.

Figure 1. Example of systematic tabulation of methods, setting, outcomes, and combined investigation procedures.

	Indicator	*Study 1*	*Study 2*	...	*Category %*
Category 1/ Methods	Indicator 1	1	0	...	50%
	Indicator 2	1	1	...	100%
	...	...	...	...	
Category 2/ Setting	Indicator 1	...	...	...	
	Indicator 2			...	
	...			...	
Category 3/ Outcomes	Indicator 1			...	
	Indicator 2			...	
	...			...	
	Indicator	*Study 1*	*Study 2*	...	*Total %*
Category Combinations	Combination 1				
	Combination 2				
	...				

Outcomes

The primary outcome of the first research question is to explore the correlations between DHT and the MWL of HCPs. The secondary outcome is to investigate the type of effect (direct/indirect) DHT has on the MWL of HCPs as well as the aspects of DHT that contribute to MWL.

The primary outcome of the second research question is the exploration of the best method to determine this relationship. Particular attention will be given to the role of eye tracking technology, which will be included as a secondary outcome.

Risk of Bias in Individual Studies

For the review, two authors will independently rate the methodological quality of the identified studies using the Joanna Briggs Institute Critical Appraisal Tool [31]. An initial screening of studies that could be included indicates a small proportion of studies with an experimental design and adequately defined criteria for conducting the study and analyzing the data. Disagreements will be resolved via discussion (LK and BB) or by a third reviewer (ML or RR), if necessary.

Data Analysis and Synthesis

After screening the search results, we do not expect to be able to conduct a meta-analysis. A first look revealed that comparing the study designs and effect measures of studies will be difficult. This may be explained by the explorative character of the review and the potentially low level of evidence, especially regarding eye tracking. Instead, we will perform a descriptive analysis to summarize the data, starting with a comparison of evaluation methods (qualitative, quantitative, or mixed methods) and survey methods. To do this, we will first compare the studies in terms of the evaluation methods used (qualitative, quantitative, mixed methods), followed by a comparison of survey methods.

For data synthesis, we use two nonquantitative approaches: tabulation and a narrative approach. Table 1 and Table 2 describe the tabular synthesis of potential findings.

In a first step, all main characteristics of each study will be extracted (ie, study design, setting of target population, sample size, age, sex, population type). Studies that do not report those main characteristics and those with a sample size under 20 participants will be excluded. We will analyze studies regarding objectives, outcomes, and assessments, as well as type of DHT. Data on overall MWL in studies, MWL levels related to DHT, quality criteria of assessments, applied eye tracking, and outcomes assessed via eye tracking will be extracted.

All included studies are evaluated with regard to their risk of bias. A textual narrative synthesis of all included studies will be made and the comparable findings will be synthesized. Additionally, a descriptive analysis of eye tracking measures is planned.

Results

As the systematic review is currently ongoing, no results are available as of yet. The preliminary searches have been completed and the piloting of the study selection process as well as the formal screening against eligibility criteria has started. We are currently analyzing the data and expect to complete the review in summer 2021.

Discussion

The aim of the review is to show which methods are currently used to measure MWL in health care and the impact of such technologies on the workload of HCPs. Additionally, the role of eye tracking should be evaluated.

In the discussion section of the review, we will discuss the results and the methodological quality of the findings, strengths and weaknesses of the review (limitations), and research gaps and opportunities for future research.

Authors' Contributions

LK conceived the study and wrote the paper. LK drafted the topic of the study and provided oversight for editing of the protocol. BB, ML, and RR revised the protocol. LK and BB are currently screening the literature. All authors approved this version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search Strings: Performed searches sorted by question and database.
[DOCX File , 30 KB - resprot_v10i8e29126_app1.docx]

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Abbreviations

DHT: digital health technology
HCP: health care professional
HIS: health information system
MWL: mental workload
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Proposal

Evaluation of the Prevalence, Regional Phenotypic Variation, Comorbidities, Risk Factors, and Variations in Response to Different Therapeutic Modalities Among Indian Women: Proposal for the Indian Council of Medical Research–Polycystic Ovary Syndrome (ICMR–PCOS) Study

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Abstract

Background: There is scanty data in India on polycystic ovary syndrome (PCOS) from several small, undersized, convenience-based studies employing differing diagnostic criteria and reporting varied regional prevalence. It is difficult to draw clear-cut conclusions from these studies; therefore, the present multicentric, well-designed, large-scale representative countrywide epidemiological study on PCOS across India was conceived with the aim to generate the actual prevalence rates of PCOS in India with a total sample size of approximately 9000 individuals.

Objective: The primary objectives of the study are to estimate the national prevalence of PCOS in India and the burden of comorbidities and to compare the variation in efficacy of standard therapeutic modalities for metabolic dysfunction in women with PCOS.

Methods: This multicentric umbrella study consists of three different substudies. Substudy 1 will involve recruitment of women aged 18-40 years using a multistage sampling technique from randomly selected polling booths across urban and rural areas to estimate national prevalence, phenotypic variation, and risk factors among regions. Substudy 2 involves recruitment of subjects from the community pool of substudy 1 and the institutional pool for quantitation of comorbidities among women with PCOS. Substudy 3, an interventional part of the study, aims for comparison of variation in efficacies of common treatment modalities and will be conducted only at 2 centers. The eligible consenting women will be randomized in a 1:1 ratio into 2 arms through a blinding procedure. All these women will undergo clinical, biochemical, and hormonal assessment at baseline and at 3 and 6 months. The data generated will be analyzed using the reliable statistical software SPSS (version 26).

Results: The study is ongoing and is likely to be completed by April 2022. The data will be compiled and analyzed, and the results of the study will be disseminated through publications.

Conclusions: The Indian Council of Medical Research–PCOS study is the first of its kind attempting to provide accurate and comprehensive data on prevalence of PCOS in India.

Trial Registration: Clinical Trials Registry–India CTRI/2018/11/016252; ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=26366

International Registered Report Identifier (IRRID): DERR1-10.2196/23437

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KEYWORDS

polycystic ovary syndrome; prevalence; metabolic aberrations; community pool; therapeutic modalities; India; metabolic dysfunction; phenotypic variations; ovarian morphology; PCOS epidemiology

Plain English Summary

Polycystic ovary syndrome (PCOS) is a multifactorial disorder with unknown etiology and numerous clinical manifestations in reproductive-aged women around the world. The metabolic abnormalities linked to this syndrome include type 2 diabetes, insulin resistance (IR) obesity, abnormal glucose tolerance (AGT), and cardiovascular diseases (CVD). The sketchy data and escalating prevalence of PCOS and associated comorbidities among Indian women led to organization of a multidisciplinary brainstorming meeting held September 11, 2014, at Indian Council of Medical Research (ICMR) headquarters, and the ensuing recommendations suggested formulation of the ICMR–PCOS Task Force to conduct a multicentric, multiphase study among Indian women with PCOS.

This is a multicentric, multispecialty study with a common comprehensive predesigned protocol involving 10 centers located in the 6 zones of the country. The women from the community (rural and urban) will be screened using a validated screening questionnaire, after obtaining a written informed consent from the subjects. The proforma will capture all details about menstrual cyclicity, acne, hirsutism, socioeconomic status, family history of PCOS, etc. The national prevalence will be calculated from the community pool for substudy 1. All biochemical and hormonal analysis will be done by standard assays using similar kits, reagents, and equipment. Ultrasonography (US) including magnetic resonance imaging (MRI) of the abdomen will be performed using a common approved protocol. The various comorbidities such as AGT, nonalcoholic steatohepatitis, and sleep apnea will be evaluated from both the pools (ie, hospital cohort and community cohort in substudy 2). The interventional randomized double-blind trial (ie, oral contraceptive pills [OCPs] vs metformin) will be conducted at only 2 centers for substudy 3. Apart from this, a knowledge, attitude, and practices survey of service providers in the public health system will be conducted to understand the training needs and gaps in the health system addressing PCOS management.

Introduction

Overview

Polycystic ovary syndrome, affecting approximately 116 million women worldwide, is now considered the commonest endocrinopathy of reproductive-aged women [1,2]. Stein and Leventhal initially described it as the association of bilateral ovaries with amenorrhea in 1935 [3,4]. Now, its association with a constellation of metabolic aberrations including obesity, AGT, IR, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, sleep apnea, stroke, CVD, neuropsychiatric comorbidities, microalbuminuria, mitogenesis, etc, in addition to cosmetic and reproductive dysfunction, is increasingly being recognized [5-9].

Global prevalence of PCOS among geographical zones is reported differently as 5%-10% in developed countries, 5%-30% in the United States, and 3.7%-22.5% across India [10-13]. Since there is no specific established treatment protocol available, early diagnosis and management is likely to reduce the risk of long-term complications of PCOS. The etiology of the disorder is being actively investigated; various reports speculate on the environmental and genetic factor interactions responsible [14-16]. Various small, regional, poorly designed studies using varying diagnostic criteria suggest a high prevalence of PCOS in India, seemingly running parallel to the epidemic of noncommunicable diseases, especially type 2 diabetes. There are no systematic representative data on the prevalence of PCOS or burden of its comorbidities among Indian women to date [17-31]. The existing data hint at the potential for large-scale epidemiological studies on PCOS across India to generate the actual prevalence and picture of the disease in the community. Therefore, there is an immense need to generate nationwide data on the prevalence of PCOS, including its

comorbidities, besides any variations in phenotypes or treatment responses among Indian women.

To address these issues concerning PCOS among Indian women, ICMR, New Delhi, has taken the initiative to conduct a nationwide multicentric study titled "Evaluation of prevalence, regional phenotypic variation, co-morbidities, risk factors and the variations in response to different therapeutic modalities among Indian women with polycystic ovary syndrome (PCOS): A Multicenter study across India" to quantitate the burden of PCOS and its comorbidities in its phase 1.

Objectives

The objectives of the proposed study are as follows:

Primary Objectives

The primary objectives are to (1) estimate national prevalence, phenotypic variations, and risk factors of PCOS in the community; (2) estimate the burden of comorbidities such as metabolic syndrome, dyslipidemia, cardiovascular complications, NAFLD, psychiatric abnormalities, sleep apnea, AGT including type 2 diabetes, and impairment of quality of life (QOL) among known cases of PCOS; and (3) compare the variation in efficacy of standard therapeutic modalities for metabolic dysfunction in women with PCOS (2 sites, All India Institute of Medical Sciences [AIIMS] and Sher-i-Kashmir Institute of Medical Sciences [SKIMS]).

Secondary Objectives

The secondary objective is to assess knowledge and management practices among service providers in the public health sector on PCOS to develop a standard screening and training modules to facilitate management of PCOS at different levels of the public health care system.

Prerequisites for Initiation of the Study

To begin with, the study required establishment of a PCOS network comprising members from the specialties and departments of endocrinology, dermatology, community medicine, biochemistry, laboratory medicine, pediatrics, internal medicine, obstetrics and gynecology, and other relevant departments based on their expertise and interest in the area of PCOS. In addition, there will be a team of national reviewers and advisors (members of the Task Force Committee) who will guide in formulating the protocol, advising on methods of assessment, and analyzing the data on relevant aspects. In view of the relevance to the project, a cardiologist (for cardiovascular risk assessment), a gastroenterologist (for NAFLD assessment), a radiologist (for devising methodology for ovarian morphology and implications of data interpretation), a psychiatrist (for assessment of psychiatric comorbidity and QOL), a pediatrician (for assessment of prepubertal risk factors and design of interventions), a dermatologist (for hyperandrogenism assessment strategies), a molecular biologist (for genetic and epidermal differentiation complex work-up), and a biostatistician (for sampling designs and final analysis) have been incorporated in the team and committee.

The following participating centers are involved in the study (Figure 1): (1) Sher-i-Kashmir Institute of Medical Sciences, Srinagar (North); (2) Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh (North); (3) All India Institute of Medical Sciences, New Delhi (North); (4) ICMR National Institute for Research in Reproductive Health (NIRRH), Seth G S Medical College and King Edward Memorial Hospital, Grant Medical College and JJ Hospital, Mumbai (West); (5) Institute of Post Graduate Medical Education & Research (IPGMER), Kolkata (East); (6) North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong (North East); (7) All India Institute of Medical Sciences, Raipur (Central); (8) Osmania Medical College, Hyderabad (South); (9) Maternal Health & Research Trust, Hyderabad (South); and (10) Government Medical College, Thiruvananthapuram (South).

Figure 1. Layout of participating centers. AIIMS: All India Institute of Medical Sciences; GMC: Government Medical College; IPGMER: Institute of Post Graduate Medical Education & Research; MHRT: Maternal Health & Research Trust; NEIGRIHMS: North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences; NIRRH: National Institute for Research in Reproductive Health; OMC: Osmania Medical College; PGIMER: Postgraduate Institute of Medical Education and Research; SKIMS: Sher-i-Kashmir Institute of Medical Sciences.

Methodological Steps and Study Design

Overview

The milestone steps to proceed with estimation of national prevalence, phenotypic variation, and risk factors involve a community-based, cross-sectional survey to recruit women belonging to the age group of 18-40 years from both rural (n=500) and urban areas (n=500) across 6 zones (ie, North, South, East, West, North East, Central India). ICMR has always been a leader in developing ethical standards for any human research considering the moral, ethical, and social values and ethos of diverse populations in the country. The proposed study will be conducted according to the Helsinki Declaration of 1975 and stands approved by the Institutional Ethics Committees at all 10 study sites. A written informed consent will be obtained from the participants assuring their understanding of the purpose of the study and obligations and consequences of their participation.

Detailed Methodology: Substudies 1 and 2

Participant Selection

Women aged 18-40 years who are not pregnant or lactating and have been residing in the area for 1 year or more will be included in the study. Women who are known to have PCOS will be recorded for the purposes of PCOS prevalence and will only be evaluated in detail for substudy 2 if they are drug-naïve. Women taking oral contraceptives, steroids, antiepileptics, or other drugs known to interfere in glucose or lipid metabolism will not be evaluated in detail and will be excluded from the study.

Substudy 1: Community Pool

The study design is a two-stage, cross-sectional, community-based study.

Study Population

Women aged 18-40 years will be recruited using a multistage sampling technique involving urban and rural areas. The polling booths will be selected randomly at the coordinating center by a random selection process. This study will be conducted in 6 zones of the country involving 10 centers that are likely to represent a majority of ethnic groups.

Inclusion Criteria

The following are the criteria for inclusion: women aged 18-40 years who are permanent residents of the area (>1 year), willing to participate in the study and sign informed consent, known to have PCOS, and not on treatment.

Exclusion Criteria

Pregnant or lactating women and those with cognitive limitations, physical limitations, or both that prevented them from answering the questionnaire will be excluded from the study.

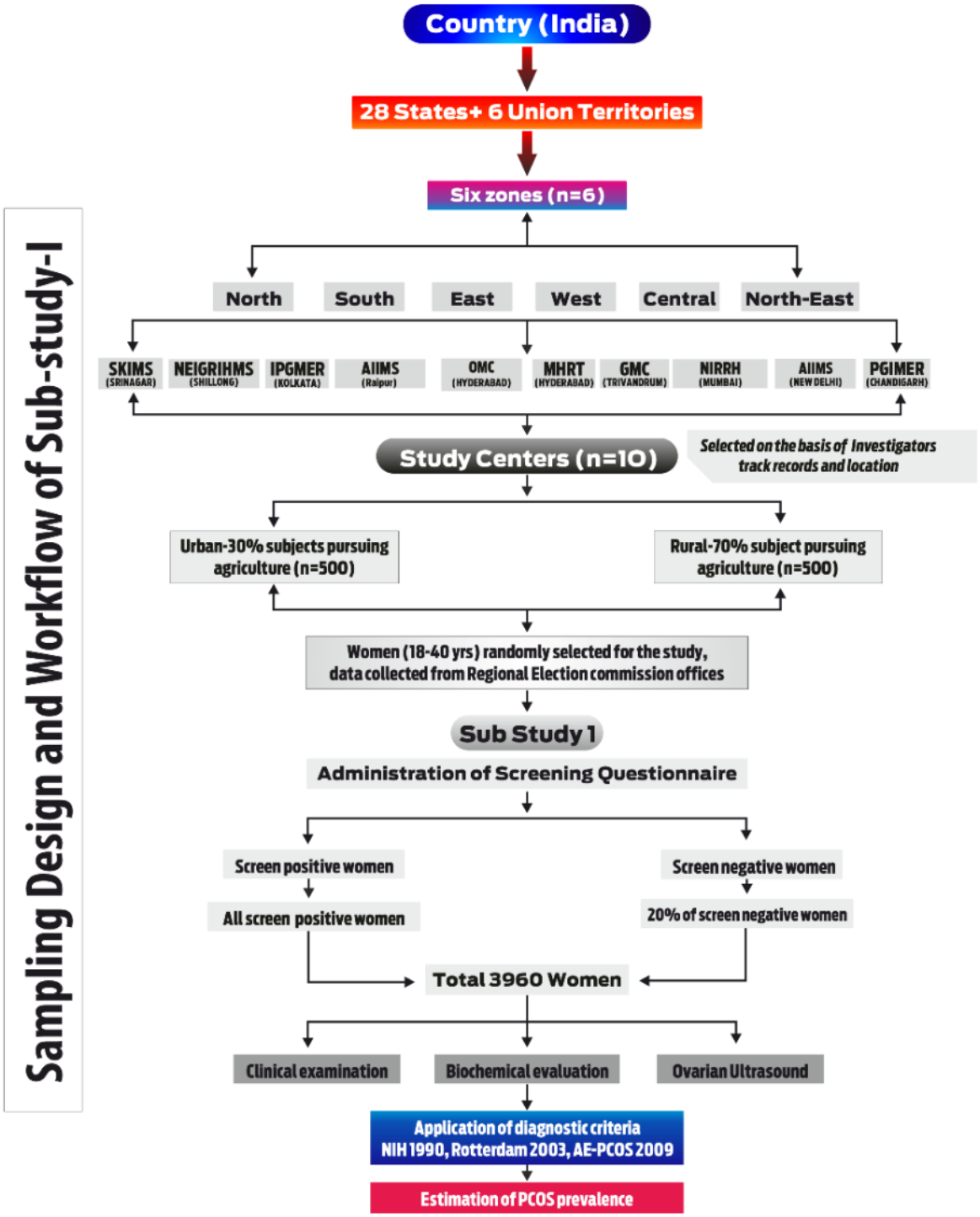
Women with a history of drug intake such as steroids, androgens, oral contraceptives, antiepileptics, or drugs known to interfere in glucose or lipid metabolism will also be excluded.

Sampling Design

A multistage cluster sampling technique is being used in this study. The first step in the sampling procedure will be to have representative data from the 6 zones (N, S, E, W, NE, and Central) of the country (Figure 1). The participating institutions from 6 zones were selected in view of location, logistics, feasibility, and the investigator profile. One urban and one rural Vidhan Sabha constituency near each institution will be selected. The choice of selection of districts and the constituencies will be given to the principal investigators at each site in order to make the study execution simpler. A rural district would mean 70% of subjects pursuing agriculture activities, while urban would mean that less than 30% have agriculture as the source of income.

After the constituencies are selected, the entire list of polling booths will be obtained from the Regional Election Commission offices. Polling booths from rural or urban constituencies will be selected to fulfill the required sample size using a random number table so that each polling booth has an equal chance to get selected. This procedure will be carried out at the coordinating center (SKIMS, Srinagar) by a third party not directly involved in the study. Next, the sites will procure the electoral roll, and voter IDs will be searched for women (aged 18-40 years) to be the potentially eligible subjects. The resulting list of women will be screened using a checklist for eligibility. If a woman is not eligible or refuses to participate in the study, the offer will go to the next woman in the list. If there is more than one eligible woman in a family, the sampling frame will also shift to the next in the voter ID list. The procedure will continue until a total of 1000 women (500 rural and 500 urban) are screened per center (Figure 2).

Figure 2. Flowchart for sampling design and workflow of the study. AE-PCOS: Androgen Excess and Polycystic Ovary Syndrome; AIIMS: All India Institute of Medical Sciences; GMC: Government Medical College; IPGMER: Institute of Post Graduate Medical Education & Research; MHRT: Maternal Health & Research Trust; NEIGRIHMS: North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences; NIH: National Institutes of Health; NIRRH: National Institute for Research in Reproductive Health; OMC: Osmania Medical College; PCOS: polycystic ovary syndrome; PGIMER: Postgraduate Institute of Medical Education and Research; SKIMS: Sher-i-Kashmir Institute of Medical Sciences.



Estimation of Sample Size for Substudy 1

Sample size was calculated, primarily to estimate the prevalence of PCOS in the country. Previously reported prevalence rates of PCOS have varied from 3.7% to 22.3% [32,33]. For the purpose of calculation of sample size, we presume the prevalence of PCOS in India to be 10%. With an assumed prevalence of 10% and an absolute error margin of 1% in a 95% 2-sided confidence interval and making allowance for about 20% refusals or nonresponse, we need to target a total of 4500 women. Further, being a cluster design and taking a design effect of 2, a total of 9000 women aged 18-40 years will be

studied from 10 centers (ie, 1000 per center, except for the 2 centers in Hyderabad, which have been designated with 500 each), half from a rural community and half from an urban community at each center.

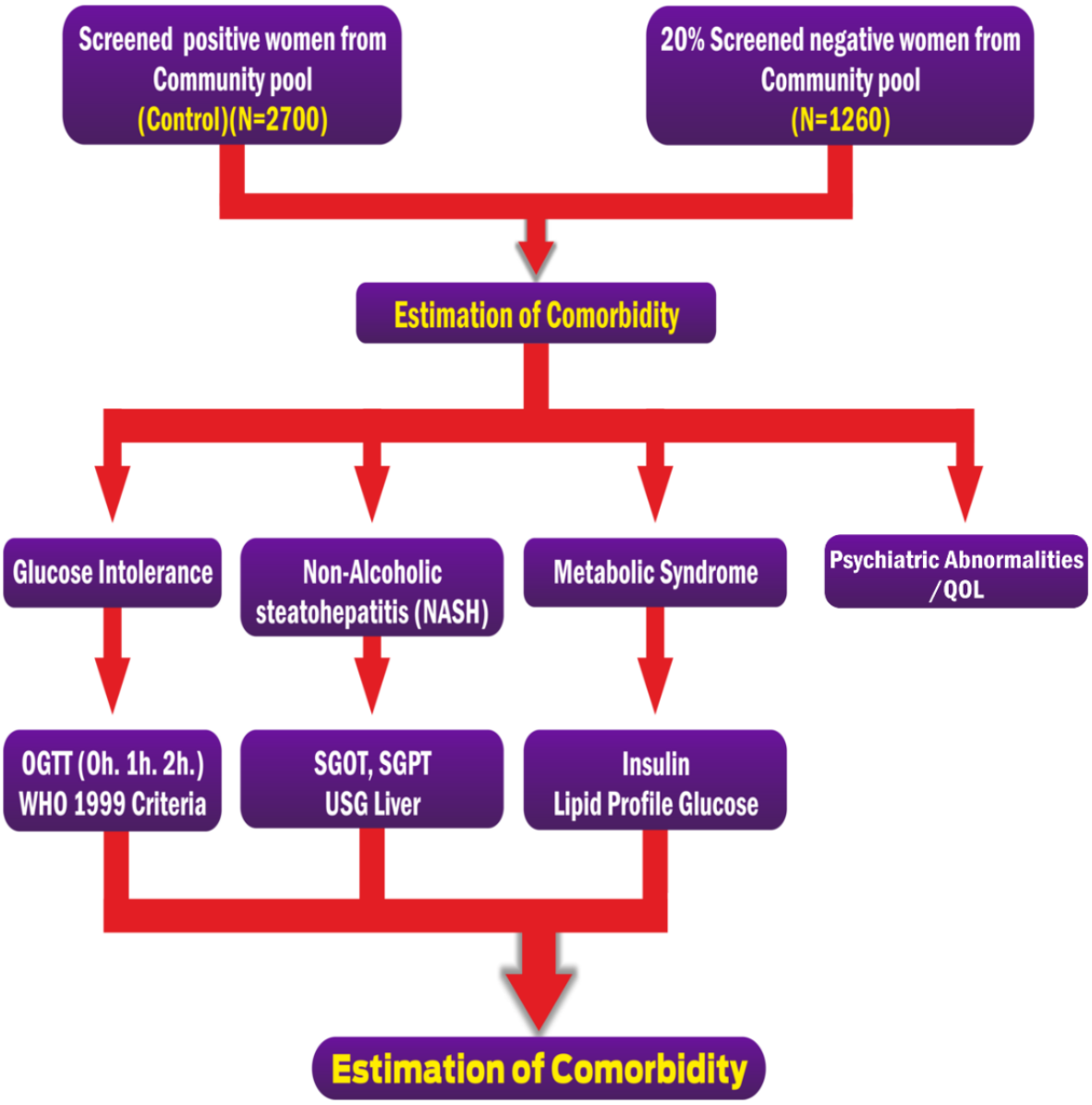
Based on a pilot study previously conducted by the chief coordinator using a similar questionnaire [34], 30% (2700/9000) of the women are expected to screen positive (likely to have PCOS) on the screening questionnaire and therefore are required to be investigated in detail. Additionally, of the 70% (6300/9000) of women expected to screen negative on the screening questionnaire, 20% (1260/6300) will require examination and investigation in detail. This will make the sample size of women requiring detailed evaluation and blood testing a total of 3960 (N=2700+1260). Keeping in view the number of centers (N=10), each participant center will screen approximately 1000 women, and a total of 440 women who will be invited for detailed examinations: 20% (140/700) of screen-negative women and all 30% (300/1000) who screen positive (Figure 2).

Evaluation Methods

Both the subgroups of women coming from the community pool and institutional pool will be evaluated as per the defined protocol for clinical, biochemical, and hormonal assessment during the second to the seventh day of the cycle. In the institutional pool, women attending endocrinology, gynecology, dermatology, or other related clinics for symptoms and signs of PCOS will be asked to report to the research staff or PCOS station for detailed evaluation as per the common protocol. Support will be obtained from the public health system for enrolling women from the community and conducting further examinations, investigations, and follow-up at their facilities in urban and rural areas. All those women who are drug-naïve will undergo clinical assessment (anthropometry, hirsutism scoring, acne, oligomenorrhea, androgenic alopecia, primary infertility), biochemical evaluation (liver function test, kidney function test, lipids, oral glucose tolerance test [OGTT]), high-sensitivity C-reactive protein (hsCRP) and cytokine tests (selected cases), 25-hydroxyvitamin D [25OHD] testing (selected cases), and hormonal estimations (thyroxine [T_4], thyrotropin, luteinizing hormone [LH], follicle-stimulating hormone [FSH], prolactin [PRL], cortisol, anti-Müllerian hormone [AMH], dehydroepiandrosterone sulfate [DHEAS], 17-hydroxyprogesterone [17OHP], sex hormone–binding globulin [SHBG], serum total testosterone and insulin at 0, 30, and 120 minutes, estradiol [E2], progesterone [P4], procollagen type I N-terminal propeptide, CrossLaps, anti–thyroid peroxidase, ferritin, B_{12}, pro–brain natriuretic peptide, and C-peptide levels). The blood samples will be transported in a cold chain to one center (SKIMS, Srinagar) for lab analysis using electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics USA). Analytes such as SHBG and serum total testosterone levels will be transported to one center (SKIMS, Srinagar) for purposes of uniformity and will be analyzed in one go. In a subset of cases (n=100), total testosterone and SHBG will be assayed by ECLIA and liquid chromatography–tandem mass spectrometry in the Department of Endocrinology, AIIMS, New Delhi.

The 1990 National Institutes of Health (NIH) consensus conference criteria will be taken as the qualifying criteria. This necessitates the presence of the following 2 criteria: (1) oligoovulation or anovulation (intermenstrual interval ≥35 days, presence of ≤8 cycles per year, or both) and (2) clinical signs, biochemical evidence, or both of hyperandrogenism after ruling out disorders with similar clinical presentation such as hyperprolactinemia, Cushing syndrome, congenital adrenal hyperplasia, and androgen-secreting tumors with specific laboratory analysis (cortisol, 17OHP, and DHEAS). To compare, the 2003 Rotterdam criteria and the 2009 Androgen Excess and PCOS (AE-PCOS) Society criteria will also be employed. Therefore, US examination to satisfy the diagnosis of PCOS by these criteria will be done. A common standard operating procedure for abdominal examination (liver, pancreas, ovary, and uterus) will be adhered to with a built-in system to minimize interobserver and equipment variations. The 2003 Rotterdam criteria necessitate the presence of 2 of the following 3 criteria: (1) oligoovulation, anovulation, or both; (2) clinical signs, biochemical evidence, or both of hyperandrogenism; and (3) polycystic ovary in US. The 2009 AE-PCOS Society criteria necessitate the presence of the following criteria: (1) oligoovulation and/or anovulation (intermenstrual interval ≥35 days, presence of ≤8 cycles per year, or both) and/or polycystic ovary in US and (2) clinical signs, biochemical evidence, or both of hyperandrogenism. To exclude etiologies that could mimic PCOS like Cushing syndrome, late-onset adrenal hyperplasia, or androgen-producing neoplasm, we will exclude thyroid disorders, renal hyperplasia, hyperprolactinemia, and late-onset congenital adrenal hyperplasia by medical history and hormone tests. This will further serve to unravel various comorbidities such as AGT, metabolic syndrome, IR, cardiovascular risk, psychiatric morbidities, and impairment of QOL (Figure 3). Besides, these women will be evaluated for risk factors such as birth weight, parental history of gestational diabetes or PCOS, risk of low birth weight, precocious pubarche, prepubertal obesity, antiepileptic drug intake, familial association with lifestyle diseases, etc. Abdominal MRI for comparing ovarian morphology will also be done at a selected center (SKIMS, Srinagar) using the predesigned uniform protocol.

Figure 3. Study design and workflow chart of substudy 2. OGTT: oral glucose tolerance test; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; QOL: quality of life; USG: ultrasonography; WHO: World Health Organization.



Study Tool: The Questionnaire

In this study, structured questionnaires will be used for capturing information. The eligibility and screening questionnaires comprise 7 and 43 questions (part 1), respectively. The screening questionnaire comprises three sections: (1) personal details, (2) menstrual history and clinical information, and (3) history of any systemic diseases. Part 1 of the questionnaires will be filled at the field site to check eligibility and identify probable PCOS on the basis of positive responses to questions. The subjects who test positive on the questionnaire (ie, probable PCOS) and 20% of those who test negative (healthy women) will be invited to the respective institutes for detailed clinical assessment. The questionnaire stands pilot-tested and modified after several rounds of investigator meetings.

Clinical Assessment

History

The subjects will be invited to nearby institutes for detailed clinical, biochemical, hormonal, and sonography assessments. These women will be assessed for clinical detail about menstruation (regularity, duration, flow, amenorrhea), weight gain, unwanted male pattern hair growth, hair fall, infertility, etc. The details about any illness will be recorded. Psychiatric morbidity will be assessed using the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria with the Mini-International Neuropsychiatric Interview, version 4.0. The details of family pedigree will also be recorded in the predesigned questionnaire.

Examination

Anthropometric assessment including measurement of height, weight, waist circumference, skinfold thickness on dorsum of hand and triceps, and blood pressure and detailed systemic examination will be undertaken. Height and weight will be measured with subjects in light clothes and without shoes, using standard apparatus. Weight will be measured to the nearest 0.1 kg on a calibrated digital scale. Height will be measured by stadiometer by standard methodology to the nearest 0.1 cm. Waist and hip circumference will be measured to the nearest 0.5 cm with a measuring tape. The waist circumference will be defined as the point midway between the iliac crest and the costal margins (lower ribs), while hip circumference will be defined as the widest circumference over the buttocks and below the iliac crest [35]. Body mass index (BMI) will be derived as weight in kg divided by the square of height in meters. Overweight will be defined using the Asian BMI range of 23.0-24.9 kg/m^2, while obesity will be defined as having a BMI equal to or greater than 25 kg/m^2 [36]. Quantitation of hirsutism by a single observer by counting 9 specific body areas for the Ferriman-Gallwey score and assessments of acne vulgaris, androgenic alopecia, and acanthosis nigricans will be performed in all subjects [37].

Radiological Examination

Ultrasonography of the abdomen will be performed to evaluate the polycystic ovary morphology and grading of fatty liver (NAFLD) and nonalcoholic pancreatic steatosis. The US will be performed at all centers, and MRI of the pelvis (n=100) will be performed primarily at SKIMS, Srinagar, to compare US and standardization of US technique by 2 independent radiologists. MRI will be done as per a randomized selection proportional to the subjects at the site.

Laboratory Evaluation

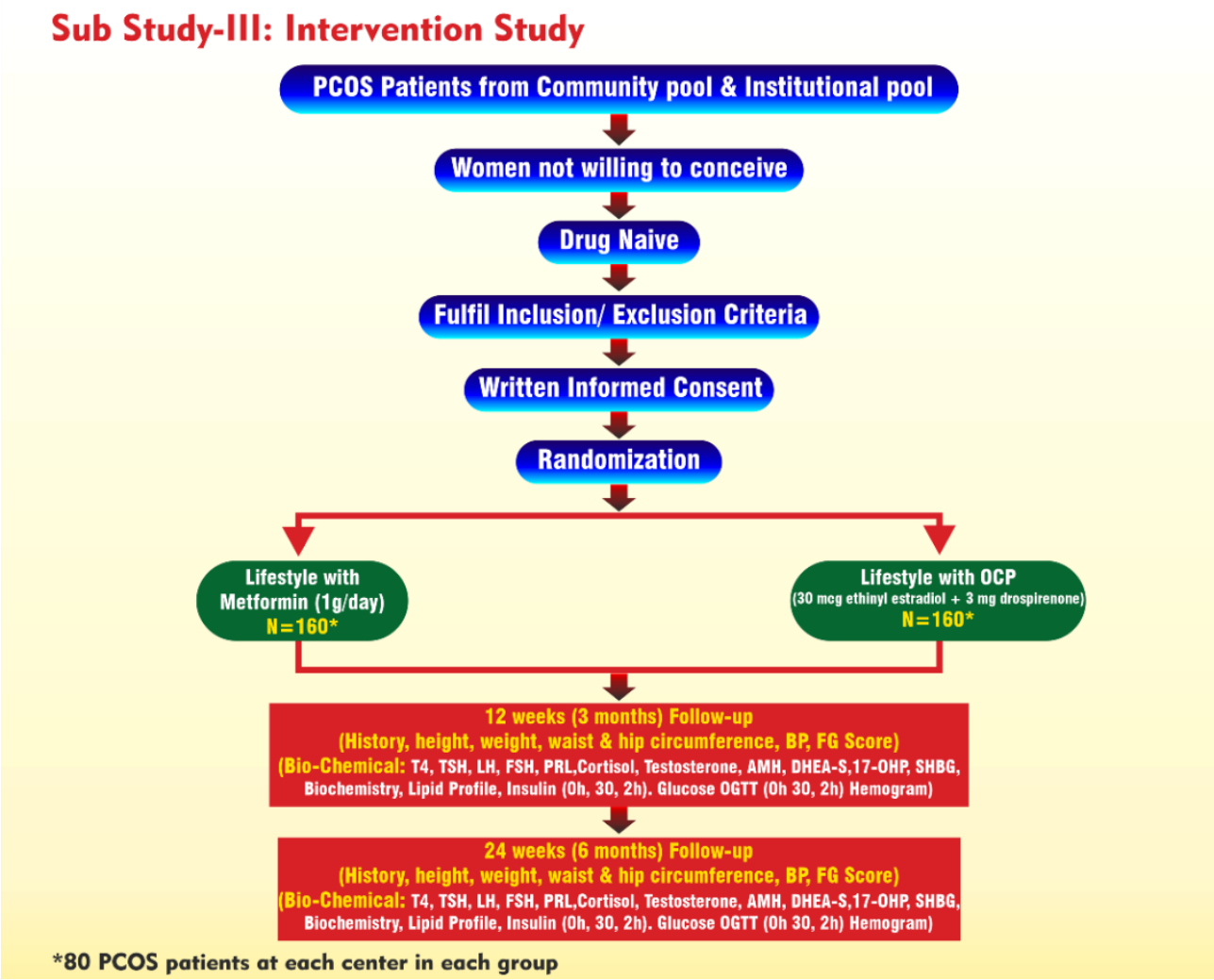
The OGTT will be performed after an overnight fast of 10-12 hours. An oral glucose load with 75 g of anhydrous glucose dissolved in 250-350 mL of water will be administered over 3-5 minutes immediately after the basal sample. The blood samples for LH, FSH, testosterone, AMH, SHBG, and DHEAS will be collected on days 3-7 (early follicular phase) of spontaneous or medroxyprogesterone-induced (in amenorrhea patients) menstrual cycle to confirm PCOS. Hematological parameters (hemoglobin, red blood cells, white blood cells, etc), biochemical tests like lipid profile, liver function, kidney function, blood glucose (OGTT), and hormonal assays like T_4, thyrotropin, LH, FSH, PRL, E2, P4, cortisol, testosterone, AMH, DHEAS, 17OHP, and insulin at 0 hours, 30 minutes, and 2 hours (optional) will be carried out at the respective centers, and special hormones like testosterone and SHBG will be done in the central facility to be created at the coordinating center (SKIMS, Srinagar). On the day of testing, women will be called after 10-12 hours of fast, and blood samples (15 ml) will be drawn. Blood will be also collected for glucose and insulin estimation after 30 minutes and 120 minutes of 75 g oral glucose challenge. Insulin samples will be immediately put in a refrigerator, separated in cold centrifuge, and stored at −20 °C until the assay. Plasma will be separated in a refrigerated centrifuge at 1560*g* for 10 minutes, and sera will be stored at −80 °C until tested.

Plasma glucose will be measured using the glucose oxidase–peroxidase method, and hormonal tests (LH, FSH, T_4, thyrotropin, PRL, E2, cortisol, testosterone, AMH, hsCRP, cytokines, and 25OHD) will use ECLIA on Cobas e411 (Roche Diagnostics USA).

Methodology: Protocol for Substudy 3

The study will be conducted only at 2 centers: AIIMS, New Delhi, and SKIMS, Srinagar. Women (aged 18-40 years) residing in the communities (rural and urban) identified in the prevalence study and those attending outpatient clinics in the departments of either endocrinology, gynecology, or dermatology of the selected institutes who are willing to participate will be recruited in the interventional part of the study. All these women will undergo clinical, biochemical, and hormonal assessment at baseline and at 3 and 6 months (Figure 4).

Figure 4. Study design and workflow chart of substudy 3. 17-OHP: 17-hydroxyprogesterone; AMH: anti-Müllerian hormone; BP: blood pressure; DHEA-S: dehydroepiandrosterone sulfate; FG: Ferriman-Gallwey; FSH: follicle-stimulating hormone; LH: luteinizing hormone; OCP: oral contraceptive pill; OGTT: oral glucose tolerance test; PCOS: polycystic ovary syndrome; PRL: prolactin; SHBG: sex hormone–binding globulin; T4: thyroxine; TSH: thyrotropin.



Sample Size Calculation for Substudy 3

On the basis of one study, metformin could improve the Homeostatic Model Assessment of IR from 2.5 (SD 0.39) to 2.79 (SD 0.39) [38]. Assuming that the baseline was similar, at an α error of 0.05 with power of 90%, and with a projected attrition rate of 20%, we need to recruit 153 women per group. To round off, we will recruit and randomize 160 women with PCOS per group (ie, a total of 320 women). A total of 160 subjects will be recruited and randomized in each of the 2 groups, with 80 subjects in each arm.

Randomization (Drug Intervention)

Eligible consenting subjects will be randomized in a 1:1 ratio into 2 arms through a blinding procedure.

Arm A compares lifestyle (32 kcal/kg diet per day with 55% carbohydrates, 20% protein, 20% fat, and 20 g of fiber with 30 minutes of brisk walking daily) and metformin (1 g /day) versus lifestyle alone (n=160; 80 per center).

Arm B compares lifestyle (32 kcal/kg diet/day with 55% carbohydrates, 20% protein, 20% fat, and 20 g of fiber with 30 minutes of brisk walking daily) and OCP (30 µg ethinyl estradiol plus 2 mg drospirenone) versus lifestyle alone (n=160; 80 per center).

Subject Selection

The subjects will be recruited from the community pool of substudy 1 and the institutional pool. The eligibility based on inclusion and the investigators will assess exclusion criteria. The institutional pool, which comprises the women attending endocrinology, gynecology, or other clinics for various complaints suggestive of PCOS, will be taken for purposes of recruitment in the intervention part of phase 1 or for further assessment in forming a long-term cohort. Potentially eligible patients will be recruited from the outpatient department services of the participating centers. If the subjects qualify on the inclusion and exclusion criteria, they will be informed about the details of the study and hence will be approached for written informed consent. All potentially eligible patients will undergo clinical, biochemical, and imaging (US) assessment to confirm PCOS. A logbook will be maintained for all patients undergo screening, randomized, eligible but not randomized along with reasons for non-randomization. For the intervention study

(substudy 3), the subjects will be recruited only from AIIMS, New Delhi, and SKIMS, Srinagar. The sleep study and carotid Doppler at SKIMS and AIIMS, New Delhi, will be conducted for 100 subjects at each site.

The drug-naïve women who qualify on the 1990 NIH criteria (from both the institutional pool and the community pool) will be invited for the study. This will be an open-label randomized intervention trial and will follow a common protocol at each participating center. Women who do not desire fertility and who furnish written informed consent (second time) will undergo a detailed clinical assessment including details of menstrual, drug, and other relevant history followed by clinical examination involving anthropometry (height, weight, waist circumference); Ferriman-Gallwey scoring for hirsutism; grading of acanthosis nigricans, androgenic alopecia, and acne vulgaris (grades 1-3); blood pressure measurement; and a brief relevant systemic examination. Biochemical and hormone estimation will be done at baseline from the second day to the seventh day of the menstruation cycle and at 3 and 6 months. The subjects will be followed up at 6 months, and all these investigations will be repeated at the follow-up. A total of 320 women for the intervention phase (ie, 80 subjects per arm and per center) will be recruited. The study will be done only in 2 participating centers (SKIMS, Srinagar, and AIIMS, New Delhi). The intervention phase will be initially done for a period of 24 weeks.

Baseline Assessment

Standardized study tools will be used to record patient name, contact details, history, family history, personal information (age of menarche, menstrual regularity information, acne severity), food habits, lifestyle habits, previous disease information, drug intake history information, and clinical details including anthropometry (height, skinfold, waist circumference) by using anthropometric tools (SECA 213 height scale, SECA 813 weight scale, SECA 203 nonstretchable tape, and calipers measuring skinfold thickness), blood pressure (using Omron blood pressure instruments), Ferriman-Gallwey score, androgenic alopecia, acanthosis nigricans, acne vulgaris, and systemic examination. Measurement of biochemical parameters (blood glucose, OGTT, lipid profile, liver function, kidney function), protein:creatinine ratio, and 25OHD (in selected cases); hormonal assays (like T_4, thyrotropin, LH, FSH, PRL, E2, P4—21st day optional, cortisol, testosterone, AMH, DHEAS, 17OHP, SHBG, and insulin); and radiological assessment will be done at baseline and after 6 months of treatment.

Follow-Up and Safety Evaluation

Patients will be evaluated for any adverse events and efficacy at 90 days (−7 days to +7 days) and 180 days (−7 days to +7 days) through follow-up. All clinical and biochemical investigation will be performed in a similar fashion as done at baseline. If the patient is not available for assessment at 180 days (−7 days to +7 days) follow-up, this will be considered a protocol deviation. The safety of different interventions will be assessed by recording the development of immediate or delayed complications recorded in a form with a prespecified list of safety parameters. Immediate reactions will include allergic reactions, diarrhea, vomiting, deep vein thrombosis, etc in a prespecified checklist.

Field Activities

Field activities will be conducted for the purposes of screening. It will include rapport building among locals and the selection of the study subjects (1 woman per household). It will be the duty of the research staff to approach the selected individuals and to make them understand their role in the study. Consenting individuals will be screened for PCOS phenotype using the predesigned structured questionnaire. The screening questionnaire will be used to obtain information on personal identification details, demographics, socioeconomic status, menstrual history and clinical information, history of any systemic disease, and QOL. The women who have hyperandrogenism or oligomenorrhea with or without obesity and acanthosis nigricans (IR) will be taken as probable cases of PCOS. Screen-positive and selected screen-negative (regular menstrual cycles, no features of hyperandrogenism or insulin resistance) individuals will be informed to visit the hospital for further investigations.

Statistical Analysis

Data will be collected on predesigned proformas. The data obtained will then be entered using pilot-tested CSPro software (version 6.2; United States Census Bureau). After assessing for approximate normal distribution, all continuous variables will be summarized as mean (SD) or median (IQR). Categorical variables will be expressed as n (%). Student *t* test and analysis of variance will be used to compare the groups. Statistical analysis will be performed using reliable SPSS statistical software (version 26; IBM Corp).

Results

The study was ethically approved and funded in November 2017 by ICMR, New Delhi, India. The subject recruitment from the community pool and implementation of the intervention for evaluating the treatment responses in a subset of PCOS subjects started in 2018 and is expected to be completed in October 2021. The study results will be compiled and statistically analyzed by April 2022 and will be published in a peer-reviewed scientific journal.

Discussion

Polycystic ovary syndrome is a multifactorial disorder with unknown etiology and numerous clinical manifestations in reproductive-aged women around the world [4-7]. The diagnostic criteria used to define PCOS include menstrual irregularity, hyperandrogenism, and polycystic ovary morphology. To date, PCOS has remained a major clinical challenge due to its poor prognosis, limited treatment options, and late diagnosis of the disease.

The prevalence of PCOS is increasing the world over and is showing a galloping increase in India. To date, there have been no systematic studies available either globally or in India. In India, there are undersized, convenience-based studies reported, which might not reflect the true status of PCOS prevalence in

the community [32,33]. It is difficult to draw a clear conclusion from this limited number of studies conducted across the country. These studies hint at the potential for large-scale epidemiological studies on PCOS across India. This ongoing study will be the first of its kind in the country to generate the actual prevalence and picture of the disease in the community.

It is the first nationwide initiative by ICMR, New Delhi, to comprehensively study the prevalence, comorbidities (obesity, AGT, IR, NAFLD, sleep apnea, stroke, CVD, neuropsychiatric comorbidities), and phenotypes of PCOS in India using robust diagnostic methodology. On its completion, the study will generate an unprecedented amount of data about PCOS and the efficacy of interventions, which will facilitate the health care professionals, policy makers, and government of India to formulate new strategies that may shift the existing treatment paradigm in the near future.

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Authors' Contributions

MAG, national chief coordinator of the study, is the first author of the study protocol. MAG and RSS conceived the proposal. Coauthors SC, V Suri, BJ, PKB, SA, NM, RS, RR, PKJ, MS, IAW, and SS provided their expertise in the design of and contributed to finalize the study protocol and are involved in data capturing. V Sreenivas provided statistical assistance and sample size calculation. All authors revised the paper and approved the final version of the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
ICMR-PCOS Study-Expert committee recommendations.
[PDF File (Adobe PDF File), 2456 KB - resprot_v10i8e23437_app1.pdf]

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Abbreviations

17OHP: 17-hydroxyprogesterone
25OHD: 25-hydroxyvitamin D
AE-PCOS: Androgen Excess and Polycystic Ovary Syndrome
AGT: abnormal glucose tolerance
AIIMS: All India Institute of Medical Sciences
AMH: anti-Müllerian hormone
BMI: body mass index
CVD: cardiovascular diseases
DHEAS: dehydroepiandrosterone sulfate
E2: estradiol
ECLIA: electrochemiluminescence assay
FSH: follicle-stimulating hormone
hsCRP: high-sensitivity C-reactive protein
ICMR: Indian Council of Medical Research
IR: insulin resistance
LH: luteinizing hormone
MRI: magnetic resonance imaging
NAFLD: nonalcoholic fatty liver disease
NIH: National Institutes of Health
OCP: oral contraceptive pill
OGTT: oral glucose tolerance test
P4: progesterone
PCOS: polycystic ovary syndrome
PRL: prolactin
QOL: quality of life
SHBG: sex hormone–binding globulin

T_4: thyroxine
US: ultrasonography; ultrasound

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Protocol

A Technological-Based Platform for Risk Assessment, Detection, and Prevention of Falls Among Home-Dwelling Older Adults: Protocol for a Quasi-Experimental Study

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Abstract

Background: According to the United Nations, it is estimated that by 2050, the number of people aged 80 years and older will have increased by 3 times. Increased longevity is often accompanied by structural and functional changes that occur throughout an individual's lifespan. These changes are often aggravated by chronic comorbidities, adopted behaviors or lifestyles, and environmental exposure, among other factors. Some of the related outcomes are loss of muscle strength, decreased balance control, and mobility impairments, which are strongly associated with the occurrence of falls in the elderly. Despite the continued undervaluation of the importance of knowledge on fall prevention among the elderly population by primary care health professionals, several evidence-based (single or multifaceted) fall prevention programs such as the Otago Exercise Program (OEP) have demonstrated a significant reduction in the risk of falls and fall-related injuries in the elderly within community settings. Recent studies have strived to integrate technology into physical exercise programs, which is effective for adherence and overcoming barriers to exercise, as well as improving physical functioning.

Objective: This study aims to assess the impact of the OEP on the functionality of home-dwelling elderly using a common technological platform. Particularly, the impact on muscle strength, balance, mobility, risk of falling, the perception of fear of falling, and the perception of the elderly regarding the ease of use of technology are being examined in this study.

Methods: A quasi-experimental study (before and after; single group) will be conducted with male and female participants aged 65 years or older living at home in the district of Porto. Participants will be recruited through the network COLABORAR, with a minimum of 30 participants meeting the study inclusion and exclusion criteria. All participants will sign informed consent forms. The data collection instrument consists of sociodemographic and clinical variables (self-reported), functional evaluation variables, and environmental risk variables. The data collection tool integrates primary and secondary outcome variables. The primary outcome is gait (timed-up and go test; normal step). The secondary outcome variables are lower limb strength and muscle resistance (30-second chair stand test), balance (4-stage balance test), frequency of falls, functional capacity (Lawton and Brody - Portuguese version), fear of falling (Falls Efficacy Scale International - Portuguese version), usability of the technology (System Usability Scale - Portuguese version), and environmental risk variables (home fall prevention checklist for older adults). Technological solutions, such as the FallSensing Home application and Kallisto wearable device, will be used, which will allow the detection and prevention of falls. The intervention is characterized by conducting the OEP through a common technological platform 3 times a week for 8 weeks. Throughout these weeks, the participants will be followed up in person or by telephone contact by the rehabilitation nurse. Considering the COVID-19 outbreak, all guidelines from the National Health Service will be followed. The project was funded by InnoStars, in collaboration with the Local EIT Health Regional Innovation Scheme Hub of the University of Porto.

Results: This study was approved on October 9, 2020 by the Ethics Committee of Escola Superior de Enfermagem do Porto (ESEP). The recruitment process was meant to start in October, but due to the COVID-19 pandemic, it was suspended. We expect to restart the study by the beginning of the third quarter of 2021.

Conclusions: The findings of this study protocol will contribute to the design and development of future robust studies for technological tests in a clinical context.

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KEYWORDS

fall prevention; technological platform; elderly; Otago Exercise Program

Introduction

According to the United Nations, it is estimated that by 2050, the number of people aged 80 years and older will have increased by 3 times [1]. Increased longevity is often accompanied by structural and functional changes occurring throughout an individual's lifespan and can be aggravated by certain behaviors, lifestyles, and environmental exposures, among other reasons. Some of the outcomes associated with these changes are loss of muscle strength, decreased balance control, and mobility impairments, which are risk factors strongly associated with the occurrence of falls in this population [2].

Globally, falls are highly prevalent in the elderly [3-5]. Although some asymmetries exist, it has been reported that about one-third of home-dwelling adults fall at least once a year, and of those who fall, two-thirds will experience another fall in the following year [4,6]. In this segment of the population, falls are complex events with multiple, dynamic interacting factors likely to lead to an increase in the frequency of such incidents with major implications on the quality of life [2]. The consequences of a fall can be extremely serious for the elderly and their families, as these falls can initiate or accelerate a vicious cycle of losses that can ultimately result in functional dependence leading to institutionalization [7,8]. Scientific research has identified several risk factors and has confirmed that the risk of falling increases with the number of existing risk factors [9]. Changes in gait and balance [2,9,10], decreased muscle strength [10], sensory deficits [2,10], functional decline [10], cognitive decline [2,9], musculoskeletal disease [4], neurological disease [2], endocrine or metabolic diseases [10], depression or depressive symptoms [9], urinary incontinence [10], the fear of falling [7,10], polymedication [2,9], and a history of a previous fall [2,4,9,10] are factors strongly associated with falls in the elderly. In a community context, research shows that the multifactorial web associated with these events also integrates risk factors present in household environments where the elderly perform their activities of daily living (ADLs) [11]; the synergistic and dynamic interaction of these risk factors with intrinsic factors increases the risk of falling.

Primary health care professionals should consider the existing evidence to develop interventions targeted at the elderly and their families [12] to identify and mitigate the environmental risks, and to promote safe behaviours. This intervention must include several programs effective for fall prevention, particularly when coupled with other approaches [9,11-13]. Changes in gait and balance are major factors associated with falls in the elderly, and rapid tests are recommended for the assessment of changes in gait and balance, such as the 30-second chair stand test (CST) [14], 4 stage balance test (4 SBT) [15], and timed-up and go test (TUGT) [9,16].

Despite the continued undervaluation of the importance of knowledge on fall prevention among the elderly population [11] by primary care health professionals, several fall prevention programs (single or multifaceted) have demonstrated a significant reduction in the risk of falls, number of falls, and fall-related injuries [6,9,13,17]. In fall prevention programs, an exercise component, either as a single intervention or integrated into multifaceted interventions, has proven effective in preventing these events and reducing associated injuries [6,9]. The Otago Exercise Program (OEP) developed at the University of Otago Medical School is an exercise program for fall prevention used in a community context internationally. The efficacy of the OEP has been attested in 4 randomized studies and 1 controlled multicenter study [6]. The focus of the OEP is to improve strength and balance with a simple, affordable, home-implemented, 12-month solution, which is monitored by a health professional through telephone interviews and home visits. The OEP was designed to be carried out autonomously by people in their homes, supported by a paper-based manual, after training with a physiotherapist for 4 individual sessions. Subsequently, other professional groups such as nurses have successfully administered the program [17,18].

Recent studies have strived to integrate technology into physical exercise programs that were revealed as effective for adherence and overcoming barriers to exercise, as well as for improvements in health and independence [19]. Currently, several technological solutions address specific aspects of the fall cycle; however, the majority of these do not address fall detection, fall risk assessment, and fall prevention simultaneously. The FRADE (Pervasive Platform for Fall Risk Assessment, Detection and Prevention) project seeks to develop a common technological platform that allows the integration of all these components. This platform consists of the use of sensors that will collect data and monitor the gait of the elderly. This platform can also send caregivers alerts and text messages in the event of a fall. The tablet application provides a set of fall prevention exercises based on the Otago Program; along with a wearable sensor, it

allows for the monitoring of user performance and evaluation of progress. This study aims to assess the impact of an exercise program supported by a technological platform on functional variables associated with risk of falling and assess the ease of use of this technology by the elderly.

Methods

Study Design

A quasi-experimental study (before and after; single group) was carried out. Two research centres were involved in the project, the Nursing School of Porto (ESEP) and the Fraunhofer Portugal Assistive Information and Communication Solutions (AICOS).

Recruitment and Sample

Participants aged 65 years or older who were living at home in the district of Porto, Portugal were recruited based on the following criteria.

The inclusion criteria are able to walk independently; cognitive impairment, as assessed by the Portuguese version of the Mini-Mental State Examination (cut-off points of 22 for 0-2 years of schooling, 24 for 3-6 years of schooling, and 27 for ≥7 years of schooling); no severe visual or hearing impairment; and willingness to participate in a physical exercise program with technological support.

The exclusion criteria are a self-reported chronic or acute illness for which exercise is contraindicated, history of hip or knee surgery or lower limb fracture in the last 12 months, current or previous participation in physical exercise programs in the last 6 months, and participation in another research study involving fall prevention programs.

After approval by the ESEP ethics committee, the recruitment of participants will start through the Living COLABORAR Network. This network is part of a Fraunhofer Portugal research center, and it participates in an organization of institutions that give social, health, and leisure support and promote the well-being of their clients, especially the elderly. Potential participants will be contacted by Fraunhofer researchers who will present the study objectives and collect information from people interested in participating in the study.

Subsequently, those willing to participate will be scheduled for an evaluation conducted at home by a rehabilitation nurse in 2 phases. The first phase involves screening potential participants based on the inclusion and exclusion criteria. Consequently, the questionnaire prepared for this study will be completed. These participants will spend a part of their days in the community center, where they will become familiar with the tablets.

The convenience sample will include at least 30 participants.

Setting

This study will be deployed in the city of Porto, within the area of Bonfim at the council in which the care center is located. The population of Bonfim is about 24,265 people, of which 27.1% are elders (>65 years old), according to the 2011 census. This day center is located in an area of the city with an aging population, in which people aged 65 years and over represent 36.3% of the population and young people represent 18.2% of the population, with a total dependency index of 54.9%.

The elderly institution has 2 modalities: long-term hospitalization (for very dependent people) and a community center. The participants for this intervention will only be enrolled from the elderly who attend the activities in the community center but live in their own homes. The intervention will take place in the houses of the participants.

Informed Consent

Participation in the study is voluntary, and participants are free to withdraw from the study at any time. All participants will provide written informed consent before data collection begins in the first home visit. The benefits, risks, and guarantee of confidentiality during data collection and information security for the participants are all explained in the consent form, in addition to the detailed explanation provided by the rehabilitation nurses.

Intervention

The physical exercise program to be implemented is based on the OEP, including exercises aimed at improving balance, gait, and muscular strength in the lower limbs. The program is carried out by the elderly independently in their homes, supported by a paper-based manual, after in-person training with a health professional. In addition to the manual, the participants will have a common technological platform consisting of an Android tablet and a wearable sensor, which will enable them to access the OEP through interfaces with interactive feedback while exercising. This technological platform also allows interactive monitoring of the 5 strength exercises and 3 balance exercises (such as knee flexion, unipedal balance, and sit-and-stand).

In the first session at the participants' homes, the rehabilitation nurse will train the participants to perform the exercises. Participants will be encouraged to carry out this program at least 3 times a week for 8 consecutive weeks. The rehabilitation nurse will provide participants with an in-person or telephone follow-up during these weeks.

The rehabilitation nurse will also instruct the elderly to wear comfortable clothes and shoes and inform the nurse if they experience joint or muscle pain. If such an event occurs, it is advisable to suspend the exercise.

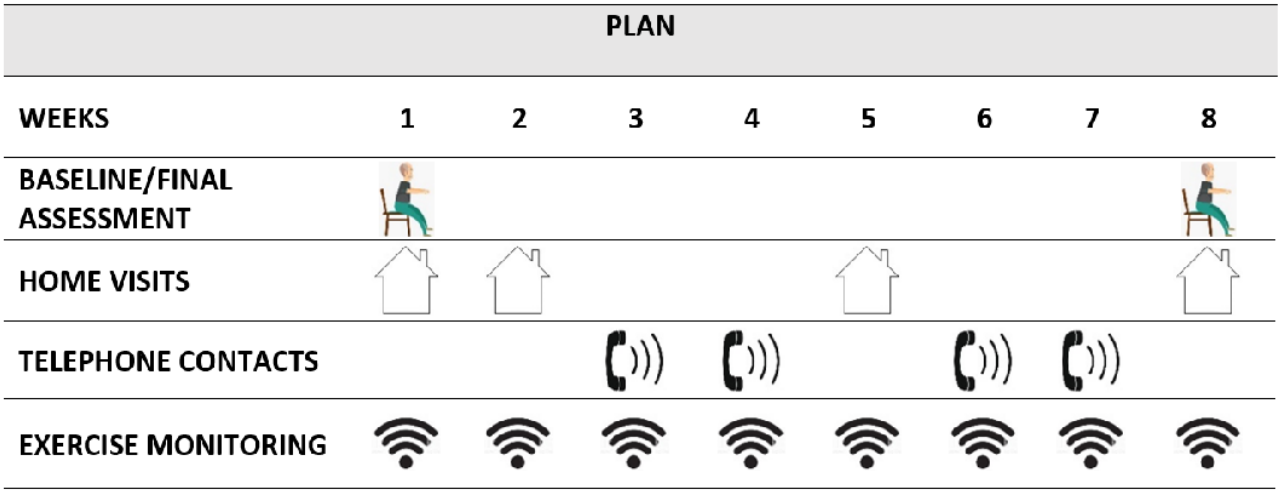
Through the technological platform, the rehabilitation nurse will prescribe the OEP exercise plan for each participant, defining the exercises to be performed and the appropriate level of each exercise along with the frequency.

Each exercise session will have 3 sequential phases: warm-up phase, main phase, and relaxation phase with stretching exercises, which is a return to the calm phase. The progression in the exercises will be guided by the rehabilitation nurse and will be adapted to the functional capacity of the elderly. Regarding the intensity of the exercises, these will be performed without weights.

The OEP exercises and phases are explained in Multimedia Appendix 1. Throughout the duration of the program, participants will be followed up in person and by telephone by

the rehabilitation nurse according to the intervention schedule (Figure 1).

Figure 1. Intervention schedule.



Outcome Measures

A rehabilitation nurse with professional experience will assess the participant at the baseline visit and after 8 weeks using a questionnaire and functional test assessment. In addition to sociodemographic or clinical (self-reported) variables and environmental risk variables, the data collection tool integrates primary and secondary outcome variables.

The primary outcome is gait (TUGT; normal step) [16]. The secondary outcome variables are lower limb strength and muscle resistance (30-second CST) [14], the 4 SBT, frequency of falls, functional capacity (Lawton and Brody - Portuguese version) [20], Falls Efficacy Scale International (FES-I) Portuguese version [21], usability of the technology (System Usability Scale [SUS] Portuguese version) [22], and environmental risk variables (home fall prevention checklist [HFPC] for older adults) [23].

The change over time in the participants is measured by improvement in the functional test scores.

Materials

The data collection instrument includes sociodemographic or clinical variables and functional evaluation variables. Lower limb strength and muscle resistance are the functional variables assessed through the 30-second CST, and mobility is evaluated with the TUGT (normal step). These functional tests, together with the 4 SBT, help evaluate the risk of a fall, which is also assessed with the fall risk screening tool using its inertial sensors to obtain information on the movements performed by the participant and related characterization. The risk of fall is then determined from parameters calculated after processing the signal from the inertial sensors during the execution of functional tests, such as walking, sitting, and standing (Figure 2).

The participants' functional capacity for instrumental activities of daily living (IADL) is assessed using the Lawton and Brody tool, FES-I, SUS, and HFPC (Figure 3).

Figure 2. Fall risk screening tool.

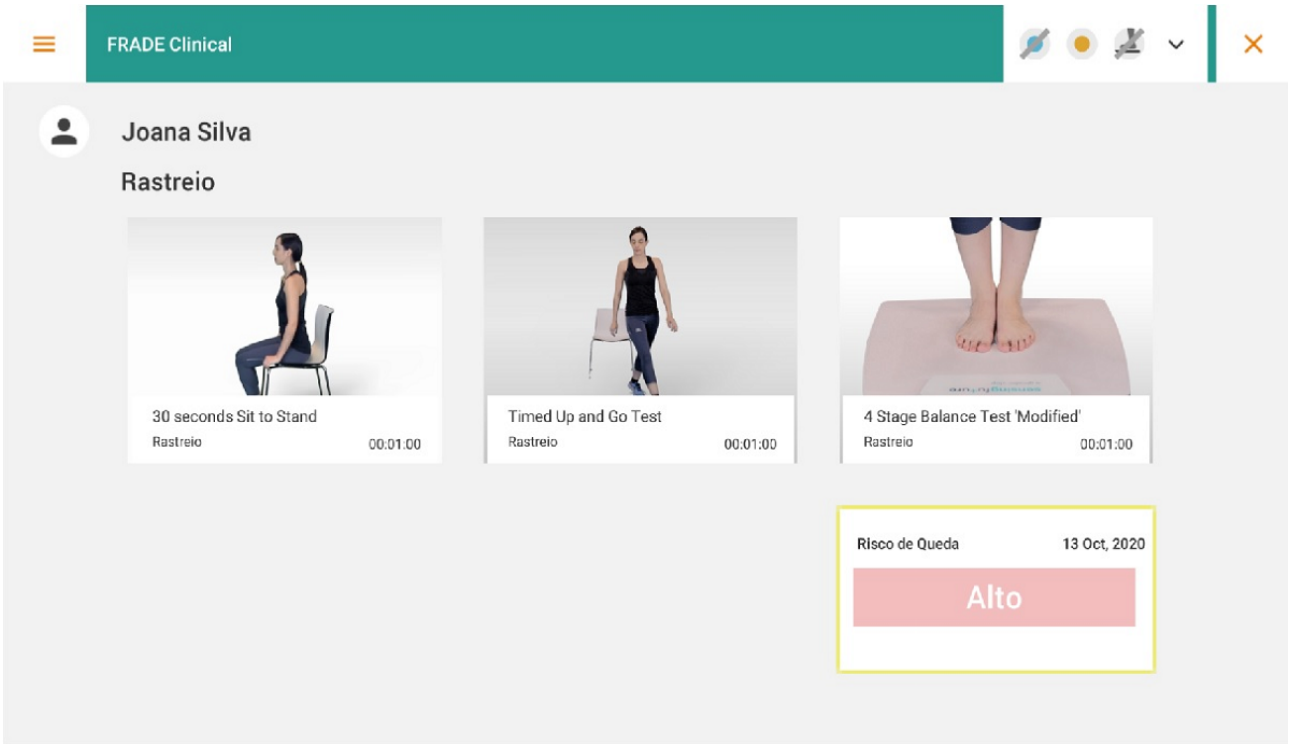
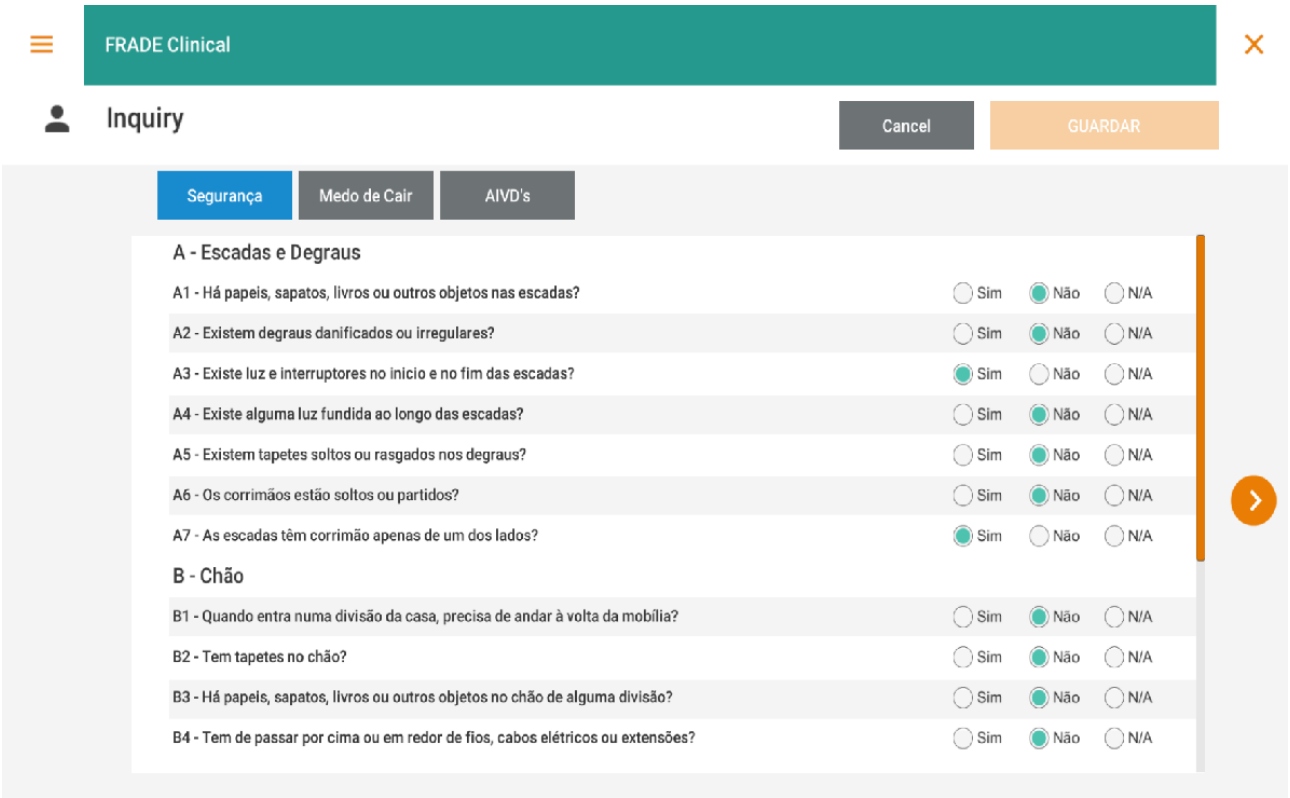


Figure 3. Data collection instrument.



Tests

The following tests will be performed to assess the outcome variables of the study.

Lower Limb Strength

The 30-second CST is a quick test that does not require a dynamometer, training, or special equipment. It is used to evaluate the strength of the lower limbs by counting the number of times the individual stands and sits in 30 seconds [14,24]. Therefore, the performance in the 30-second stand-and-sit test is used as a measure of the strength and muscle resistance of the lower limbs, specifically of the extensor muscles of the knee [25,26].

Mobility

The TUGT (normal step) measures, in seconds, the time an individual takes to stand up, walk a distance of 3 meters, return, and sit down in the same chair. Individuals who complete the test in <20 seconds are reportedly independent in manual handling transfer, and individuals who complete the test in >30 seconds tend to be dependent for this task [27]. It has also been reported that the time spent on the TUGT performance is related to scores on the Berg Balance Scale (r=–0.72), walking speed (r=–0.55) and the Barthel ADL index score (r=–0.51). The TUGT is a useful and practical measure for assessing mobility in the frail elderly and is easy and quick to apply without the need for special equipment or training.

Static Balance

The 4 SBT is used to track impairments in the static balance of the elderly. Several authors have reported that the test has excellent test-retest (r=0.97) and interevaluator reliabilities (kappa=0.92) [28,29]. According to the guidelines issued by the Centers for Disease Control and Prevention, the test must first be demonstrated to the participants by a nurse or physiotherapist, allowing the participants to perform a trial test to ensure correct performance. Participants are instructed to perform the four 10-second stages of the test sequentially. If the participant manages to perform 1 stage in 10 seconds, without moving the feet, losing balance, or needing support, the participant can move on to the next stage. If the participant fails this test, it is terminated [30]. The success of fall prevention programs is measured by comparing the positions achieved in 10 seconds in the pre- and postprogram evaluations [17].

Participants are instructed to be in an orthostatic position and perform the 4 different feet positions sequentially: position 1 is a side-by-side stance; position 2 is a semitandem stance (preferred foot forward with the instep foot touching the hallux of the other foot); position 3 is a tandem stance (one foot in front of the other, the heel of one foot touching the toes of the other); position 4 is a one-legged stance (using the preferred leg for support).

The final score will be the number of positions that are completed without loss of balance. Participants who cannot maintain position 3 for 10 seconds have a high risk of falling [30].

Functional Ability

The Lawton and Brody scale assesses the level of independence in performing IADLs, which include daily tasks such as using the telephone, shopping, cooking, housekeeping, washing clothes, using transport, preparing medication, and handling finances. It is an easy-to-administer tool that can be used in community and hospital settings [31-33].

In this study, the Portuguese version [20] of the Lawton and Brody scale is used, including the same items as in the original version, but with a polychotomic score (0, 1, 2, 3, or 4) instead of the original dichotomic version (0 and 1). This allows for a better description of an individual's ability to perform the tasks, with a different score for each response option. The total score of the scale can be between 0 and 23, with a lower score corresponding to worse performance. In a validation study for this scale conducted with a sample of elderly people living in urban and rural settings, good metric qualities were shown when applied in a community setting, with a Cronbach alpha indicative of good reliability (0.94) and correlations between the scale items and the total scale between r=0.77 and r=0.86. In a study on the convergent validity of this scale, a strongly positive and statistically significant correlation with the Barthel Index was observed.

Fear of Falling

The FES-I evaluates the fear of falling. The elderly may have problems expressing their fear of falling. The assessment of this fear is highly relevant because it is associated with adverse effects on elderly mobility and quality of life [34-36].

One of the instruments used to evaluate the fear of falling is the FES-I [37] developed by ProFaNE (Prevention of Falls Network Europe Group) based on the original version of the FES developed in 1990 [38]. The FES-I incorporates 16 activities, including some daily activities slightly more complex than those in the original version, with others more targeted at the social life of elderly to strengthen some of the weak points mentioned in the literature about the original version. Its adaptation to different languages and cultural contexts (following the protocol recommended by the ProFaNE group) has allowed the scale to be widely applied, along with comparison of the results in different populations and contexts.

Because this scale provides an understandable measure of the fear of falling in the elderly and has excellent metric properties, the FES-I was chosen to measure the fear of falling in our study [39-41].

The Portuguese version of the FES-I [21] showed excellent internal consistency (Cronbach alpha=0.978) and test-retest reliability ($ICC_{2.1}$=0.999). Concurrent validity assessed using the activities-specific balance confidence (ABC) scale showed results indicative of good concurrent validity (r_s=–0.85; P<.001). Based on these results, the authors consider the Portuguese version of FES-I a reliable and valid measure to assess the fear of falling among the Portuguese community-dwelling elderly population.

Technology Usability

Technology usability will be analyzed using the SUS. The original author of the test describes it as a quick tool to assess the usability of a particular product or service [42]. According to some authors, this test has several features that provide good assessment of the overall usability, such as the flexibility to evaluate interface technologies, interactive voice response systems, and hardware used in more traditional computer interfaces and websites. Ease and speed of use, both by participants and system administrators; ease of operation of scoring; and free access are characteristic of this test [43].

The original SUS consists of 10 statements that are scored on a 5-point Likert scale (Strongly disagree – Strongly agree). The final score can vary from 0 to 100 points, with higher scores indicating better usability [42]. In this scale, an excellent score is above 90; a good score is above 80, and an acceptable score

is above 70; scores below 70 indicate usability problems [44]. In 2015, a group of Portuguese researchers [22] began the translation and cultural adaptation of this scale along with the subsequent evaluation of its metric qualities. The same authors stated that the SUS could be used to distinguish between usable and nonusable applications.

Procedures

Developing the Intervention

Meetings will be held between main investigators and rehabilitation nurses to present the study protocol. Subsequently, meetings will be held between rehabilitation nurses and the engineers who developed the applications. The first meeting will aim to present the clinical application (FallSensing Clinical App) to nurses. At the second meeting, the application to be used by the elderly in the home context (FallSensing Home App) will be presented, and a final meeting will be held to present the web platform. A screening test session will also be performed using all the tools.

The rehabilitation nurses will be provided with a checklist to standardize the procedures during the intervention phase, both for in-person and telephone follow-ups.

Ensuring the Safety of the Intervention

During the exercise program, the participants will be instructed to follow safety measures, such as performing the exercises in a large space without obstacles, along with wearing loose and comfortable sports clothes.

The nurse will evaluate the best ergonomic place in the house to perform the exercises.

In March 2020, the World Health Organization declared COVID-19 an international pandemic. Following this event, several important measures must be adopted to contain the spread of the disease, namely the use of a mask, social distancing, and hand hygiene. Strict measures will be added to prevent the spread of COVID-19 in the nurses' procedures when dealing with home-dwelling elderly, specifically during the execution of the physical exercise program. This means wearing a surgical mask, protective gown, and gloves; the personal protective equipment will be discarded after each contact.

Technological Platform

The technological solutions to be used to support the physical exercise program consist of 3 applications.

The FallSensing Clinical App requires the use of a Windows computer, 2 wearable devices with inertial measurement units, and a pressure platform to obtain information about the movement and balance of the user while performing the CST, TUGT, and 4 SBT. The application also allows the creation of a personal profile for each participant, in which the participants' answers to questionnaires for the assessment of several risk factors for falls, such as the IADL or FES-I home hazards questionnaires, can be saved. Additionally, the application will enable the prescription of OEP exercises and scheduling for each participant through a dedicated exercise prescription interface. This exercise prescription will be sent automatically to the FallSensing Home application.

The interactive FallSensing Home App, based on the OEP, aims to improve physical functionality. The application features 8 exercises from the program that are static, easy, and well accepted, with interactive feedback for the execution of the movement. The application can also motivate participants who perform the exercises at home. The application requires an Android tablet, support for the tablet, 2 wearable inertial devices, and the respective chargers. The users will be guided through a weekly exercise plan, which they will be able to select through the tablet interface where the instructions for executing each exercise will be presented, as well as an interface with visual feedback during the execution of each exercise (Figures 4 and 5).

Figure 4. FallSensing Home App.

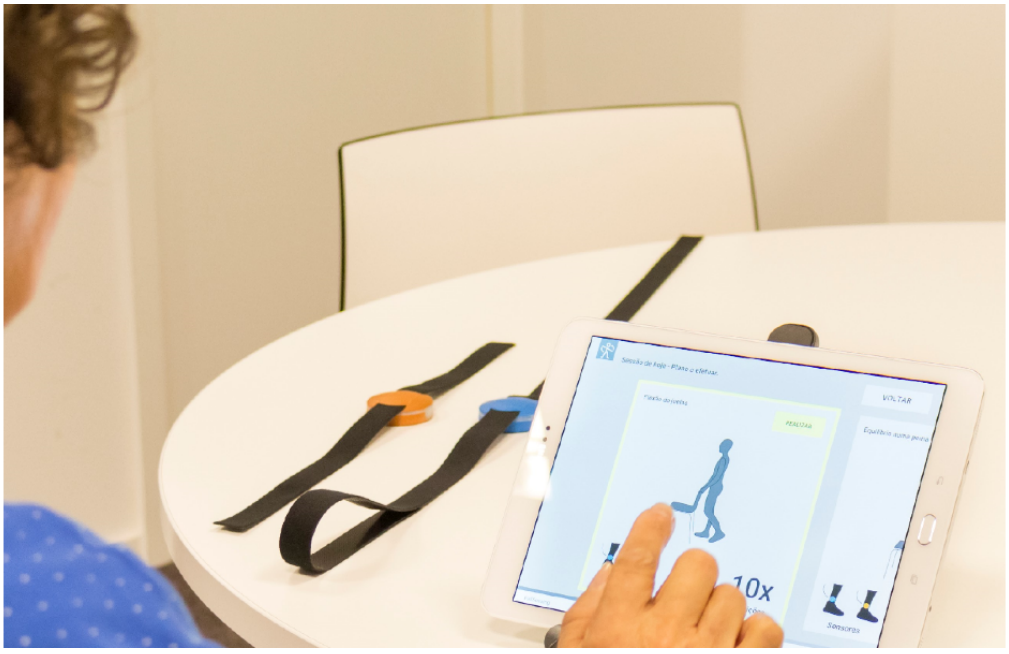
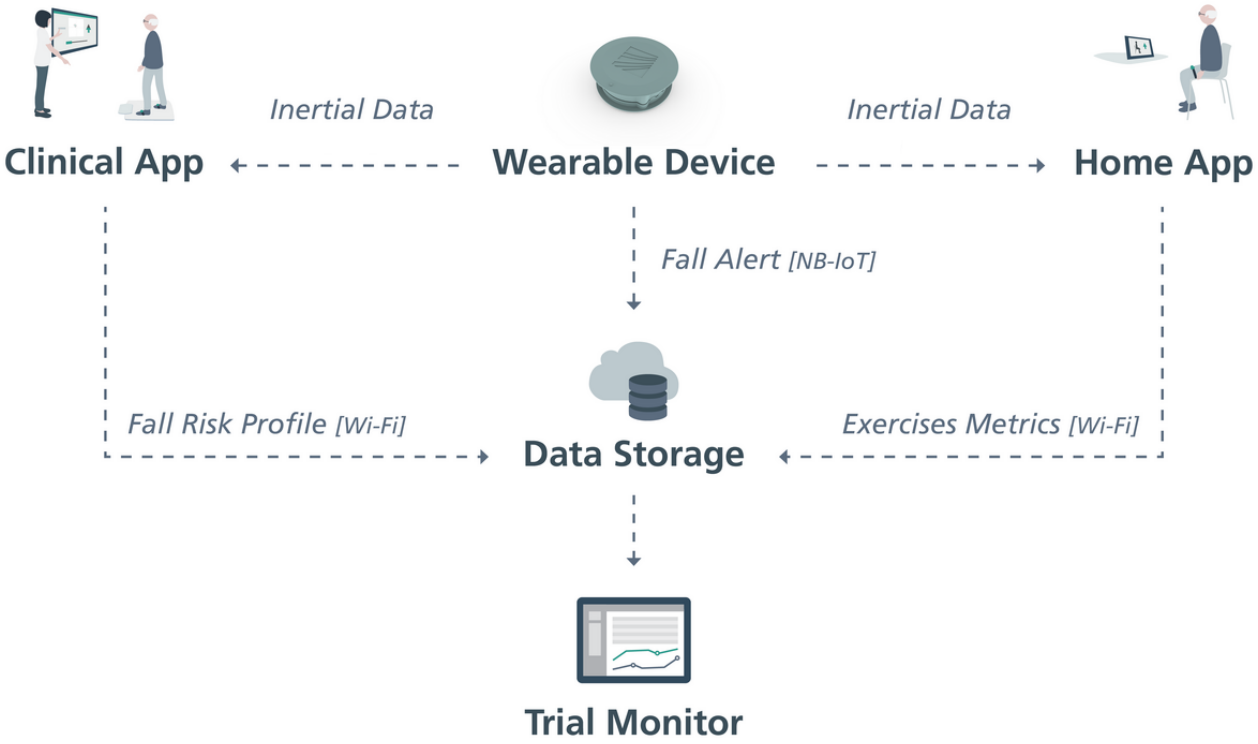


Figure 5. Demonstration of exercises through the FallSensing Home App.

The wearable fall detection device contains an automatic fall detection algorithm and offers features such as the sending of alarms through the wearable device, which can be placed discreetly on the belt, in the pocket, or on the chest of the user. If a fall event is detected, a notification will be sent to a backend that in turn sends a text message and email to a set of predefined emergency contacts. Communication between the device and the backend is via Narrow Band-IOT (Internet-of-Things). The device also triggers an audible alarm to attract the attention of people nearby, featuring an emergency button that allows the cancellation of false alarms. The device works independently of a smartphone or other resource and only needs to be charged via an induction charger, which will be supplied with the device.

Figure 6 facilitates a better understanding of the process of the technological platform.

Figure 6. Process followed by the technological platform. NB-IoT: Narrow Band-Internet of Things.



Statistical Analysis

Data processing will be carried out with SPSS software (IBM Corp, Armonk, NY). In the first approach, the data will be analyzed using descriptive statistics in order to classify the group of participants based on their sociodemographic, clinical, functional, and body processes data, using measures of frequency, central tendency, and dispersion. For inferential statistics, nonparametric statistics will be used, considering the sample size and sample type (nonrandom), with statistical significance set at $P<.05$. The prospective differences in the primary and secondary outcome variables, based on the 2 repeated measurements, will be tested using nonparametric tests equivalent to the *t* test for paired samples (Wilcoxon or McNemar procedure for quantitative and qualitative variables, respectively).

Results

The recruitment process was meant to start in October 2020; however, due to the COVID-19 pandemic, it was suspended. We expect to restart the study by the beginning of the third quarter of 2021. The study results are expected to be published after this. This research will be carried out by a partnership between the ESEP and Fraunhofer Portugal. From this collaboration emerges a multidisciplinary team of nurse researchers, rehabilitation nurses, and engineers. This research seeks to obtain health gains for the elderly population.

This study was approved by the Ethics Committee of ESEP on October 10, 2020 (António Bernardino de Almeida, 4200-072 PORTO - Portugal; ref annex 2 meeting minutes no. 6/2020).

Discussion

The study will provide an objective measurement of fall risk factors and movement-based metrics obtained during the OEP exercises, such as strength of the lower limbs, mobility, and balance impairment

A quasi-experimental study protocol will be developed, focusing on the OEP, involving home-dwelling elderly, and using a common technological platform, with follow-up by a rehabilitation nurse 3 times a week over 8 weeks.

Throughout the intervention, the follow-up of participants through regular home visits, coupled with telephone contact, will contribute to better monitoring of the evolution of the condition of the participant and will increase their confidence and security, as a determinant for the recognition of the role of the nurses.

The technological platform will allow the centralization of all relevant variables in a unified and secured database, which will be accessible through a web portal and made available for the nurses supervising the study. In addition to the variables retrieved by the clinical application (eg, personal profile, medical conditions, medication, answers to the questionnaires, and scores of the 3 functional tests, the home application will allow the measurement of the range of motion along with the number of repetitions and durations of ascending and descending movements for the 8 exercises of the OEP, namely, knee flexion, knee extension, hip abduction, knee bending, toe raises, calf raises, sit-to-stand, and one-leg standing exercises. Previous studies have set a background for the technological solutions used in this study [45,46].

This study has some limitations, namely, the use of a nonrandom sample and the absence of a control group. Additionally, the recruitment process was hindered by the COVID-19 outbreak, even though all the National Health Service guidelines were followed. Additionally, the funding agency provided a relatively short time for the development of the study.

As for the technological aspect, we consider that the technological literacy of each participant may affect an individual's use of the platform and that some limitations are likely to arise during the 8-week intervention program since some of the sessions will be performed by the elderly alone at home. To attempt to overcome these limitations, frequent contact between the nurses and the elderly will be established along with remote guidance whenever deemed necessary.

In conclusion, the findings of this study protocol will contribute to the design and development of future robust studies for technological tests in a clinical context.

Acknowledgments

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Authors' Contributions

FA and MNN contributed to the design of the study protocol and drafting the manuscript. FA, MNN, and JS contributed with critical revisions to the paper for important intellectual content. FA, MNN, and JS obtained the funding. JS described the technological solutions used in the study. SR contributed to the definitions of participant recruitment and ethical considerations.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Otago Exercise Program exercises and phases.
[DOC File , 34 KB - resprot_v10i8e25781_app1.doc]

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Abbreviations

ABC: activities-specific balance confidence
ADL: activities of daily living
AICOS: Center for Assistive Information and Communication Solutions
CST: chair stand test
ESEP: Escola Superior de Enfermagem do Porto
FES-I: Falls Efficacy Scale - International
FRADE: Pervasive Platform for Fall Risk Assessment, Detection and Prevention
HFPC: home fall prevention checklist
IADL: Instrumental Activities of Daily Living
OEP: Otago Exercise Program
ProFaNE: Prevention of Falls Network Europe Group
SBT: stage balance test
SUS: System Usability Scale
TUGT: timed-up and go test

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Protocol

Use of Home-Based Connected Devices in Patients With Cystic Fibrosis for the Early Detection and Treatment of Pulmonary Exacerbations: Protocol for a Qualitative Study

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Abstract

Background: Early detection of pulmonary exacerbations (PEx) in patients with cystic fibrosis (CF) is important to quickly trigger treatment and reduce respiratory damage. We hypothesized that using home-based and wearable connected devices (CDs) and educating patients to react in case of abnormal variations in a set of parameters would allow patients to detect and manage their PEx early with their care team.

Objective: This qualitative study aimed to assess the feasibility and appropriate conditions of a new PEx management process from the users' point of view by analyzing the experience of patients and of CF center teams regarding the education program, the use of CDs, and the relationship between the patient and the care team during PEx management.

Methods: We have been conducting a multicenter pilot study involving 36 patients with CF aged ≥12 years. The intervention was divided into 3 phases. In phase 1 (3 months), patients were equipped with CDs, and their parameters were collected on 3 nonconsecutive days each week. Phase 2 involved the development of a "React to PEx" educational program aimed at providing patients with a personalized action plan. A training session to the educational program was organized for the physicians. Physicians then determined the patients' personalized alert thresholds by reviewing the data collected during phase 1 and their patients' clinical history. In phase 3 (12 months), patients were educated by the physician during a clinic visit, and their action plan for reacting in timely fashion to their PEx signs was defined. Education and action plans were revised during clinic visits. At the end of the project, the patients' experience was collected during semistructured interviews with a researcher as part of the qualitative study. The experience of CF teams was collected during focus groups using a semistructured guide once all their patients had finished the study. The interviews and focus groups were recorded and transcribed verbatim to be analyzed. Data from educational sessions were collected throughout the educational program to be put into perspective with the learnings reported by patients. Analyses are being led by 2 researchers using NVivo (QSR International).

Results: The study received the favorable reception of the Committee for the Protection of Persons (CPP NORTH WEST III) on June 10, 2017 (#2017-A00723-50). Out of the 36 patients included in phase 1, 27 were educated and entered phase 3. We completed collection of all data from the patients and care providers. Qualitative analysis will provide a better understanding of users' experience on the conditions of data collection, how useful CDs are for detecting PEx, how useful the PEx action plan is

for reacting quickly, what patients learned about PEx management, and the conditions for this PEx management to be sustainable in routine care.

Conclusions: This study will open new perspectives for further research into the implementation of an optimal PEx care process in the organization of care teams in order to support patient self-management.

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KEYWORDS

cystic fibrosis; pulmonary exacerbation; connected devices; patient education; self-management

Introduction

Pulmonary exacerbations (PEx) are the main cause of lung function decline in patients with cystic fibrosis (CF) leading to respiratory failure. Identifying warning signs of PEx is a priority to trigger early treatment and reduce respiratory damage [1]. Some authors have attempted to define scores based on symptoms felt and expressed by patients, particularly during telephone contact with their doctor, in order to standardize treatment [2]. However, the lack of consensus led the EuroCareCF Working Group to recommend that the medical decision regarding the prescription of an antibiotic treatment (or antibiotic modification) associated with PEx-like symptoms remains the gold standard definition of PEx in clinical trials [3].

Recently, the Standardized Treatment of Pulmonary Exacerbations (STOP) study conducted at 11 CF centers in the USA was intended to serve as a basis for future interventional studies aimed at improving the outcomes of exacerbations [4]. West et al [5] pointed out the significant heterogeneity in physicians' decisions regarding antibiotic treatments used to treat an exacerbation. Indeed, a study testing various scenarios for designing interventions led to the conclusion that a combination of mean change in Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) and in absolute forced expiratory volume in 1 second (FEV1) in liters predicted from treatment initiation should be used for performing interventional studies targeting CF exacerbations [6,7]. Whether these indicators can be used to detect and manage patients' PEx early in routine care remains an open question. The prospect of using connected devices (CDs) to measure physiological parameters and patient perceptions at home turns this question into a matter of feasibility, reliability, and sustainability in a real-life context.

Previous studies have shown that a combination of physiological parameters and patient-reported perceptions (PRP), such as weight loss, decreased spirometry, increased cough, or increased sputum production reported daily, helps to diagnose PEx episodes and trigger early treatment [8,9]. A study aimed at establishing a consensus approach (Delphi) identified 10 signs of PEx (Tables 1-2) frequently perceived by patients and 10 indicators most often cited by caregivers [10], 4 of which were shared between professionals and patients. It was further found that professionals relied more on measurements of physiological parameters, while patients relied on perceptions and difficulties to perform their daily activities.

Table 1. Indicators of an exacerbation from a Delphi survey in adults with cystic fibrosis: mean scores, SD, and rank order of each statement [10]. Scores with the same average rating were given the same joint ranked position.

Statement	Score, mean (SD)	Rank order
A large decrease in lung function (greater than 10% FEV1[a])	9.33 (0.784)	1[b]
Feeling more short of breath than usual	8.52 (1.087)	2[b]
Trouble breathing	8.52 (1.805)	2
Feeling the need to do more airway clearance than usual	8.37 (1.115)	4
An increase in symptoms at night	8.22 (1.450)	5
Producing more sputum	8.19 (1.388)	6[a]
Finding it harder than normal to do usual exercise	7.96 (1.581)	7
Finding it harder than normal to do usual activities	7.93 (1.838)	8
Feeling more exhausted than usual	7.85 (1.703)	9
More coughing than usual	7.85 (1.610)	9[a]

[a]FEV1: forced expiratory volume in 1 second.

[b]Also ranked in the top 10 by cystic fibrosis health care providers.

Table 2. Indicators of an exacerbation from a Delphi survey in cystic fibrosis health professionals: mean scores, SD, and rank order of each statement [10].

Statement	Score, mean (SD)	Rank order
Increased sputum	8.84 (1.027)	1[a]
A large decrease in lung function (greater than 10% FEV1[b])	8.84 (1.263)	1[a]
More shortness of breath than usual	8.32 (1.141)	3[a]
Increased inflammatory markers (for example CRP[c] and white cell count)	7.92 (1.124)	4
Fever or increased temperature	7.89 (1.269)	5
Increased respiratory rate at rest	7.82 (1.557)	6
Decreased oxygen saturation	7.79 (1.510)	7
Hypoxia/hypoxemia	7.76 (1.807)	8
Change in the color of sputum	7.61 (1.636)	9
New changes on chest x-ray	7.47 (1.767)	10
Increased coughing	7.47 (1.466)	10[a]

[a]Also ranked in the top 10 by adults with cystic fibrosis.

[b]FEV1: forced expiratory volume in 1 second.

[c]CRP: C-reactive protein.

At present, patients with CF do not routinely monitor their lung function at home, as few are equipped with devices to track variations in their physiological parameters or perceptions over time. Clinical observations also show that changes in physiological parameters and PRP related to PEx differ according to age and degree of lung function impairment [11]. Consequently, PEx may be diagnosed with a delay as symptoms progress while remaining unnoticed and patients seek medical care late. A few studies have been initiated in CF with daily monitoring of PEx symptoms and a few clinical parameters, mainly spirometry and oxygen saturations, together with a symptom diary [12,13]. Data were transmitted to the clinical staff who analyzed the variations and decided what course of action to take in case of an alert. These studies generally used the same alert thresholds for all patients although it is known that patients with CF have different thresholds for these indicators [9,11]. These findings have opened the way into investigating a more personalized approach to help patients self-manage their indicators at home for identifying and treating PEx early.

Our hypothesis is that an intervention that combines the provision of CDs with personalized alert thresholds and patient education by a physician may enable patients to detect early PEx signs and initiate the management of a PEx episode in a timely manner. In order for this self-management process to lead to the effective development of appropriate patient behavior, it is further hypothesized that it is essential to teach patients how identify alerts defined as abnormal variations in their parameters and to react to them.

Adults with CF report significant and unmet needs for information on the disease [14], and it has been shown that patient adherence to treatment recommendations appears to be greater when patients have a better understanding of these recommendations [15]. Shared decision-making is built on the principle that patient participation in decisions regarding their health and treatments is associated with better adherence to treatment and healthier behavior [16]. Patients therefore need to have greater control over the decisions and actions affecting their health.

In France, the CF patient education group, Groupe Éducation Thérapeutique et Mucoviscidose (GETTHEM), has been working for more than 10 years to develop patient education programs, including an educational program entitled “React to the warning signs of an exacerbation” [17]. This program aims to achieve a co-construction between patient and clinician of a clinical semiology anticipating PEx signs and to establish a shared action plan to increase self-efficacy in PEx management. Thus, recommendations regarding the optimal regimens, route and frequency of antibiotic administration, start and duration of other drug administrations, and intensification of physiotherapy at home can be discussed preventively and reassessed regularly during clinic visits.

The intervention in this study was designed by combining the use of home-based CDs and connected wearables with a patient education program derived from React—renamed React CDs—which includes alerts and personalized action plans for patients shared with their physician. Analyzing the variations in patient parameters using a cumulative sum control (CUSUM) charts may help determine and revise patient alert thresholds when needed. Engaging patients through a patient education program may result in increased awareness of PEx detection, increased commitment to treatment implementation, and thus a better ability to react early to a PEx episode. In this patient-centered approach, the goal is to achieve the most effective outcomes by integrating a better understanding of the disease into each patient’s unique experience [18]. It is a useful approach to implement new interventions based on patients’

needs using information reported from their lived experience [19].

As part of the overall research project, this qualitative study will contribute to the assessment, from the users' point of view, of the feasibility and appropriate conditions for the use of home-based CDs by patients educated in the early detection and treatment of PEx. This assessment will be based on the experience and skills of patients or parents (of adolescents) in the self-management process of PEx, on their relationship with the care team, and on the experience and workload of the CF center teams for this protocol. The qualitative method enables us to consider the patient as a whole by exploring the patient's subjective perceptions, beliefs, representation, or opinions of an object or a phenomenon [20,21].

Currently, we know that adherence to connected devices by patients with a chronic condition is limited: nonusage, misuse, and dropout are frequent [22]. However, we have little information regarding the use of connected devices by patients in a real-life context and the perceived barriers to their use. The qualitative study of this research project will therefore be implemented to gain in-depth understanding of how patients use connected devices in a real-life context.

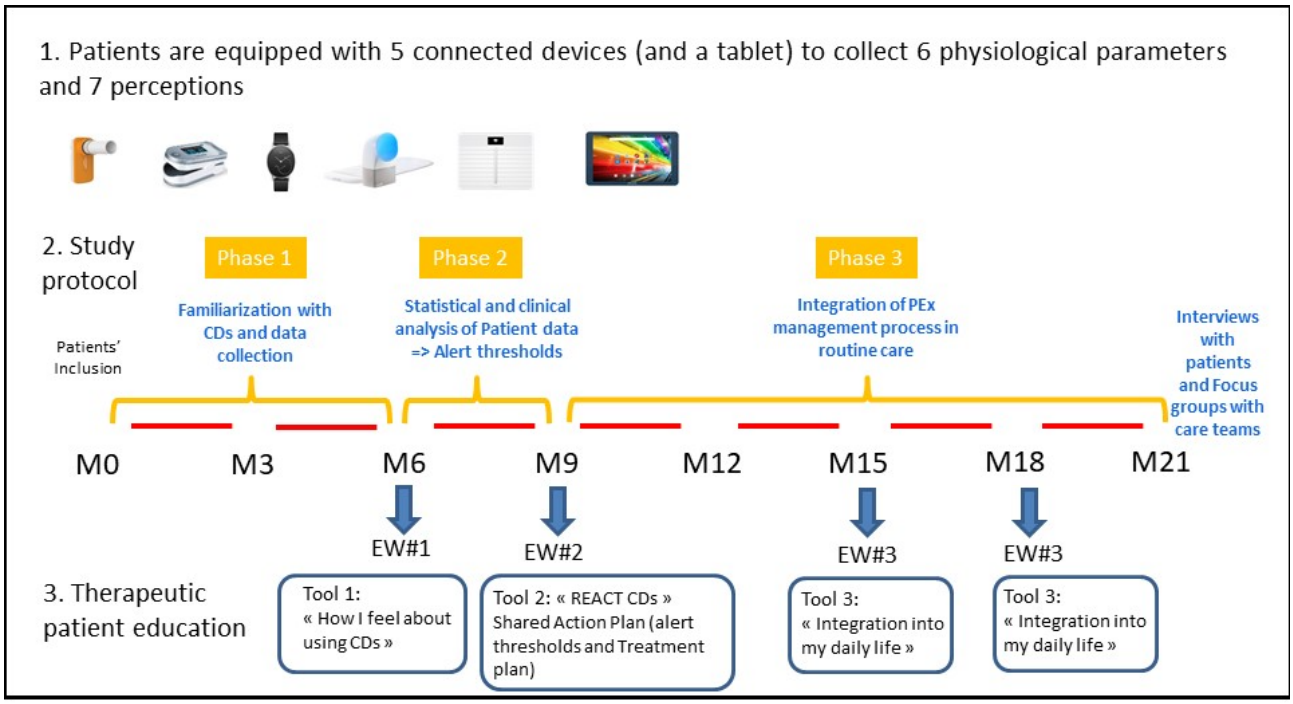
If conclusive, this study may provide new prospects for further research into the optimal organization for this PEx care process to take place in the CF centers and into the evaluation of the impact on patient health and health economic outcomes.

Methods

Study Intervention

This 3-year pilot study was based on an intervention combining the following measures (see Figure 1).

Figure 1. Study intervention. CD: connected device; EW: educational workshop; PEx: pulmonary exacerbations.



Providing Patients With CDs

In 2015, a group of French CF investigators including physicians, nurses, and physiotherapists was established to select CDs capable of collecting relevant parameters with a focus on PEx detection. This group started with a literature review on parameters of interest for the detection of PEx and CF experiences on the use of CDs to collect these parameters. Five devices from two French companies (Lamirau and Withings) were selected after a market analysis conducted by a consultant specialized in telemedicine in France [23]: (1) The Oxymeter model PO3M measures blood oxygen. (2) Spirobank Smart determines the flow and volume and produces graphs to analyze the quality of the measurements. The recording of (PRPs) is proposed after the flow measurement. (3) Body cardio scale measures full body composition (weight, lean body mass) and heart rate. (4) The Activity Pop watch tracks the number of steps, distance walked, and calories burned. (5) The AURA device consists of an under-mattress sensor combined with a lamp that acts as an alarm clock. It measures the heart frequency during sleep and tracks sleep stages, the number of times the person wakes up during the night, and total sleep time.

For the study, these CDs were used to collect 13 parameters, comprising 6 physiological parameters, including FEV1, cardiac frequency, SaO2, weight, sleep duration (minutes/night), and physical activity (step count/day); and 7 PRPs, including trouble breathing, need for more airway clearance, increased symptoms at night, difficulty to perform usual activities, experience of greater fatigue, loss of appetite, and change in sputum (color or quantity).

Defining Personalized Alert Thresholds for Patients Through Statistical and Clinical Analysis of Patient Data

A statistical process control analysis of patient data was performed by the statistician (Institut National de la Santé et de la Recherche Médicale [INSERM]) on the data collected during the 3-month phase 1 in order to guide the physician in defining patient alert thresholds and to inform the discussion with the patient during the patient education session. CUSUM charts were then used to detect abnormal changes in physiological parameters and perceptions of each patient by comparing these variations to thresholds considered as the upper control limit or lower control limit. An automatic alert generation program was configured. In phase 3, an email was sent to the patient each time a parameter deviated from its normal limits.

Educating the Patient to Interpret and React to Alerts of an Acute PEx by Taking the Actions Agreed Upon With Their Clinicians to Resolve the PEx Episode.

The initial patient education program "Warning signs of a PEx in CF" was adapted by a group of expert clinicians together with a patient and a parent from a French CF patient education group (GETHEM) to take into account the patient's alert thresholds. The new program was named "React CDs" and consisted of 3 educational workshops.

In educational workshop 1, titled "How I have felt about my daily life with connected objects since this research project started," the patient education program started with a semistructured interview with patients conducted by the clinical research assistant (CRA) at the CF center at the end of phase 1. It was designed to gather patient feedback on this first phase and to identify patient needs and expectations regarding the next educational session. Their feedback, their overall understanding of the data collected, and their motivation to continue the study were explored using open-ended questions (Multimedia Appendix 1).

In educational workshop 2, titled "Symptoms, parameters, and action plan", the patient education session was organized during the next clinic visit involving the CRA and the physician with the patient (or with the parent when the patient was under 18 years of age) using the React CD tool (Multimedia Appendix 2). It began by reviewing the signs and variations in the patient's PEx for each parameter as collected from the observations made during phase 1. Next, the patient's understanding of the course of a PEx and of the necessary gradual actions to be undertaken were explored together with the physician, as well as the barriers that may prevent the patient from seeking treatment. Finally, the patient's alert thresholds were defined, and an action plan in the event of an alert was agreed upon by the physician and the patient. The frequency of measurement with the CDs was defined according to the patient's daily schedule. The action plan specified gradual actions, such as intensifying physiotherapy, increasing hydration, taking additional lung clearance medication, starting oral or nebulizer antibiotics prescribed conditionally in case of PEx calling the center to make an appointment, and so on. This educational session was planned to last approximately 45 minutes with each patient.

In educational workshop 3, patient education was reviewed after 6 months, mid–phase 3, and during subsequent clinic visits, based on what had happened and whether the patient had reacted effectively. The action plan could be revised to take into account any changes in the patient's lifestyle or health status.

Qualitative Study Objectives

As part of the overall project, the qualitative study aims are to assess the feasibility of this PEx management process as routine care from the user's point of view. As a pilot study, the objective is to identify the utmost difficulties expressed by users on every topic important to them or related to the context that could prevent or limit the subsequent adoption of this process in their routine care.

The context included technical aspects using CDs or internet access, patient lifestyle, accessibility to the CF care team, and health complications that may arise during the course of the study. The following themes were explored during the interviews: the acceptance of both the CDs and measurement workload for the patient, the relationship with the care team during a PEx episode, what patients learn about PEx, healthy behaviors, and the implementation of timely treatments.

In order to improve our understanding of the feasibility and conditions of this process in routine care, 2 researchers (MM and DP) will analyze the patients' feedback at the end of phase 1 and 3, together with the documents produced during the patients' educational sessions with the physicians, the transcripts of patient or parent interviews, and the documents from the focus groups with the clinical teams at the end of phase 3.

Study Population

Sample Size

For this pilot study, the number of participants was based on the recruitment capacities of the centers, the logistical constraints, and the possibility of observing a saturation phenomenon on the qualitative study. The saturation point in qualitative studies is usually reached between 20 and 30 interviews [24]. This sample is increased by 20% to cover the risk of patients dropping out during the study. The population at inclusion was set at 36 patients.

Eligibility Criteria

The study population was defined to include various profiles in nontransplanted patients, adolescents or adults, living in different regions and followed in different CF centers, all with a pulmonary function status not suggesting that a transplant could be required during the course of the study (FEV1% > 50% at inclusion).

The participant inclusion criteria were as follows: 12 years of age or older, in a clinically stable condition (no PEx requiring intravenous antibiotics within the past 4 weeks), with at least 1 PEx within the past 12 months, currently being followed in a participant CF center (and not planning to change centers during the course of the study), no history of having undergone solid organ transplants, prescribed at least 1 pulmonary medication (eg, inhaled mucolytic, inhaled or oral antibiotic therapy,

hypertonic saline), French speaking, able to connect a tablet to Wi-Fi, and having signed written informed consent.

Patients were deemed ineligible if they wished to participate in another therapeutic study planned at the center.

Study Setting

Multicenter Study

Patients were recruited in 7 centers from 4 different geographical areas: 3 pediatric centers (4 patients per center) and 4 adult centers (6 patients per center; Table 3). These centers offer various contexts regarding the social situation of patients, for instance, if they are city dwellers or more rural dwellers, or if they live close to or far from their center.

Recruitment Process

Clinic staff emailed all potentially eligible patients or parents (in pediatric settings) to present them the study and offer the opportunity to opt out. Patients or parents who opted out of the study were asked to complete a questionnaire anonymously about the reasons for opting out and provided demographic data. The items were inspired by previous publications from the Pew Internet Research Center and previous research on patients with CF [25]. This questionnaire was also used for patients who dropped out of the study.

Study staff then phoned patients or parents who wished to participate and optionally patients or parents who had not opted out. They checked their eligibility, gave them information, answered their questions, and asked for verbal informed consent. The inclusion visit was then scheduled for the next clinic visit.

Participant Timeline for the Study

M0: Inclusion Visit

Upon inclusion, a written informed consent form was signed by all adults or parents of adolescents; an information letter was given to the children. Quality of life and anxiety-depression scores were collected using the Health Anxiety Depression Scale (HADS) and Cystic Fibrosis Questionnaire-Revised (CFQ-R) scale. Each patient was given the 5 CDs and a tablet dedicated to the research. The CDs were synchronized with the patient's tablet, and the necessary apps were downloaded via an anonymous ID by the CRA. Patients received a demonstration and written instructions on how to use the CDs (including cleaning and disinfection) and a maintenance support number (hotline).

M0-M3: Data Collection for 3 Months (Phase 1)

Patients were asked to use their CDs at home on 3 nonconsecutive days each week and to synchronize them with their tablet at least once a week. During the M3 clinic visit, quality of life and anxiety-depression data were collected using the HADS and CFQ-R scale. The number and date of diagnosis of acute PEx, FEV1, weight, respiratory symptoms, and antibiotic treatments prescribed were collected from the electronic patient record and transferred into the e-clinical research file.

M4 to M9: CUSUM Analysis and Education Program Setup (Phase 2)

During the clinic visit (M4-M5), patient feedback on the first phase was collected by the CRA (educational workshop 1). The ensuing educational session took place (educational workshop 2) during the next clinic visit (M9). Quality of life and anxiety-depression data were collected using the HADS and CFQ-R scale.

M9-M21: Data Collection and PEx Management for 12 months (Phase 3)

During the third phase, physiological parameters and PRPs were continuously collected by CDs. In the event of an alert, patients were automatically notified by email. Patients attended their clinic visits as usual. During clinic visits, their action plan was reviewed with their physician. Adherence to CD usage was measured from the audit trail that recorded each time a device was used. The number of acute PEx and the time between 2 acute PEx, FEV1, weight, respiratory symptoms, and antibiotic treatments prescribed during the period were collected in the e-clinical research file at the CF Centre.

Final Clinic Visit (M21)

Quality of life and anxiety-depression data were collected using the HADS and CFQ-R scale. Patients kept the CDs at the end of phase 3. Patient feedback on phase 3 was collected by the CRA (therapeutic patient education #3). Within 3 months, the final interview was conducted individually over the phone by a researcher to discuss the patients' overall experience of this PEx management process.

Qualitative Data Collection

There were 2 sources of data for the qualitative study. One was the data collected from patients and professionals by the CRA during the educational program with the physician; the documents completed by the patient with the CRA were transferred to the research team in charge of the qualitative analysis and stored in a secured environment. The other was data collected during patient or parent interviews and focus groups with the care teams at the end of phase 3; all interviews were recorded and transcribed verbatim for content analysis.

Patients' experience was collected in semistructured interviews using an 8-item open-ended question interview guide (Textbox 1) derived and adapted from validated protocols for patient narrative elicitation in outpatient care experiences [20].

The experience and workload of care teams were explored in focus groups using a 5-item open-ended interview guide (Textbox 2).

Textbox 1. Guide for semistructured interviews with patients or parents.

1. For you, what are the most important aspects in the management of your respiratory exacerbations in your daily life?
2. How do you rate the conditions for managing exacerbations during the study (based on what is most important to you)?
3. Can you tell us about a positive experience you had during this study concerning the management of your exacerbations? What happened and how did it make you feel? Did you do anything in particular after this positive experience (eg, change your attitude or behavior)?
4. Can you tell us about an experience that turned out differently than you expected? What happened and how did you feel at the time?
5. Regarding this last experience where you wished things had turned out differently, did you or your doctor do anything to rectify the situation?
6. Did your participation in the study change your outlook on the way you manage your exacerbations?
7. What do you think would be the best way to integrate this type of long-term follow-up so that it addresses the aspects that are most important to you in the management of your exacerbations?
8. Is there anything else you wish to tell us about (eg, COVID 19)?

Textbox 2. Guide for the focus group with care teams.

1. From the point of view of the health care team, what are the most important aspects in the management of respiratory exacerbations in patients, particularly in their daily lives?
2. In your opinion, how have the proposed monitoring methods, including connected objects and patient education, addressed these priorities, or within what limits?
3. During this research project, what changes have you noticed in the way the team works or in its workload with regard to monitoring patients for the management of their exacerbations? Have you noticed a change in your relationship with the patients' physiotherapist in town?
4. What difficulties or bad experiences have you had in the process of managing patient exacerbations using connected objects?
5. Do you feel that you had positive experiences during this study with the management of patient exacerbations? How would you rate these experiences in relation to the most important aspects of the management of respiratory exacerbations?
6. In your opinion, should this type of long-term patient follow-up be included in the management of exacerbations or in other aspects of their management? If so, what would be the best way to integrate it, and for which patients and with which objectives?.
7. Is there anything else you wish to tell us about (eg, COVID-19)?

Qualitative Analysis of Data Collected With Patients or Parents

All interviews have been transcribed verbatim and are being subjected to a descriptive qualitative analysis. The research team will collaborate early on in the process to develop a preliminary coding framework that will be modified to incorporate additional emerging content until saturation of data is evident [24]. A grounded dimensional analysis of the patient or parent data will be performed by 2 researchers, taking into account their evolution over the course of the study and the various natures and production conditions of the collected material while constantly comparing the data within and across patients and parents [26].

Qualitative Analysis of Data Collected With Care Teams

The data from the focus groups will be exploited (coding, categorization), processed (analysis, validity), and interpreted according to the standard thematic content analysis protocol [27]. The categories resulting from the care teams will be put into perspective within the conceptual model derived from the patients' verbatim analysis in order to identify similar topics and specificities expressed by both categories of participants.

Implementation of the Study

Training the Educators and Interviewers

The CRAs were trained in the use of the CDs and taught how to set them up for each patient included in the project. They were supported by the companies' (Withings and Lamirau) maintenance services and hotlines in order to resolve any technical problems with the patients' equipment.

The CRAs and the physicians who were already trained in the methodology of patient education were trained in the entire "REACT with CDs and alerts" educational program in a 1-day session for pediatric teams and a 1-day session for adult teams. The CRAs tested the interview guide in a simulated interview with a patientlike participant during the training session.

Process Evaluation and Monitoring

The implementation of the protocol was carried out by representatives of the promoter (INSERM). The monitoring visits were carried out by the CRA from the promoter according to the procedures and the level of risk that had been attributed to this protocol. All CF centers were monitored. At the end of the study, a monitoring and closing visit was carried out. At the end of each visit, a report was written by the CRA. Quality control procedures are described in detail in the research monitoring plan.

Ethics Approval and Consent to Participate

Before carrying out this research, the promoter submitted the project to evaluation by a Committee for the Protection of Persons designated randomly under conditions provided for in the Public Health Code (Article L. 1123-14). Free and informed consent was collected before any act related to research was undertaken.

This research is being carried out in accordance with the reference methodology MR 001 approved by the National Commission for Computing and Liberties on July 21, 2016, and with which INSERM is committed to comply (receipt #1764311 v. 0 on January 16, 2017).

Results

Ethics and Approval

The whole study, including the quantitative and qualitative research, received the favorable reception of the Committee for the Protection of Persons (CPP NORTH WEST III) on June 10, 2017 (#2017-A00723-50).

Funding

Funding for this study is from 2 main sources: Fondation pour la Recherche Médicale (FRM), who provided €173,970 (US $205,925), and Grant Vertex Pharmaceuticals, who provided €12,105 (US $14328). The Nokia Foundation (Withings) donated the CDs used for the study.

Inclusions

In all, 36 patients have been included: 14 are children and 22 are adult patients. By the end of phase 1, 12 dropped out (5 children and 7 adults), 6 of whom participated in educational workshop 1. Finally, 24 were educated with the React CD tool (educational workshop 2) and entered phase 3 (9 children and 15 adults). Figures by centers are presented in Table 3.

Table 3. Number of patients involved in the study.

CF[a] center investigator	Patients included (n=36), n	Patients educated (n=24), n
Pediatric centers		
Versailles	4	3
Paris R. Debré	5	2
Nantes	5	4
Adult centers		
Lille	8	4
Nantes	6	6
Reims	3	3
Roscoff	5	2

[a]CF: cystic fibrosis.

Expected Benefits for the Participants

At the end of the study, we expect to observe new learnings in patients or parents regarding the physiological parameters impacted by a PEx, a more consistent perception of variations in these parameters [10,28], and a better understanding of the importance of early treatment to prevent degradation and possibly avoid intravenous (IV) intervention or hospitalization.

We expect to see an increased interest for patient education within the care teams despite the time-consuming nature of this activity and a stronger therapeutic collaboration between physician and patient leading to faster initiation of treatments. We intend to show that this process of care for patients equipped with CDs at home is acceptable in their daily workload or to identify the conditions necessary to make it acceptable. We hope to assess the teams' level of satisfaction regarding the PEx action plan shared with the patients, its implementation by the patients in the event of an alert, and the positive evolution in the patients' quality of life.

We hope to see an improvement in the evolution in PEx treatments, with lower antibiotic IV interventions for oral or nebulized antibiotics, as early diagnosis is known to allow a better recovery of previous lung function [29]. This would also result in reduced hospitalization costs, as IV cures are often initiated in hospital. We cannot anticipate the evolution of the number of PEx detected for a patient or the change in time interval between 2 successive PEx.

Qualitative analysis will provide a better understanding of the subjective experience of using such devices in a real-life context. It will allow us to identify the benefits and pitfalls of using CDs and alerts at home to detect PEx and react early, as well as the impact on the partnership between the patient and their care team.

Discussion

Innovation in CF Care Delivery

The use of home-based CDs is rapidly growing, and their clinical contribution to the diagnosis and resolution of PEx in patients with CF, as well as their acceptance by users deserves to be fully evaluated. The intervention in this study was designed by combining the use of home-based CDs and connected wearables with a patient education program which includes alerts and personalized action plans shared with their physician. Engaging

patients through a patient education program may result in increased awareness of PEx detection, strengthened commitment to treatment implementation, and thus an improved ability to react early to a PEx episode. In this patient-centered approach, the goal is to achieve the most effective outcomes by integrating a better understanding of the disease into each patient's unique experience [18]. This approach differs from other studies in which alerts are used by the care teams to drive actions, as our intervention focuses on ensuring that patients initiate actions themselves when alerted.

Patient Education and Partnership With the Care Team

Patient education is a critical component of chronic care and is recognized to improve self-management. All investigative centers in France have been involved in the care quality improvement program deployed since 2011 [30]. This program has promoted patient education as an integral part of CF care to improve not only the care provided at the center but also self-care at home. Despite this involvement, not all patients have been educated to "React to signs of an exacerbation." The educational part of this protocol will promote access to this education in the context of the use of CDs and will engage physicians with their patients as an additional benefit of the study.

Nevertheless, if patients do not follow the action plan agreed upon with their physician, their treatment of PEx may not begin earlier. An alternate process could then be envisaged to increase effectiveness, in which alerts are sent to the clinical teams and used by them to drive actions with the patient. In routine care, the process leader may switch from the patient to the care team at certain critical times when the patient's condition worsens.

Perspective for a CF-Integrated eHealth Solution

The use of several CDs from 2 different companies (Lamirau and Withings) led to the combination of 2 different systems for the extraction and transmission of data to the research server at INSERM. The return transmission of alerts to the patients was conducted via an email account set up for the research. This configuration does not allow the patient to use a single dashboard to gather their history of physiological parameters and PRPs or information on their treatment over the different periods. The development of a CF application that can display patient data collected from various CDs in a single dashboard is becoming increasingly necessary due to the continual emergence of new and more efficient CDs capable of measuring lung function parameters, as well as nutritional status and glycemia, which is a comorbidity in approximately 30% patients with CF and that should be part of the CF patient follow-up [31].

Conceptualization of a Model for Health Behavior Adoption During an eHealth Intervention

Previous studies have highlighted that the use of information technology depends on its perceived usefulness and perceived ease of use [32], as well as on personal (age, gender, and previous experience) and contextual factors, including facilitating conditions, social influence, hedonic motivations, and price value [33]. The adoption of wearable devices for health self-quantification also involves "task-technology fit" characteristics, such as connectivity and healthcare infotainment, as well as a good level of perceived data privacy [25,34]. During the qualitative analysis, the researchers refer to these theoretical models when eliciting verbatim test categories from patients, which may include the perceived ease of use of CDs and alerts to manage PEx, the perceived role of education to feel at ease with the use of CDs and alerts, the perceived usefulness of gaining better control over one's own health, or the perceived usefulness of linking one's own perceptions to the measures given by CDs and possibly developing the ability to anticipate crises and manage them independently. Moreover, in the field of chronic care, the relationship with the care team will be addressed as an element of the model. Certain conditions facilitating or hindering the use of technology related to technical problems, the very design of the intervention, or events in the patient's life or health will be explored. A conceptual model will be proposed for the design of interventional research on eHealth related to the phenomenon under study.

Limits and Measures Taken

Our feasibility study includes a small sample of patients from several CF centers, which will result in a variety of situations and cases with no statistical weight. The patients included were selected on the basis of their motivation to participate in the study as solicited during the recruitment process. The small number of patients included in this pilot study will not make it possible to specify the characteristics of patients best suited to this care process using CDs at home.

Technical difficulties in the usage of CDs or with internet connections at home, depending on where the patient lives and the maturity of the device, have discouraged patients from collecting their data as regularly as needed. We had planned to recruit 36 patients at inclusion and expected 30 patients to remain until the end of the study. This expectation proved to be overly optimistic due to the technical problems encountered with the selected devices, especially regarding spirometry.

Perspective for Further Research

This pilot study will help to define the conditions for a further trial aimed at evaluating the potential generalization in the organization of care teams and the cost-effectiveness of this care process on patient health outcomes and hospital costs in terms of the number of clinic visits, hospitalizations, and patient transportation costs.

Acknowledgments

We wish to acknowledge the CF care teams and particularly the CRAs, who managed to solve the technical problems with the CD suppliers, thus spending more time on the study than initially planned. We further acknowledge the patients and their parents, who faced technical problems and participated actively in their resolution, having to go back to the CF center to replace some CDs, and who also collaborated with the CRAs to reflect on what solutions could be found.

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This research was also supported by a grant from Withings (formerly Nokia Health), who provided all the CDs that were allocated free of charge to the patients in the CF centers.

Authors' Contributions

MM and DBP cowrote the whole article. GR, VD, and DPB conceived the study and defined the qualitative study design. GR and DPB coordinated the study. VD and AP provided expertise on patient therapeutic education in cystic fibrosis and on the design of the patient educational tool, and provided training for its use during the project to the professionals involved. GR provided pedagogical expertise and advice in the field of e-learning, and GR was the clinical scientific coordinator. All the authors contributed to the accuracy of the study protocol and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
React CDs: How I feel about my daily life with connected devices.
[DOC File , 108 KB - resprot_v10i8e14552_app1.doc]

Multimedia Appendix 2
React CD's symptom parameters action plan.
[DOC File , 80 KB - resprot_v10i8e14552_app2.doc]

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Abbreviations

CDs: connected device
CF: cystic fibrosis
CFQ-R: Cystic Fibrosis Questionnaire-Revised
CFRSD-CRISS: Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Infection Symptom Score
CPP: Committee of Protection of Persons
CRA: clinical research assistant
CUSUM: cumulative sum control
FEV1: forced expiratory volume in 1 second (liters)
FRM: Fondation Pour la Recherche Médicale
GETTHEM: Groupe Éducation Thérapeutique et Mucoviscidose
HADS: Health Anxiety Depression Scale
INSERM: Institut National de la Santé et de la Recherche Médicale
IV: intravenous
PEx: pulmonary exacerbation
PRP: patient-reported perceptions
STOP: Standardized Treatment of Pulmonary Exacerbations

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Protocol

An Ecological Monitoring and Management App (EMMA) for Older Adults With Chronic Pain: Protocol for a Design and Feasibility Study

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Abstract

Background: Chronic pain is a complex problem for many older adults that affects both physical functioning and psychological well-being. Mobile health (mHealth) technologies have shown promise in supporting older persons in managing chronic conditions. Cognitive behavior therapy is recommended for older people with chronic pain. However, web-based treatment programs for chronic pain are not aimed at the needs of older people and offer standard therapies without providing tailored treatment for this population.

Objective: To address this problem, we aim to develop a psychological web-based intervention for ecological monitoring of daily life experiences with chronic pain called EMMA to support self-management of chronic pain in older adults.

Methods: The key clinical and engagement features of the intervention were established through the integration of evidence-based material from cognitive behavioral therapy for the treatment of chronic pain in older adults. The development process uses a co-design approach and actively involves end-users in the design process by incorporating feedback from focus groups with older adults in order to inform a user-centered intervention design. For the co-design process, we will include 10 older adults with chronic pain, who will discuss the requirements for the app in workshops in order to ensure suitability of the app for older adults with chronic pain. In order to test the feasibility and acceptability of the intervention, we will include a sample of 30 older adults with chronic pain who will test all features of the intervention for a period of 8 consecutive weeks. After the trial period, validated instruments will be used to assess usability and acceptability, as well as influence on pain levels and associated physical and psychological symptoms. Participants will be invited to take part in a semistructured telephone interviews after the trial period to explore their experiences using the app.

Results: Digitalization of the pain diary and psychotherapeutic content has started. Recruitment of participants for the co-design workshops will start as soon as we have a functioning prototype of the electronic pain diary and EMMA intervention, which is expected to be in September 2021. The feasibility study will start as soon as the co-design process is finished and required changes have been implemented into the pain diary and the EMMA intervention. We expect to start the feasibility study early in 2022.

Conclusions: Required changes to assure usability and acceptability will be directly implemented in the app. EMMA brings together a strong body of evidence using cognitive behavioral and self-management theory with contemporary mHealth principles, allowing for a cost-effective intervention that can be used to target chronic pain anywhere and anytime by older adults. Given the ubiquity of mHealth interventions for chronic conditions, the results of this study may serve to inform the development of tailored self-management interventions.

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KEYWORDS

chronic pain; older adults; mHealth; online intervention; self-management

Introduction

This paper presents a new psychological web-based intervention for chronic pain in older adults in the form of a web-based self-guided intervention called EMMA (Ecological Monitoring and Management App) to support self-management of chronic pain.

Chronic pain is one of the most common conditions affecting older adults over the age of 65 [1]. Previous studies [2] on pain in older adults have reported prevalence rates from 24% to 72% and a high prevalence among residents of nursing facilities. Older adults with chronic pain are likely to experience more physical impairments and interference with activities than young people, and pain locations tend to spread over the whole body with age [3]. Commonly occurring pain disorders that affect older adults include back pain, osteoarthritis, rheumatoid arthritis, musculoskeletal pain, and various neuropathies from diabetes, herpes zoster, chemotherapy, or surgery [3]. Pain is also common in the advanced stages of many chronic diseases, such as congestive heart failure, end stage renal disease, and chronic obstructive pulmonary disease [3]. Furthermore, many joint repair and replacement surgeries are performed annually, and a percentage of patients undergoing these procedures report chronic pain despite surgery [4].

Unrelieved pain in older adults has been shown to cause or increase depression, anxiety, and sleep disturbance; decrease mobility; and increase social isolation [5], as well as being a significant risk factor for decreased functional capacity and onset and progression of disability in old age [3]. The global burden of chronic pain is projected to increase as prevalence rates for pain increase as the global population continues to age. Older patients are the most likely of all age groups to receive inadequate pain treatment [6]. Internationally, there has been increasing recognition of the importance of developing nonpharmacological interventions for older adults with chronic pain [7].

Current best practices for the management of chronic pain in older adults involves multidisciplinary cognitive behavioral interventions that focus on fostering self-management [8]. Studies in older adult chronic pain have shown that comprehensive interactive face-to-face psychoeducational interventions lead to symptom reduction and improved health-related quality of life compared with care that is strictly medication focused, with a postulated mechanism being enhanced self-efficacy and empowerment over disease and symptom management [9]. Self-care strategies for managing stress, facilitating positive coping behaviors, or reducing anxiety may be especially effective for mediating psychological and social components of pain management; evidence supporting self-management treatments in improving pain and pain-related disability in older individuals with chronic pain is strong [10]. However, cognitive behavior therapy techniques are underutilized, particularly among older adults with chronic pain [11]. Access to effective pain management programs is often limited, due to lack of services, lack of patients' resources, and fear of stigmatization [11]. Other barriers to treatment include physical symptoms that limit mobility, clinic distance, transportation requirements, and cost constraints. Self-management interventions, such as web-based interventions, are a promising alternative to traditional treatments and have the potential to overcome barriers and improve the availability of effective psychological treatments.

Several studies [12] have piloted web-based self-care interventions for chronic conditions in older adults such as diabetes, dementia, and osteoarthritis [12]. Results from these studies suggest that the benefits of these web-based self-care interventions appear to be comparable to in-person interventions [12,13]. There is a growing number of mobile pain management apps available in app stores such as the Apple App store and the Google play store. Several systematic reviews confirmed a beneficial effect of these apps for pain management in terms of reduced pain intensity and increased quality of life [14,15]. However, most apps did not use evidence-based strategies and were developed without the involvement of health care practitioners, and none included end-users in the development process [14]. Furthermore, to the best of our knowledge, no web-based self-management interventions with a specific focus on chronic pain in older adults exist. A recent review [16] on the quality and usability of arthritic pain self-management apps for older adults concluded that only a few of the currently available pain apps offer a comprehensive pain self-management approach incorporating evidence-based strategies in accordance with published guidelines and take into account the needs of older adults in terms of usability.

The aim of this paper is to describe the development of a theoretically sound psychological web-based self-management intervention based on ecological monitoring of daily life experiences. The EMMA intervention will address all etiologies of chronic pain in older adults. The EMMA intervention will be adapted to the needs and challenges of older adults with respect to psychological content, as well as web design. The

developmental process will follow methods in accordance with the Medical Research Council framework for development and evaluation of complex interventions [17].

Methods

Overview

The study will be subdivided into 2 phases, namely, (1) the development of the clinical content of the web-based intervention, including the digitalization process, and (2) the feasibility study.

The goal of EMMA is to provide automated support, in terms of self-management for chronic pain in older adults, that has been carefully designed alongside members of the target population, as these are key drivers of app usage within the Ritterband model [18], the state-of-the-art model for the development of web-based interventions. We defined a clear set of requirements for the development of the app based on literature reviews [19]: The app must be capable of (1) meeting the needs of older adults in terms of presentation, user-friendliness, acceptance, and user guidance by using a user-centered design and actively involving older persons in the development process, (2) supporting both major mobile operating systems (Apple iOS and Google Android), (3) allowing clinicians to access the pain data in a graphical format for patient care in clinic using either the app or the web, and must be (4) compliant with data protection laws in Switzerland, including the Swiss Federal Data Protection Law [20] for the privacy and security of protected health information, as well as European Union Medical Device Regulation [21] and (5) usable as a stand-alone treatment or incorporated in a multidisciplinary pain management practice. EMMA provides psychoeducational material and comprehensive modules to teach self-management strategies for chronic pain in the older adults to enhance self-efficacy, a primary determinant of behavior change [22].

Development Aims

Features

Currently, there are no widely accepted frameworks or clinical guidelines recommending the key components of a pain self-management program in general or for older adults specifically [23]. Based on a systematic review [16] of self-management programs on chronic pain in older adults, previous web-based interventions for chronic pain [15], and our own clinical practice, we selected tools that were known to be effective, relevant, and usable. The clinical content of EMMA, is grounded in cognitive behavioral therapy [24], the biopsychosocial model of chronic pain [25], and self-management theory [26]. Furthermore, we put an emphasis on experiential learning, given that older adults have been shown to learn more from active training than from didactic content [24]. Although the number of randomized controlled trials investigating mind-body interventions (mindfulness-based stress reduction, yoga) for older adults with persistent pain is small [27], research suggests that these interventions are effective for enhancing well-being, mood, and pain acceptance [27]. Therefore, we aimed to incorporate mind-body techniques such as breathing techniques, mindfulness and gratitude practices, and yoga for older adults in our program.

The EMMA intervention will contain psychoeducational material in video format, a digital pain diary, and self-management treatment modules.

Psychoeducation is an essential part of pain management for older people [6]. Therefore, we will include psychoeducational information in short, easy-to-understand explanatory videos with a maximum duration of 120 seconds. The videos will be high contrast, limited to the most important information, and provided with subtitles to be accessible to older adults with hearing and visual loss. The videos will be embedded in the app and will contain information about the development of chronic pain, the pain-self-management process, medication use, communication with health professionals, adaptive coping strategies, fatigue, sleep, fear of falling, importance of activity, emotion regulation, attitudes and beliefs about pain, psychological issues management, and emotion regulation. There will also be a section on the influence of pain on the family, partners, or others. The video material will be based on validated psychoeducational pain management courses [28] and adapted to address the specific needs of older adults. The content will be digitalized with the help of research assistants in Psychology at the University of Fribourg.

The digital pain diary is based on a paper-and-pencil diary that was developed in a pilot study on the experience of chronic pain in daily life at the University of Fribourg and tested in a sample of 60 patients with chronic pain and 40 healthy individuals [29]. The diary covers different aspects of the painful sensation (sensory, affective, cognitive and behavioral). The following data will be collected by the pain diary: (1) pain intensity, (2) quality of painful sensation, (3) emotional state, (4) thoughts, (5) stress, and (6) activity. The content of the diary will be digitized as part of the project and adapted to provide an original set of questions that we know will be suitable for repeated questioning during everyday life for ecological momentary sampling. The content of the paper-and-pencil diary has been found suitable for repeated questioning during everyday life for ecological momentary sampling; therefore, it will be converted to a digital form as part of the project. Because regular monitoring of pain levels and associated symptoms and experiences is the foundation upon which other changes in behavior are built, reminders will be added to the app, that prompt users to log their pain 4 times per day (by default: after waking up, noon, evening, before going to bed) [30]. Pain logs for self-monitoring are a useful source of clinically relevant information about pain intensity and quality; key activities; emotional state, stress, and thoughts; and the relationship between them and the context in which they occur. This method allows the measurement of pain and related factors in real-world settings, which possibly enhances accuracy and detail of measurement and helps to identify potential mediators and moderators of pain in older populations. Prior studies [31] have found strong support for the feasibility and application of this method in healthy older adults, people with clinical disorders, and patients with chronic pain. Furthermore, studies emphasize the importance of self-observation methods for understanding the different factors that influence the pain sensation instead of

drawing further attention to the pain sensation [32]. Pain intensity score is known to be a poor indicator of clinically important pain [33]; therefore, we aim to assess pain impact on daily life experiences and factors that impact pain experiences, which has been reported to be a much more promising approach [34]. Summarizing these data is the simplest way to provide personalized feedback. The advantage of digitalization is the ability to instantly aggregate patient-generated data. Dynamic charts will be built into the app to allow individual relations between pain, emotional, behavioral responses, and coping strategies to be displayed. If the patient wishes, pain data can be shared with their health care provider through a secure portal.

EMMA will be designed to incorporate 8 web-based self-management treatment modules, which is consistent with the design of other face-to-face or web-based self-management programs for chronic pain [35-38]. The lessons are completed over an 8-week period, each week a lesson is unlocked. The 1-week gap between lessons will allow participants time to revisit the content in each lesson, view the resources, and practice the skills. The EMMA intervention will specifically target a number of important aspects of pain self-management relevant for older adults. The EMMA modules will contain: (1) information about realistic goal setting and progress monitoring; (2) chronic pain and self-management strategies; (3) the role of the attention focusing and shifting attention with guided meditation; (4) the role of negative thoughts or beliefs and learning to change them by engaging in pleasant meaningful activities; (5) the role of relaxation and stress management; (6) the role of physical activity, safe ways of getting active, yoga, stretching for older adults, pacing activities, improving well-being through mindfulness, and savoring; (7) learning to regulate emotions, dealing with pain flare-ups and setbacks, psychiatric comorbidities relevant for older adults with chronic pain and (8) and self-management strategies, when to seek help, decreasing social isolation, and incorporating strategies to learn to live with the pain. Patients will receive daily task lists with 3 to 5 small tasks to fulfill in 1 week in order to complete the entire lesson, which will encourage accountability and keep participants motivated. All participants will receive regular email communications to notify them that a new lesson is available.

Development Process

In order to maximize usability and acceptability, end-users should be active partners in the design of the product [39]. The development of the platform will follow a user-centered design framework, which includes the user in all phases of system development in an iterative manner. This project will also use a participatory design approach (also called co-design), which allow users to become cocreators of the final system [40]. Indeed, this approach brings all the people involved in the development (eg, researchers and developers), clinicians, and end-users together. EMMA will be built as an embedded web app, appearing to the user as a native app while allowing for compatibility on most mobile devices and rapid updates when necessary. The app will be designed to work on different screen size of devices (responsive web design for phones, tablets, and laptops). The app comprises information shown to the user and input from the users. The web app will be developed using Angular framework that is typescript and HTML-based for the front-end. The back-end it will be developed using Django, a Python-based framework. The connection will be made using an application programming interface that connects the front-end and back-end. The database is based on a MySQL server that is administrated through the Django administration tool.

The project will follow European [22] and Swiss [21] Guidelines for data privacy and security as well as on Responsible Research and Innovation. Privacy by design will be accomplished by putting technical measures in place from the start.

Co-development

We will actively involve older adult participants in the developmental process to test the first prototype of the app, after a demonstration of the main features, for 2 consecutive weeks. We will include 10 older adults with chronic pain who use a smartphone or tablet device and meet the following inclusion criteria: (1) age 65 and older; (2) able to read, write, and communicate in French; and (3) able to give written consent. After a testing period for 2 consecutive weeks, a workshop with all study participants will be organized for the co-design process. In order to establish important features of app design for older people, the following topics will be discussed: easy handling of the app, navigation problems, age-appropriate design, auditory support, and other supportive measures. All 3 features (psychoeducational video content, digital pain diary, and self-management modules) will be tested. A meeting (face-to-face or via telephone) will be organized with all consenting participants in order to download and set up the EMMA app on the participant's personal device, provide participants with app training, and brief them to use the app for 14 days. Participants will be shown all features of the app, until they are comfortable, by research assistants of the University of Fribourg. In addition, participants will be advised to contact one of the investigators if they require assistance when using the app throughout the 14-day period. Participants will be advised to use the app as desired during the testing period but will be asked to use the app at least once daily, perform a daily pain or mood log entry, and go through all psychoeducational content and modules. It is important to note that, during this testing period, there is no requirement of how much participants must use the app. The user feedback will be implemented in the app, and modifications will be discussed in the subsequent group meeting. From previous experience, we expect 2 to 3 rounds will be necessary.

Feasibility Study

Study Purpose and Specific Aims

Feasibility studies are carried out prior to a main study to estimate important parameters required to design the main study, whereas a pilot study is a smaller version of the main study carried out to evaluate if all of the components of the main study can work together [41]. The primary goal of this study is to evaluate the feasibility, usability, and acceptability of the EMMA intervention in a sample of older adults with chronic pain. Because this is a feasibility study, a sample size calculation is not appropriate. However, consistent with other comparable studies [42-44], a target of 30 older adults will be used. Study

protocol, intervention, participant information, and informed consent will be reviewed by the Ethics committee of the Canton Vaud, and all participants will provide written informed consent. The study will be conducted according to the principles of the 2013 Declaration of Helsinki.

Participants

We plan to include older adults with chronic pain who meet the following inclusion criteria: (1) age 65 years or older; (2) with a chronic pain condition based on International Classification of Disease 11th revision [45] defined as persistent primary pain, persistent posttraumatic or postsurgical pain, persistent neuropathic pain, persistent malignant pain, persistent headache and orofacial pain, persistent visceral pain, and persistent musculoskeletal pain; (3) no signs of neurocognitive disorder (Mini Mental State Examination [46] score >23); (4) able to read and write in French; (5) able to give written informed consent. Exclusion criteria: (1) a current psychiatric disorder (other than depression or anxiety) (2) suicidal thoughts, or (3) a diagnosed neurocognitive disorder. The app's download and use are free for the participants.

Procedure and Design

Screening, recruitment, and consenting processes for this study will be carried out by trained research assistants from the University of Fribourg. Prospective participants will be sought from associations catering to older adults such as *Gerontopôle Fribourg* or *Pro Senectute*, using flyers, brochures, and informational talks given at the associations and at the Department of Neuroscience and Movement Science at the General Hospital Fribourg (JC). To facilitate online recruitment, a Facebook page will be created for the entire project. Interested participants will screened to assess eligibility. Eligible participants will be asked to provide written informed consent.

Screening and Diagnostic Measures

All participants will undergo the same screening procedure, including a standardized questionnaire to test the general inclusion and exclusion criteria, a structured clinical psychiatric interview for the diagnosis of mental disorder (Structural Clinical Interview for Diagnostic and Statistical Manual for Mental Health [47]), and Mini Mental State Examination [46]. The assessment will be performed by trained research assistants from the University of Fribourg and will be supervised by a senior clinician (KL). We will ask participants to provide sociodemographic data (including age, sex, education, marital status), information on their smoking, drinking, physical activity, self-perception of aging, basic and instrumental activities of daily living, and health care use associated with the pain problems in the past 3 months. Basic and instrumental activities of daily living are each measured with 7 in a modified version of the OARS Multidimensional Functional Assessment Questionnaire [48].

Intervention Delivery

All participants will receive individual in-person training on how to use the mobile app in order to minimize possible errors of manipulation. Participants will be advised to use the EMMA app as desired to complete the EMMA intervention (8-week web-based program). Furthermore, participants will be asked to complete the daily diary in the app, assessing pain levels and psychological symptoms including mood, stress, thoughts, behaviors, and activities 3 times per day for 2 weeks before the intervention and 2 weeks after the EMMA intervention in line with other ecological momentary assessment protocols in chronic pain research [49]. Participants will receive an alarm 3 times a day (morning, afternoon and evening) at times determined by the participant, with the requirement that the chosen times be at least 3 hours apart and at least 3 hours after awakening in the morning to allow adequate sampling of variables across the course of the day. Each log will be date- and time-stamped in the app. Studies [50] of participants using electronic devices typically show high rates of adherence at the time of the scheduled prompts; in clinical populations, 85% or more of prompts were answered. We will inform the participants (during the coaching session for the use of the app) about the importance of regularly entering data; participants with less than 50% of data entries will be excluded from analysis. We will continuously monitor the participants on the regularity of their responses to the prompts, and in case of nonadherence, we will contact them and remind them about the importance of entering the data regularly.

Outcome Measures

Study measures were chosen based on psychometric properties, including sensitivity to change, brevity, and appropriateness for use with community-dwelling older adults with chronic pain as well as in accordance with recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials group [51]. Outcomes will be measured before and after the intervention with exception of the usability and acceptability measures, which will be measured only after the intervention.

The primary outcome is the Pain Disability Index [52]. The intensity of symptoms associated with pain and depression, including pain, fatigue, and sleep disturbance, will be assessed using the Pain Disability Index [52] to measure the degree to which pain interferes with function in major life areas.

Secondary outcomes will also be measured. The Brief Pain Inventory short form [53] is a validated, widely used, self-administered questionnaire developed to assess the severity of pain and the impact of pain on daily functions. For this study, pain intensity is measured by calculating the mean of 4 items in which respondents are asked to rate their average, current, least, and worst pain during the previous week on a scale from 0 (no pain) to 10 (pain as bad as you can imagine [54]).

The Hospital Anxiety and Depression Scale [55] is a 14-item Likert scale measure; 7 items assess the severity of depression, and 7 items assess the severity of anxiety.

The Geriatric Depression Scale [56] is a 30-item self-report measure specifically designed to assess depressive symptoms in older persons. Good sensitivity and specificity for detecting depression in geriatric psychiatric and medical outpatients has been demonstrated (84%-100% sensitivity, 73%-96% specificity) [57]. The Geriatric Depression Scale was selected because of its screening efficiency with geriatric outpatient populations and its focus on affective rather than physical symptoms.

The World Health Organization Quality of Life [58] 26-item questionnaire measures quality of life in 4 domains, with a 5-point Likert Scale: physical health, psychological health, social relationships and environment

The Pain Coping Strategies Questionnaire [59] is one of the most widely used measures for pain coping and catastrophizing. Measures derived from the Pain Coping Strategies Questionnaire have been shown to be associated with various measures of functioning among patients with different pain conditions [60-62]. The Pain Coping Strategies Questionnaire has demonstrated reliability and validity in several samples of older adults, including those who are older than 75 [63].

Usability and Acceptability

After the trial period, participants will complete questionnaires to evaluate the usability and acceptability of the EMMA intervention in healthy older adults, using the Technology Acceptance Model [64] and its version adapted for older adults [65], System Usability Scale [66], and the Emotional Metric Outcomes scale [66]. In addition, all participants will be invited to take part in a semistructured telephone interview at the end of the intervention period. The semistructured interview will focus on evaluating the acceptability of the intervention. Participants will specifically be asked about patterns of app use, including frequency and timing, and their experiences, attitudes, and perspectives on integrating the EMMA intervention into their pain self-management strategies. Participants' perceptions of the barriers to and facilitators of use of the intervention will be explored. The interviews will be audiorecorded and transcribed verbatim for analysis.

Statistical Analysis

We will utilize SPSS software (version 27 or higher; IBM Corp) for management and analysis of data and the latest version of HLM for the Ecological monitoring data (version 8; Scientific Software International Inc). Before analysis, all outcome variables will be tested for normality using the Kolmogorov-Smirnov test and, if necessary, transformed to obtain a normal distribution. Differences in variables (demographic, diagnostic, pain-related) will be compared using *t* tests for continuous variables and chi-square tests for categorical variables. For the primary and secondary outcomes, participants self-reported pain disability, pain severity and impact of pain on daily function, depression, anxiety, quality of life, and pain coping strategies will be compared before and after the intervention. Data from the pain diary yield intensive longitudinal data that are clustered as they represent series of measurements that stem from different individuals. in keeping with current consensus [67] on how to analyze experience sampling data, we will use a multilevel approach to analyze these data, which takes into account clustering and provides flexible tools to investigate within-subject phenomena, such as responses to stressors or pain shifts. We will use software (the latest version of HLM software) that allows for simultaneous within-subject and between-subject modeling, examination of associations among individual difference variables, and examination of individual differences within-subject parameters. In line with similar studies [42], we will use an inductive thematic content analysis for the qualitative interviews. Transcribed interviews will be read and reread to promote immersion in the data and close examination of the interview content. Preliminary themes and subthemes will be generated and continually refined.

Results

The study is currently ongoing. Development of the digital pain diary has started. Psychotherapeutic web-based app content has been digitalized. Recruitment of participants for the co-design workshops will start as soon as we have a functioning prototype of the electronic pain diary and EMMA intervention, which is to be expected in September 2021. The feasibility study will start as soon as the co-design process is finished and all required changes have been implemented into the pain diary and the EMMA intervention. We expect to start the feasibility study at the beginning of 2022.

Discussion

General

This article describes a research protocol for a development and feasibility study of a web-based psychological intervention for older people with chronic pain to support pain self-management. We will develop a self-guided web-based program for chronic pain that consists of an electronic pain diary and a web-based smartphone app with psychotherapeutic treatment modules that will be tested for feasibility as well as providing the first indicators of efficacy. The EMMA intervention combines a strong body of evidence using cognitive behavioral intervention designs with contemporary mHealth principles, allowing for the intervention to be used when and where it matters the most. Potential benefits for older adults with chronic pain are invaluable as this app will address most barriers for effective treatment of older people with chronic pain. This feasibility study should provide information for further optimization of the intervention, and if successful, this app will be tested in an RCT and could become a model to address the needs of older people with chronic pain in Switzerland.

We believe that developing an web-based self-management tool for pain that is suited for older adults will address a major gap for the treatment of pain in older adults. This system could serve as a tailored and customized education tool for individualized services and as a social support and social engagement tool for enhanced pain management. Furthermore, this system could be a potential method of communicating more effectively with health care providers, with the caveat that providers might not have adequate time. Relaying real-time pain status to providers may provide a support tool for patients to convey the daily pain status to their social network and prompt their network for motivation and coping strategies. Furthermore, we also aim to empowering users with this system by supporting them in actively managing their own condition, at their convenience, by self-monitoring to develop a set of self-management strategies.

Limitations

Discomfort With Technology

Although many older adults use mobile technologies, many do not. Moreover, those who do use these technologies often use fewer features than young adults and are easily confused by the wealth of potential apps [68]. Therefore, we will incorporate older adults in the development process to ensure that the app can be navigated easily. We will also provide brief orientation sessions for each participant, where they learn to navigate the app's features. This process will be continued until the participant is comfortable with their ability to access and navigate the app interface. Most importantly, we aim to minimize these limitations during phase 1 by receiving and iterating on participants feedback related to the app. We will use Web Content Accessibility 2.0 guidelines to ensure to meet the needs of older people (in terms of visibility, design, and navigation). In particular, we will use a large font for text in form fields and other controls to accommodate older adults with visual impairments. Because some older adults lose contrast sensitivity, we will adapt high contrast colors will be used. For the videos, transcripts will be provided to account for eventual hearing loss, background noise, and distractions. Due to possible cognitive decline and inexperience with browsing habits, navigation, and presentation of the program, the organization of pages will be kept as simple as possible. Furthermore, pop-ups, new windows, and tabs will be limited to avoid confusion. Lastly, there will be no time restrictions to complete the transactions.

Operational Challenges

Conducting this study will involve several operational challenges. The first challenge is the recruitment of an adequate number of older people with chronic pain who are willing to participate. The second challenge is the nonuse of the intervention. Previous studies have shown that nonadherence is a common problem in web-based interventions [69]. To prevent nonusage, we have taken several measures. Patients will receive reminders when they have not logged into the web-based app. The app includes daily inspirational quotes and blogs to encourage daily use. In addition, log data enable us to track the amount of time patients spend using the intervention. Finally, guidance by the study personnel is offered throughout the intervention to motivate patients, answer questions, and overcome difficulties.

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Authors' Contributions

KL significantly contributed to the development of the EMMA intervention. KD and RC contributed to the technical design of the web-based intervention. KL wrote the first draft of the manuscript. All authors contributed to and have improved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

mHealth: mobile health

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Protocol

Evaluating the Impact of COVID-19 on the Adoption of Virtual Care in General Practice in 20 Countries (inSIGHT): Protocol and Rationale Study

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Abstract

Background: In recent decades, virtual care has emerged as a promising option to support primary care delivery. However, despite the potential, adoption rates remained low. With the outbreak of COVID-19, it has suddenly been pushed to the forefront of care delivery. As we progress into the second year of the COVID-19 pandemic, there is a need and opportunity to review the impact remote care had in primary care settings and reassess its potential future role.

Objective: This study aims to explore the perspectives of general practitioners (GPs) and family doctors on the (1) use of virtual care during the COVID-19 pandemic, (2) perceived impact on quality and safety of care, and (3) essential factors for high-quality and sustainable use of virtual care in the future.

Methods: This study used an online cross-sectional questionnaire completed by GPs distributed across 20 countries. The survey was hosted in Qualtrics and distributed using email, social media, and the researchers' personal contact networks. GPs were eligible for the survey if they were working mainly in primary care during the period of the COVID-19 pandemic. Descriptive statistical analysis will be performed for quantitative variables, and relationships between the use of virtual care and perceptions on impact on quality and safety of care and participants' characteristics may be explored. Qualitative data (free-text responses) will be analyzed using framework analysis.

Results: Data collection took place from June 2020 to September 2020. As of this manuscript's submission, a total of 1605 GP respondents participated in the questionnaire. Further data analysis is currently ongoing.

Conclusions: The study will provide a comprehensive overview of the availability of virtual care technologies, perceived impact on quality and safety of care, and essential factors for high-quality future use. In addition, a description of the underlying factors that influence this adoption and perceptions, in both individual GP and family doctor characteristics and the context in which they work, will be provided. While the COVID-19 pandemic may prove the first great stress test of the capabilities, capacity, and robustness of digital systems currently in use, remote care will likely remain an increasingly common approach in the future. There is an imperative to identify the main lessons from this unexpected transformation and use them to inform policy decisions and health service design.

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KEYWORDS

primary care; telemedicine; virtual care; digital-first models; quality of care; patient safety

Introduction

Background

Even before the COVID-19 pandemic, virtual care (a broad term that encompasses all the ways health care providers remotely interact with their patients) was on the rise, with many health care systems developing strategies to facilitate the adoption of this approach [1]. Yet, despite digital remote care having long been anticipated to play an increasingly important role in supporting primary care, its mainstream usage remained suboptimal and piecemeal in many countries, often limited by cultural, regulatory, industrial and technical, knowledge, financial, and market-related barriers, among others [2,3].

COVID-19 has brought an abrupt end to this unhurried introduction. Over the course of a short few weeks, primary care worldwide rapidly transitioned from face-to-face consultations to virtual care solutions [4,5]. In less than 1 year, virtual care approaches have taken center stage, triaging and monitoring patients with COVID-19 and other acute conditions in primary care, as well as ensuring access and continuity of care for those with long-term conditions (eg, diabetes, hypertension, asthma, psychiatric illnesses, chronic pain) [6-8]. Consequently, existing digital technologies and systems supporting virtual care suddenly faced an immense challenge, both in their ability to cope with the surge in use and the new myriad of clinical tasks they were now expected to fulfil. However, COVID-19 also presented a unique opportunity and a catalyst for furthering the deeper integration of virtual care into the modern primary care landscape [9,10].

One year on from this initial mass transition, there is a growing need to review the impact of widespread digital-first model usage on patients, carers, primary health care providers, and health systems worldwide. Much uncertainty remains surrounding whether systems now in place adequately address the diverse range of clinical needs found in primary care, as well as their effects on quality and safety of care delivery. Some efforts to promote remote care were based on the assumption

that a considerable proportion of visits can be managed sufficiently remotely without compromising safety or quality of care [11]. However, this remains to be clearly demonstrated [12,13], and concerns have been raised regarding remote physical assessments [14]. It is also unclear whether the use of digital remote care will dissipate or attenuate after the pandemic is resolved [9] and whether general practitioners (GPs) and family doctors have the necessary training and support to comfortably deliver remote care [12,13]. Past research exploring this topic was largely built upon theoretical models such as the Technology Acceptance Model and Expectation Confirmation Model to gauge users' acceptance or desire to continue using novel information technologies in relation to their perceived convenience and usefulness [15-17]. COVID-19 has provided an opportune moment to apply these conceptual constructs and assess whether they continue to hold true in real-life circumstances at scale and across varying primary care contexts worldwide.

As primary users of virtual care technologies, ascertaining feedback from GPs is imperative to understanding the extent of the use of these remote care technologies as well as evaluate their practical implications on quality and safety of care in order to inform guidance and policies concerning their continued use into the future. GPs' experience during the pandemic is valuable as digital-first models no longer serve just as a backup to traditional face-to-face consultations, but rather act as an essential means for GPs to interact with their patients [18], among other reasons to protect the vulnerable and most sick, a role and responsibility not originally envisaged when virtual systems and technologies were first adopted. The lessons learned will likely outlast the pandemic and serve as a watershed moment in transforming how primary health care can be remotely delivered for decades to come.

Aims

This study aims to explore GPs' perspectives on the (1) use of virtual care during the COVID-19 outbreak, (2) impact of virtual care on quality and safety of care, and (3) critical factors for high-quality and sustainable use of virtual care technologies in the future.

Methods

The study will use an online cross-sectional questionnaire completed by GPs. Online surveys have been successfully used in health care professional research and was chosen in this case to ensure widespread geographical coverage [19]. Recruitment started in June 2020 and was completed at the end of September 2020. The study adheres to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline for cross-sectional studies [20].

Study Population

The inSIGHT Research Group is a collaborative research group of primary care researchers, aiming to explore the impact of the COVID-19 pandemic on the adoption of digital remote technologies in general practice/primary care. The research is conducted by a consortium spread across 20 countries (Australia, Brazil, Canada, Chile, Colombia, Croatia, Finland, France, Germany, Ireland, Israel, Italy, Poland, Portugal, Slovenia, Spain, Sweden, Turkey, the United Kingdom, and the United States).

Sampling

Each local lead was asked to email an invitation to take part in the survey to GPs in their country, using their personal contact networks. The invitation included the participant information sheet as well as a link to the website hosting the survey. GPs were eligible for the survey if they were working mainly in primary care during the period of the COVID-19 pandemic. Recruitment of health care professionals during the COVID-19 pandemic posed significant challenges; additionally, low survey response rates are common in primary care [21]. Thus, local leads who had difficulty achieving the total minimum number (n=386) were asked to use snowballing, a recognized technique for recruiting hard-to-reach populations in health studies, to increase the number of responses [22,23]. Upon consenting to participate in the study, the survey remained active for the participant to complete for 2 weeks.

Sample Size

The total population of GPs in the countries included was calculated using a combination of publicly available resources (Table 1).

Table 1. Proportionate allocation sampling estimate

Country	Total number of general practitioners (N=527,970)	Proportionate allocation sampling estimate (N=901)
Australia	36,938 [24]	63
Brazil	7149[a] [25]	12
Canada	43,500 [26]	72
Chile	20,361 [27]	35
Colombia	522 [28]	2
Croatia	984 [29]	2
Finland	2362 [30]	5
Germany	47,708 [31]	82
Ireland	3378 [32]	5
Israel	5052 [33]	9
Italy	42,987 [34]	72
Poland	8439 [35]	14
Portugal	7768 [36]	14
Slovenia	1237 [37]	2
Spain	29,743 [38]	51
Sweden	6195 [39]	12
Turkey	24,082 [40]	42
United Kingdom	35,146 [41]	58
United States	204,419 [42]	348

[a]All doctors working in primary care settings were considered in this analysis, including those that had not completed formal training in general practice/family medicine.

Published response rates with medical practitioners are often lower than 30% [43]. Based on this estimated population and an expected response rate of 30%, sample size was estimated using the following formula, where N = population size, e = margin of error (percentage in decimal form), and z = z-score [44].

Anticipating an expected response rate of 30%, a total sample size of ≥901 responses was calculated to be sufficient to provide us with a confidence level of 95% and a margin of error of 5%. Sample sizes per country were determined via proportionate sampling calculations (Table 1). Under most conditions, fixed effects and their standard errors are unbiased; however, with fewer than 5 cases per group and fewer than 50 groups, standard errors for fixed effects will be too small (ie, increased Type I errors), and random effects (variances) and their standard errors may be underestimated. In a recent review, McNeish and Stapleton [45] suggested a minimum cluster size of 50, especially if fixed model estimation is used. Thus, to mitigate any potential issues of underrepresentation for smaller countries due to their resultant lower sample size estimates, all country leads were instructed to recruit a minimum of 50 participants to ensure a representative sampling of their GP population was collected. Given the 30 items in the questionnaire, this is also in excess of the rule by Hair et al [46] requiring a sample size to be at least 10 times that of the number of variables.

Survey Development

The study was designed by investigators at the Patient Safety Translational Research Centre and Department of Primary Care and Public Health at Imperial College London (ALN, EL, GF, JC, AM, AD) in March 2020. The questions were generated from expert consultation, including both GPs and academics and researchers with experience in digital health and health services research. A draft survey was developed by the first author and subsequently reviewed by other co-authors prior to being finalized. The questionnaire (in English) was piloted by the national leads of the 20 inSIGHT Research Group member countries in May 2020 to identify statements that needed adaptation for cultural or organizational contexts at a national level. In order to improve participation rates, the questionnaire was translated into 5 additional languages (Portuguese, Spanish, French, Italian, and German) by inSIGHT Research Group local leads. Translation was carried out in a standardized way, with medically qualified native speakers of the local languages and fluent in English performing “forward” translations. The questionnaires were made available online using Qualtrics.

Description of the Questionnaire

The questionnaire included an introductory section with participant information and 30 questions divided into 4 sections: (1) basic participant demographics, (2) use of digital-first models

before and during the COVID-19 pandemic, (3) experience and impact of using digital-first models during the COVID-19 outbreak, (4) future of digital-first models in primary care.

The introductory section included the purpose of the study, a link to the participant information sheet, and an introduction to the concept of remote digital care (Multimedia Appendix 1). The first part included questions about participants' individual characteristics (eg, age, gender, country, years of experience), as well as practice characteristics (eg, country; urban, rural, or mixed setting). The digital maturity of the practice was also evaluated using the Patient-Centred Framework for Evaluating Digital Maturity of Health Services [47].

The second part explored participants' use and experience using virtual care approaches before and during the pandemic. Questions focused on the use of 8 virtual care solutions, selected after performing a rapid review evaluating the main tools used during the first months of the pandemic: (1) telephone consultations, (2) video consultations, (3) chat consultations, (4) online triage, (5) remote clinical monitoring technologies, (6) patient-initiated digital services (eg, scheduling, health education activities, prescription renewal, test requests), (7) secure messaging systems, and (8) remote access to electronic health records. Participants were asked about the availability and number of hours spent using each solution before and during the COVID-19 pandemic as well as the training, and guidance available or undertaken. In the third part, participants were asked about their overall experience and perceived impact of digital remote technologies on quality and safety of care. To evaluate impact on quality and safety of care, we adopted the definitions of the 6 dimensions of quality (ie, patient-centeredness, effectiveness, efficiency, safety, timeliness, and equity), as defined by the Institute of Medicine [48]. In this section, participants were also asked about the main benefits of, challenges to, and barriers to future use of digital remote technologies in primary care (free-text questions). The fourth and last section explored GPs' perceptions on the future of digital remote models in primary care. In particular, participants were asked how they would like the adoption of these tools to evolve in the future and to identify the key aspects to ensure high-quality adoption of digital remote care in the future once the COVID-19 pandemic has resolved. A complete copy of the survey is provided in Multimedia Appendix 2.

Statistical Analysis

For quantitative data, descriptive statistics will be calculated, including absolute (n) and relative frequencies (%) for categorical variables and mean (μ) and SD for continuous variables. At a first stage, differences in adoption of the various remote care technologies before and after the pandemic will be reported as the proportion of users before and during the pandemic. Potential associations with patients' characteristics will be explored using Kruskal-Wallis tests and effect sizes calculated using Cramer v. If possible, we will explore the potential of using structural equation modelling (ie, partial least squares path modelling) to impute the relationships between unobserved constructs (latent variables) and observable variables [49]. The significance level for all statistical tests will be set at $P<.05$.

For qualitative analysis, free-text answers will be analyzed; online surveys are a recognized qualitative research tool [50]. The framework analysis method was used, which includes 5 main stages: familiarization, identifying a thematic framework, indexing, charting, and mapping and interpretation [51]. The charting stage is applied as a principle for developing the coding framework through a process of abstraction to ensure that coding elements that might have been missed with an a priori approach are adequately captured [51]. Coding will be performed by at least two independent researchers, and the coding framework was kept both deductive and inductive, allowing the ongoing inclusion of emergent themes. All themes identified will be supported by quotations, and results will be presented both as conceptual maps and textboxes. Qualitative analysis will follow the Consolidated Criteria for Reporting Qualitative studies (COREQ) to ensure the study meets the recommended standards of qualitative data reporting [52].

Dissemination

Sharing information about the project will take place throughout the duration of the work. Results will be published in peer-reviewed scientific journals as well as shared as preprints and in conference presentations. Local leads will be encouraged to publicize the project findings within their universities and health services, for example in newsletters, websites, meetings, and local journal publications. Additionally, patient partners will be included in the interpretation of our results, the co-development of a dissemination strategy, and summarizing the research findings into lay summaries and reports, in order to raise awareness and stimulate public participation on this topic.

Results

Ethical approval was provided by the Imperial College Ethics Research Committee (ICREC) in April 2020. Data collection took place from June 2020 to September 2020. As of the submission of this manuscript, a total of 1605 GP respondents participated in the questionnaire. Both qualitative and quantitative data analyses are currently ongoing, with an anticipated publication date of the first results in mid-late 2021.

Discussion

This study will provide novel insights into GPs' perspectives on the availability of digital-first models before and during the COVID-19 outbreak. We will investigate their perceptions on their impact on quality and safety of care, as well as the critical factors surrounding high-quality, sustainable use of digital technologies in the future.

Despite the size and diversity of the sample, it remains a nonprobability, convenience sample that might have implications for representativeness, external validity, and overall generalizability of the study's findings. As local leads recruited GPs at a national level using a range of methods, including convenience and snowballing sampling, there is an inherent risk of selection bias. Additionally, while online surveys have been successfully used in health care professional research and allow for widespread geographical and demographic coverage [53],

their use also comes with possible selection bias, potentially favoring the participation of subjects who likely are more research-inclined and who have greater access to and are more familiar with digital technologies. It is also important to note that there is an unequal distribution of the number of GPs in total among countries (ie, high variance), which may introduce bias. The survey was translated in 5 languages, not in all the languages of the countries included in the survey, and the fact that it is not made available in the participant's native language may influence both uptake and response behavior. Finally, it is important to consider that the questions evaluating the availability of digital-first solutions only capture self-reported availability rather than actual availability and thus are likely to introduce some level of reporting bias.

To our knowledge, this is the first study, both before and during the COVID-19 pandemic, to explore the availability of virtual care solutions in primary care and the perspectives of GPs regarding their impact on quality and safety of care at an international level. Being at the frontline of primary care delivery, GPs are ideally placed to identify the main pragmatic benefits and challenges of using digital tools for remote care as well as their impact on care quality and safety. Additionally, the study has included a large sample size, estimated based on sample power calculations and representing a variety of participants, health care settings and systems, and countries. An extensive description of the sample will be performed to explore the factors associated with the availability of remote care solutions and their perceived impact on quality and safety of care. Finally, the questionnaire was carefully developed and piloted with several national leads, capitalizing on their experience as frontline GPs working during the COVID-19 pandemic to ensure its relevance and ability to capture data necessary to address the study objectives.

The inSIGHT study will provide a comprehensive overview of the use of remote care technologies both before and after the onset of COVID-19 across 20 countries from the GPs' perspectives, as well as attempt to capture the underlying factors in individual GP characteristics and the contextual characteristics in which they work, to better explain any findings observed. It will afford new knowledge about what digital tools worked well in the past and what is in dire need of improvement. While the COVID-19 crisis may prove the first great stress test as to the capabilities, capacity, and robustness of digital systems currently in use, remote care as a whole will likely remain an increasingly prevalent consultation method for years to come. It is therefore critical to reflect upon the main lessons to be learned from this global real-life experiment and capitalize on this transformative moment to improve the means upon which primary care will increasingly depend as we progress towards an increasingly digital future.

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Authors' Contributions

ALN, EL, GF, JC, AM, and AD contributed to the conception and design of this work. ALN and EL wrote the manuscript with input from all authors. All authors approved the version submitted for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant information sheet.
[PDF File (Adobe PDF File), 197 KB - resprot_v10i8e30099_app1.pdf]

Multimedia Appendix 2
Survey questions.
[PDF File (Adobe PDF File), 491 KB - resprot_v10i8e30099_app2.pdf]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
GP: general practitioner
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Digital Technology Tools to Examine Patient Adherence to a Prescription-Only Omega-3 Polyunsaturated Fatty Acid Therapy To Mitigate Cardiovascular Risk: Protocol for a Prospective Observational Study and Preliminary Demographic Analysis

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Abstract

Background: Sustained adherence and persistence with prescription medications is considered essential to achieve maximal treatment benefit for patients with major chronic, noncommunicable diseases such as hyperlipidemia and lipid-associated cardiovascular disease. It is widely documented, however, that many patients with these conditions have poor long-term adherence to their treatments. The population of Russia is affected by poor adherence in the same ways as populations elsewhere and continues to have high rates of cardiovascular disease.

Objective: The purpose of this study was to examine patient adherence to a prescription-only preparation of highly purified omega-3 polyunsaturated fatty acids (1.2 to 1 eicosapentaenoic acid to docosahexaenoic ratio, 90% purity) in a large sample of patients at risk for cardiovascular diseases using digital technology to monitor patient behavior and as an outreach facility for patient education and engagement.

Methods: We conducted a 6-month prospective observational study (DIAPAsOn) at >100 centers in the Russian Federation. A bespoke electronic data capture and patient engagement system were developed with a well-established Russian technology supplier that enables information obtained during clinic visits to be supplemented by remote patient self-reporting. Other aspects of the program included raising patients' awareness about their condition via educational materials available in personal patient accounts in the electronic system.

Results: From an initial cohort of 3000 patients, a safety population of 2572 patients (age: mean 60 years) with an equal proportion of men and women has been characterized. There was widespread concomitant cardiovascular pathology and commensurate use of multiple classes of cardiovascular medication, notably lipid-modifying and antihypertensive drugs. The program was completed by 1975 patients, of whom 780 were prescribed highly purified omega-3 polyunsaturated fatty acid supplements for secondary prevention after myocardial infarction and 1195 were prescribed highly purified omega-3 polyunsaturated fatty acid supplements for hypertriglyceridemia. Data collection and analysis have been completed.

Conclusions: DIAPAsOn will provide insights into patient adherence with prescription-grade omega-3 polyunsaturated fatty acid therapy and perspectives on the role of mobile technology in monitoring and encouraging adherence to therapy.

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KEYWORDS

omega-3-acid ethyl esters; myocardial infarction; hypertriglyceridemia; adherence; compliance; persistence; mHealth; eHealth; patient-reported outcomes

Introduction

Low-density lipoprotein cholesterol (LDL-C), the primary lipoprotein component of total cholesterol, is recognized as the most important lipid risk factor for coronary heart disease [1]. An extensive array of clinical trials has demonstrated the value of lowering LDL-C as a means of prevention (especially secondary prevention) of major cardiovascular events, including myocardial infarction and stroke; meta-analyses [2,3] exemplify the influence of LDL-C levels on cardiovascular risk—every 1 mmol/L (39 mg/dL) reduction in LDL-C leads to a decrease in overall mortality of 12%, a 19% reduction in coronary mortality, and a 17% reduction in the incidence of stroke, with the effect size relating closely to the absolute reduction in LDL-C achieved and evident across the continuum of LDL-C levels. These findings underpin the status of statins as first-line therapies to reduce cardiovascular risk via modulation of LDL-C levels.

Nevertheless, in a meta-analysis [2], 5-year event rates in statin-treated patients were 14% (compared with 18% in the reference group), and even higher residual risk was apparent in patients with preexisting coronary heart disease or type 2 diabetes. It has been estimated that some 50% of individuals with acute coronary syndrome do not have elevated LDL-C, indicating that other factors account for a sizeable proportion of total cardiovascular risk [4].

The existence of residual risk in patients whose LDL-C is well controlled with medication [5,6] has focused attention on additional contributors to that persisting risk, including elevated plasma triglyceride levels [7]. Demonstration of a causal link between elevated triglycerides and cardiovascular risk has been a matter of controversy, with evidence of an association between triglyceride levels and cardiovascular risk often being attenuated after adjustment for other factors [8-12]. Considerations such as the reciprocal relationship between levels of triglyceride and levels of high-density lipoprotein cholesterol (HDL-C), which is a correlation that persists even when triglyceride are low [13], as well as appreciation of qualitative metabolic interplay between triglyceride-rich lipoproteins and HDL-C fractions, have nevertheless established a strong prima facie case for triglyceride levels as one factor influencing residual cardiovascular risk in statin-treated patients, especially in patients characterized by a high triglyceride to HDL-C ratio. Various national and international guidelines recognize that elevated triglyceride may be implicated in the overall risk of coronary heart disease [14-16], notably so in patients with type 2 diabetes, obesity, or metabolic syndrome [17-20].

Highly purified long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs), available as prescription-only medications, are approved in various countries for the management of elevated triglyceride. These preparations are qualitatively distinct from dietary supplements of n-3 PUFAs [21]. One such prescription n-3 polyunsaturated fat preparation (OMACOR, Market Authorization Holder Abbott Laboratories GmbH), is available in Russia as 1 g capsules containing 840 mg of ethyl esters of omega-3 fatty acids—a 1.2 to 1 ratio (eicosapentaenoic acid to docosahexanoic acid, 90% purity)—and 160 mg of excipients. This preparation (hereafter designated OM3EE) is approved for doses of 2 to 4 g per day, for the regulation of triglyceride levels, and at a daily dose of 1 g, for the secondary prevention of major cardiovascular events in patients after myocardial infarction; the latter indication was supported by the findings of a randomized clinical trial [22] and corroborated by a recent Cochrane review [23].

Continued therapy is central to the attainment of the full and sustained benefit in cardiovascular prevention and a range of other major noncommunicable diseases. Patients' ownership of their situation, and the accompanying empowerment, can be an important determinant of willingness to persevere with a course of therapy [24]. This can be a particular challenge when dealing with initially symptomless conditions such as hyperlipidemia, where the connection between aberrations in blood lipid levels and later major cardiovascular events can seem abstract.

Previous trials [22,25] have highlighted the importance of long-term adherence to omega-3–based therapy in cardiovascular preventive medicine. The highly purified n-3 PUFAs are generally considered to be well tolerated and largely free of substantial adverse effects but even so a sufficient degree of patient adherence to therapy outside the framework of a controlled clinical trial cannot be taken for granted. This consideration—combined with the evidence from GISSI-Prevenzione [22] and the JELIS study [25] that good adherence maintained over a course of years can deliver clear clinical benefits—makes better understanding of treatment adherence in real-world circumstances desirable.

The emergence of widely available digital and internet technologies with the potential to provide rapid or immediate bidirectional communication between health care professionals and patients may be an important new resource for promoting long-term adherence to therapies [26]. DIAPAsOn was designed to study patient adherence to OM3EE therapy using digital technology tools.

Methods

Overview

DIAPAsOn was a nonrandomized prospective study (Clinicaltrials.gov NCT03415152) conducted at >100 centers in the Russian Federation to assess adherence to OM3EE prescribed as either a secondary preventive medical therapy for patients with a history of recent myocardial infarction (approved dose 1 g per day) or for lipid level regulation in patients with endogenous hypertriglyceridemia who have had insufficient responsiveness to either dietary modification or other drug therapy (approved dose 2-4 g per day). Because the objectives of the program are exploratory, there was no formal study

hypothesis and no formal calculation of sample size; however, we planned to enroll 3000 patients.

There was no control group in DIAPAsOn and patients did not undergo diagnostic tests or interventions other than those that are currently accepted standards of medical care.

We used digital technology to facilitate patient-initiated data collection. Patients accessed a customized electronic system that allowed them to enter data, including daily records of OM3EE administration, and to complete various questionnaires relating to, for example, health-related quality of life and product usability on a 4-level scale (very good, good, moderate, poor). If the reported grade was moderate or poor, patients were asked to provide narrative details. This system included an option for patients to set up reminders to take the study medication. Patients were also able to report side effects in their personal accounts or to indicate if they had undergone any cardiovascular-related, new angina pectoris, or nonfatal myocardial infarction hospitalizations.

Recruitment of Study Centers and Patients

Selection of investigators and sites to participate in the program was based on the ability to properly conduct the program, including capacity to complete an electronic case record form, and existence within the study center of a cohort of adult (≥18 years) patients with a history of myocardial infarction not earlier than 6 months for whom OM3EE was prescribed as part of a medical secondary prevention regimen or existence within the study center of a cohort of patients with a diagnosis of hypertriglyceridemia not adequately controlled by a hypolipidemic diet.

Patients satisfying these criteria at the selected sites were eligible to participate in DIAPAsOn if they had been taking OM3EE for no more than 14 days at the time of enrollment and if they were considered capable, either personally or with the assistance of immediate relatives, of submitting data through a mobile phone app or web browser. The use of this system was voluntary, and once enrolled, patients remained part of the study whether or not they used the system or withdrew during the observation period. No a priori assumption was made regarding any possible changes in treatment or follow-up related to the use of the system.

Candidates for enrollment were excluded if they were taking other prescription-only n-3 PUFAs or nutrition supplements containing omega-3 polyunsaturated fats at screening or had taken such compounds within the previous 6 months. Other exclusion criteria were being pregnant or breastfeeding; having a known sensitivity to the active substance, excipients, or soy; having been diagnosed with exogenous hypertriglyceridemia (Frederickson type I hyperchylomicronemia); participating in any other clinical or observational study at the same time as DIAPAsOn or within the previous 30 days; or having any other clinical state that, in the opinion of the center investigator, made the patient unsuitable for inclusion.

Schedule of Visits and Data Collection

DIAPAsOn included 3 principal clinic visits (Figure 1). At each visit, patients were asked about their adherence to OM3EE using the Questionnaire of Treatment Adherence [27]. This instrument, which has been used to investigate adherence to antihypertensive medication among Russian patients, produces a numerical indication of adherence: 12 to 15 points is very high, 8 to 11 points is high; 4 to 7 points is moderate, and 0 to 3 points is low. Concomitant diseases at the first visit were classified according to International Classification of Diseases, tenth revision (ICD-10) codes.

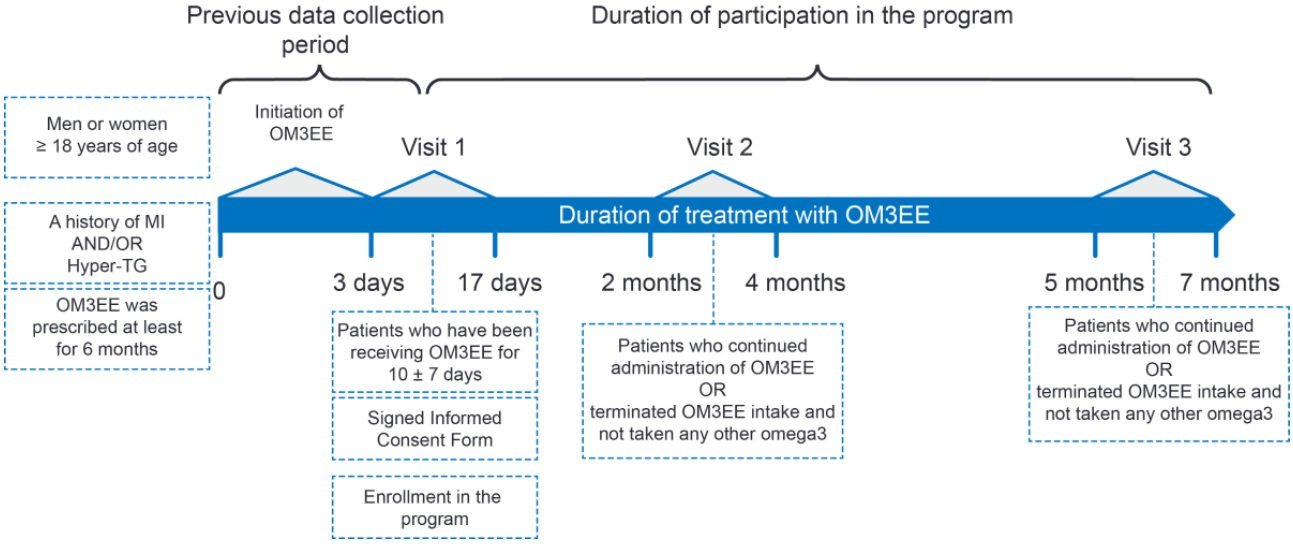
At these visits, information about concomitant therapies, blood pressure, and heart rate were also obtained. Because OM3EE was administered within the frames of normal medical practice rather than being supplied by the sponsor, information about the batch number and shelf life of the supplement were recorded at each visit.

Blood lipid profile was determined at each study visit. No central laboratory procedures were performed. All laboratory tests were conducted in accordance with routine local clinical practice.

Safety and adverse events data were recorded at each visit. In the event of a patient discontinuing the study, enquiries were made about the reason (adverse drug reaction; lack of effect; inconvenient to use; not available in pharmacies; other).

The principal clinic visits were supplemented by monthly investigator-led phone calls that focused on adherence to therapy and safety. The investigator asked the patient for information about medication batch number and expiry date if this information was not collected during regular physician visits.

Figure 1. Design and chronology of the DIAPAsOn study. MI: myocardial infarction; TG: triglyceride.



Mobile Patient Engagement Technology

The electronic patient engagement and data collection system used in DIAPAsOn was developed in collaboration with the medical online platform ROSMED [28], which has extensive experience in the development and operation of such facilities in the Russian Federation, including the Russian Severe Asthma Registry (RSAR NCT03608566), the all-Russian register of patients with hearing impairment and the integrated support program (anticipated recruitment 12 million people), and the Russian Register of patients aged >80 years with acute coronary syndrome, and maintenance, on behalf of the Russian Glaucoma Society, of the first Russian pharmaco-epidemiological study of the treatment of glaucoma patients with retinoprotective interventions and adherence to therapy [28]. The platform satisfies current requirements of Russian legislation pertaining to the management of personal data and the implementation of observational studies, primarily Russian Federal Law 152, and is included in the Russian Unified Register of computer programs and databases of the Ministry of Communications of Russia; certification of quality management and information security management has been conducted in accordance with ISO 9001:2015 and ISO/IEC 27001:2013 [28].

The system devised for DIAPAsOn was configured to minimize technical and ergonomic barriers to participant adoption and use. Contributing patients could work with the web version (configured to work with all popular browsers) or download the smartphone app (Apple iOS or Android).

Obligatory form fields for remote completion by patients included (1) medication consumption on a daily basis; (2) assessment of quality of life using the SF-36 questionnaire [29] (every 3 months); (3) evaluation of medication usability (month 1); and (4) reason for termination of the treatment, specifying adverse effects, lack of effect, inconvenience of use, nonavailability, or other. Optional form fields included (1) adverse effects (if “Yes,” the electronic system sent a notification message to the attending physician and the patient received the message, “Your doctor received the message about changes of your health”); (2) hospitalizations for cardio-vascular reasons, new cases of stenocardia, or nonfatal myocardial infarction; and (3) tests of patient’s knowledge of the problem or disease based on acquaintance with study materials available in the electronic system of the program.

Operational domains of the digital platform (Figure 2) consist of an administrative tier, occupied by the service manager and the study sponsor, and an executive tier, which includes dedicated areas (cabinets) for use by patients and physicians (Figure 3; these screenshots have been translated into English, and the examples shown here have also been anonymized).

The landing page for the Patient Cabinet (Figure 4) displays 5 drop-down menus designed to allow patients easy access to the full range of services. These include access to notices and push-reminder services (Figure 5) and an internal social network (Figure 6). The patient registration page was deliberately kept simple to minimize set-up friction and encourage patient enrollment (Figure 7).

Figure 2. User interactions.

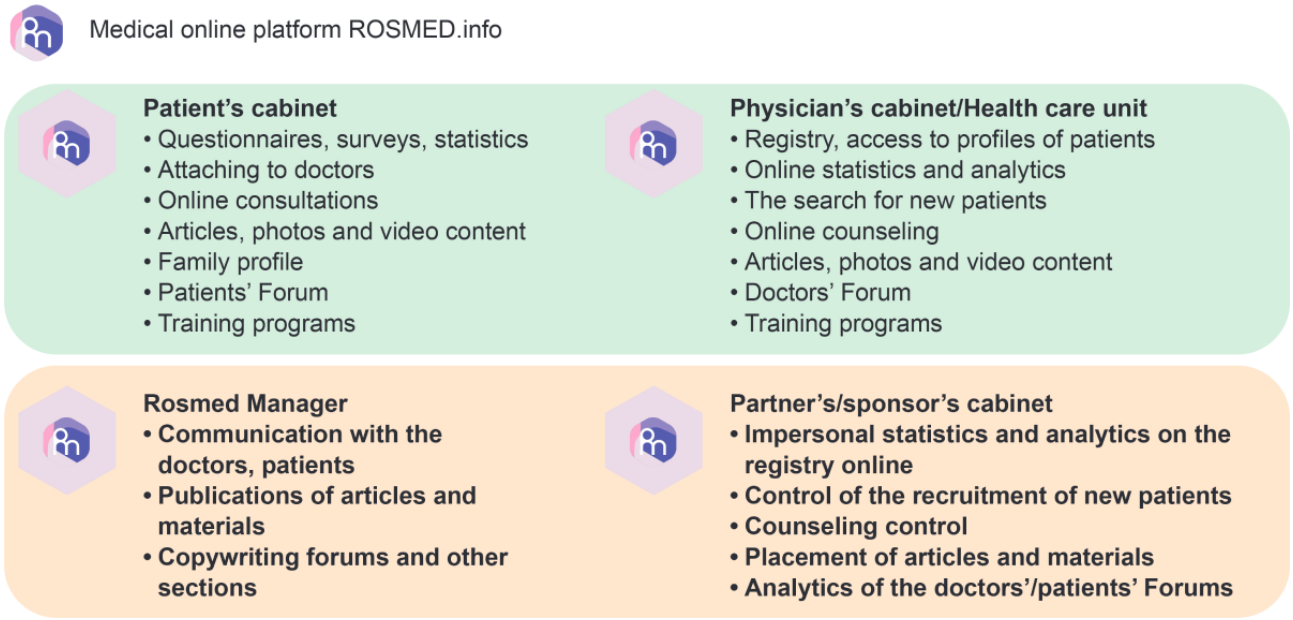


Figure 3. Physician's cabinet graphical user interface.

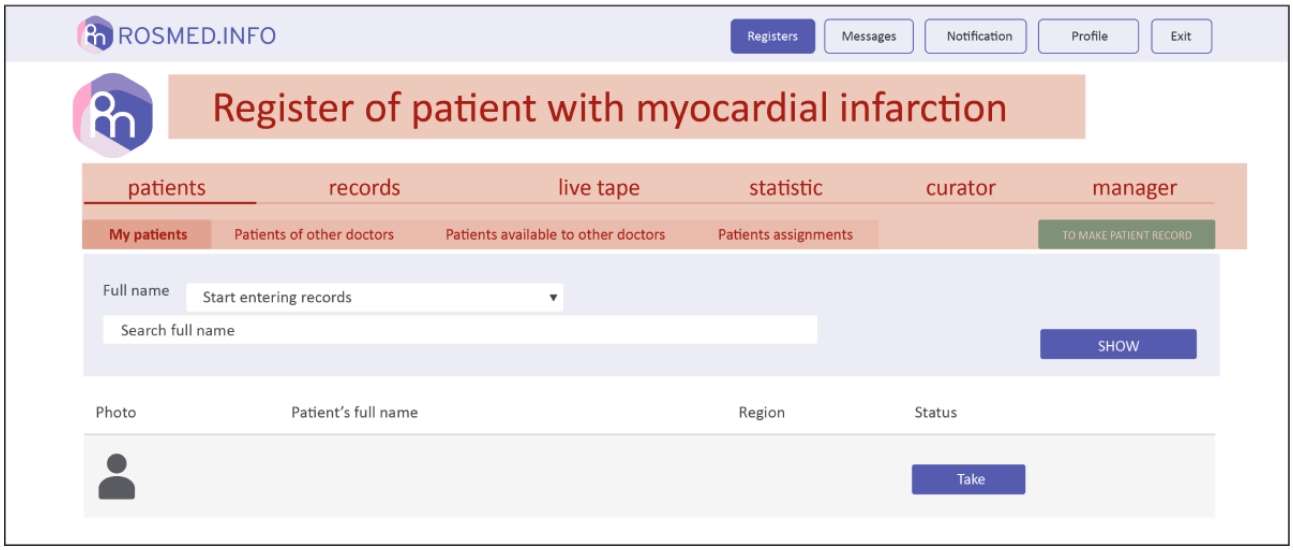


Figure 4. Patient's cabinet.

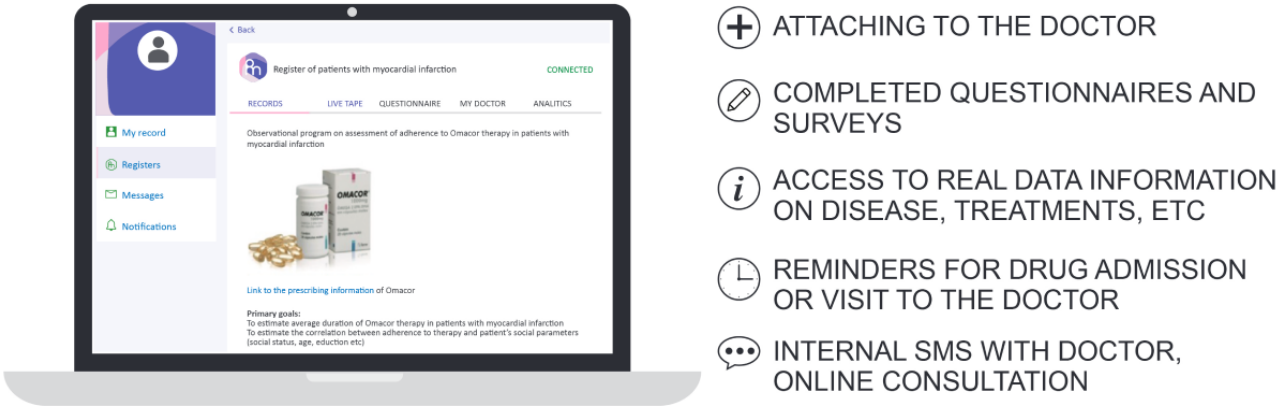


Figure 5. Notices and push-reminder messages.

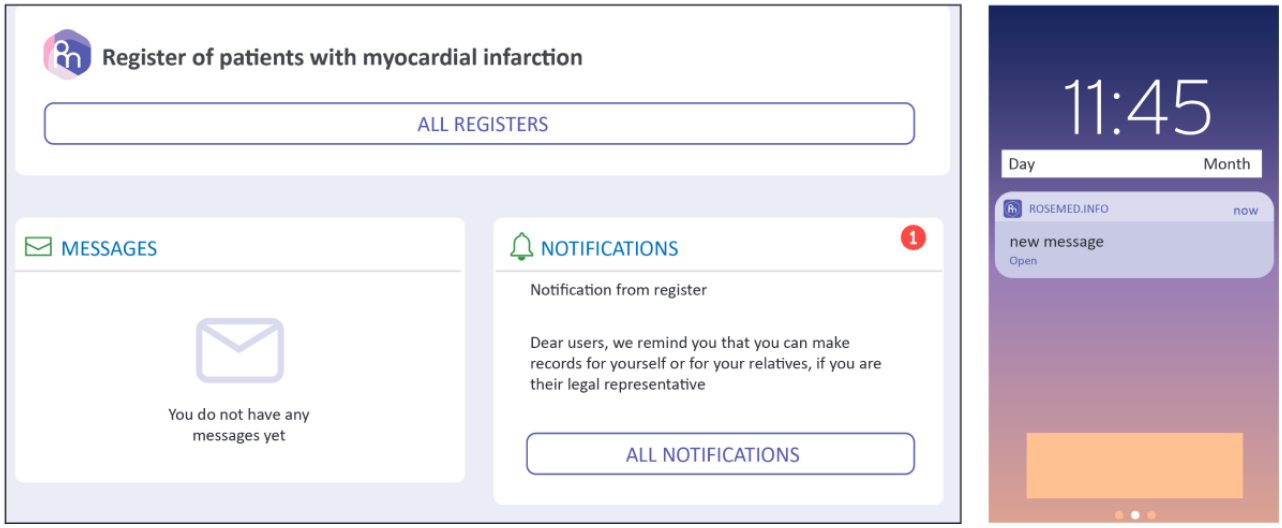


Figure 6. Internal social network.

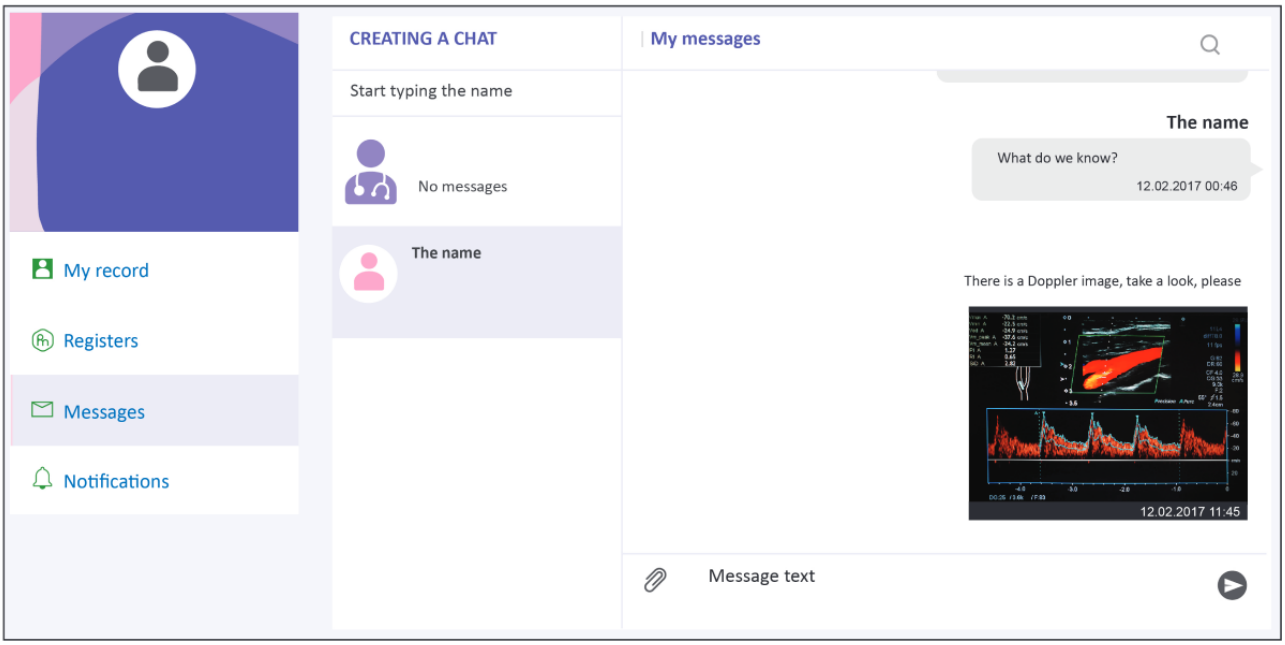
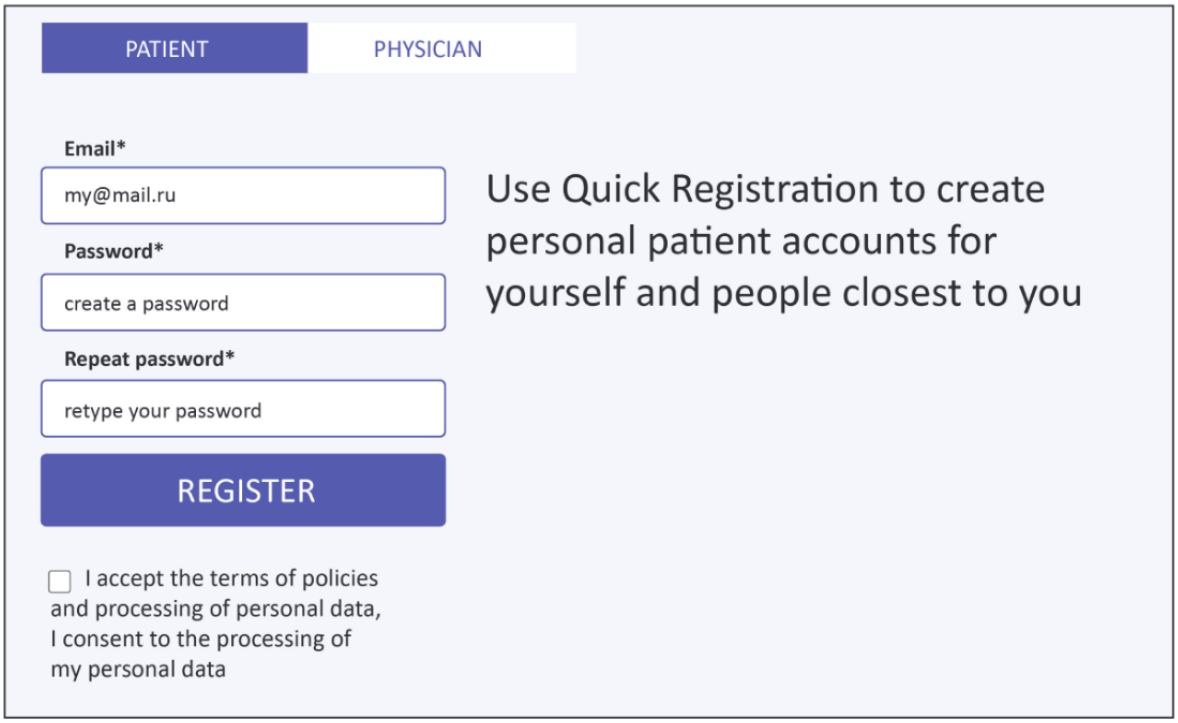


Figure 7. Simplified patient registration.



Statistical and Analytical Plans

Statistical analysis was performed in accordance with a preapproved Statistical Analysis Plan, using R (version 3.4.3; The R Project).

We used the 2-tailed paired *t* test for dependent samples for continuous data and the McNemar test for categorical data for comparisons between scheduled visits. For all comparisons, statistical significance was calculated at the threshold of $P<.05$.

For applicable endpoints, further analysis was performed in subgroups of patients with different adherence rates (ranked on a 0-1 scale) at visits 2 and 3.

The primary endpoint was assessed per-protocol (all patients for whom data were collected), at least at visit 2. The safety population included all patients who completed at least visit 1. This population was used to record reports of adverse drug reactions, serious adverse drug reactions, and other safety information.

Analysis of the primary endpoint included (1) determining the mean adherence rate, calculated as the sum of days when the patient took the full prescribed dose of highly purified omega-3 polyunsaturated fatty acid supplement during the specified period divided by the total number of days in that period, at the end of the study (visit 3); and (2) mean score on the National Questionnaire of Treatment Compliance, determined at the end of the study (visit 3).

Ethics

Ethical oversight of the study was exercised by the independent Interuniversity Ethics Committee. Initial written approval was issued on October 19, 2017, before the start of the study. The study was then implemented in accordance with the protocol version of November 8, 2017.

The study conformed to the requirements of Good Clinical Practice and to all applicable national standards relevant to the rights, safety, and well-being of all study participants in accordance with the provisions of the Declaration of Helsinki and all relevant national legislation and related provisions. Informed written consent was obtained from the patient to use and disclose personal and medical information. Prospective patients were apprised of their right to decline further participation in the study at any time and for any declared reason (or for no reason) without prejudice to any subsequent treatment.

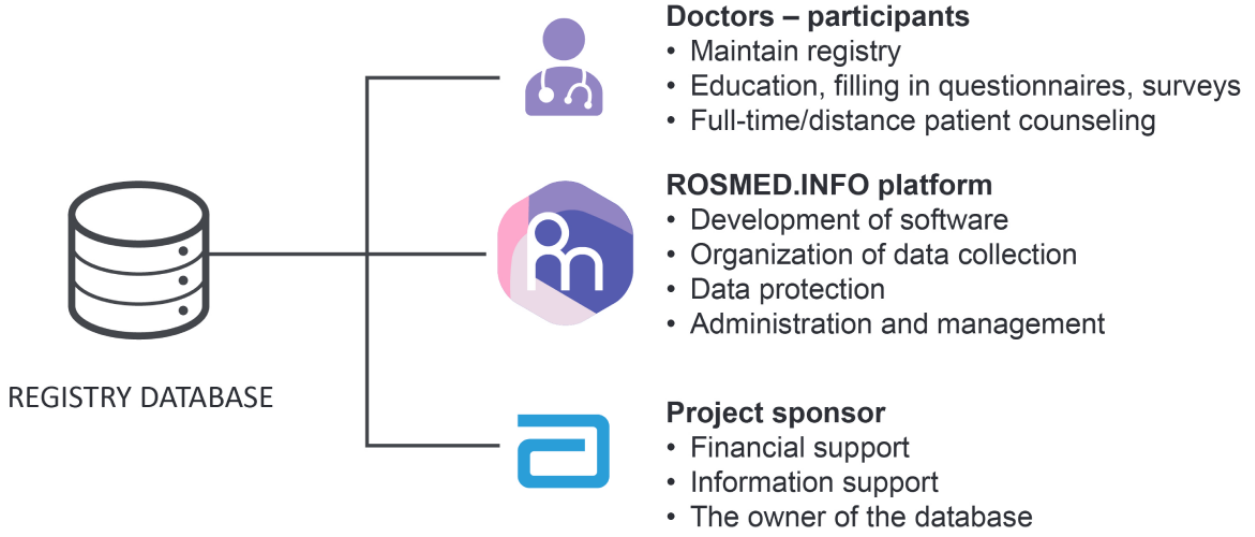
Individual center investigators were responsible for ensuring quality control; execution of the program; and the collection, documentation, and submission of data in accordance with the protocol, standards of Good Clinical Practice, and all applicable local laws.

Administrative Structure

The tripartite functional organization of the project is illustrated in Figure 8. A list of 107 investigators at participating centers is presented in Multimedia Appendix 1.

Abbott Laboratories (Moscow), in its role as study sponsor led the development of the protocol, subject to endorsement by the investigators, and discharged statutory responsibilities with respect to drug safety and adverse events monitoring. Abbott Laboratories (Moscow) did not supply highly purified omega-3 polyunsaturated fatty acid supplement, which was prescribed in the context of routine clinical practice. Results were collated and analyzed by an independent external biostatistician. Financial compensation for physicians was reasonable and represented local fair market value for the services provided. Patients in the study did not receive any financial compensation.

Figure 8. Functional scheme of the project.



Results

A total of 3000 patients were initially included in the program, but 428 (14.3%) were excluded because visit 1 data were incomplete. Valid and complete data from visit 1 were available for 2572 of the 3000 patients (85.7%), who constituted the safety population (Table 1), and data from a per-protocol contingent of 2167 patients were accrued (Table 2); 405 patients failed to complete at least visit 2.

Within the per-protocol population, 41.4% (898/2167) were prescribed OM3EE for secondary prevention after myocardial infarction, and 58.6% (1269/2167) for hypertriglyceridemia. The program was completed by 1975 patients, 780 of whom were being treated for secondary prevention, and 1195 of whom were being treated for hypertriglyceridemia. Our protocol stipulated that discontinuation of the study medication was not a reason to withdraw a patient from the study.

Men accounted for 52.8% (1145/2167) of the total population and 67.7% (608/898) of the subgroup prescribed OM3EE for secondary prevention postmyocardial infarction; conversely, most of the patients prescribed OM3EE for hypertriglyceridemia were women (732/1269, 57.7%). The study population was almost exclusively Caucasian (2118/2167, 97.7%), and almost all other patients (43/2167, 2.0%) were Asian.

Patients' mean age was 59.9 years (SD 11.6), and overall mean BMI was 29.9 kg/m^2 (SD 5.6). Slightly more than one-quarter of all patients (613/2167, 28.3%) smoked actively. In the secondary prevention subgroup, the mean time since the index myocardial infarction to the start of study therapy with highly purified omega-3 polyunsaturated fatty acid supplement was 3.04 months (SD 1.7).

The most frequently recorded concomitant diseases were hypertensive diseases (ICD-10 codes: I10-I15), recorded in 63.8% (1383/2167) of patients. Within those categories, most patients were diagnosed with hypertensive heart disease without congestive heart failure (725/2167, 33.5%) and essential hypertension (328/2167, 15.1%). Coronary heart disease (ICD-10 codes: I20-I25) was recorded in 17.9% of patients (388/2167), other heart disease (ICD-10 codes: I30-I52), including unspecified atrial fibrillation and atrial flutter, was recorded in 16.2% (352/2167) and diabetes was recorded in 7.1% of patients (154/2167). Metabolic disorders (ICD-10 codes: E70-E90) were recorded in 10.8% of patients (235/2167).

Therapies prescribed during the 12 months preceding enrollment were mostly lipid-modifying agents (1600/2167, 73.8%). The single most frequently prescribed drug in this category was rosuvastatin (906/2167, 41.8%), followed by atorvastatin (601/2167, 27.7%). Combinations of lipid-modifying drugs accounted for 6.9% (150/2167) of prescriptions. Over half of the patients (1140/2167, 52.6%) had been prescribed antiplatelet agents, primarily aspirin (n=583), and 40.6% (879/2167) had been prescribed beta-blockers, predominantly bisoprolol (n=586). In addition, 694 patients (694/2167, 32%) received angiotensin-converting enzyme inhibitors, either as monotherapy (n=438) or in combination with other classes of antihypertensive drugs, including diuretics and calcium-channel blockers. Perindopril was the most widely prescribed angiotensin-converting enzyme inhibitor (n=325).

Variations were apparent in the 2 indication-specific subgroups. The use of anticoagulants was recorded in 96.4% (866/898) of patients who received OM3EE for secondary prevention postmyocardial infarction. The use of beta-blockers was recorded in 62.9% (564/898), the use of angiotensin-converting enzyme inhibitors was recorded in 31.9% (286/898), and the use of lipid-modifying agents was recorded in 73.6% (661/898). Prestudy use of lipid-modifying agents was at a similar level in patients with hypertriglyceridemia (939/1269, 74.0%) but the use of above-specified classes of agents was at a lower level.

Baseline mean systolic blood pressure was 133.7 mmHg (SD 17.3) and baseline mean diastolic blood pressure was 81.4 mmHg (SD 8.8). Some patients, 21.4% in the overall cohort (463/2167) and 23.6% in the hypertriglyceridemia subset (299/1269), but only 18.0% of those in the postmyocardial infarction subgroup were considered to have clinically relevant elevation of systolic blood pressure. Approximately 13% (hypertriglyceridemia: 165/1269; postmyocardial infarction:

117/898) were considered to have clinically relevant elevation of diastolic blood pressure.

Table 1. Safety population characteristics (participants with data available from visit 1).

Characteristic	Overall population (n=2572), mean (SD)	Secondary prevention postmyocardial infarction (n=1171), mean (SD)	Hypertriglyceridemia (n=1401), mean (SD)
Age (years)	59.9 (11.6)	61.8 (10.3)	58.2 (12.4)
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight (kg)	87.1 (16.9)	86.0 (15.1)	88.0 (18.1)
BMI[a] (kg/m^2)	29.9 (5.6)	28.5 (4.1)	31.0 (6.4)

[a]BMI: body mass index.

Table 2. Per-protocol population sociodemographic characteristics.

Characteristic	Per protocol (n=2167), n (%)	Secondary prevention postmyocardial infarction (n=898), n (%)	Hypertriglyceridemia (n=1269), n (%)
Sex			
Male	1145 (52.8)	608 (67.7)	537 (42.3)
Female	1022 (47.2)	290 (32.3)	732 (57.7)
Education			
Some secondary	17 (0.8)	13 (1.4)	4 (0.3)
Secondary general	238 (11.0)	86 (9.6)	152 (12.0)
Secondary vocational	673 (31.1)	280 (31.2)	393 (31.0)
Higher	1199 (55.3)	504 (56.1)	695 (54.8)
Supplementary vocational	40 (1.8)	15 (1.7)	25 (2.0)
Work status			
Working	1199 (55.3)	445 (49.6)	754 (59.4)
Not working	968 (44.7)	453 (50.4)	515 (40.6)
Marital status			
Single	91 (4.2)	33 (3.7)	58 (4.6)
Married	1744 (80.5)	669 (74.5)	1075 (84.7)
Divorced	124 (5.7)	60 (6.7)	64 (5.0)
Widowed	208 (9.6)	136 (15.1)	72 (5.7)
Smoking status			
Smokes	613 (28.3)	284 (31.6)	329 (25.9)
Does not smoke	1554 (71.7)	614 (68.4)	940 (74.1)

Discussion

Rates of death from coronary heart disease have been falling in Russia in recent decades [30], but the rate of decline has been less marked than in other European countries, and age-standardized mortality rates remain markedly higher than those in other nations [31]. Data from other investigations suggest that not all of this discrepancy in declines can be explained by blood lipid levels (alcohol appears to exert a notable influence [32]), but lipid levels are regarded as central determinants of risk [33]. Additional efforts to improve the management of coronary risk are, therefore, warranted; a focus on patient adherence to secure maximum benefit from available therapies is one logical dimension of that response.

It is clear from CEPHEUS II data that failure to reach targets for lipid-based risk reduction is widespread in Russia [34]. Patient-related factors associated with nonattainment of targets identified in that study included patients considering it acceptable to miss prescribed doses more than once per week.

In response to these deficits, we developed digital technology tools designed to stimulate patient engagement and education and recruited 3000 patients to study the effectiveness of this mobile health technology. We believe this research in preventive cardiovascular medicine to be the first of its kind undertaken at scale in Russia: it may provide a model for further studies in this field.

The patient population of DIAPAsOn was large and was recruited from a wide geographical area. This gives us the confidence that the demographic profile and extensive use of concomitant cardiovascular medications reported herein are likely an accurate reflection of the patient population in the Russian Federation that are likely to be candidates for prescription-grade n-3 PUFA therapy. As such, we are optimistic that the findings of DIAPAsOn may be instructive about the routine use of prescription-grade n-3 PUFA therapy throughout the Federation, which has a population of 145 million.

The limitations of this study must be recognized. The absence of a control group precludes any determination of cause and effect, and the potential for biases in any trial of this type must be acknowledged. A retrospective calculation of the Nichol score [35] for DIAPAsOn confirmed that our study rated favorably in the *Disease-Related Criteria* and *Compliance Definition and Measurement Criteria* subcategories but scored less strongly in the *Study Design Criteria* subcategory. The duration of follow-up was appropriate for an initial evaluation of a technical innovation in the management of chronic cardiovascular risk [36], but a substantially longer period of observation (we conjecture at least 1 year) will be needed to demonstrate whether our strategy for digital patient engagement translates into a robust, sustained, and meaningful improvement in long-term adherence. The web-based resources were developed and presented in Russian, and the study population was highly homogeneous: those factors may restrict the extrapolation of findings from this study to other countries. We did not perform a prestudy evaluation of the web-based services used in DIAPAsOn using, for example, the Mobile App Rating Scale, or a prefatory feasibility study, such as that reported by Paldán et al [37].

These reservations notwithstanding, experience and insight from this prospective study of a digital technology and patient self-reporting platform to enhance adherence may inform further development of mobile health engagement technologies for Russian populations to improve adherence to medications and thereby reduce the risk of clinical cardiovascular events.

Acknowledgments

The investigators thank the Ethics Committee of Pirogov Russian National Research Medical University for its advice and guidance on the development of the research protocol. Manuscript preparation was assisted by Hughes associates (Oxford, United Kingdom). ROSMED [28] was responsible for the development and maintenance of software for the digital data collection and adherence facilities, and for data collection and protection. Contract research services were provided by RSMI LLC (Moscow, Russian Federation), and data statistical services were provided by Sciencefiles LLC (Yekaterinburg, Russian Federation). The study was sponsored by Abbott Laboratories (Moscow, Russian Federation), which is the legal owner of the registry database of digital information generated during the study.

Conflicts of Interest

The study was supported by Abbott. GPA has not received any educational grants from any companies and has not received any fees or nonfinancial support from health care companies related to this study. GPA reports receiving honoraria for professional lectures at regional/national medical educational events from health care companies, including Abbott, Bayer, Boehringer Ingelheim, and Servier. AGA has not received any educational grants from any companies and has not received any fees or nonfinancial support from health care companies related to this study. AGA reports receiving honoraria for professional lectures at regional/national medical educational events from health care companies, including Abbott, Bayer, Boehringer Ingelheim, and Servier.

Multimedia Appendix 1
DIAPAsOn center investigators.
[PDF File (Adobe PDF File), 58 KB - resprot_v10i8e29061_app1.pdf]

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Abbreviations

BMI: body mass index
HDL-C: high-density lipoprotein cholesterol
ICD-10: International Classification of Diseases, tenth revision
LDL-C: low-density lipoprotein cholesterol
n-3 PUFA: omega-3 polyunsaturated fatty acid

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Protocol

Implementation of Patient Engagement Tools in Electronic Health Records to Enhance Patient-Centered Communication: Protocol for Feasibility Evaluation and Preliminary Results

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Abstract

Background: Patient–physician communication during clinical encounters is essential to ensure quality of care. Many studies have attempted to improve patient–physician communication. Incorporating patient priorities into agenda setting and medical decision-making are fundamental to patient-centered communication. Efficient and scalable approaches are needed to empower patients to speak up and prepare physicians to respond. Leveraging electronic health records (EHRs) in engaging patients and health care teams has the potential to enhance the integration of patient priorities in clinical encounters. A systematic approach to eliciting and documenting patient priorities before encounters could facilitate effective communication in such encounters.

Objective: In this paper, we report the design and implementation of a set of EHR tools built into clinical workflows for facilitating patient–physician joint agenda setting and the documentation of patient concerns in the EHRs for ambulatory encounters.

Methods: We engaged health information technology leaders and users in three health care systems for developing and implementing a set of EHR tools. The goal of these tools is to standardize the elicitation of patient priorities by using a previsit "patient important issue" questionnaire distributed through the patient portal to the EHR. We built additional EHR documentation tools to facilitate patient–staff communication when the staff records the vital signs and the reason for the visit in the EHR while in the examination room, with a simple transmission method for physicians to incorporate patient concerns in EHR notes.

Results: The study is ongoing. The anticipated completion date for survey data collection is November 2021. A total of 34,037 primary care patients from three health systems (n=26,441; n=5136; and n=2460 separately recruited from each system) used the previsit patient important issue questionnaire in 2020. The adoption of the digital previsit questionnaire during the COVID-19 pandemic was much higher in one health care system because it expanded the use of the questionnaire from physicians participating

in trials to all primary care providers midway through the year. It also required the use of this previsit questionnaire for eCheck-ins, which are required for telehealth encounters. Physicians and staff suggested anecdotally that this questionnaire helped patient–clinician communication, particularly during the COVID-19 pandemic.

Conclusions: EHR tools have the potential to facilitate the integration of patient priorities into agenda setting and documentation in real-world primary care practices. Early results suggest the feasibility and acceptability of such digital tools in three health systems. EHR tools can support patient engagement and clinicians' work during in-person and telehealth visits. They could potentially exert a sustained influence on patient and clinician communication behaviors in contrast to prior ad hoc educational efforts targeting patients or clinicians.

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International Registered Report Identifier (IRRID): DERR1-10.2196/30431

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KEYWORDS

electronic health record; patient portal; patient–physician communication; agenda setting; patient priorities; patient engagement; health care teams; electronic health record documentation; standard work; digital health

Introduction

Systematic reviews of the essentials for improving health care delivery have emphasized the importance of patient–physician communication [1,2]. Many efforts have been undertaken to improve patient–physician communication, including the use of a booklet to elicit patients' agendas before visits and facilitating teach-back during visits [3], and implementing a systematic training program on patient-centered communication at the organizational level [4]. Efficient and scalable approaches are needed to empower patients to speak up and to prepare physicians to respond [3]. A component of an effective communication strategy is agenda setting, which aims to prioritize the items to discuss in a visit [4,5]. Agenda setting has been shown to improve patients' health outcomes, satisfaction, and physicians' time management [6]. However, it can be challenging for physicians to incorporate agenda setting in their workflow [7-10] even though doing so can facilitate visit management [11] without lengthening the visits [12].

The patient's role in patient–physician communication is equally important. As electronic health records (EHRs) become an integral part of health care [13,14] patients often use the patient portal to communicate with their providers [15]. We created and implemented a set of EHR-based tools to facilitate joint agenda setting between patients and physicians and to ease the task of documenting patient priorities by physicians in the EHRs. We trained staff and physicians on the use of the tools as a part of an ongoing multicenter randomized control trial (ClinicalTrials.gov IHS-1608-35689). The aim of this paper is to report the design and implementation of our EHR tools into clinical workflow that facilitates patient–physician communication and present some preliminary interim results from the study.

Methods

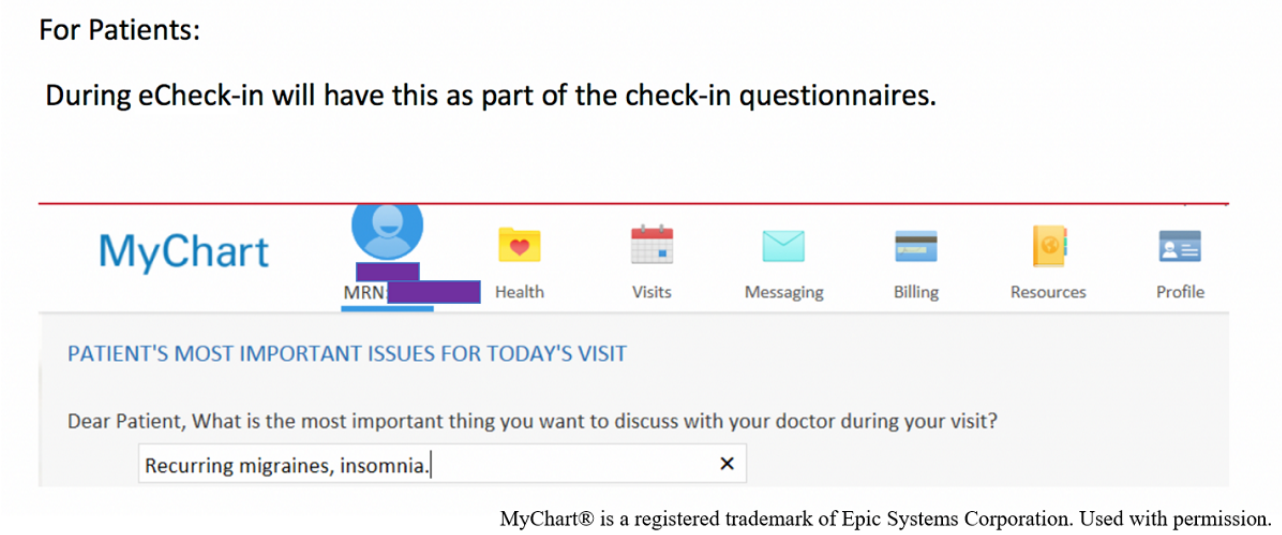
EHR Tools

The research team collaborated with health information technology leaders at the University California San Diego Health (UCSDH), Sutter Health, and Reliant Medical Group to design, build, test, and implement the EHR tools for the study. All three health systems use a commercial EHR from the same vendor (Epic Systems). Representatives from across the three health systems attended weekly meetings to coordinate the patient-facing and care team–facing components during the EHR building and workflow implementation processes. The key components of the EHR built at UCSDH included the following: (1) a patient previsit questionnaire; (2) a new rooming tab for the staff; and (3) a documentation shortcut (SmartPhrase in Progress Notes) to enable physicians to see what the patient entered and incorporate it into the visit note. Considering organizational preferences, variations in the workflow existed across the three health systems. In addition to providing descriptions of these EHR tools, we present preliminary data on the feasibility of implementing these EHR tools in real-world primary care practices in diverse health systems located in Southern California, Northern California, and Central Massachusetts. Similar to other studies on the feasibility of Internet-based health interventions [13,14], we measured feasibility by seeking to understand participants' acceptance of our tools, perception of the tools' value in improving patient–clinician communication, and potential issues with their use. As the study is ongoing, the preliminary findings on the feasibility presented in this paper are informal. More formal analyses of user surveys involving clinicians, clinical staff, and patients will be performed after we complete data collection.

Patient Previsit Questionnaire

The previsit questionnaire (Figure 1) was added as a check-in questionnaire in the EHR's patient portal, known as "MyChart," when a patient scheduled an appointment. The question, "What is the most important thing you want to discuss with your doctor during your visit?" appeared during the eCheck-in process. The text box was limited to 250 characters.

Figure 1. Previsit patient important issue questionnaire in MyChart.



MyChart® is a registered trademark of Epic Systems Corporation. Used with permission.

At Reliant, previsit patient questionnaires were attached automatically to appointments with primary care providers (PCPs) who were study participants when the visit was scheduled and released no sooner than 2 weeks before the visit date. Because legacy appointments could not automatically have the questionnaire, the Sutter and UCSDH teams manually attached it for the first 2 months of the study. As new appointments were scheduled, the questionnaire was automatically attached.

Use of Patient Responses to the Previsit Questionnaire by Rooming Staff

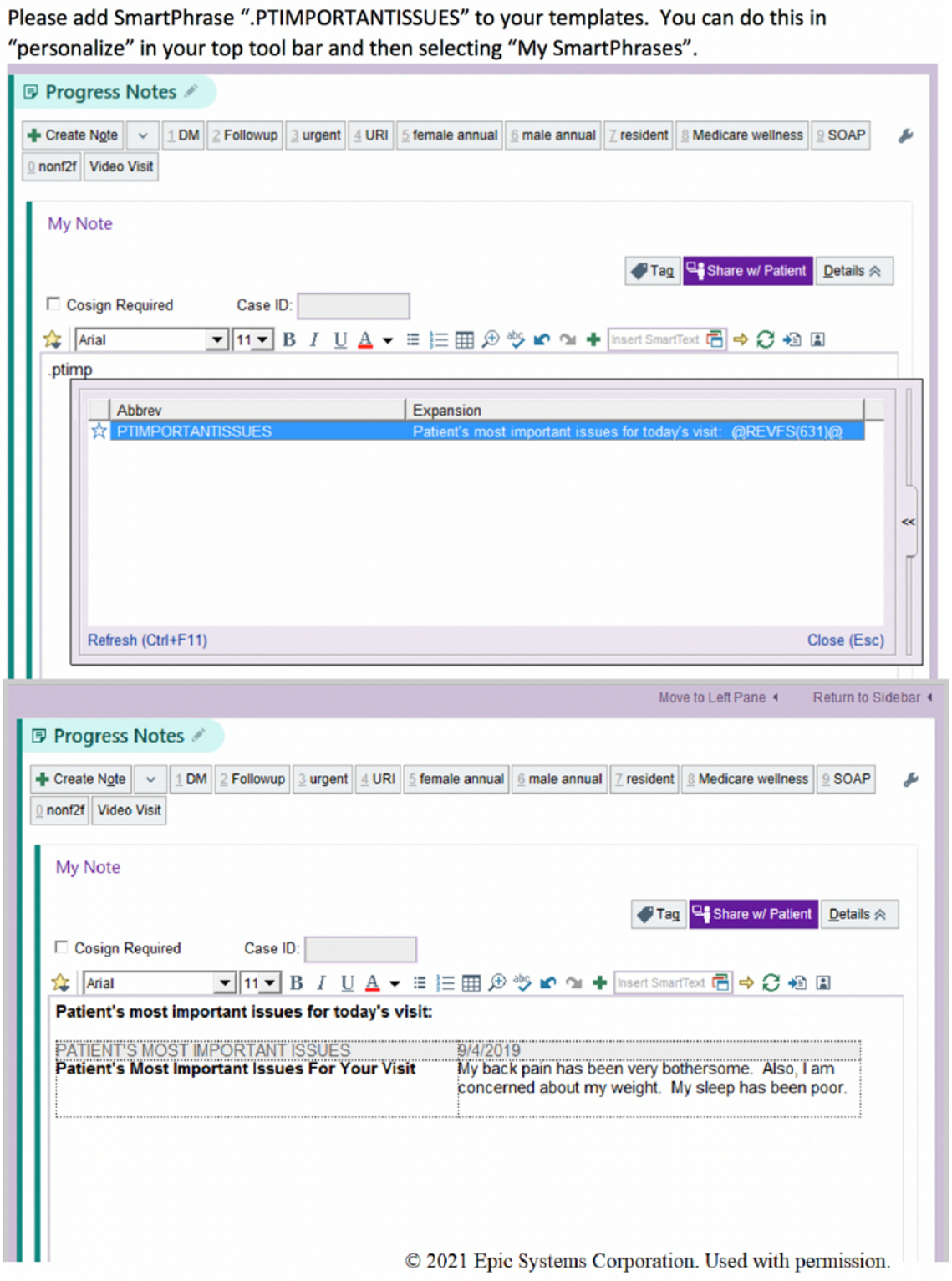
Prior to meeting their physicians, patients are routinely greeted by clinic staff for visit preparation involving measuring vital signs and eliciting patients' reasons for visiting. This process is commonly known as rooming. At UCSDH, once the patients arrived for their appointments, the rooming staff would see a new tab in rooming called "Patient Important Issues" in the EHR. This separate tab was created so that it would not be buried in the main rooming tab. The questionnaire also appeared before the EHR field called "Chief Complaint" so that it could be easily found. If the patients had already filled out the questionnaire, the staff could confirm the important issues with the patients. If the patients had changes or new issues to add, the staff could edit them accordingly. If the previsit questionnaire had not been completed, the staff could elicit and enter the patients' responses.

No new tab was created at Reliant or Sutter. Early implementation at Reliant relied on the staff to copy and paste the patient's response from the questionnaire into the "Chief Complaint" field and edit it as needed. Subsequently, the process was modified so that the patient's response was automatically pulled into the rooming note if the staff used a documentation shortcut template for rooming. Use of this template was strongly encouraged but not required. Then, the staff could edit directly in the rooming note. At Sutter, the staff could see if the patient had completed the questionnaire in the visit schedule and proceed to view the response for that particular visit in the patient's record. The staff verified the response with the patient and updated the record as needed.

Integration of Patient Previsit Questionnaire Responses by Physicians

A documentation shortcut named "PTIMPORTANTISSUES" was created for physicians at UCSDH. Physicians were asked to add the shortcut to their documentation templates in the EHRs by personalizing their tool bar (Figure 2). Although it was also possible to add patients' responses in notes during the appointment, physicians were encouraged to include the shortcut in their usual templates because it automatically added patients' responses in their workflow, so they did not have to remember to look for them. After the patients were fully checked in, the physician could refresh the progress notes to see the patients' most important reason (s) for their visit. This information is in a table format at UCSDH. Therefore, if the patient had responded to the questionnaire for previous visits, the physician could see a history of the issues by appointment date (Figure 2).

Figure 2. Documentation shortcut for physicians.



At Sutter, patient responses to the previsit questionnaire were incorporated into a shortcut "ENCQNR," which physicians were encouraged to add to their documentation templates. A physician could designate the location in the progress notes by typing "ENCQNR," and the previsit questions and patient responses would appear in a table format. The specific location of the patient response could vary based on the physician's preference. As mentioned earlier, no new documentation shortcut was created specifically for the study at Reliant, but all the PCPs' staff members were encouraged to use the shortcut for the rooming note template, which populated the patient's responses to the questionnaire automatically at the top of the note.

Interface With Telehealth During the COVID-19 Pandemic

Since the national declaration of the COVID-19 Pandemic in March 2020, all three systems rapidly increased clinical services

delivered using telehealth [16]. The patients must state their important issues in the previsit questionnaire, as they are required for video visits in all the relevant clinics participating in the study at UCSDH. The UCSDH physicians have also added the documentation shortcut known as "SmartPhrase" to telehealth documentation templates. At Sutter, modifications were made to the existing previsit questionnaire to automatically attach the questionnaire for telehealth services with the participating PCPs. Furthermore, modifications were made to the physician's documentation to include telehealth. At Reliant, the patient responses to the previsit questionnaire are available for telehealth services as they are for in-person visits.

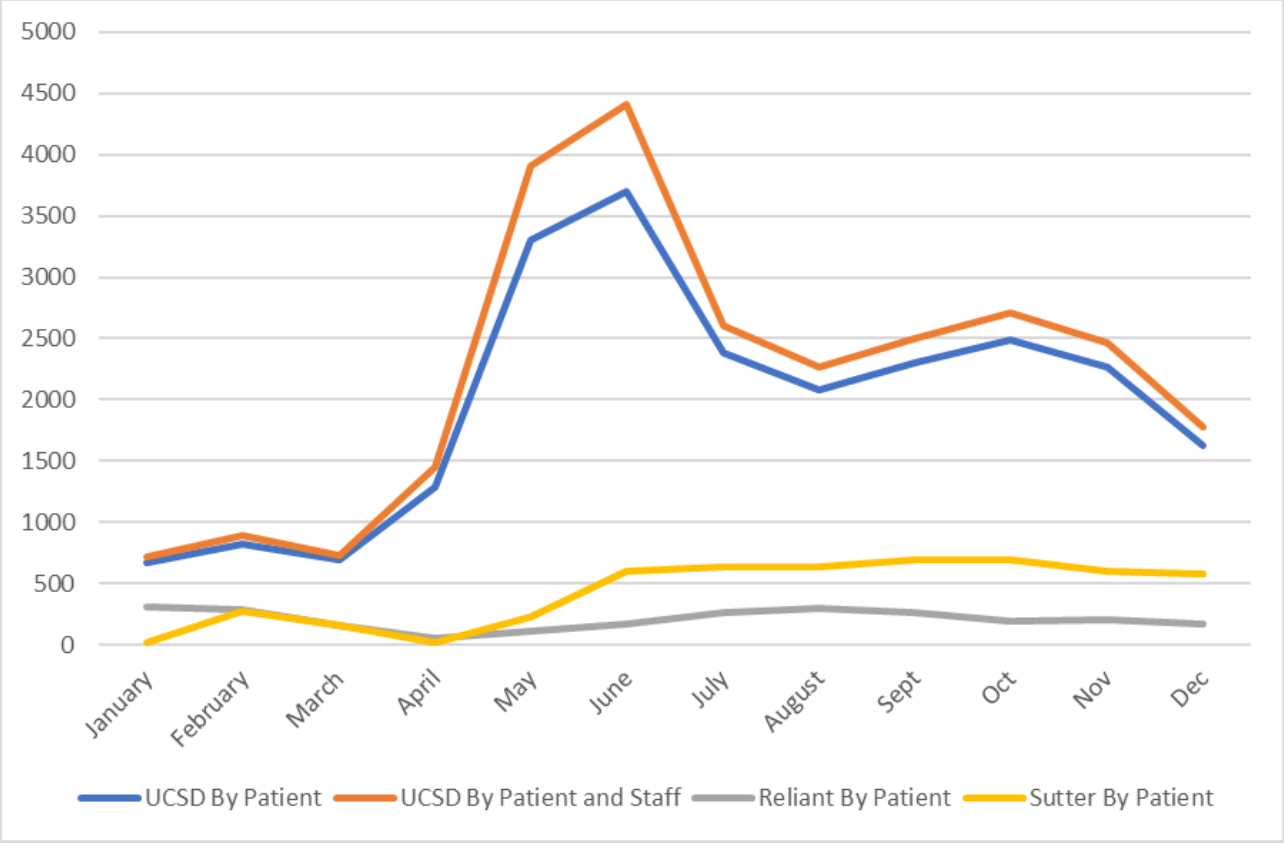
Results

Survey Data Collection

The study is ongoing. The anticipated completion date for survey data collection is November 2021. We report interim findings on the adoption of patients' most important issues into the EHR clinical workflow in the three health care systems.

Between January 1 and December 31, 2020, the previsit questionnaire was used in 26,441 UCSDH visits, 5136 Sutter visits, and 2460 Reliant visits (Figure 3). At Sutter and Reliant, the previsit questionnaire was used only for the patients of the PCP participants involved in the study. UCSDH started with PCPs participating in the study and expanded it to all primary care visits at the request of the health system in June 2020. Because the questionnaire is required for eCheck-in before televisits, the increase in televisits at UCSDH during the surge of COVID-19 cases in the community could explain the pronounced upsurges in the use of the previsit patient questionnaire from April to July 2020.

Figure 3. Responses to the previsit patient questionnaire across the three health systems in 2020. UCSD: University of California San Diego Health.



Feedback From Physicians and Staff

We have received informal comments and anecdotes from physicians. Three preliminary themes have emerged: acceptance of our tools; perceived values of the tools in improving patient–clinician communication, and potential issues with their use. Regarding acceptance of our tools, we heard comments such as "For the most part, patients have said this questionnaire was easy to use."

The following comments reflect the perceived values of our tools in improving patient–physician communication:

There are no curve balls - I know what the patient wants to talk about before I see them.

For some of my more difficult/rambling patients, it may have provided a bit of focus.

It helps them focus and get more out of their medical visits.

I knew ahead of time what the issues were that we were going to discuss … have a form ready… made the appointment more efficient.

The patients listed something that they did not bring up so I was able to ask them about it.

> *Many patients are slightly anxious the first video visit so having a list to review made it easier to get started.*

The staff also noted that the ease of incorporating patient responses into the rooming workflow empowered them to facilitate communication between the patients and health care team.

A few potential issues in using the tools were noted:

> *The biggest challenge is making sure the nurses are trained in pulling this question in. Some are familiar with the workflow and some are not, especially float nurses who are brought in as temporary help.*

> *What I should have done was put it into my regular note but I kept losing track of the dot phrase. And this again tells me that I should fix this up to work better because it was helpful when it worked.*

The staff reported that some patients entered health issues that they wanted addressed during their upcoming annual health exams. Although these visits are intended for preventive care rather than for addressing specific health issues [17], patients may view these as opportunities to discuss what matters to them with their primary care physicians. Physicians appreciate knowing these issues ahead of time as they can convert the annual health exams to office visits so that they are oriented to specific health issues that patients consider the most important during that visit. This helps promote patient-centered care. Identifying the patients' important issues enables physicians to "take a step back and get their patients ready for the next time when they would undergo their annual health exam."

Discussion

Our study suggests that it is feasible to design and implement EHR tools to facilitate patient–physician communication, from joint agenda setting to documentation of patient priorities in physicians' notes at the point of care. Consistent with the principles of translational informatics [18], our multilevel intervention nudges patients and clinicians with easy-to-use tools. It is in harmony with the "Meaningful Use" criteria, which emphasize patients playing an active role in their care via the patient portal [15]. The innovation of incorporating the patients' most important issues into the EHR was intentionally designed for simplicity and ease of implementation. It has the potential to overcome the challenge of patient priorities not being integrated into the workflow [8]. Although each system has a different shortcut and method of using the previsit questionnaire, we show that this approach is feasible and can be implemented on a larger scale. Furthermore, for new digital tools and workflows, acceptance by end users is important. The acceptance level of our approach is illustrated by UCSDH's application of the questionnaire more broadly to all primary care visits. Beyond our study, Epic has adopted this workflow on its platform and called it "Patient's Most Important Issues" for all eCheck-ins to help identify patients' reasons for scheduling an appointment.

We acknowledge that the central role of the patient portal in this effort may limit its reach to patients who do not use the patient portal either owing to limited access to the Internet or mobile phones. As a nation, digital infrastructure needs to be more accessible to all people regardless of where they live, and their health status, age, race, and education [19].

Our work demonstrates how a patient-centered communication intervention designed for a study, when implemented in alignment with health care delivery needs, can significantly benefit both endeavors. Furthermore, our approach is like OpenNotes [20], which enables patients, caregivers, and providers to jointly create clinical notes and care plans within the shared EHR. As more organizations adopt OpenNotes, where clinical notes are shared with patients [21,22], EHR interventions such as ours could empower patients to become more engaged in their health care.

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Conflicts of Interest

Authors MM and CL are affiliated with UCSDH; AC, with Sutter Health; and LG, with Reliant Medical Group. The other authors have no conflicts of interest to declare.

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Abbreviations

EHRs: electronic health records
PCORI: Patient-Centered Outcomes Research Institute

PCPs: primary care providers
UCSDH: University California San Diego Health

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Protocol

Muscular Assessment in Patients With Severe Obstructive Sleep Apnea Syndrome: Protocol for a Case-Control Study

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Abstract

Background: Myofunctional therapy is currently a reasonable therapeutic option to treat obstructive sleep apnea-hypopnea syndrome (OSAHS). This therapy is based on performing regular exercises of the upper airway muscles to increase their tone and prevent their collapse. Over the past decade, there has been an increasing number of publications in this area; however, to our knowledge, there are no studies focused on patients who can most benefit from this therapy.

Objective: This protocol describes a case-control clinical trial aimed at determining the muscular features of patients recently diagnosed with severe OSAHS compared with those of healthy controls.

Methods: Patients meeting set criteria will be sequentially enrolled up to a sample size of 40. Twenty patients who meet the inclusion criteria for controls will also be evaluated. Patients will be examined by a qualified phonoaudiologist who will take biometric measurements and administer the Expanded Protocol of Orofacial Myofunctional Evaluation with Scores (OMES), Friedman Staging System, Epworth Sleepiness Scale, and Pittsburgh Sleep Quality Index questionnaires. Measures of upper airway muscle tone will also be performed using the Iowa Oral Performance Instrument and tongue digital spoon devices. Evaluation will be recorded and reevaluated by a second specialist to determine concordance between observers.

Results: A total of 60 patients will be enrolled. Both the group with severe OSAHS (40 patients) and the control group (20 subjects) will be assessed for differences between upper airway muscle tone and OMES questionnaire responses.

Conclusions: This study will help to determine muscle patterns in patients with severe OSAHS and can be used to fill the gap currently present in the assessment of patients suitable to be treated with myofunctional therapy.

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International Registered Report Identifier (IRRID): PRR1-10.2196/30500

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KEYWORDS

myofunctional therapy; sleep apnea; sleep disordered breathing; speech therapy; phenotype; sleep; therapy; protocol; muscle; assessment; case study; exercise; airway; respiratory

Introduction

Background

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a significant public health issue characterized by repetitive episodes of airway obstruction during sleep associated with snoring, sleep fragmentation, daytime sleepiness, and increased cardiovascular risk [1,2]. It is well established that the most effective treatment for OSAHS is continuous positive airway pressure (CPAP) [3], which has variable patient compliance. CPAP virtually eliminates OSAHS and snoring, reduces daytime sleepiness, and improves subjective sleep quality [3,4].

The etiology of OSAHS is multifactorial, including anatomical and physiological factors. The upper airway dilator muscles are crucial for maintaining pharyngeal patency and may contribute to the incidence of this medical condition [5,6].

Other treatments for OSAHS include a mandibular advancement device (MAD), conventional surgery, CO_2 or radiofrequency laser, or hypoglossal nerve stimulation. There is also some evidence for pharmacological treatments with oxybutynin and atomoxetine, which are currently showing promising results [7]. Clinical trials have been carried out with theophylline, acetazolamide, and desipramine to reduce the collapse of the upper airway, but without clear effectiveness [8,9].

Myofunctional therapy is a treatment applied to patients with orofacial myofunctional disorders that can interfere with the development or functioning of orofacial structures and functions [10]. Reviews of studies on myofunctional therapy show benefits by promoting changes in dysfunctional muscles of the upper airway [11]; therefore, this treatment has been proposed to reduce the severity of OSAHS and associated symptoms in adults [12]. Myofunctional therapy also has potential to promote a decrease in the Apnea-Hypopnea Index (AHI), reduce snoring [13], and improve quality of life [14]. In addition, it can be considered as an adjuvant therapy and an intervention strategy to support CPAP adherence [15].

However, it is currently unknown which patients are the best candidates for myofunctional therapy. Although there are instruments available for patient selection such as the Expanded Protocol of Orofacial Myofunctional Evaluation with Scores (OMES), involving functional exploration of all of the stomatognathic functions to obtain a score, this has proven to be inferior in patients with OSAHS compared with controls [16,17]. A myofunctional therapist uses this evaluation to improve the examined items that are in deficit and subsequently performs specific exercises to improve them. However, the OMES test is based on subjective evaluations, contains many items, and is difficult to reproduce. In our opinion, a more concise, objective, and reproducible evaluation is required. This opinion stems from our experience of measurements with the Iowa Oral Performance Instrument (IOPI) of the genioglossus muscle and the orbicular muscle [18,19]. Together with measurement of the motor tone of the genioglossus muscle using a tongue digital spoon (TDS) [20], these simple measurements may provide patients with information about their condition, serve as therapy response parameters, and objectively transmit results between professionals, which can also be based in electronic health facilities [21].

Aim

The aim of this study is to evaluate the muscle patterns of patients with severe OSAHS. The use of the OMES protocol can be complemented by the values obtained through the IOPI and the TDS.

Objectives

The main objective is to evaluate the function of the stomatognathic musculature of patients with OSAHS by using the OMES protocol, TDS, and IOPI.

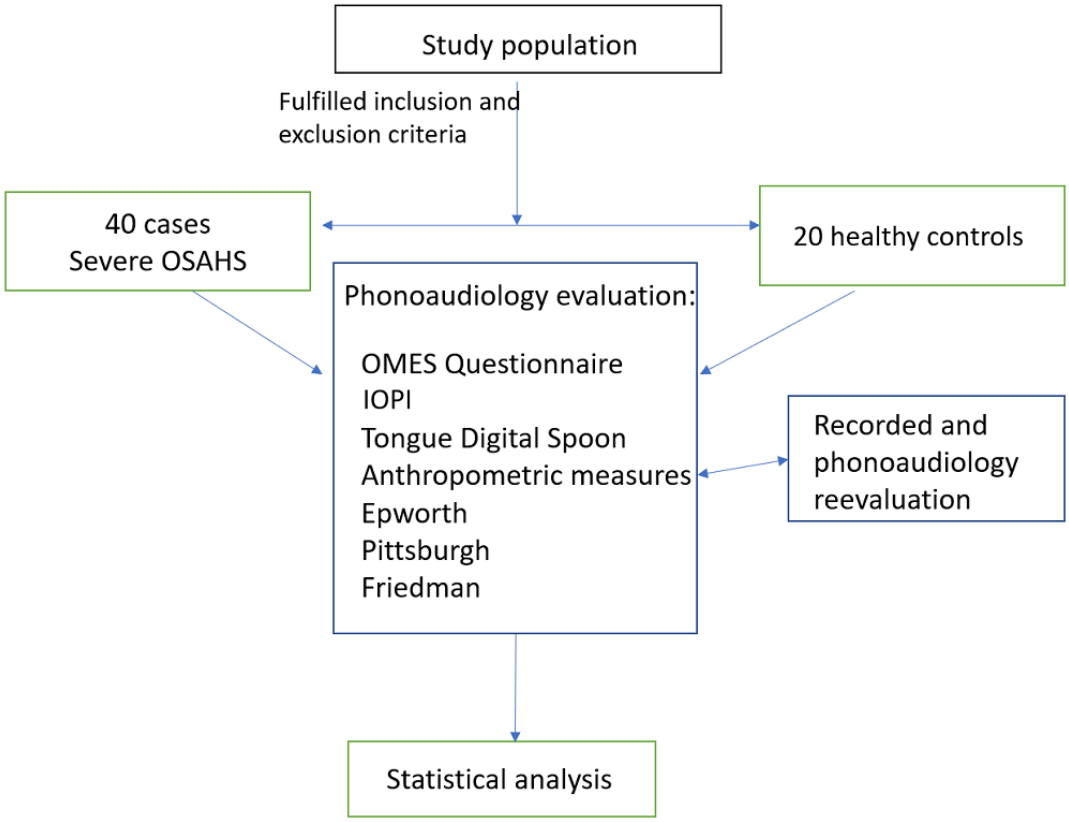
The secondary objectives are to: (1) use this protocol to evaluate whether there are differences between the muscles of patients with OSAHS and healthy controls; (2) use the IOPI to measure tongue strength and resistance with the genioglossus and buccinator muscle tone, and evaluate whether there are differences from those of healthy patients; and (3) use the TDS to measure tongue pressure and evaluate whether there are differences from healthy patients.

Methods

Design

We designed a prospective controlled quasiexperimental pilot study on patients with severe OSAHS (Figure 1).

Figure 1. Flow chart of the study process. IOPI: Iowa Oral Performance Instrument; OMES: Orofacial Myofunctional Evaluation with Scores; OSAHS: obstructive sleep apnea-hypopnea syndrome; TDS: tongue digital spoon.



Scope of the Study

This study will involve patients diagnosed and/or treated at the Pneumology and Otorhinolaryngology Departments of Quirónsalud Hospital in Marbella (Malaga, Spain) or Hospital Campo de Gibraltar (Palmones, Cadiz, Spain) where the study will also be performed.

Study Population

This study will include patients diagnosed with sleep apnea-hypopnea at the participating hospitals and who agree to participate in the project.

Inclusion Criteria

For cases, adults (aged 18-75 years) who have received a diagnosis of severe OSAHS (AHI>30) without previous experience of the condition and not undergoing treatment owing to different circumstances, who had not undergone any previous treatment for OSAHS, and signed the informed consent form will be included.

For controls, adults with adequate sleep hygiene, no complaints of snoring or daytime sleepiness, and scoring <7 points on the Epworth Sleepiness Scale will be included.

Exclusion Criteria

Cases and controls alike with a cognitive or neurological deficit, inability to answer questionnaires, severe alcohol abuse, presence of craniofacial malformations, active neoplastic disease, or a history of prior orofacial muscle rehabilitation therapy and any prior apnea treatment that may modify the study results (surgery, MAD, CPAP) will be excluded.

Sample Size and Sampling Procedure

The effectiveness of use of the OMES protocol in the evaluation of patients with moderate to severe apnea-hypopnea syndrome will be evaluated from data previously published in studies using this protocol. Following the literature review, patients will be recruited. The sample size will be 60 subjects (40 in the experimental group and 20 in the control group). The sample size was calculated using the XLSTAT statistical software for Excel.

The variables that we are going to measure in all patients are reflected in the data collection table shown in Multimedia Appendix 1 using SPSS Info software, including age, sex, weight, height, ethnicity, BMI, abdominal circumference (at the level of the navel), neck circumference (using a flexible tape around the most prominent part while the patient is standing with their arms by their sides, head erect, and eyes looking ahead), IOPI measurement of tongue strength and the buccinator muscle, AHI, nighttime oxygen desaturation index, lowest overnight oxygen saturation levels, digital spoon measurement of tongue strength, and OMES protocol.

A series of questionnaires will be applied to both groups: Friedman Staging System, Epworth Sleepiness Scale, and Pittsburgh Sleep Quality Index (see Multimedia Appendix 2).

An information sheet and information consent will also be provided and signed by patients.

Procedures

Experimental Design

A myofunctional evaluation of patients diagnosed with OSAHS will be performed in the same week as the polysomnography is performed. During this evaluation, patients will be blindly examined by a speech therapist and their examination will be recorded on video for subsequent evaluation.

The patient will sit 1 meter away from the camera with their feet flat on the floor and their back supported by the backrest. The camera (Sony CCD-TRV138 Handycam camcorder) will be placed on a tripod at face and shoulder height.

Evaluation with the OMES protocol (see Multimedia Appendix 3) will then take place, based on the analysis of the following parameters: (1) appearance/posture; (2) mobility; and (3) functions, including respiration, deglutition, and mastication.

As a result of this evaluation with the already validated protocol, the higher the score, the more normal the patient's stomatognathic system.

IOPI Evaluation

The IOPI objectively measures maximum tongue and lip strength. Tongue strength is assessed by measuring the maximum pressure exerted when a person presses a disposable, standard-sized tongue bulb against the roof of the mouth. Lip strength is assessed by measuring the maximum pressure when the bulb is located between the cheek and closed teeth, and the patient contracts the buccinator muscle without biting the bulb. Reference values have been obtained for a healthy population and are provided by the manufacturer [18].

Tongue strength is measured by obtaining maximal tongue elevation pressures. The patient is instructed to "place this bulb in your mouth on the midline of your tongue and push it against the roof of your mouth as hard as you can." To maximize standard placement, the examiner demonstrates how to place the bulb along the central groove of the tongue blade. Previous research [18] indicates that maximal measures of tongue strength and endurance are best assessed with an unconstrained jaw; participants will be encouraged to gently rest the incisors on the tubing of the IOPI bulb. Each test lasts 7-10 seconds, and all participants will be given verbal encouragement from the examiner for the entire test. The test will be performed three times by each participant, with a brief rest of about 30 seconds between each test while the examiner records the peak pressure obtained. The highest pressure across the three trials will be used as the maximal isometric pressure instead of the mean pressure, which has been used by other researchers [22]. Given the high correlation between the average and maximal pressure and that both are similarly related to oral-phase swallowing function, the use of maximal pressure is more efficient in a clinical setting because it requires no calculation.

Subsequently, the muscle tone of the genioglossus muscle and the buccinator muscle are evaluated, taking three measurements of each and using the highest value.

TDS Evaluation

Finally, the tone of the tongue muscles will be measured with a digital spoon, taking three measurements and using the highest obtained. A digital spoon is a kitchen tool used to estimate the weight of food. To develop the TDS, we used the Soehnle Cooking Star Digital Measuring Spoon with graduation from 0.1 grams to 500 grams (ID ID20005876833). This is a handheld instrument with a spoon that can be found on online shopping platforms, consisting of a handle where the "tare" and "hold" buttons are located. Pressing the "hold" button helps to obtain the highest tared value, equivalent to the IOPI peak pressure. To carry out the measurements, the spoon is inverted and a 1-cm^2 circular sticker is placed on the back to obtain a marked circumference. To measure tongue strength, the subject holds the spoon by the handle and, with their elbow resting on a flat surface, brings the spoon closer to the tongue with an elbow angle of approximately 30°. The subject must then tare the device by pressing the "hold" key, marking 0.0 grams. The subject then presses on the marked circumference with the tip of their tongue. Once done, with the index finger of the hand that is holding the handle, the subject presses the "hold" button. This test is performed entirely by the subject to avoid movements on the spoon that may interfere with the results [20].

The recordings and the data obtained will also be analyzed by another blinded examiner.

Distribution of Hospital Visits

Selection Visit

A patient diagnosed with OSAHS at a pulmonology laboratory by means of an initial sleep study (with measurement of baseline AHI, nighttime oxygen desaturation index, and the lowest nighttime oxygen saturation figures) will be evaluated with respect to the inclusion and exclusion criteria and then informed about the study. After reading the information and having any doubts resolved, the patient will accept and sign the inform consent form in duplicate, taking one copy home.

One-off Visit

The patient will be evaluated by the speech therapist and fill in the sleepiness questionnaires, following which the OMES protocol will be applied and the evaluation will be carried out with the IOPI and the TDS.

Statistical Analysis

The data of the study variables will be collected in a database created for the development of the study. In the statistical analysis, the sample will be described through the distribution of frequencies for the categorical variables, and through measures of central tendency and dispersion such as the mean (SD) and median (IQR) for quantitative variables. The distribution of quantitative variables will be examined using the Kolmogorov-Smirnov test. Bivariate analysis of the association between categorical variables will be carried out using the χ^2 test or Fisher exact test when necessary. The differences between quantitative variables will be analyzed using the Student *t* test or analysis of variance for two or more samples, respectively, and nonparametric tests (Mann-Whitney or Kruskal-Wallis test) will be used if the variables to be

analyzed do not follow the normal distribution. The possible correlations between the OMES protocol evaluation and the IOPI values and TDS will be assessed using the Spearman rank correlation coefficient. The consistency and stability of the intra- and interrater measurements (reliability coefficient) will be determined using the split-half method. The level of statistical significance will be set at $P<.05$.

Ethical Aspects

The Research Ethics Committee of the Hospital Provincial de Málaga reviewed and approved the protocol and the informed consent model for the patients (AWGAP-2021-02). Before performing any of the procedures specified in the study protocol, the participating subjects will have signed and dated the informed consent form approved by the Research Ethics Committee.

Access to Data and Protection of Data Obtained from the Study

To guarantee the confidentiality of the study data, the original data will be stored at the hospital and only researchers and the Research Ethics Committee will have access.

This project will be carried out following the guidelines of the Declaration of Helsinki (Fortaleza, Brazil, 2013) [23] and the Standards of Good Clinical Practice. Personal data will be processed according to Regulation (EU) 2016/679 of the European Parliament and of the Council (April 27, 2016) on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and Organic Law 3 (December 5, 2018) on the protection of personal data and guarantee of digital rights.

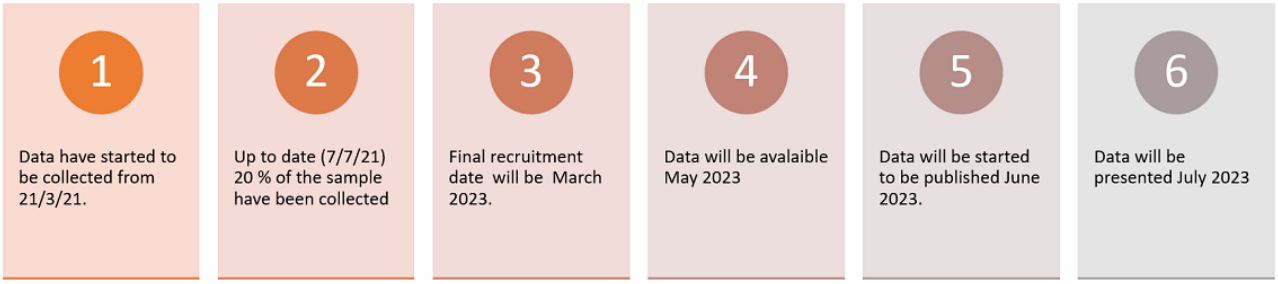
Usefulness and Applicability

The selection criteria for patients with OSAHS may improve depending on which therapy is more suitable.

Results

The authors plan to publish the study findings in a peer-reviewed journal and at topic-related conferences (to be determined at a later date). All listed authors or contributors are compliant with guidelines outlined by the International Committee of Medical Journal Editors for author inclusion in a published work. Furthermore, to support research transparency and reproducibility, we will share the deidentified research data after publication of the study results. We will also share the deidentified data on Figshare, a repository where users can make all of their research outputs available in a citable, shareable, and discoverable manner. To date, we have collected data for 20% of the planned sample. The timeline for data collection to completion of the study is given in Figure 2.

Figure 2. Summary of the results.



Discussion

Projected Significance

Although Eckert [24] proposed that one of the phenotypes responsible for initiating sleep apnea is the hypotonic pattern in 2016, studies have yet to be performed to confirm this proposal. It is well known that patients with this phenotype can benefit from treatment with a hypoglossal pacemaker, myotonic medication such as desipramine, and myofunctional therapy. We consider that our study will help to identify certain patients with severe OSAHS according to distinct anthropometric and myofunctional features from those of conventional patients (ie, individuals with obesity or with anatomical issues such as big tonsils). Following our experience using the IOPI [18], we consider that patients with a normal BMI, neck and bell circumference, and anatomy of the upper airway will show no relationship with the position of the tongue or the soft palate. We previously demonstrated that Friedman stage is independent from the tone of the muscle of the genioglossus as measured by the IOPI [18].

The patients' main anomaly will be determined by their responses to the OMES questionnaire, and with the measures of the upper airway muscles using the IOPI and TDS.

The TDS is a simple, reproducible, and affordable method to measure the muscle tone of the tongue for this patient group. We have pioneered the use of this domestic tool to allow patients to obtain immediate feedback of their success in performing myofunctional therapy exercises. In our opinion, the OMES questionnaire is a suitable tool to make a diagnosis for these patients, but can only be performed by specialized phonoaudiologists and requires considerable time. In most countries, there is a lack of phonoaudiologists and the demand on their time means that consultations are short. We contend that we can provide this information with the assistance of the IOPI and TDS that do not require any special training.

The information provided by these two instruments can be correlated with the information obtained by the OMES. In this case, these two measures are fast, simple, reproducible, and provide objective information to both the patient and examiner.

Limitations

One of the limitations of this study is that although we are going to identify patients according to their singular characteristics, we are not going to be able to demonstrate the effectiveness of the exercises performed with myofunctional therapy. Theoretically, these patients should improve with myofunctional therapy, a hypoglossal pacemaker, or inotropic medication. We intend to perform that study as a continuation of this proposed trial.

Our main concern is that if these patients have myofunctional disorders (ie, low OMES, IOPI, or TDS scores), the therapist is obliged to correct the deficits simultaneously with the use of CPAP. We are strongly opposed to any surgery in patients where there is a demonstrated myofunctional disorder.

Comparison With Prior Work

No previous work directed at this matter has been performed for effective comparison.

Conclusions

This study will help determine the muscle patterns in patients with severe OSAHS and may be used to fill the current gap in the identification of patients suitable to be treated with myofunctional therapy.

Authors' Contributions

PFB, COR, JMI, and ER made significant contributions to data collection, and writing and editing assistance. FD, CCA, and PFB assisted with translation. GP and MTGI made significant contributions in the design of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PowerPoint presentation with database.
[PPTX File , 3292 KB - resprot_v10i8e30500_app1.pptx]

Multimedia Appendix 2
Information sheets; informed consent; and Pittsburg, Friedman, and Epworth questionnaires.
[PDF File (Adobe PDF File), 6303 KB - resprot_v10i8e30500_app2.pdf]

Multimedia Appendix 3
OMES questionnaire.
[PDF File (Adobe PDF File), 249 KB - resprot_v10i8e30500_app3.pdf]

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Abbreviations

AHI: Apnea-Hypopnea Index
CPAP: continuous positive airway pressure
IOPI: Iowa Oral Performance Instrument
MAD: mandibular advancement device.
OMES: Orofacial Myofunctional Evaluation with Scores
OSAHS: obstructive sleep apnea-hypopnea syndrome.
TDS: tongue digital spoon

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Protocol

Health Impacts of Perchlorate and Pesticide Exposure: Protocol for Community-Engaged Research to Evaluate Environmental Toxicants in a US Border Community

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Abstract

Background: The Northern Arizona University (NAU) Center for Health Equity Research (CHER) is conducting community-engaged health research involving “environmental scans” in Yuma County in collaboration with community health stakeholders, including the Yuma Regional Medical Center (YRMC), Regional Center for Border Health, Inc. (RCBH), Campesinos Sin Fronteras (CSF), Yuma County Public Health District, and government agencies and nongovernmental organizations (NGOs) working on border health issues. The purpose of these efforts is to address community-generated environmental health hazards identified through ongoing coalitions among NAU, and local health care and research institutions.

Objective: We are undertaking joint community/university efforts to examine human exposures to perchlorate and agricultural pesticides. This project also includes the parallel development of a new animal model for investigating the mechanisms of toxicity following a “one health” approach. The ultimate goal of this community-engaged effort is to develop interventions to reduce exposures and health impacts of contaminants in Yuma populations.

Methods: All participants completed the informed consent process, which included information on the purpose of the study, a request for access to health histories and medical records, and interviews. The interview included questions related to (1) demographics, (2) social determinants of health, (3) health screening, (4) occupational and environmental exposures to perchlorate and pesticides, and (5) access to health services. Each participant provided a hair sample for quantifying the metals used in pesticides, urine sample for perchlorate quantification, and blood sample for endocrine assays. Modeling will examine the relationships between the concentrations of contaminants and hormones, demographics and social determinants of health, and health status of the study population, including health markers known to be impacted by perchlorate and pesticides.

Results: We recruited 323 adults residing in Yuma County during a 1-year pilot/feasibility study. Among these, 147 residents were patients from either YRMC or RCBH with a primary diagnosis of thyroid disease, including hyperthyroidism, hypothyroidism, thyroid cancer, or goiter. The remaining 176 participants were from the general population but with no history of thyroid disorder.

The pilot study confirmed the feasibility of using the identified community-engaged protocol to recruit, consent, and collect data from a difficult-to-access, vulnerable population. The demographics of the pilot study population and positive feedback on the success of the community-engaged approach indicate that the project can be scaled up to a broader study with replicable population health findings.

Conclusions: Using a community-engaged approach, the research protocol provided substantial evidence regarding the effectiveness of designing and implementing culturally relevant recruitment and dissemination processes that combine laboratory findings and public health information. Future findings will elucidate the mechanisms of toxicity and the population health effects of the contaminants of concern, as well as provide a new animal model to develop precision medicine capabilities for the population.

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KEYWORDS

community-engaged research; endocrine disruption; environmental contaminants; health disparities; toxic metal contamination; perchlorates; pesticides; population health; thyroid disease

Introduction

The Center for Health Equity Research (CHER) at Northern Arizona University (NAU) is conducting community-engaged health research in Yuma County, Arizona (Yuma, Somerton, San Luis, Rio Colorado). The primary community health stakeholders include the Yuma Regional Medical Center (YRMC), Regional Center for Border Health, Inc. (RCBH), Campesinos Sin Fronteras (CSF), Yuma County Public Health District, and several nongovernmental organizations (NGOs) working on border health issues. These stakeholders identified the most important regional priorities for joint health research [1]. One high-priority request was to examine basic epidemiology and conduct targeted translational research on environmental toxicants that impact communities in the border region.

Following discussions, literature reviews, and matching local needs with NAU research resources, we constructed this project as a joint community/university effort to examine the impact of human exposures to perchlorate, a water-soluble contaminant [2,3], and toxic metals such as cadmium, copper, lead, manganese, and mercury [4-11], which are active ingredients of currently or formerly used pesticides in the region. Results from the exposure assessment will be related to the health outcomes of Yuma residents. This project also includes the development of a new animal model for investigating the mechanisms of toxicity following a “one health” approach [12]. The ultimate purpose of this community-engaged effort is to develop interventions to reduce exposures and impacts of contaminants in Yuma populations.

In 2017, Yuma County had a population of 207,534 and an additional estimated 90,000 winter visitors/residents [13]. The race and ethnicity of the year-round population comprised 63.9% Hispanics, 30.8% White non-Hispanics, 2.7% African Americans, 2.3% Native Americans, 1.5% Asians, and 0.3% Native Hawaiians or other Pacific Islanders. The Yuma region sustains a large agricultural labor force [14] and frequent cross-border interactions with migrant farm workers from Mexico. In addition, Yuma County is home to two federally recognized tribes (Cocopah and Quechan). The United States Department of Labor’s Bureau of Labor Statistics ranked the unemployment rate of 387 metropolitan areas in November 2018 and found that Yuma had the second highest unemployment rate in the country, at 14.9% [15].

Yuma County is bounded by the Colorado River to the west and the US border with Mexico to the south (Figure 1). The Colorado River is the primary source of irrigation and drinking water throughout the region. The Colorado River, and thus the water used for irrigation and drinking, was contaminated with perchlorate that originated from a production facility in Nevada [16]. Perchlorate is a water-soluble and highly persistent environmental contaminant [17] that acts as an endocrine disruptor by outcompeting iodide at the sodium-iodide symporter of the thyroid gland, leading to hypothyroidism [18]. Perchlorate-induced hypothyroidism poses a particular risk during early development and has been linked to a significantly altered thyroid status in Yuma neonates [16]. In addition to affecting thyroid health, our research group discovered that perchlorate disrupts sexual development in laboratory animal models [19-23] and may therefore be a factor influencing the development of certain human reproductive problems. The animal model work also revealed that perchlorate can act as an obesogen, and therefore, it may play a role in the current obesity epidemic [24,25]. Because obesity in Hispanic immigrant populations is a high public health priority [26], this element of the proposed project may have strong implications for obesity-related programs.

Yuma County is often referred to as “the lettuce capital of the United States” and is a national source of winter vegetables (lettuce, cabbage, broccoli, kale, radish, and yellow squash), melons (cantaloupe, honeydew, and watermelon), citrus fruits (oranges and grapefruit), and dates. All these crops are a potential source of perchlorate exposure in the US food supply chain. The economy of the Yuma area is based upon year-round agriculture with intensive use of pesticides. Therefore, this project also focuses on exposure to toxic metals used in pesticides currently or in the past, such as mercury, lead, manganese, and copper. These metals are potent neurotoxicants when present at high concentrations and some also disrupt the endocrine system. Collectively, the population mix and environmental conditions in Yuma County provide a unique

opportunity to investigate the health consequences of exposure to perchlorate, toxic metals, and pesticides.

In summary, Yuma is a medically underserved community that has historically experienced elevated exposure to perchlorate [16] and pesticides [27]; consequently, residents may face a higher-than-average risk of exposure but have poor access to resources and information to address this risk. The cultural diversity of Yuma County, combined with extensive intermediate-term residency (snowbirds) and the proximity of the United States–Mexico border, makes this a scientifically significant venue for implementing the protocol explained in this paper.

Figure 1. Map of the study region.

This pilot study was designed and conducted following a series of consultations with our community partners. We committed to examine the relationships between contaminant exposures and consequent health outcomes. We hypothesize that individuals with greater exposure to perchlorate will be more vulnerable to thyroid disorders, reproductive disorders, and obesity. Moreover, individuals with greater exposure to toxic metals have higher chances of experiencing neurological disorders. These hypotheses will be subsequently tested and published in later manuscripts. The current paper explains the feasibility of a community-engaged approach to field research in difficult-to-access populations and illustrates the success of the sampling methodology used to achieve our research aims.

Methods

Community-Approved Research Aims

The NAU investigators and the leadership from our community partners participated in a series of consultations about the purpose, design, and research protocols of this study. The study addresses community priorities regarding health equities for the Yuma region.

Community-Endorsed Aim

This pilot research protocol focused on comparing patients with thyroid disorders (n=147) that may be due, in part, to perchlorate exposure, with participants (n=176) having no known history of thyroid disease. Participants provided urine samples for the quantification of perchlorate, hair samples for the quantification of toxic metals, and blood samples for the quantification of thyroid and stress hormones. We will statistically model the associations between perchlorate and metal concentrations in

individuals with their health outcomes, degree of endocrine disruption, and variables such as residency patterns, economic status, occupation, ethnicity, gender, and age.

Chart Audits

The staff at the YRMC and RCBH reviewed the medical charts of patients to determine their eligibility for either the clinical group or the control group using a prescreening tool. The prescreening tool was designed to be culturally and linguistically appropriate by the research team in collaboration with community partners and was administered by the members of the research team. Participants were recruited based on the following eligibility requirements: over 18 years of age, year-round resident of the Yuma service region, and either experiencing a health problem under study (thyroid disease) or having no known history of thyroid diseases. A research team member then engaged with potential participants in either English or Spanish in the informed consent process. Participants voluntarily consented to participating in the research. Additional control participants from the community were recruited through CSF. The control participants had no record of thyroid disease. All participants were able to understand the informed consent process and the content of the survey.

Recruitment

The recruitment, enrollment, and data collection process followed basic community-engaged research principles [28] and will follow these principles in terms of the analysis and dissemination of results at the individual, community, and scientific levels. Recruitment and data collection were accomplished by bilingual personnel from the YRMC, RCBH, and CSF. Survey questions were jointly vetted by community and university investigators, and feasibility measures were used to determine the possibility of scaling up the project.

Participant recruitment occurred at the following three sites: (1) YRMC: It is a not-for-profit health care system located in the city of Yuma, which is geographically centered between Phoenix and San Diego. The organization has 24/7 hospitalists and intensivists, more than 2000 employees, over 450 medical staff, and a family and community residency program accredited by the Accrediting Council for Graduate Medical Education (ACGME). The organization provides a comprehensive range of medical services at its main campus and facilities throughout the Yuma area. (2) RCBH: It has fully integrated behavioral and primary care rural health clinics in Somerton and San Luis, including an urgent care and a diagnostic medical facility. RCBH is the regional center for the Western Area Health Education Center, with offices in Yuma, La Paz, and Mohave Counties. RCBH also operates vocational technical schools called the “College of Health Careers” throughout its service area. (3) CSF: It was established in 1999 by a group of farmworkers who intended to address social, health, and environmental justice issues for migrant and seasonal farmworker families in Arizona. CSF is a 501(c)(3) not-for-profit, grassroots advocacy organization with a mission to promote self-sustainability for farmworker families, new immigrants, and low-to-moderate income individuals by providing and facilitating access to health care, behavioral health and social services, housing rehabilitation, counseling, immigration services, citizenship assistance, environmental education, and workforce development.

All participants completed the informed consent process in their language of choice. The informed consent included information on the purpose of the study, a request for access to participant health histories and medical records, and a brief survey. Following the informed consent process, in a single visit to the YRMC or RCBH, each participant was weighed and measured for BMI, and sampled for blood, urine, and hair. Whole blood (5 mL) was collected by venipuncture into a heparinized vacutainer and separated into plasma and cellular fractions via centrifugation; the plasma fraction was frozen and maintained at -80 ºC until assayed for hormone concentrations. Each participant also provided a single urine sample, which was stored at -20 ºC until analyzed for perchlorate concentration. Hair (~150 mg) was clipped close to the surface of the skin at the back of the neck using scissors and stored in paper envelopes at room temperature for later analysis of metals and metalloids. All sampling followed established quality assurance/quality control measures including the use of chain of custody and bio-banking forms.

Survey Development

All consented participants completed a survey that included demographic data (age, gender, income, household composition), sources of drinking and cooking water, social determinants of health, a health status screen (eg, family history of diseases of the thyroid and reproductive organs), health care utilization information and access to care, and occupation and occupational exposure to environmental contaminants. This personal and population health information is being modeled with the measured levels of contaminants, endocrine function, and health status as determined from electronic medical records. Together, the findings will result in a clearer picture of the population health effects of contaminants and reveal the potential for developing precision medicine capabilities for the population.

Electronic Medical Record Audit

For those individuals who consented to sharing their medical records, we transferred the data housed in NAU’s high-security server (in compliance with the Health Insurance Portability and Accountability Act [HIPAA] and National Institute of Standards and Technology [NIST]) through a Redcap (HIPAA-compliant) data transfer protocol. All data were de-identified prior to analyses, which were conducted behind the firewall of the secure information technology (IT) server.

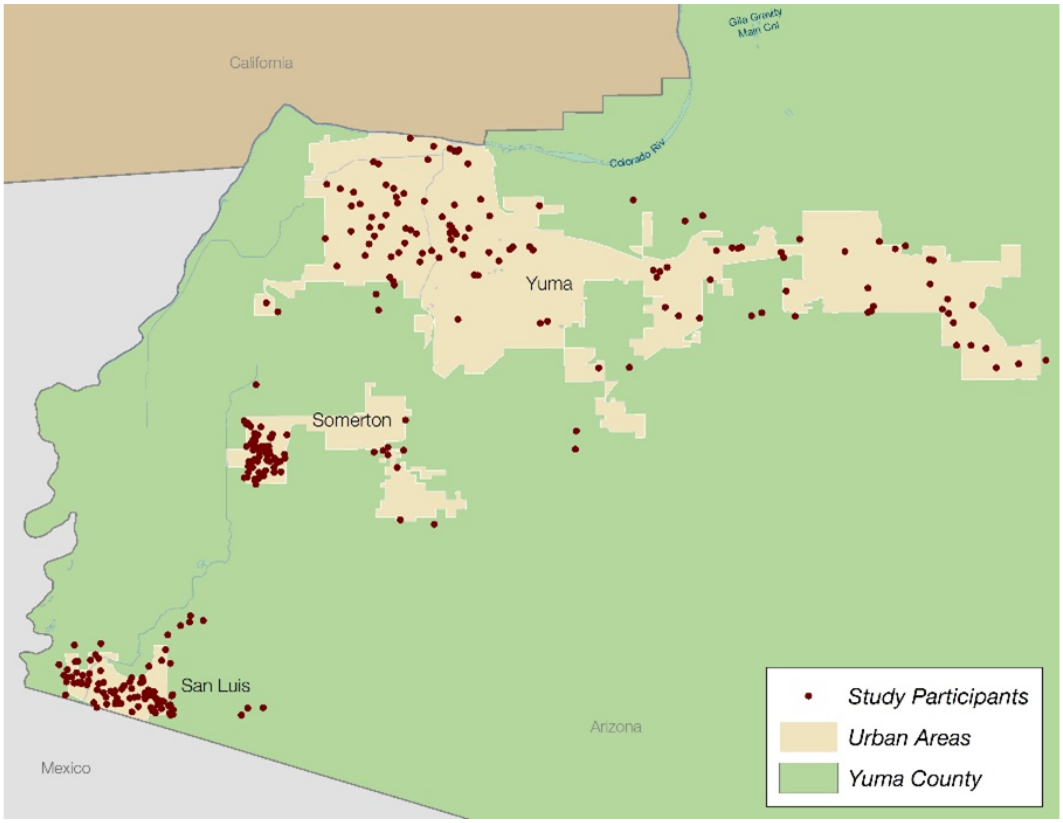
Data from medical records were extracted through manual chart audits. The primary variables of interest comprised physical health diagnoses including thyroid conditions, cancers, obesity, diabetes, and hypertension; mental health diagnoses including anxiety, depression, sleep disorders, substance use disorders, and attention deficit disorders; medication history; and BMI.

Results

We determined the feasibility of our recruitment and data collection process. We recruited, consented, enrolled, and surveyed 323 adults residing in Yuma County (Figure 2).

Among them, 147 residents were patients from either the YRMC or RCBH with a primary diagnosis of thyroid disease, including hyperthyroidism, hypothyroidism, thyroid cancer, or goiter. The remaining 176 participants were from the general population but with no history of thyroid disorder. We recruited 22 males and 123 females for the clinical sample, and 46 males and 132 females for the community sample. Most participants were Whites (251/323, 78%), and Hispanics or Latinos (286/323, 89%).

Figure 2. Geographic distribution of participant residences.



The participant demographics are presented in Tables 1 and 2. The clinical and community samples differed somewhat in terms of the percentage of male and female respondents, and the overall age profile of the samples, but were congruent in terms of the time of residence in the Yuma region, residence types, and household sizes. More women participated in the study than men (Table 1); nearly all participants had lived in Yuma County for over 5 years (Table 2), and participants in the clinical sample were older (mean 53.27; SD14.29) than participants in the community sample (mean 44.89; SD 15.25). Among the participants enrolled in the clinical sample (ie, those with documented thyroid disorders), over 50% (92/145) reported a diagnosis of hypothyroidism. Additionally, obesity (169/318, 53%), high cholesterol (132/323, 41%), hypertension (107/323, 33%), diabetes (87/323, 27%), depression (73/321, 23%), and anxiety (68/320, 21%) were the most frequently cited chronic conditions across all participants. Although most participants reported having health care insurance (281/323, 87%) and access to medical care (307/323, 95%), self-reported health statuses were more variable with approximately half of the participants indicating “fair” to “poor” health.

Although there were slight variations in the participants’ marital status (married=197/323, 61%) and residence type (own homes=266/323, 82%), the size of the household and number of children ranged between 1 to 22 and 0 to 11, respectively. Most participants had completed high school (191/323, 59%) with approximately one-third reporting a college or postgraduate degree (98/323, 30%).

Over half of the participants were currently employed (170/323, 53%), with 14% (46/323) reporting that they worked as a farmer, rancher, or agricultural worker in the last year and 17% (55/323) reporting that they were exposed to pesticides in the workplace. The most cited occupations included homemakers (ama de casa) (87/323, 27%), medical assistants (21/323, 8%), students (13/323, 4%), and farmworkers (11/323, 3%). Annual household incomes ranged from less than $5,000 to over $70,000 with most participants earning between $10,000 and $40,000.

Table 1. Clinical and community sample numbers by gender (N=323).

Sex	All, n (%)	Clinical, n (%)	Community, n (%)
Male	68 (21)	22 (15)	46 (26)
Female	255 (79)	123 (85)	132 (74)
Total	323	145	178

Table 2. Clinical and community sample numbers by residence time in Yuma County.

Sample	<6 months, n (%)	6 months to 1 year, n (%)	1 to 3 years, n (%)	3 to 5 years, n (%)	>5 years, n (%)
Community (N=178)	1 (0.6)	2 (1.1)	8 (4.5)	6 (3.4)	161 (90.4)
Clinical (N=145)	1 (0.7)	1 (0.7)	3 (2.1)	4 (2.8)	136 (93.8)

One key element of our protocol was to assess the feasibility of our community-engaged design and recruitment within the context of the need for systematic public health and population health data collection and analysis. We followed a community-engaged (modified community-based participatory research [CBPR]) logic model described by Belone et al [29] to increase our understanding of the factors that contribute to successful partnerships, including contexts, group dynamics/equitable partnerships, intervention, and research and outcomes. The full description and results of this community-engaged approach are forthcoming, but the key elements supporting the overall conclusion of successful engagement are summarized in Table 3, obtained from our ongoing evaluation of the protocol.

One of the primary areas of assessment was the overall partnership "health" measure provided by ongoing monitoring of the stability of the developed relationships and group dynamics focused on common goals. A critical area of process evaluation was monitoring community and researcher views on appropriate levels of collaborative research development (Table 3). The key elements that constituted the bulk of the process evaluation for the project were monitoring community and researcher views on appropriate levels of collaborative research development, especially in the areas of "context," "group dynamics," and "research processes," as well as determining the level of satisfaction with the dissemination of findings and relevance of the primary outcomes for the research project from community and researcher perspectives. Although the overall dissemination is still in process for the partner and scientific communities, our assessment of the impact is consistently positive.

Table 3. Key elements of successful engagement with community partners.

Key element	Illustrative quotes from community partners
Context: This dimension focuses on factors that influence partnerships, including historical contexts of trust/mistrust between universities and communities, the salience of health issues to the community, and the capacity and readiness to engage in a project.	Community priorities and salience of health issues – *-We were interested because it discussed the environment and how it might be impacting you.* *- I was interested in participating because of how the findings could inform us about the health and well-being of our community.*
Group dynamics: This dimension focuses on relationships, the partnering process, and the importance of structural agreements among partners to assure community benefits. Benefits might include increased capacity in community leadership and in research performance.	Partnership length and trust – *- We had been working with members of the NAU[a]team for years and knew them from involvement in the ABRC[b]advisory board/steering committee.* Staff and care coordinators appreciated that one team member delivered the project introduction in Spanish. *Listening to each other and respecting each other, as equal partners and valuing the information that each brings makes a big difference.* Shared responsibility - The division of labor fell out naturally. CSF[c], the advocacy organization for the farmworkers, primarily recruited farmworkers, whereas the hospitals (YRMC[d], RCBH[e]) recruited patients and collected clinical data and samples; NAU researchers conducted the laboratory analytical work and statistical analyses.
Intervention/research: This dimension includes the extent to which community partners have a voice in terms of how their cultural norms and knowledge are integrated into the research in designing interventions, methods, or instruments or the extent of bidirectional translation, implementation, and dissemination.	Partnership synergy – *Really being open with each other, listening to each other and respecting each other as equal partners and valuing the information that each brings again that makes a big difference...throughout the years, I learned yes you guys know a lot about research and different things but you don't know about my community, you don't know about the things that we live on a daily basis, the challenges we face so that makes me an expert on my own issues and then I can speak up and be at the table speaking to you with the same level of authority.*
Outcomes: This dimension ranges from intermediate systems (i.e., policy and capacity changes, power relation changes, sustainability, and increased cultural renewal) to improved health and social justice outcomes.	Capacity to create desired community changes – *I learned so much about the process of research and how heavy metals and materials could affect the health of the community.* *This project has the potential to improve the health of individuals in the community. We will be able to apply the findings of this research in our work at the hospital.* *Knowing sources and causes can help prevent poor health. They need tools and choices. We need to empower individuals. If our community is exposed to things and they can do something to change it, we need to give them choices.*

[a]NAU: Northern Arizona University.

[b]ABRC: Arizona Biomedical Research Commission.

[c]CSF: Campesinos Sin Fronteras.

[d]YRMC: Yuma Regional Medical Center.

[e]RCBH: Regional Center for Border Health.

Discussion

This pilot study lays the groundwork for future research designed to reduce contaminant exposures and health disparities of Yuma residents. Based on a community engagement model, we have committed to measuring the concentration of perchlorate in urine samples, measuring toxic metals in hair samples, quantifying a variety of hormones in blood samples, and comparing these findings with medical records and self-disclosure health surveys from each of the individuals recruited. We are statistically modeling the associations between the concentrations of the contaminants in individuals and their health outcomes, degree of endocrine disruption, and variables such as residency patterns, economic status, occupation, ethnicity, gender, and age. The ongoing collaboration with our community partners has allowed relatively rapid data collection with strong feasibility measures, as noted in our preliminary results described above. Establishing the levels of exposure to environmental toxicants in the Yuma region will allow us to examine the relationships between contaminant concentrations and adverse health outcomes. Developing a locally available animal model for testing the hypotheses related to contaminant

concentrations and health outcomes will potentially lead to future translational studies and evidence-based public health policy development. Additionally, this pilot project was intended to improve research capacity in a community-engaged framework for border populations, and our process education measures support this endeavor.

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Conflicts of Interest

None declared.

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Abbreviations

ACGME: Accrediting Council for Graduate Medical Education
CBPR: community-based participatory research
CHER: Center for Health Equity Research
CSF: Campesinos Sin Fronteras
HIPAA: Health Insurance Portability and Accountability Act
IT: information technology
NAU: Northern Arizona University
NGOs: nongovernmental organizations
NIST: National Institute of Standards and Technology
RCBH: Regional Center for Border Health, Inc.
YRMC: Yuma Regional Medical Center

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Protocol

Cyberbullying Among Traditional and Complementary Medicine Practitioners in the Workplace: Protocol for a Cross-sectional Descriptive Study

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Abstract

Background: Cyberbullying is becoming prevalent among health care professionals and may cause a variety of mental health issues. Traditional and complementary medicine practitioners remain an important pillar of the health care system in Malaysia.

Objective: This paper presents a study protocol for an online survey (Cyberbullying Among Traditional and Complementary Medicine Practitioner [TCMPs]) that will collect the first nationwide representative data on cyberbullying behavior among traditional and complementary medicine practitioners in Malaysia. The objectives of the survey are to (1) evaluate the cyberbullying behavior among traditional and complementary medicine practitioners in Malaysia, (2) identify sociodemographic and social factors related to cyberbullying, and (3) evaluate the association between cyberbullying behavior, sociodemographic, and social factors.

Methods: A snowball sampling strategy will be applied. Traditional and complementary medicine practitioners who are permanent Malaysian residents will be randomly selected and invited to participate in the survey (N=1023). Cyberbullying behavior will be measured using the Cyberbullying Behavior Questionnaire (CBQ). Data on the following items will be collected: work-related bullying, person-related bullying, aggressively worded messages, distortion of messages, sending offensive photos/videos, hacking computers or sending a virus or rude message, and threatening messages about personal life or family members. We will also collect data on participants' sociodemographic characteristics, social factors, and substance abuse behavior.

Results: This cross-sectional descriptive study was registered with Research Registry (Unique Identifying Number 6216; November 05, 2020). This research work (substudy) is planned under a phase 1 study approved by the Research Management Centre, Xiamen University Malaysia. This substudy has been approved by the Research Ethics Committee of Xiamen University Malaysia (REC-2011.01). The cross-sectional survey will be conducted from July 01, 2021, to June 30, 2022. Data preparation and statistical analyses are planned from January 2022 onward.

Conclusions: The current research can contribute to identify the prevalence of workplace cyberbullying among Malaysian traditional and complementary medicine practitioners. The results will help government stakeholders, health professionals, and education professionals to understand the psychological well-being of Malaysian traditional and complementary medicine practitioners.

Trial Registration: Research Registry Unique Identifying Number 6216; https://tinyurl.com/3rsmxs7u

International Registered Report Identifier (IRRID): PRR1-10.2196/29582

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KEYWORDS

cyberbullying; traditional medicine; workplace; practitioners; medical professional

Introduction

Background

Adverse consequences of cyberbullying behavior in the workplace are well-documented [1,2]. The negative effects of cyberbullying behavior are harmful or aggressive communications [3], expressing negative emotions [4], and e-harassment [5]. Cyberbullying is a severe threat to the workplace that results in job dissatisfaction, mental strain [6], and perceived organizational injustice, which in turn increases the perceived job stress that eventually results in cyberbullying [3]. Cyberbullying is defined as a repetitive negative (harmful) behavior by a person (perpetrator) to intentionally hurt an individual (affected party) through technological means, such as SMS text messages or email. In most cases, this involves an imbalance of power between the perpetrator (usually anonymous) and the affected individual. The perpetrator's action is generally considered more severe in the public domain than in the private domain [7].

The prevalence of cyberbullying in the workplace has raised some serious global public health concern. A Swedish survey estimated the prevalence of workplace cyberbullying to be 9.7% [8], based on Leymann's cut-off criterion [9]. Gardner et al [10] performed a study on predictors of workplace bullying and cyberbullying in New Zealand, and found that among the total study participants (N=826), 15% (n=123) experienced bullying and 2.8% (n=23) experienced cyberbullying (2.8%) within the last 6 months. Workplace bullying in different countries among different staff members have been reported in many studies; for example, the prevalence of bullying among hospital employees in Austria was reported to be 26.6% [11], among university employees in Finland to be 16.9% [12], and among health and welfare managers in Norway to be 8.6% [13]. Bullying in workplace is also reported from studies conducted in Ireland (16.9%) [14] and Portugal (33.5%) [15,16]. By contrast, there is very limited research on workplace cyberbullying.

Cyberbullying behavior has psychological effects on the affected individual, such as social anxiety [17], emotional distress [18], and depression [19]. However, the exact biological mechanism underlying cyberbullying remains unknown. Cabrera et al [20] reported on the role of cortisol in cyberbullying behavior, with the level of this hormone being higher among affected individuals due to increased activity of the hypothalamic–pituitary–adrenocortical axis, which plays an important in the management of stress.

The World Health Organization has expressed concern with the prevalence of bullying among students and employees globally [21-23]. Recently, The United Nations Educational, Scientific, and Cultural Organization and the Government of Ireland, Dublin City University, have developed a partnership to increase institutional capacities on cyberbullying awareness through knowledge sharing and collaborative work [24]. The International Labour Organization sets benchmarks for defining, preventing, and responding to violence at the workplace and recognizes bullying under "aggressive behavior" [25].

Objectives

Using the workplace Cyberbullying Behavior Questionnaire (CBQ), this study aims to provide the first nationally representative data on cyberbullying behavior among traditional and complementary medicine practitioners in Malaysia. Objectives of the CBQ survey are to (1) evaluate the cyberbullying behavior among traditional and complementary medicine practitioners in Malaysia, (2) identify sociodemographic and social factors related to cyberbullying, and (3) evaluate the association between cyberbullying behavior, sociodemographic, and social factors. In the following sections, we discuss the research design and methods and present an overview of methodological challenges, strengths, and limitations related to the study design and sampling strategy.

Methods

Study Design

This is a cross-sectional descriptive study performed using the Cyberbullying Behavior Questionnaire (CBQ and its short version [CBQ-S]), which was administered to traditional and complementary medicine practitioners in Malaysia. The questionnaire includes 32 questions (see Multimedia Appendix 1) in a closed-ended question format. The standardized checklist for the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations was used to ensure that all the elements recommended were addressed within this section to participate in the study, including a link to the platform where all the information related to the project, its objectives, and expected outcomes can be found [26]. Traditional and complementary medicine practitioners will receive an online invitation using SurveyMonkey to participate in the study, including a link to the platform where all the information related to the project, its objectives, and expected outcomes can be found [27]. The online survey will follow the CHERRIES guideline [28] to maintain the quality of the web-based survey. Malaysia is a highly digitally networked nation, with nearly 90% of households using the internet, mostly through mobile broadband plans on smartphones. The rationale to conduct an online survey is the ease of internet availability in Malaysia [29].

Study Population

Individuals were selected for study participation according to the following inclusion criteria: traditional and complementary medicine practitioners working in the public and private sector in Malaysia; and currently practicing in any one of the practice areas recognized by the Ministry of Health Malaysia (Traditional Malay Medicine, Traditional Chinese Medicine, Traditional Indian Medicine, homeopathy, chiropractic, osteopathy, and Traditional Islamic Medicine).

All eligible participants will be contacted through official Facebook pages of the Malaysian Society for Complementary

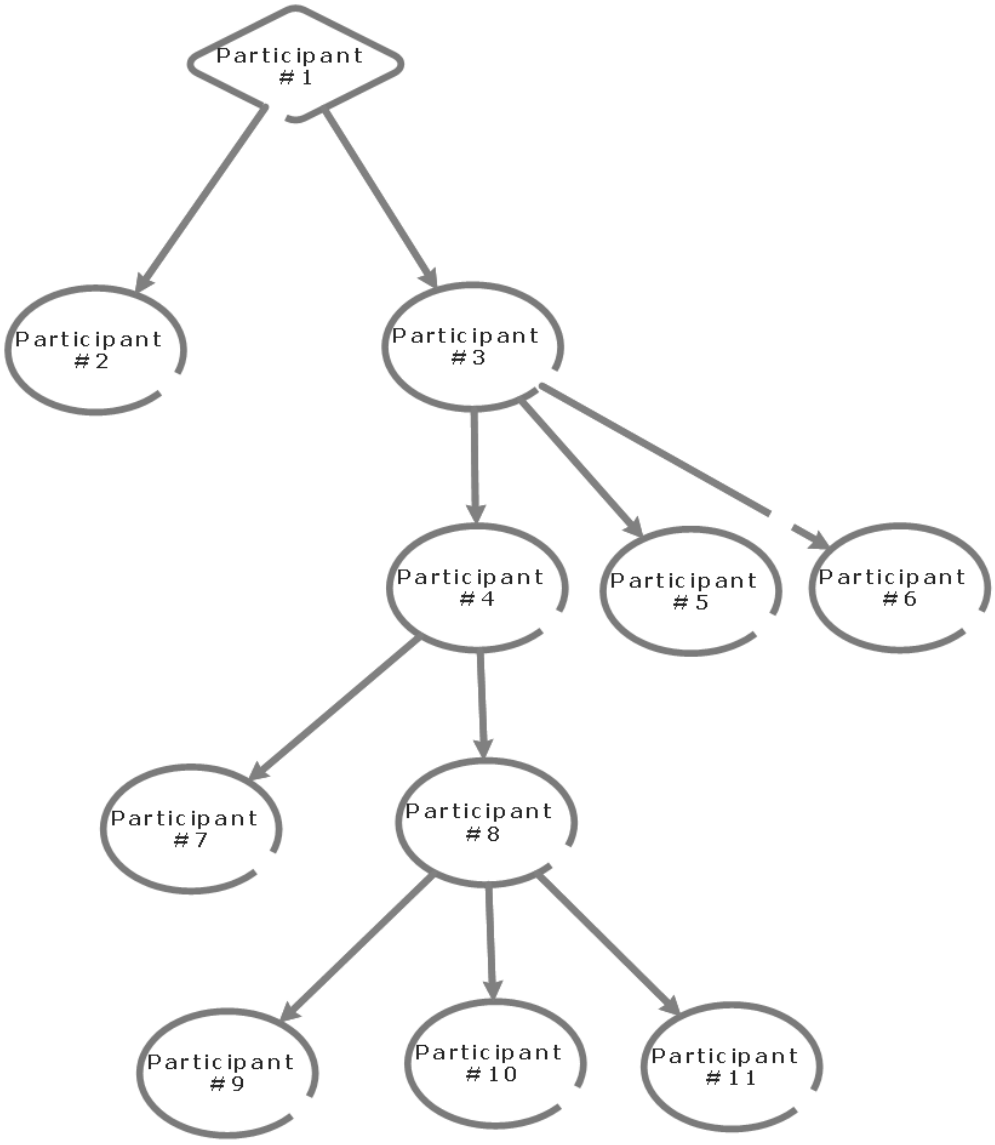
Medicine, Federation of Chinese Physicians and Acupuncturists Associations Malaysia, Malaysian Chinese Medical Association, TCM & Western Naturopathic Malaysia, Traditional Malay Medicine Association, Majlis Perubatan Homeopathy Malaysia, Association of Chiropractic Malaysia, Malaysia Osteopathy Association, and Malaysian Health Qigong Association.

Individuals were excluded from study participation according to the following exclusion criteria: not traditional and complementary medicine practitioners in one of the recognized practice areas and practitioners who did not give consent.

Sampling Strategies

Using traditional sampling strategies to recruit hard-to-reach population faces several hurdles. In this regard, a snowball sampling method is valuable. It is a technique to find research participants with the help of name suggestions from a single participant: initially, 1 participant is identified and then a chain of participants related to the first one is identified. This remains one of the valuable sampling strategies in descriptive studies [30]. We will use snowball sampling on the Facebook pages of official traditional and complementary medicine practitioner associations (Figure 1). A list of well-known associations is mentioned above (see inclusion criteria).

Figure 1. Overview of the snowball sampling strategy.



Sample Size

Traditional and complementary medicine practitioners will be selected from both public and private sectors in Malaysia. The total number of traditional and complementary medicine practitioners in Malaysia is approximately 15,000 (data as of 2011) [31]. However, no data are available on how many practitioners are serving in the general and urban population. Because of the COVID-19 pandemic, we cannot directly contact the practitioners. Therefore, we will conduct a nonprobability snowball sampling involving 1023 participants (3% precision and 95% confidence level).

Data Protection and Ethical Approval

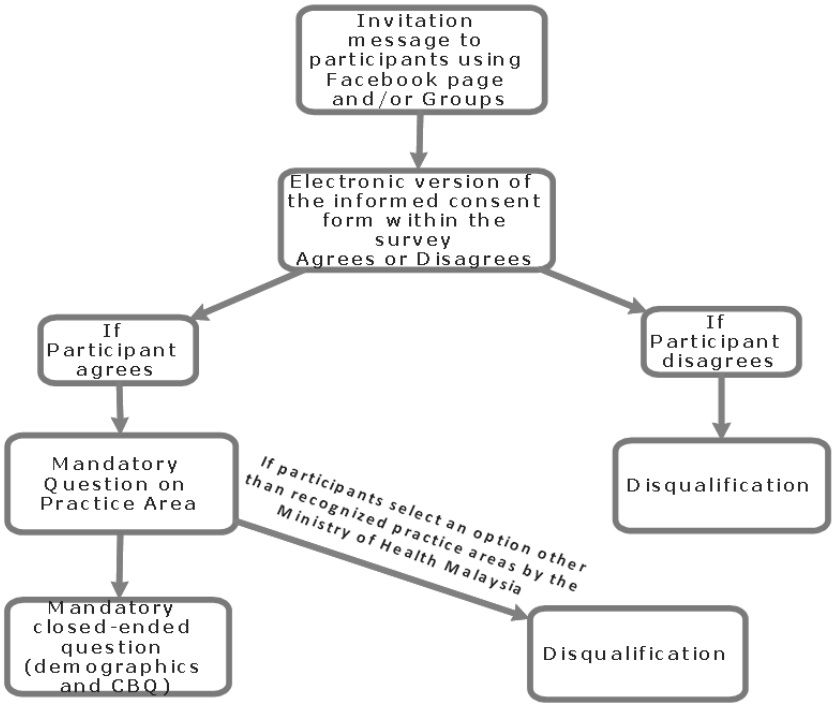
All data are stored in a password-protected electronic format on OneDrive cloud (Microsoft). To ensure participant

anonymity, the survey will not contain any information that will personally identify the participants. The study results will be used for research purposes only. This study will be conducted according to the Declaration of Helsinki and the guidelines of the National Committee for Clinical Research [32]. The study has been approved by the Research Ethics Committee of Xiamen University Malaysia (REC-2011.01). Data collection is expected to happen between July 01, 2021, and June 30, 2022. Duration of the online survey is 15-20 minutes. All participants will be given a study information sheet. An electronic version of the informed consent form will be made available within the survey (SurveyMonkey [27]).

Data Collection and Data Handling

Participants will use SurveyMonkey to accept or decline participation. Participants will be invited via Facebook pages of medical associations. There will be a reminder every 2 weeks to follow-up on the status of the questionnaire with participants. Figure 2 presents an overview of the study flow and informed consent procedure.

Figure 2. Overview of the study flow and informed consent procedure.



Measurements

The items in the questionnaire were chosen according to previous studies by Einarsen et al [33], Farley [34], and Forssell [8,35] and aimed for a comprehensive assessment of all aspects of workplace cyberbullying among traditional and complementary medicine practitioners in Malaysia (Table 1). There will be no public involvement in the design of this study. The results will be presented in scientific meetings worldwide and published in peer-reviewed open-access journals to disseminate the outcomes. The Cronbach α values for CBQ and CBQ-S in the study by Forssell et al [35] were .76 (Swedish sample) and .95 (American sample). The Negative Acts Questionnaire-Revised (NAQ-R) has a Cronbach α value of .90. Therefore CBQ, CBQ-S, and NAQ-R are reliable and valid instruments for the evaluation of workplace cyberbullying [8,33].

Table 1. Overview of the topics and measures applied in the Cyberbullying Behavior Questionnaire (N=31 items).

Topic/parameter and measure	Source	Number of items	Assessing objectives[a]
Sociodemographics			
Sex, age group, and current relationship status	N/A[b]	3	2
Education			
Level of education	N/A	1	2
Socioeconomic status			
Household income	N/A	1	2
Health status			
Substance abuse	Pattern of Substance and Drug Misuse Among Youth in Malaysia [36]	1	2
Geography			
Working sector, location (city)	N/A	2	2
Working status			
Community participant work, current job level, practice area	Official Portal of Traditional and Complementary Medicine Division [37]	3	2
Cyberbullying Behavior Questionnaire			
Work-related bullying, person-related bullying	Negative Acts Questionnaire-Revised [33]	11	1 and 3
Aggressively worded messages, distortion of messages	The Measurement and Impact of Workplace Cyberbullying [34]	2	1 and 3
Posted offensive photos/videos, hacking computer or sending virus or rude message, attaching or threatening messages about personal life or family	Forssell Cyberbullying Behavior Questionnaire [8]	7	1 and 3

[a]Objective 1: To evaluate the cyberbullying behavior among traditional and complementary medicine practitioners in Malaysia; objective 2: To identify sociodemographic and social factors related to cyberbullying; and objective 3: To evaluate the association between cyberbullying behavior, sociodemographic, and social factors.

[b]N/A: not applicable.

Data Management, Data Preparation, and Data Analysis

Descriptive statistics and exploratory structural equation modeling will be used to assess sociodemographic and social factors related to cyberbullying and evaluate the association between cyberbullying behavior, sociodemographic, and social factors. Statistical analysis will be performed using SPSS (version 26) and SPSS AMOS/ADANCO (IBM).

Results

This cross-sectional descriptive study was registered with Research Registry (Unique Identifying Number 6216; November 05, 2020). This research work (substudy) is planned under a phase 1 study approved by the Research Management Centre, Xiamen University Malaysia, whose protocol has already been published [38]. This substudy has been approved by the Research Ethics Committee of Xiamen University Malaysia (REC-2011.01). Data preparation and statistical analyses are planned from January 2022 onward.

Discussion

This exploratory study will provide the first nationally representative data on workplace cyberbullying for traditional and complementary medicine practitioners in Malaysia. The data collected and analyzed will explore the relationship between workplace cyberbullying and social factors. A significant strength of the study is the use of a validated measurement tool (CBQ and CBQ-S), which is a combination of different instruments validated for different population groups (Swedish and American) [35]. Compared with the Copenhagen Psychosocial Questionnaire (COPSOQ III) [39], which encompasses a broad range of psychosocial aspects of modern work life, the CBQ possesses an excellent Cronbach α value of .95 when applied in an American population.

CBQ and CBQ-S are specifically administered to evaluate cyberbullying behavior in the workplace. Understanding the prevalence of cyberbullying is the first step in the formulation of evidence-based interventions for promoting the mental health of both perpetrator(s) and affected individual(s). Our sampling strategy has both strengths and limitations. Participants will be conveniently selected from the Facebook pages of various

professional associations of traditional and complementary medicine practitioners using the snowball sampling method [40]. The survey will also follow CHERRIES guidelines [28] for the design, obtaining of informed consent, development, survey administration, response rates evaluation, and analysis. Because of time constraints, it is not feasible to perform a nonresponder bias survey, which could help identify the factors associated with the lack of response [41,42].

The CBQ survey results will provide data to identify the prevalence of workplace cyberbullying among traditional and complementary medicine practitioners, identify a correlation between social factors and cyberbullying behavior, and guide the implementation of related interventions for traditional and complementary medicine practitioners in a Malaysian context. Data from this survey will help improve mental health strategies to promote mental health education among health care professionals.

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Authors' Contributions

YJK, LQ, and MSA conceptualized the study, formulated the methodologies, and are responsible for project administration and funding acquisition. MSA accomplished data curation and original draft preparation. MSA and YJK performed the review and editing of this protocol. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Cyberbullying Behavior Questionnaire.
[PDF File (Adobe PDF File), 219 KB - resprot_v10i8e29582_app1.pdf]

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Protocol

Developing a Risk Governance Framework on Radiological Emergency, Preparedness, and Response for Emergency Responders: Protocol for a Mixed Methods Study

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Abstract

Background: Risk governance involves processes and mechanisms to understand how risk decisions are taken and executed. This concept has gained a reputation over time as being essential for emerging comprehensive management that defines the success of an organization. While guiding documents that explain the use of risk management related to nuclear safety and security are available worldwide, few locally conducted studies have explained risk governance practices in areas where hazard usage is known, such as in radiological emergencies.

Objective: This paper describes a protocol that was used to determine several factors that influence emergency responders' perceptions toward radiological risk practices and visualize the risk radiological framework for emergency preparedness and response.

Methods: A mixed methods study with a convergent design was performed. A qualitative analysis was performed using a case study approach where 6 key informants were purposely sampled for in-depth interview, and a cross-sectional study involving a self-administered questionnaire was conducted among approximately 260 emergency respondents from national regulatory, research, and services organizations. NVivo (version 12, QSR International) was used to analyze the interview transcripts and emerging themes were identified through abductive coding. Simultaneously, multiple logistic regression analysis was used to determine significant predictors that form the equation model.

Results: The study is still underway. Qualitative findings were based on transcript-coding that informed the relevant thematic analysis, while statistical analyses including multiple logistic regression analysis measured the adjusted odds ratio of significant variables for the equation model. The study is expected to conclude in late 2021.

Conclusions: Important emerging themes and significant factors that are related to the emergency responders' perceptions regarding radiological governance practices were determined through the convergent design. This potentially facilitated the development of a plausible radiological risk governance framework. Furthermore, our results will provide key insights that can be used in future studies.

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emergency; preparedness; radiological; risk governance; risk practices

Introduction

Background

The philosophy of governance, existing since medieval times, has come a long way. Far from being perfect, practices have evolved from a simplistic stewardship theoretical approach to a more complex dynamic model and may continue to develop in parallel with globalization [1]. Despite its popularity in the corporate, business, and economic sectors in certain fields, the application of governance may not be well-known or is unrecognized. However, previous studies have shown that governance plays an integral part in numerous organizational managements and is considered the main foundation for organizational sustainability.

One particular area where governance is gaining popularity is within working sectors that use certain materials that are known to be hazardous to health and have the potential to cause disasters if not managed properly. For example, in the medical fraternity, the concept of governance has led to the development of a documented manual by the World Health Organization, entitled "Rapid Risk Assessment of Acute Public Health Events," which serves as a guide for a systematic process of rapid and defensible decision-making to deal with hazardous events of a biological or chemical nature and re-emerging diseases [2]. This manual also addresses multidisciplinary players and stakeholders in prevention and control, including effective communication to improve national preparedness. Similarly, this concept was adopted by Schmidt et al [3] for better and more effective management to combat challenges in vector-borne diseases. It has been observed that when governments or organizations develop new services in combatting disasters, other uncertainties such as financial risks, time risks, or psychological risks may arise and should be considered. Conscious management of the transparent process can promote a more successful service-related outcome [4].

In the context of health and safety, the concept of risk management involves valued judgments that reflect the probability and consequences of the occurrence of an event [5], which is a common misnomer to risk governance. Under these circumstances, risk management does not equate to risk governance as it may have relatively minimal focus on other areas such as financial and legal sectors and interaction of the Internet of Things, which rely on a clear and robust code of practice for the entire management [6]. Therefore, the term "risk governance" has been explicitly described by the International Risk Governance Council as a nonprofit organization that facilitates a better understanding of risks and their scientific, political, social, and economic contexts and translates the core principles of governance to the context of risk and risk-related decision-making of an organization [7,8].

To establish a system in radiological emergency preparedness and response (EPR), the International Atomic Energy Agency (IAEA) has developed a few documents that recommend what forms the basis of and the requirements for an adequate level of preparedness and response for a nuclear or radiological emergency. In addition, these documents have also described the necessary implementation of specific safety requirements; for example, guidelines on a coordinating mechanism and communicating with the public in emergency preparedness and response considering certain circumstances. All these can be seen as the gold-standard guide for any of the IAEA member states to develop its own radiological governances that encompass all the requirements. However, local studies have mainly focused on the characteristics of EPR itself from an operational perspective, but few studies have implemented a governance perspective.

It is currently speculated that the available local radiological framework focuses on the legislative and organizational components with minimum information on risk practices and community involvement. It was also revealed that under the Radiological Emergency Preparedness and Response Training and Capability Development in Southeast Asia, certain countries still had issues related to radiological EPR, where recommendations were made to improve the integration of radiological responses into an all-hazards approach and related interagency interoperability [3].

Thus, having a proper framework encompassing relevant factors, areas, and people is key to success especially in radiological EPR, and it is speculated that such studies have been deemed necessary to evaluate local governance practices that are in place for radiological EPR management. Here we describe a protocol used to determine relations among sociodemographic, occupational, cultural, social, ethical values, decision-making, and trust factors that influence emergency responders' perceptions toward radiological risk practices. Additionally, this protocol would help researchers develop a more customized radiological risk governance framework.

Underpinning Theory

Two major components that constitute governance are system and people; accordingly, this study adopted 2 types of theoretical models. The first model is the Social Action Theory mooted by one of the pioneer sociologists Max Weber in the early 1900s, which examines the actions of people in the context of meanings assigned to them and their relationship with the actions of others. This is important in determining one's perception of risk as it is based on subjective assessment of an individual's frame of reference developed over time, with respect to risk management. This influences the evaluation of the probability of a specified type of accident occurring and how concerned a person is with the consequences.

The second theory is based on the risk governance framework developed by the International Risk Governance Council—a Switzerland-based private, independent, nonprofit foundation established in 2003—and represents a system that uses the following 5 elements [9]:

1. Risk preassessment: early warning and "framing" of risk to provide a structured definition of the problem to describe how it is framed by various stakeholders and how it can be managed optimally.
2. Risk appraisal: combining a scientific risk assessment (of the hazard and its likelihood) with a systematic concern assessment (of public concerns and perceptions) to provide a knowledge base for subsequent decisions.

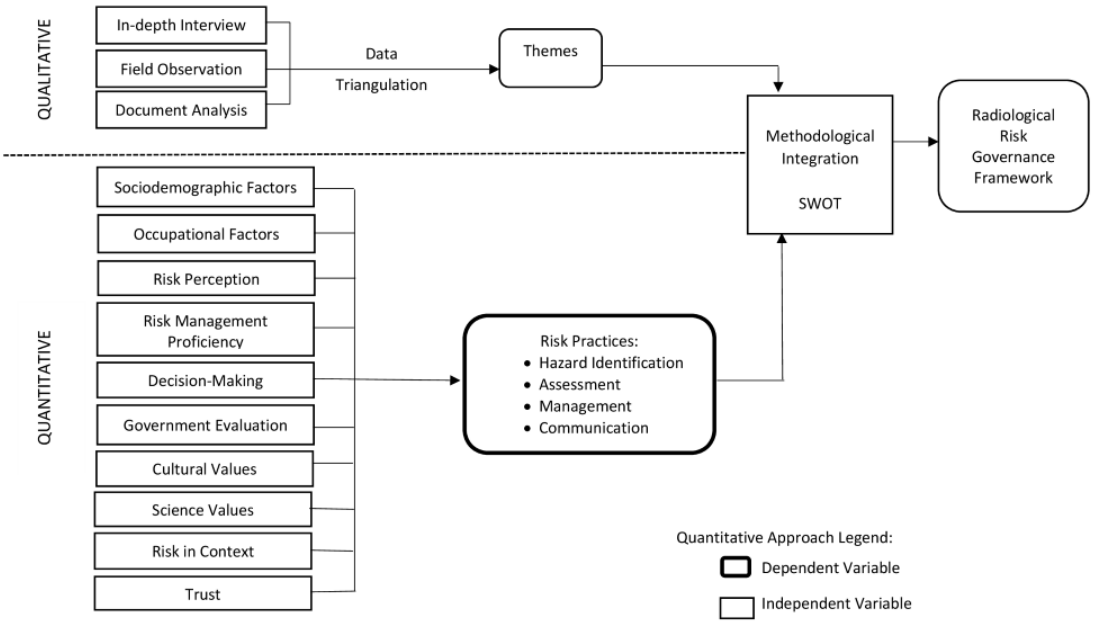
3. Characterization and evaluation: scientific data and a detailed understanding of risk-affected societal values are used to evaluate the risk as acceptable, tolerable (requiring mitigation), or intolerable (unacceptable).
4. Risk management: actions and remedies required to avoid, reduce, transfer, or retain the risk.
5. Risk communication: how stakeholders and civil society understand the risk and participate in the process of risk governance.

The use of these 2 theories provided insight into the research conceptual framework.

Methods

This was one of the earlier proposed local studies that is focused on radiological risk governance practices, and the application of both quantitative and qualitative assessments is important to further support the evaluation of risk governance that is in place for the management of radiological technology. Furthermore, the philosophical assumption of mixed methods studies is often referred to as the third methodological approach that has attracted both academics and researchers who were primarily either positivists or interpretivists [10]. Based on the theories that were considered, the conceptual framework of our study is shown in Figure 1.

Figure 1. Conceptual framework of the study. SWOT: strengths, weaknesses, opportunities, and threats.



Klang Valley was selected as the study location as it is the prime area where most radiological applications and activities are concentrated and where radiological EPR will be activated (if it occurs). Table 1 illustrates the mixed methods approach in terms of its aim, design, extension, sample size, instrument to be used, analysis, and interpretation.

The selection of respondents/informants was based on the following criteria where those aged ≥18 years old, those working as emergency responders at an organization, those involved in radiological governance policy-/decision-making, or those having experience related to radiological risk governance were eligible to participate in the study. In contrast, those who were absent during study data collection (eg, international travel/training) and those who refused to participate in the study were excluded.

Table 1. Characteristics of the mixed methods approach.

Characteristics	Quantitative research	Qualitative research
Aim	Provide an understanding of the research questions	Proves research hypothesis
Design	Cross-sectional study	Case study approach
Extension	Breath view	In-depth view
Sample size	Sample size is calculated using a sample size formula for a number to estimate prevalence on the basis of proportion [11] and with a known (finite) population of 500 emergency responders within the study area [12]. Total=260 respondents.	Generally smaller; until achieving a saturation point
Sample selection	Simple random sampling	Purposely involving the 7 governmental agencies
Instrumentation	Standard questionnaire	In-depth interview
Analysis and interpretation	Through statistical analysis including bivariate analysis as well as correlation and prediction using multiple logistic regression analysis	Identify research themes
Reporting guidelines or protocol	Strengthening the Reporting of Observational Studies in Epidemiology checklist	Consolidated criteria for reporting qualitative research checklist

The qualitative approach used an in-depth interview technique through a semistructured interview protocol that included the following core questions:

1. What is the general governance's framework in radiological EPR?
2. How does the emergency responder perceive the use of current governance's framework in radiological EPR?
3. How to improve the current governance's framework in radiological EPR?

A total of 6 key informants were purposely chosen as they represent each responsible organization that fit with the aforementioned selection criteria. The entire interview was audiotaped, and transcripts were analyzed using NVivo (version 12, QSR International) which provided the basis for thematic analysis.

The quantitative method utilized a standard questionnaire adopted from previous risk governance studies on climate change, radiation emitted from mobile phones, and radioactive waste [13,14]. This questionnaire has been validated among 1547 respondents through face-to-face interviews and was widely accepted as a reliable method (Cronbach α on reliability analysis ranging .58-.89). The 5-point Likert Scale questionnaire aimed to provide hypothetical reasoning in the field of risk management, which encourages theoretical understanding. A precalculated sample of 260 respondents were administered a self-administered questionnaire. Independent variables comprising both continuous and categorical data were input in the statistical analysis using IBM SPSS software version 25. Logistic regression analysis was used to exhibit the association between the independent variables and radiological risk practices as the dependent variable. Based on simple logistic regression analysis, variables with significant *P* values of <.25 were selected for subsequent multiple logistic regression analysis to determine predictors with significant *P* values of <.05 regarding radiological risk practices.

Finally, research ethic approvals were gained from 2 organizations, namely the Medical Research Ethics Committee at Universiti Putra Malaysia (UPM/TNCPI/RMC/JKEUPM-2018-014) and the Medical Research Ethics Committee of the Ministry of Health, Malaysia (NMRR-18-1922-40686). Informed formal consent was also obtained from each respective organization where the respondents were sampled from.

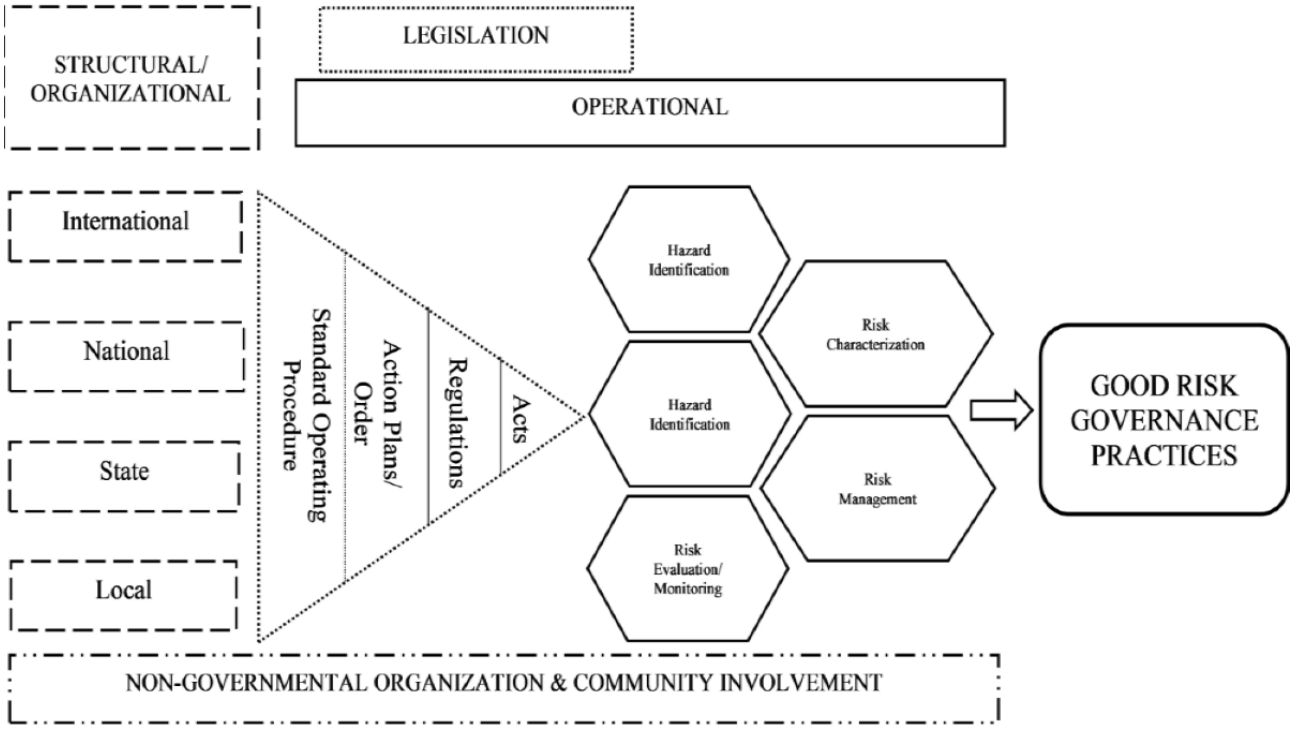
Results

The qualitative result was based on interviews from 6 key informants describing the relevant thematic analysis, while quantitative data were presented as descriptive statistics and analyzed using multiple logistic regression analysis, which yielded adjusted odds ratios for significant variables for the equation model. The hypothesized relationship was depicted in a multiple regression equation as follows:

$$\text{Odds (radiological risk practices)} = b_1x_1 + b_2x_2 + \ldots + b_nx_n + c$$

Converging the 2 findings in the form of a joint display table facilitated further interpretation among various factors and addressed all research objectives as data integration is a key element for mixed methods analysis. Based on all findings, a proposed radiological risk governance framework was tabled out with a preliminary version. Furthermore, the framework was also aligned with the national sustainable development goals to be cohesive, transparent, accountable, and relevant with time [15]. Figure 2 shows the preliminary framework. The study is still underway and is expected to conclude in late 2021.

Figure 2. Proposed risk governance framework on radiological emergency, preparedness, and response for emergency responders. SWOT: strengths, weaknesses, opportunities, and threats.



Discussion

Principal Findings

This paper describes a protocol that was used to address governance concepts and practices, particularly in the field of radiological EPR. Through this convergent research design, this study aimed to understand and evaluate the current governance, with quantitative methods, using statistical analysis that includes relationship testing. The hypothesized significant relationship between the studied factors and emergency responder perception on radiological governance potentially revealed significant factors such as risk perception, risk management proficiency, organization, and government involvement, and analysis was depicted in a model that represented the hypothesized causal/predictive relations. Through in-depth interviews, the qualitative approach possibly reveals explanatory and textual emerging themes that may not have been discovered before, and this can be viewed as a part of an ongoing process that helps improve performances for current and future management to achieve desired outcomes.

It is known that risk governance plays a pertinent role in the technological use of radioactive material in various fields because of its potential for global impact. The Atomic Energy Licensing Act was passed in 1984 [16] owing to the rapid development of the applications of radioactive material and activities in Malaysia, which require effective control, enforcement, and ensuring of safe and peaceful use. Furthermore, National Security Council directive 20 emphasizes the policy and mechanism of an integrated management system for disaster and relief management on land, which includes radiological emergencies before, during, and after disaster stages as well as determining roles and responsibilities of various agencies involved in disaster management [17]. Similarly, several international documents from the IAEA have explained the safety standards in terms of fundamentals and requirements that are necessary for preparedness and response for a nuclear or radiological emergency [18,19] right until the termination of the emergency response [20]. Simultaneously, a reference manual on the generic procedures for the initial response toward a radiological accident by each organization and different phase responses is also available from among the IAEA technical documents [21]. Regarding communication, this component should also concur with international recommendations for a transparent and accurate provision of official information as well as having a practicable coordinated response [22].

Limitations

The involvement of multiple stakeholders from several organizations that are currently involved in radiological EPR, such as enforcement agencies, the police, armed forces, firefighters, medical teams, and university and research centers, while potentially adding more data value, took a long time and required plenty of resources and support. Another challenge was related to data integration and the finalization of interpretive findings as there are still limited resources that can support an overall comprehensive governance framework.

Conclusions

Important emerging themes and significant factors related to emergency responders' perceptions on radiological governance practices were determined through the convergent design. This potentially facilitated the development of a plausible radiological risk governance framework to strengthen the existing process as this is in tandem with good governance practice that promotes continuous improvement for prevention and control in radiological emergency, preparedness, and response.

Authors' Contributions

AAR curated the literature and drafted and critically revised the manuscript. RAM and PYL provided technical inputs and reviewed the manuscript. SS and MHJ provided methodological and technical inputs on the study.

Conflicts of Interest

None declared.

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Abbreviations

EPR: Emergency Preparedness and Response
IAEA: International Atomic Energy Agency

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Proposal

Effect of Preconception Care Intervention on Maternal Nutritional Status and Birth Outcome in a Low-Resource Setting: Proposal for a Nonrandomized Controlled Trial

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Abstract

Background: The provision of preconception care approaches such as maternal assessments and education on healthy lifestyle (including physical activity, nutrition, and dietary supplements such as folic acid), general and sexual health, avoidance of high-risk behavior, and immunizations has been shown to identify and reduce the risk of adverse birth outcomes through appropriate management and preventive measures.

Objective: The goal of the study is to determine the effect of an integrated preconception care intervention on delivery outcomes, which is a novel challenge for lowering unfavorable birth outcomes in India's low-resource setting. The main objectives are to investigate the relationship of birth outcomes to both maternal and paternal preconception health and determine the effect of preconception care intervention on improvement of maternal nutritional status and reduction of the risk of adverse birth outcomes such as prematurity, low birth weight, and maternal and neonatal complications.

Methods: A nonrandomized controlled trial design will be used for comparing 2 groups: preconception care with a standard maternal health care (MHC) program and an integrated MHC program (without preconception care). Two rural field areas of Khordha district, Odisha, will be selected for conducting the study. The study will enroll 782 married women between the ages of 18 and 35 years with their spouses, with 391 women in each group. The couples will receive preconception care based on their health circumstances, and they will be followed up at 3-month intervals before pregnancy. Following pregnancy, they will be followed up for 8 prenatal monitoring and care visits as well as 6 weeks after delivery as part of the standard MCH program. The preconception care intervention package includes couples counseling, contraceptive education and distribution, sex education, lifestyle modification, and nutritional supplementation of iron and folic acid, along with multivitamins if needed.

Results: The proposal was approved by the institutional ethical committee for conducting the study in June 2020 (Ref No: T/EMF/Nursing/20/6). Participants were enrolled in phase 1 in April 2021, phase 2 of offering preconception services will begin in August 2021, and study outcomes will be measured from 2023 to 2024.

Conclusions: Through preconception care and counseling, the eligible couples will recognize, embrace, and implement the actions to improve their preconception health. Finally, it is expected that maternal and paternal health will have a significant impact on enhancing maternal nutritional status and birth outcomes.

Trial Registration: Clinical Trials Registry–India CTRI/2021/04/032836; http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=48239&EncHid=&userName=CTRI/2021/04/032836

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KEYWORDS

preconception care; maternal nutritional status; birth outcome; paternal preconception health; childbirth; birth outcomes; maternal and child health; maternal health; maternal and child nutrition; health education; pediatrics

Introduction

Maternal health care (MHC) is a cost-effective and clinically helpful method of preventing unfavorable birth outcomes. However, adverse birth outcomes remain a significant public health concern around the world, contributing to substantial morbidity, mortality, and increased health care costs [1]. The majority of this adverse effect happens in low- and middle-income countries (LMICs), with mortality rates being higher in rural and low-resource populations. Starting prenatal treatment late in the first trimester may make it more difficult to check for risk factors and prevent a negative birth result. The importance of maternal health prior to pregnancy (preconception care) is becoming more well acknowledged, and improving a woman's health and preparation prior to conception may prevent or reduce the risk of adverse birth outcomes.

Preconception care for all women, as well as women with particular risk factors such as maternal obesity, diabetes, hypertension, depression, substance misuse, and occupational variables, has been shown to improve maternal and newborn health in the long run [2-4]. On the other hand, much less is known regarding fathers' preconception influences on delivery outcomes. Paternal health variables, such as obesity, cardiovascular health, and job circumstances [5], have been linked to birth outcomes, notably birth weight [6-9] in some studies. More research is needed to understand how paternal health affects birth outcomes, as well as whether this process occurs independently or in tandem with maternal health [10].

According to the US Centers for Disease Control and Prevention [1] and American College of Obstetrics and Gynecology guidelines [11], preconception care intervention included maternal assessment, screening, supplementation with folic acid and iron, vaccination, lifestyle modification, and counseling. Improved pregnancy and delivery outcomes, such as fewer low birth weight or preterm infants, congenital abnormalities, and intrauterine growth restriction, are all examples of good preconception health [1,12,13]. The Centers for Disease Control and Prevention also recommends that preconception care be improved and consumer-focused research be conducted to promote preconception health and reproductive knowledge. The implementation of comprehensive preconception care in low-resource areas in the Indian situation has not been researched on a wide scale. More study is needed to discover best practices and the most efficient ways to administer integrated preconception care components in remote areas. Our research will be conducted in the rural communities of Odisha, India. One of the most significant challenges facing Odisha's health system is reducing maternal and infant fatalities. With many efforts from the state under the Reproductive, Maternal, Newborn Child, and Adolescent Health campaign, the state maternal mortality ratio and infant mortality rate have decreased over time, according to the sample registration system reports from 2015 to 2017. The present rate of decline, however, is insufficient to meet the 12 5-year plan goals. According to India's National Family Health Survey–4 (2015-16), the prevalence of low birth weight infants is high in tribal-dominated states, with Odisha reporting the highest number of low birth weight newborns compared to the national average [14]. Inadequate antenatal care services, a low number of antenatal visits, and poor health-seeking behavior, such as delaying timely intervention and accessing emergency obstetric care, were recently linked to the occurrence and prevalence of obstetric complications like preterm deliveries, prolonged labor, and low birth weight babies, according to a population-based study conducted in Khordha district of Odisha [15].

Despite the fact that there are 8 or more scheduled visits of standard prenatal care without preconception care, which is considered insufficient, 99% of maternal and neonatal death occurs in LMICs like India, with the majority of deaths occurring in rural and low-resource communities. As a result, an integrated MHC program has been proposed, which includes a specific plan throughout the preconception and prenatal periods, in order to determine its impact on improving maternal health and reducing adverse birth outcomes such as prematurity, low birth weight, and maternal and neonatal complications as well as to investigate the relationship between birth outcomes and both maternal and paternal preconception health.

Methods

Research Design and Study Setting

A nonrandomized controlled trial design will be used to assess the impact of a preconception care intervention plan for maternal nutritional status and birth outcome among married women aged 18 to 35 years. The research will be conducted in the Khordha district of Odisha, which is located in India's eastern rural community. Khordha district has a population of 22.52 lakh (2.25 million) people, accounting for 5% of the total population of Odisha. The district's rural population accounts for 52% of the total population, with females accounting for 48% and males accounting for 52% [16].

Study Participants

Married pregnant women aged 18 to 35 years, gravida and parity of less than 5 and who will attend a minimum of 8 scheduled visits of prenatal monitoring will be recruited into the standard MHC group. The integrated MCH program will enroll married nonpregnant women aged 18 to 35 years with their partners, gravida and parity of less than 5, who intend to have a child within 1 year and will attend at least 3 preconception appointments and get preconception care at least once every 3 months.

Participants who will not able to attend the scheduled preconception visits and antenatal visits will be excluded from the study. The sample size for the study will be 652 couples, which was calculated by using sample size calculation software (Epi Info, CDC) for sample size estimation of nonrandomized controlled trials with 95% confidence level and 80% power and

risk/prevalence ratio (0.42) of low birth weight baby as an adverse birth outcome associated with preconception care in a previous study [17]. We expect 20% to be lost to follow-up; therefore, the total required sample size is rounded to 782, and each group will be enrolled with 391 women with their partners.

Recruitment Process

A nonrandomized cluster sampling will be used to select the population samples from the targeted population. Each rural community health center will be considered as a cluster and will be listed in the sampling frame. In the first stage, 2 clusters will be selected randomly from a sampling frame of all rural health centers, Khordha district, Odisha, and all eligible participants fulfilling the sampling criteria in those clusters will be listed in the sampling frame. One cluster will be exposed to the integrated MHC program (ie, women with their partners who will receive preconception care and prenatal care), and another cluster will receive the standard MHC program (ie, women who received prenatal care without preconception care). In the next stage, eligible couples will be selected in each cluster by a convenience sampling technique proportionate to the sample size. After obtaining consent for enrollment, the selected eligible couples will be interviewed, and preconception health will be assessed by a team of research groups consists of a research coordinator, field data collectors, nurse-midwife, and doctor. The preconception service will be given to the eligible couples and they will be followed up at 3-month intervals before pregnancy and then up to 8 scheduled visits of prenatal monitoring and delivery as provided under the standard maternal health care program.

Measures

In the initial phase, data on preconception sociodemographics, health conditions, and health behaviors of the participants and their partners will be measured and will be followed until their delivery. In the next phase, the characteristics of the pregnancy and birth outcomes will be assessed.

- Sociodemographic characteristics: parent ages, educational level, socioeconomic status, previous pregnancy, and birth characteristics
- Preconception health conditions: 4 variables are included: BMI, diabetes, high blood pressure, depression. Screening of cases for identifying diabetes and high blood pressure and also diagnosed cases will be classified as having diabetes and high blood pressure. Depression will be measured using a depression scale. BMI will be calculated by measuring height and weight and categorized according to standard categories of normal weight, underweight, overweight, or obese
- Preconception health behaviors: maternal and paternal health behaviors such as substance use, fast food consumption, and physical activity are included in the study, which will be assessed through a structured self-reported format. Substance abuse will be measured in the form of the frequency of taking alcohol or drugs or smoking. Consumption of fast food will be measured by respondents' reports of the number of days per week in which they typically eat fast food. Physical activity will be measured by responses to a series of items which ask if the participant is engaged in a variety of activities, such as bicycling, doing aerobics, playing team sports, participating in individual sports, walking, or any physical work
- Pregnancy characteristics and birth outcomes: pregnancy characteristics, nutritional status of the mother, and birth outcome are the outcome variables. The nutritional status of the mother will be measured in the form of BMI and hemoglobin level anemia. The birth outcome will be measured using the gestational age of the baby, birth weight, maternal and neonatal complications, and mode of delivery (normal vaginal delivery and cesarean delivery)

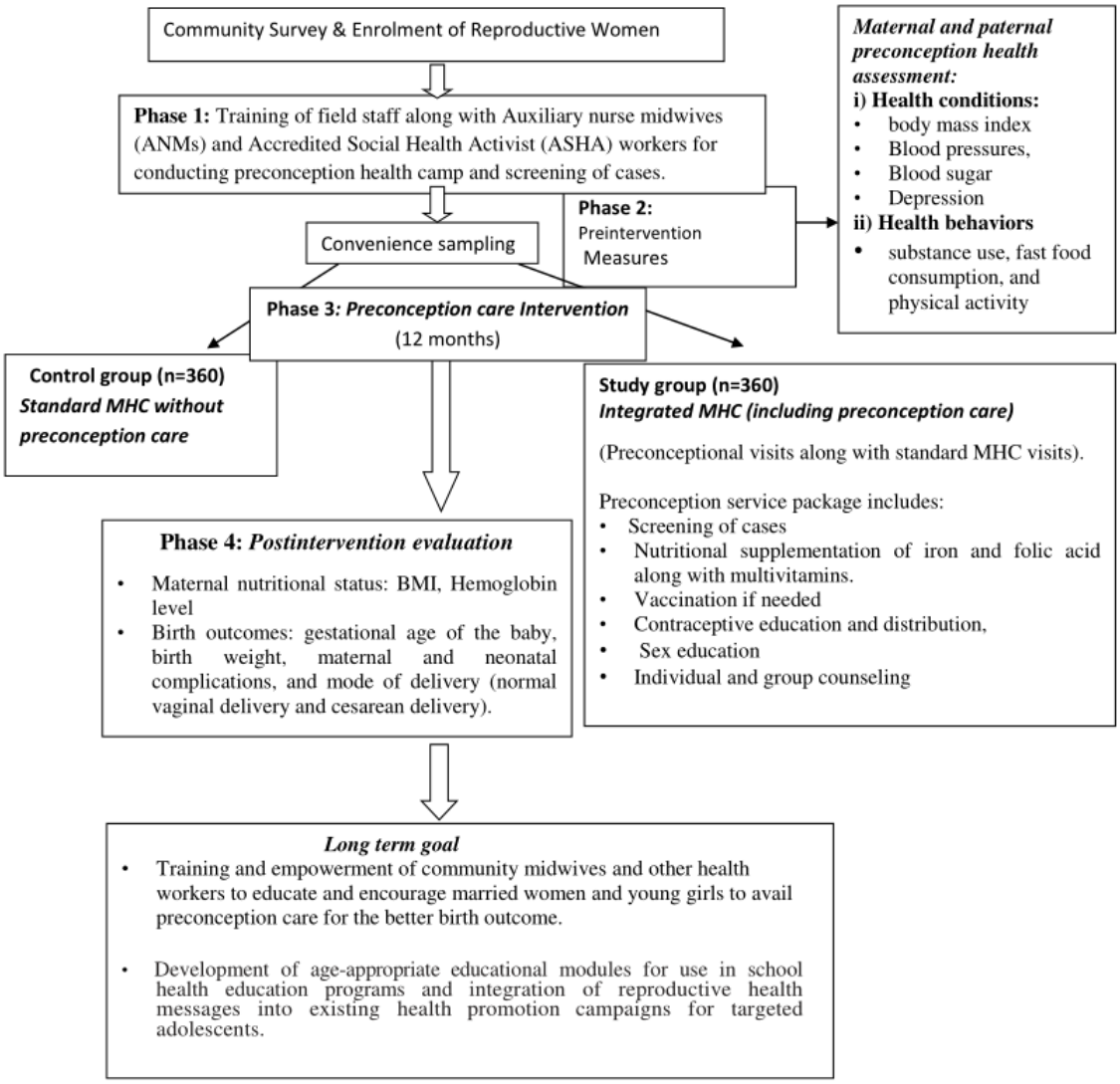
Ethical Consideration

The proposal for conducting the study has been approved by the institutional ethical committee (Ref No: T/EMF/Nursing/20/6). Detailed information about their preconception health assessment and testing will be given to the study participants, and written consent will be obtained from them before proceeding to data collection. No such risks are involved in delivering the routine preconception advice and care related to pregnancy, and it will be given under the guidance of an obstetrician and nurse-midwife. Most women will be counseled and educated about their planned pregnancy and preparing for a better outcome. This trial is registered at the Clinical Trials Registry–India [CTRI/2021/04/032836].

Project Implementation Plan

Figure 1 depicts the phase-wise research implementation plan.

Figure 1. Phase-wise study work plan. ANMs: auxiliary nurse midwives; MHC: maternal health care.



In the first phase, this project will collaborate with selected rural health centers for the implementation of effective preconception care intervention. Due permission will be obtained from the chief district medical officer, Khordha district, Odisha, and concerned community health workers such as accredited social health activists. Auxiliary nurse midwives will be involved in identifying eligible participants in their locality and bringing those couples for preconception advice and care at a free preconception health camp. Qualified data collection teams will be assigned to do the data collection in the targeted areas. The selection of the interviewers will be based on set criteria such as having a medical background or medical knowledge, familiarity with the region, fluency in the local language, and familiarity with surveys and data collection. All data collectors and field supervisors will be trained on questionnaires/assessment tools, processes of data collection, and ethical issues of the survey based on an already developed training plan. Also, community midwives will be trained and certified as trainees for trainers so that they will continuously involve the same type of preconception health assessment in their areas.

In the second phase, a preconception health camp will be conducted at their locality on a weekly basis until reaching the sample size to collect baseline data on preconception sociodemographics, screening of health conditions, and health behaviors of the enrolled participants. Community field testing for risk assessment will be done by the project team by involving community health workers.

In the third phase, preconception care service will be provided to the couples based on their health conditions and they will be followed up at 3-month intervals before conception. After conception, they will be followed up for 8 scheduled visits of prenatal monitoring and care and 6 weeks after delivery as provided under the standard MCH program. The detailed preconception care intervention plan is presented in Table 1 and includes couples counseling, contraceptive education and distribution, sex education, lifestyle modification, and nutritional supplementation of iron and folic acid along with multivitamins if needed. The preconception care training manual and its digital app will be available as technological support for women who prefer a self-directed approach for maintaining good preconception health for the better birth outcome.

In the fourth phase, a postintervention assessment will be done for measuring outcome variables such as the nutritional status of the mother during pregnancy and birth outcome. Maternal nutritional status includes BMI and hemoglobin level, and birth outcome includes gestational age of the baby, birth weight, maternal and neonatal complications, and mode of delivery (normal vaginal delivery and cesarean delivery).

Table 1. Preconception care intervention plan.

Service	Screening activities	Plan of action
Reproductive history and contraception	Inquire about previous pregnancies: • Preterm birth, preeclampsia • Congenital anomalies, stillbirth/miscarriage • Gestational diabetes • Caesarean birth, uterine anomalies, high/low birth weight Inquire about contraception: • Interventions to delay age at first pregnancy and interpregnancy intervals	Provide appropriate referrals. Discuss family planning and conception. Advise women with prior cesarean delivery to wait at least 18 months prior to conception. Recommend folic acid 5 mg daily prior to conception and for 12 weeks after conception if positive history of neural tube defects. Recommend >12 and <60 month interpregnancy interval.
Sexual health	Sexually transmitted diseases	Provide treatment according to sexually transmitted infection guidelines. Inform women with genital herpes of the risk of vertical transmission.
Chronic medical conditions	Screen for diabetes, high blood pressure	Manage as per medical protocol
Mental health	Screen for the following conditions: • Depression • Anxiety • Family history of mental health issues	Counsel women with mental health diagnoses of risks of pregnancy and relapse. Strategize management. Stabilize/optimize mood and anxiety level. Discuss risks and benefits of medications.
Medications	Screen for teratogenic medication use: • Prescribed medications • Over-the-counter medications • Complementary and alternative therapy (herbal, natural, weight loss, athletic products or supplements, etc)	Potentially teratogenic medications should be changed to safer options. Women should be counseled not to stop prescribed medications without consulting with their provider. Recommend folic acid 5 mg daily prior to conception and for 12 weeks after conception for women taking folate antagonists (eg, methotrexate, sulfonamides, and antiepileptic).
Nutrition	Screen for issues regarding access to food, nutrition, storage, cooking facilities, and folic acid. Screen for iron-deficiency anemia if at risk.	Recommend folic acid 0.4-1.0 mg daily (through a multivitamin or supplement) and a folate-rich diet prior to conception and throughout pregnancy. Recommend calcium 1000 mg daily through food and/or supplements. Recommend an essential fatty acid–rich diet, including omega 3 and 6. Recommend avoiding raw/undercooked meat and fish and unpasteurized milk and cheese. Limit caffeine to <300 mg/day. Recommend vitamin D 600 IU (15 µg) supplementation daily. Recommend 2.6 µg of vitamin B12 daily through supplement or multivitamin. Provide referral to a dietitian or appropriate community agencies for nutritional support.
Vaccinations	Rubella, hepatitis B, varicella	Provide all immunizations required prior to conception with the exception of the flu vaccine, which can be administered before and/or during pregnancy.
Family and genetic history	• Family history of a genetic condition such as consanguinity (first cousins or closer) or children who died at a young age (may reveal a metabolic condition) • History of sudden unexplained death (may indicate cardiomyopathy or metabolic condition) • History of infertility, multiple miscarriages (>3) • Congenital malformations, birth defects • Developmental delays, learning disabilities	Recommend folic acid 5 mg daily prior to conception and for 12 weeks after conception if positive family history of neural tube defects or high-risk ethnic group. Provide referral to a specialist for those with family and genetic history risk factors.

Service	Screening activities	Plan of action
Weight status	Screen BMI (kg/m^2) annually.	• Underweight (BMI <18.5) • Overweight (BMI 25-29.9) • Obese (BMI >30) Recommend folic acid 5 mg daily prior to conception and for 12 weeks after conception for obese individuals. Discuss recommended healthy weight gain diet plan as per the BMI during pregnancy. Provide appropriate referrals for management.
Physical activity	Assess series of items in which the participant engages in a variety of activities, such as walking, doing other physical work, etc.	Recommend at least 150 minutes of moderate to vigorous aerobic physical activity per week in episodes of 10 minutes or more. Add muscle and bone-strengthening activities at least 2 days per week.
Substance use	Screen for tobacco (all forms), tobacco exposure (secondhand smoke), alcohol, other substances.	Counsel women with tobacco addictions of risks to pregnancy. Strategize management as required. Recommend an extra 35 mg of vitamin C daily for smokers. Provide brief intervention and appropriate referrals. Inform women of available patient resources.

Data Analysis Plan

The data will be cleaned, validated, and analyzed using SPSS (version 20, IBM Corp). Descriptive statistics for continuous variables (mean and standard deviation) or categorical variables (frequencies) will be presented for participant characteristics and the outcome measures. Regression analysis will be used to examine potential associations between maternal and paternal preconception health and birth outcomes. Inferential statistics will be used for testing the effectiveness of preconception care intervention on maternal nutritional status and birth outcome.

Expected Outcomes

There will be a strong impact of maternal and paternal health on birth outcomes such as gestational age of the baby, birth weight, maternal and neonatal complications, and mode of delivery (normal vaginal delivery and cesarean delivery). The preconception care intervention will improve birth outcome and nutritional status of the mother. The eligible couples will recognize, accept, and include the measures to improve their preconception health through preconception counseling and health teaching. Ultimately, it is anticipated that community midwives will be trained for disseminating effective preconception care in low-resource setting communities, which may bring better birth outcomes.

Results

The proposal was approved by the institutional ethical committee for conducting the study in June 2020. Enrollment of participants to phase 1 began in April 2021, phase 2 of providing preconception service will begin in August 2021, and study outcomes will be measured from 2023 to 2024.

Discussion

Summary

Preconception health is associated with infant birth outcomes, which in turn influences health status throughout the lifetime. Some of the prepregnancy health conditions such as underweight, history of chronic hypertension, poor prepregnancy physical function, and smoking before pregnancy increase the risk of preterm birth and prematurity [18]. Maternal and paternal diabetes status demonstrated some of the strongest relationships with infant birth weight and gestational age. Interestingly, maternal diabetes was associated with increased birth weight, but paternal diabetes was associated with decreased birth weight [9,19-21]. Nationally, diabetes is becoming more common among young adults [18]; accordingly, diabetes management will become even more important for preconception care. The presence of elevated blood pressure in the mother was linked to a higher child birth weight. High blood pressure before conception [19,22] and during pregnancy [23,24] has been linked to a lower birth weight in previous research. Our research will also look into how preconception health issues like BMI, diabetes, and blood pressure affect delivery outcomes.

A prospective longitudinal study was conducted to see how maternal and paternal preconception health factors and behaviors affect infant birth weight and gestational age. Infant gestational age was found to be marginally lower for infants born to mothers with greater levels of depression and slightly lower for infants born to fathers with diabetes and greater levels of fast food consumption [25]. The goal of this study is to see if there's a link between maternal and paternal diabetes, maternal hypertension, maternal alcohol use, mother depression, and paternal fast food intake and newborn birth outcomes. Preconception health promotion activities can target these characteristics in order to enhance birth outcomes, which will benefit the health of future generations.

Maternal nutritional deficiencies, particularly iron and folates, are common in LMICs. Anemia in women from LMICs is due to low dietary intake of bioavailable iron combined with endemic infectious diseases such as helminthiasis, which puts women at increased risk during pregnancy. Low preconception hemoglobin and ferritin levels increase the risk of poor fetal growth and low birth weight [26]. Similarly, folate deficiency can lead to the development of neural tube defects in the fetus. Other micronutrients such as zinc, vitamin B, and calcium have been found to improve maternal and newborn outcomes when

supplementation is provided during pregnancy; however, their impact during the preconception period has not been established [27]. The findings of this study will support the idea of increasing women's preconception nutritional status by delivering critical nutritional supplements throughout the preconception period, which can assist women to start their pregnancy in the best possible health.

Improved reproductive health and planning is the fundamental component of preconception care, and starting early interventions in the preconception period may improve the participants' knowledge and self-efficacy toward the need for better health before and during pregnancy, which may contribute to those favorable outcomes. Although policies and guidelines on preconception care are available, this study intends to implement the recommendations and good clinical practice guidelines in a low-resource rural community setting of India. So this study will fill the gap in the continuum of care, particularly for women who are not pregnant. Evidence also indicates that prenatal care is frequently too late to prevent negative health consequences for developing fetuses. The goal of the study is to introduce nutrition and other lifestyle interventions during the preconception period, which will be the best time to promote maternal health and ensure a healthy pregnancy. This intervention is cost-effective but at the same time will be very challenging to implement before pregnancy in India's low-resource setting.

Limitations

The study will be a nonrandomized clinical trial which may limit the validity of the study outcome, and the study setting will be limited to one district of the Odisha state, India. The study needs a long duration of a minimum of 2 years to measure the effects on birth outcome; hence, there is more possibility of nonadherence to the preconception services as well as noncompliance for routine antenatal care. However, those cases will be followed up by the local community nurse-midwives and research team members, and necessary counseling sessions will be conducted for adherence to care. Additionally, preconception care needs tremendous effort and cooperation from the field health care women and their partners. Thus, exploring facilitators and barriers to the implementation of the preconception care intervention is a vital step of this proposed project.

Future Plans

As an extension of the outcome of this study, training can be provided to concerned community health workers who will provide extensive support to the women using this preconception care intervention for better health outcomes, mostly in a low-resource community setting. Also, the development of age-appropriate educational modules for use in school health education programs and integration of reproductive health messages into existing health promotion campaigns for targeted adolescents is a long-term goal.

Conclusions

The eligible couples will adopt strategies to improve their preconception health through preconception care and counseling. Structured preconception care in community settings has the potential to prevent unfavorable pregnancy and childbirth consequences. Finally, maternal and paternal health are likely to have a significant impact on maternal nutrition and birth outcomes.

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Conflicts of Interest

None declared.

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Abbreviations

LMICs: low- and middle-income countries
MHC: maternal health care

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Protocol

Association of Postoperative Clinical Outcomes With Sarcopenia, Frailty, and Nutritional Status in Older Patients With Colorectal Cancer: Protocol for a Prospective Cohort Study

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Abstract

Background: Older patients account for a significant proportion of patients undergoing colorectal cancer surgery and are vulnerable to a number of preoperative risk factors that are not often present in younger patients. Further, three preoperative risk factors that are more prevalent in older adults include frailty, sarcopenia, and malnutrition. Although each of these has been studied in isolation, there is little information on the interplay between them in older surgical patients. A particular area of increasing interest is the use of urine metabolomics for the objective evaluation of dietary profiles and malnutrition.

Objective: Herein, we describe the design, cohort, and standard operating procedures of a planned prospective study of older surgical patients undergoing colorectal cancer resection across multiple institutions in the United Kingdom. The objectives are to determine the association between clinical outcomes and frailty, nutritional status, and sarcopenia.

Methods: The procedures will include serial frailty evaluations (Clinical Frailty Scale and Groningen Frailty Indicator), functional assessments (hand grip strength and 4-meter walk test), muscle mass evaluations via computerized tomography morphometric analysis, and the evaluation of nutritional status via the analysis of urinary dietary biomarkers. The primary feasibility outcome is the estimation of the incidence rate of postoperative complications, and the primary clinical outcome is the association between the presence of postoperative complications and frailty, sarcopenia, and nutritional status. The secondary outcome measures are the length of hospital stay, 30-day hospital readmission rate, and mortality rate at days 30 and 90.

Results: Our study was approved by the National Health Service Research Ethics Committee (reference number: 19/WA/0190) via the Integrated Research Application System (project ID: 231694) prior to subject recruitment. Cardiff University is acting as the study sponsor. Our study is financially supported through an external, peer-reviewed grant from the British Geriatrics Society

and internal funding resources from Cardiff University. The results will be disseminated through peer-review publications, social media, and conference proceedings.

Conclusions: As frailty, sarcopenia, and malnutrition are all areas of common derangement in the older surgical population, prospectively studying these risk factors in concert will allow for the analysis of their interplay as well as the development of predictive models for those at risk of commonly tracked surgical complications and outcomes.

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KEYWORDS

sarcopenia; frailty; nutritional status; urine metabolomics; surgery; geriatric medicine

Introduction

Background

There are numerous preoperative factors that affect surgical patients. In particular, older patients undergoing surgery have age-related factors that can affect their surgical outcomes. This is particularly important in the context of colorectal cancers, which are the third most diagnosed malignancy and the fourth leading cause of cancer death worldwide [1]. The majority of colorectal cancers are still diagnosed after the age of 65 years [2]. As populations continue to age, the incidence of major colon and rectal resections for cancer in the older population are projected to increase dramatically [3]. This makes it important to understand surgical risk factors in older adults and implement timely intervention where possible. Further, three of the most important age-related preoperative factors in older surgical patients are frailty, sarcopenia, and malnutrition. Although each has been studied individually, there is little information on their associations in older surgical patients.

Frailty

At present, while there are no universally agreed upon consensus criteria for defining frailty, it can be thought of as physiologic decline and an increased risk of poor health resulting from aging [4]. There are numerous definitions, which vary from clinical phenotypes with specific required criteria to operational definitions (eg, the tally of an accumulation of deficits in older patients) [5,6].

Regardless of the definition used, preoperative frailty has been shown to be associated with poor postoperative outcomes in major colorectal surgery, such as an increased number of postoperative complications, an increased length of hospital stay, higher readmission rates, and decreased long-term survival rates [7]. Frailty is also associated with an increased cost of elective surgical care [8].

Two simple-to-use frailty assessments are the Clinical Frailty Scale (CFS) and the Groningen Frailty Indicator (GFI). Each of these assessments can be rapidly performed and have been validated with multiple cohorts [9,10].

Sarcopenia

Sarcopenia is the age-related loss of muscle mass and function [11]. It is often associated with physical frailty, yet being clinically frail is not always a prerequisite for a sarcopenia diagnosis. It is also associated with malnutrition, although the two entities can occur separately [12].

Muscle function is often measured through hand grip strength, while lower extremity and torso muscle mass can be evaluated through numerous mechanisms, including computerized tomography (CT) morphometric analysis [13,14].

Sarcopenia has been associated with an increased risk of postoperative complications in patients undergoing gastrointestinal tumor resection, and it has a potential role in preoperative risk stratification if both muscle mass and function are assessed [15].

Malnutrition

Malnutrition refers to deficiencies, imbalances, or excesses in a person's intake of energy and nutrients [16]. In patients undergoing major abdominal surgery, malnutrition is associated with worse outcomes, including increased lengths of stay, increased in-hospital mortality rates, and higher costs of care [17]. The identification of malnutrition often relies on clinical screening tools that are reliant on various amounts of subjective recall [18]. A promising new strategy for making an objective diagnosis of dietary patterns that indicate a risk for malnutrition is urine metabolomics analysis [19]. This may play a role in assisting clinicians with identifying patients who may benefit from perioperative nutritional support.

Study Overview

The objective of our feasibility study is to prospectively study older patients undergoing elective colorectal cancer resection and to provide informative data for further large-scale intervention studies. This study will evaluate the risk of postoperative complications (primary outcome), length of hospital stay (secondary outcome), and mortality (secondary outcome), with the following risk factors: frailty, sarcopenia and nutritional status.

The data obtained from this study may allow for the development of novel management strategies and targeted therapies of older surgical patients who experience a combination of frailty, sarcopenia, and malnutrition.

Methods

Setting

The Older Persons Surgical Outcomes Collaboration is a collaboration of surgeons, geriatricians, and epidemiologists

who collect data on surgical outcomes in older individuals through multicenter research studies [20]. This collaborative collects data across the United Kingdom (sites include Cardiff, Bristol, Bath, Glasgow, Manchester, London, and Aberdeen) from all phases of surgical care, including longitudinal follow-ups. This study will initially enroll patients at three sites—Cardiff, Bristol, and Bath. It will then be registered on the Health & Care Research Wales Clinical Portfolio in order to allow other sites to enroll their patients. Cardiff University is acting as the study sponsor.

Study Design

Our study is a prospective, multicenter, UK cohort study of older (aged ≥65 years) patients with colorectal cancer undergoing surgical resection. The objectives are to determine the association between clinical outcomes and frailty, nutritional status, and sarcopenia.

The inclusion criteria include patients with a diagnosis of colorectal cancer, those who plan to undergo surgical treatment for colorectal cancer, those aged ≥65 years, those with an abdominal CT scan that was taken prior to surgery (current standard of care), and those with the ability to understand the participant information sheet and are therefore able to provide written informed consent. Patients will be excluded if their procedural treatment is not performed with curative intent (including palliative colorectal stent insertion or the treatment of locally advanced tumors not amenable to curative resection) or if they are participating in another research study.

Subject Recruitment

Patients will be identified by the usual clinical team as part of the routine, preoperative, multidisciplinary team meeting (the cancer multidisciplinary team). After patients are identified by screening, they will be approached by the colorectal clinical nurse specialist (CNS) by phone to discuss the study. If a patient agrees to discuss the study, the CNS will send the patient a participant information sheet via postal mail to allow for time for reviews and the further consideration of participation prior to the patient attending their preoperative assessment clinic (POAC) appointment. As the POAC is a routine standard-of-care appointment for evaluating a patient's appropriateness for undergoing anesthesia and surgery, it does not subject patients to unnecessary visits. The CNS will also inform the study team about patient interest, so that a member of the study team can attend the POAC to answer patients' questions and obtain written informed consent.

Sample Size Justification

Based on an a priori power analysis, we will estimate the true postoperative incidence of complications (estimated to be 20%) with a 95% CI of ±11%. To achieve this, 50 patients will be enrolled. Due to the nature of the study, we anticipate that all patients will be followed up.

Enrollment will occur over a 12-month period beginning in winter 2020.

Data Procurement and Management

Routine clinical data will be prospectively collected, including baseline demographics (age, sex, and race), height, weight, BMI, and medical comorbidities. Standard-of-care POAC laboratory results will be obtained, including full blood counts, basic metabolic panels, liver function test results, and C-reactive protein levels. Data on study specific characteristics, including urinary biomarkers for the assessment of dietary intake, radiographic muscle evaluations, and frailty assessments, will be recorded. At 90 days following surgery, the following specific outcomes will be reviewed: the length of hospital stay, readmissions to the hospital within 30 days, postoperative complications (evaluated using the Clavien-Dindo classification system), 30-day mortality, and 90-day mortality [21].

Each research site will maintain separate databases, and electronic records will be stored via standard National Health Service encryption. If hard copy data exist, they will be stored securely by each participating site's principal investigator. All data shared with the centralized coordinating center will be deidentified and shared through a secure electronic database. All identifiable participant data will be deidentified by assigning research numbers to participants. Clinical data (including images) will be anonymized and securely stored centrally at Cardiff University for long-term storage in accordance with local guidelines (stored for 15 years). Consent forms will be stored centrally at Cardiff University.

Outcomes

Coprimary Outcomes

The primary feasibility outcome is the estimation of the incidence rate of postoperative complications. The primary clinical outcome is the association between the presence of postoperative complications and frailty, sarcopenia, and nutritional status.

Secondary Outcomes

The secondary outcomes include the length of hospital stay, hospital readmission at 30 days, mortality at day 30, and mortality at day 90.

Measuring Outcomes

Primary Outcome (Postoperative Complications)

Postoperative complications will be recorded and graded using the Clavien-Dindo classification system, categorized as grade 1 or grade 2 complications, and compared to grade 3 or higher complications [21].

Secondary Outcomes

Standard surgical and clinical outcomes (the length of stay, readmission to the hospital, and returns to theatre) will be tracked and recorded 90 days after surgery through a review of medical records.

Measuring the Predictors

CT Morphometric Analysis

It is standard care for patients with colorectal cancer undergoing curative surgical resection to undergo preoperative CT scans for the evaluation of metastatic disease [22]. CT morphometric software allows for body composition analysis, in which the accurate estimation of total body muscle mass by using a single

CT scan slice is performed [13,23]. Preoperative low muscle mass has been shown to be a predictor of poor outcomes for numerous surgical populations [15,24,25].

In order to identify radiographic evidence of sarcopenia, we will perform the CT morphometric assessment of the psoas and abdominal wall skeletal muscles in order to calculate the skeletal muscle index and psoas muscle index. This will be done by using SliceOmatic software (version 5.0, revision 7; TomoVision).

To calculate the total skeletal muscle cross-sectional area (cm^2), all axial skeletal muscles (the psoas, paraspinal, and abdominal wall muscles) of a single CT slice at the third lumbar vertebra (where both transverse processes are visible) will be identified by using established Hounsfield unit attenuation thresholds (−19 to 150 Hounsfield units) for skeletal muscle. A skeletal muscle index (cm^2/m^2) will then be calculated by normalizing the total skeletal muscle cross-sectional area to the squared height of the patient. This same technique can be used to calculate a psoas muscle index (cm^2/m^2).

Urine Metabolomics Analysis

As previously stated, urine metabolomics provides clinicians with the ability to objectively measure dietary intake over time. Urine metabolomics profiles provide more objective results than dietary logs and questionnaires. Urine metabolomics profiles have been shown to vary among patients with controlled feeding conditions and can be used to classify the dietary intake of free-living individuals [26]. It has also been shown that urine metabolic profiles of individuals at home who are not undergoing strict dietary control can be quantified [27]. Multiple spot urine collections, such as the collection of a first-morning void, can provide metabolic profiles that are similar to those of 24-hour and temporally phased cumulative collections, thereby allowing for less rigorous requirements during home participation [28].

Urine samples will be collected over 4 separate, week-long time points; 3 samples will be collected during each time point, resulting in a total of 12 samples. The four time points consist of the week following the POAC visit, the immediate postoperative week, postoperative week 4, and postoperative week 8.

Participants will be provided with urine collection kits and prepaid, preaddressed envelopes so that they can return the samples by postal mail after each collection time point. If the participant is an inpatient for a given week, research staff will assist with sample collection. Patients will be phoned by the study team to remind patients about urine collections when they are outside of their hospital. If the patients are at home, each batch of the 3 samples will be stored in a domestic fridge until the end of the collection week.

Urine metabolomics analysis will be performed based on previously published methods [29]. Urine samples will be corrected for intraindividual variance by using specific gravity adjustments, and individuals' samples will be pooled together for each collection week. Following extraction, the nontargeted metabolomics fingerprints of samples will be generated via flow infusion electrospray high-resolution mass spectrometry. The quantification of dietary biomarkers for measuring habitual dietary exposure and nutritional status will be performed by using liquid chromatography-triple quadrupole mass spectrometry via both the reverse phase and hydrophilic interaction liquid chromatography methods. Approximately 60 biomarkers that correspond to the intake of dietary components that are commonly consumed within the United Kingdom will be measured [30].

Frailty and Functional Assessments

Multiple frailty and functional assessments will be performed at the POAC to evaluate a patient's baseline status. The following two frailty assessments will be performed: The Canadian Study of Health and Aging CFS assessment and the GFI assessment.

The CFS is a 7-point scale that is used to score patients (from 1 to 7) based on the symptom burden of comorbidities and patients' dependence on others for activities of daily living [10]. Patients with a score of 1 to 4 will be considered as "nonfrail," while those with CFS scores of between 5 and 7 will be considered as "frail."

The GFI is a simple, 15-point questionnaire that can be easily completed by clinical staff [31]. These assessments will be repeated during patients' 8-week postoperative appointments to evaluate changes in frailty over time.

In addition to frailty assessments, numerous adjunctive functional tests will be performed at the POAC appointment. Strength will be assessed by using a hand grip dynamometer with the patient's dominant hand and averaging the best results of 3 trials [5]. Mobility will be evaluated with a 4-meter walk test (measured from a starting standing position, at a normal walking pace, and with any usual walking aids) [32]. As strength and mobility are key components of frailty and the loss of muscle function is a key component of sarcopenia, these two tests will provide adjunctive information to both our frailty assessments and measured muscle masses. These functional assessments will also be repeated at the 8-week postoperative appointment to evaluate changes over time.

Finally, as an adjunct to both frailty evaluations and urine metabolomics analyses, the Mini Nutritional Assessment–Short Form will be used at both the POAC and 8-week follow-up visits. The Mini Nutritional Assessment–Short Form is a quick screening tool that is used to identify older patients that are malnourished or at risk of malnutrition [33], which has been shown to be associated with frailty in hospitalized patients [34]. Its use in this study will allow for comparisons between this subjective malnutrition assessment and objective urine metabolomics profiles.

Data Analysis

A baseline descriptive analysis will be carried out for all patients who consent to the study, and this will be used to summarize the extent of missing data [35].

Primary Outcome: Estimating the Incidence of Postoperative Complications

This primary outcome will be estimated by using an asymptotic method to summarize the incidence of postoperative complications and calculate the associated 95% CIs.

Primary Outcome: Associating Risk Predictors With Postoperative Complications

A crude logistic regression model will be used to estimate the odds ratios for postoperative complications and will be fitted by comparing risk factors (eg, frailty).

Secondary Outcomes

Dichotomous outcomes will be analyzed in a similar manner as the primary outcome. If fewer than 8 cases are observed, the analysis will be reverted to a Fisher exact test.

The length of hospital stay will be shown by using a Kaplan-Meier plot with a survival function and will be analyzed via a Cox proportional hazards regression. Patient deaths will be censored on the date of death.

Missing Data and Populations Under Investigation

Missing data will be summarized, and the reasons will be explained.

Subgroup Analyses

Whether descriptive analyses will be carried out for subgroups will be determined at the time of analysis.

Software

Stata, version 15 (or later; StataCorp LLC) will be used to conduct the statistical analysis.

Results

Our study was approved by the National Health Service Research Ethics Committee (reference number: 19/WA/0190) via the Integrated Research Application System (project ID: 231694) prior to subject recruitment.

Cardiff University is acting as the study sponsor.

Our study is financially supported through an external, peer-reviewed grant from the British Geriatrics Society and internal funding resources from Cardiff University.

The results will be disseminated through peer-review publications, social media, and conference proceedings.

Discussion

Older patients represent a unique subset of patients who require major oncological surgery, as they are predisposed to a number of preoperative risk factors that are not often seen in younger patients. The purpose of our study is to evaluate older patients undergoing elective colorectal cancer resection by focusing on the three aforementioned perioperative factors—frailty, sarcopenia, and nutritional status. Following a series of sequential objective measurements, associations between each risk factor as well as associations between risk factors and common postoperative outcomes of interest will be examined.

Our preliminary study will provide data on the feasibility of obtaining serial urine samples for the metabolomics analysis of nutritional status in the perioperative period. We also believe that the data obtained from our study (and subsequent larger studies) will enable clinicians to identify older surgical patients who are the most at risk for poor surgical outcomes. These data will help establish which preoperative risk factors would be most beneficial to target in the future and will help clinicians provide better care to older surgical patients through more personalized and bespoke medicine.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

CFS: Clinical Frailty Scale
CNS: clinical nurse specialist
CT: computerized tomography
GFI: Groningen Frailty Index
POAC: preoperative assessment clinic

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Protocol

Matching Registered Nurse Services With Changing Care Demands in Psychiatric Hospitals: Protocol for a Multicenter Observational Study (MatchRN Psychiatry Study)

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Abstract

Background: The quality of care is often poorly assessed in mental health settings, and accurate evaluation requires the monitoring and comparison of not only the outcomes but also the structures and processes. The resulting data allow hospital administrators to compare their patient outcome data against those reported nationally. As Swiss psychiatric hospitals are planned and coordinated at the cantonal level, they vary considerably. In addition, nursing care structures and processes, such as nurse staffing, are only reported and aggregated at the national level, whereas nurse outcomes, such as job satisfaction or intention to leave, have yet to be assessed in Swiss psychiatric hospitals. Because they lack these key figures, psychiatric hospitals' quality of care cannot be reasonably described.

Objective: This study's purpose is to describe health care quality by exploring hospital structures such as nurse staffing and the work environment; processes such as the rationing of care; nurse outcomes, including job satisfaction and work-life balance; and patients' symptom burden.

Methods: Match^{RN} Psychiatry is a multicenter observational study of Swiss psychiatric hospitals. The sample for this study included approximately 1300 nurses from 113 units of 13 psychiatric hospitals in Switzerland's German-speaking region. In addition, routine patient assessment data from each participating hospital were included. The nurse survey consisted of 164 items covering three dimensions—work environment, patient safety climate, and the rationing of care. The unit-level questionnaire included 57 items, including the number of beds, number of nurses, and nurses' education levels. Routine patient data included items such as main diagnosis, the number and duration of freedom-restrictive measures, and symptom burden at admission and discharge. Data were collected between September 2019 and June 2021. The data will be analyzed descriptively by using multilevel regression linear mixed models and generalized linear mixed models to explore associations between variables of interest.

Results: The response rate from the nurse survey was 71.49% (1209/1691). All data are currently being checked for consistency and plausibility. The Match^{RN} Psychiatry study is funded by the participating psychiatric hospitals and the Swiss Psychiatric Nursing Leaders Association (Vereinigung Pflegekader Psychiatrie Schweiz).

Conclusions: For the first time, the Match^{RN} Psychiatry study will systematically evaluate the quality of care in psychiatric hospitals in Switzerland in terms of organizational structures, processes, and patient and nurse outcomes. The participating psychiatric hospitals will benefit from findings that are relevant to the future planning of nurse staffing. The findings of this study will contribute to improvement strategies for nurses' work environments and patient experiences in Swiss psychiatric hospitals.

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KEYWORDS

quality of care; psychiatric hospitals; nurses; patient routine data; work environment; Switzerland

Introduction

Background

As of 2016, approximately 1 billion people worldwide were affected by mental illness [1]. Although mental illnesses account for 7% of the global disease burden [2] and about 13% of total health expenditures in European Union countries [3], methods for assessing the quality of mental health care are considerably less advanced than in other health services areas [4].

We define quality of care as a measure of how fully the provided services lead to the desired outcomes [5]. Measurements of the quality of care cover various dimensions, such as structures; processes of care; and outcomes, including clinicians' and patients' perspectives [6,7]. To monitor the quality of care, measurements must be relevant for patients, health care providers, and policy makers and have an acceptable reporting burden [8]. On the basis of the structure-process-outcome (SPO) model by Donabedian [6], the International Psychiatric Association has concluded that differences in structures and processes are insufficiently assessed or otherwise considered in psychiatric settings. In addition, systematically monitored patient outcomes are scarce [9]. In mental health care, because research regarding structures, processes, and outcomes is limited, the quality of care in psychiatric hospitals is inadequately depicted, leaving triggers for quality improvement efforts absent.

In Switzerland, the structures of psychiatric care are planned at the cantonal level. As a result, the structures and processes of psychiatric hospitals vary considerably [10], offering the possibility to assess the impact of various structures and processes on outcomes. However, little is known about psychiatric hospitals' nursing care structures, processes, or outcomes. For example, no requirements stipulate the number of nurses or skill or grade mix per unit, and no data are required regarding, for example, nurse well-being or job satisfaction. In contrast, patient outcomes and characteristics are well monitored. This imbalance provides a rare opportunity to examine how various structures and processes affect patient and nurse outcomes in psychiatric hospitals at the national level. By assessing them, we hope to help improve the interpretation of the mandatorily measured and reported patient outcomes. Specifically, we will provide and analyze data at the unit level, which is crucial for monitoring and describing the quality of care [11,12].

Swiss Psychiatric Hospitals: Structures and Processes

In 2018, the 50 participating psychiatric hospitals housed 7772 beds [13] and registered 76,097 patient admissions [14], with an average stay length of 3.4 days [15]. Although the raw figures regarding the health professionals employed for 2018 were well documented (eg, 6399 full-time equivalent nurses and 1906 doctors [13]), no data were gathered on nurse staffing, skill or grade mix, or the quality of the nurse work environment [10], all of which would be highly significant to quality improvement strategies.

Higher nurse staffing is positively associated with patient safety and nurse outcomes in general hospitals [12]. This positive association between nurse staffing and patient safety is also known, but less studied, in psychiatric settings [16,17]. In addition to nurse staffing, work environment factors, including nurses' perceived workload, relationship with physicians, and leadership, are reported as structural factors that influence patient and nurse outcomes in psychiatric hospitals [18].

In addition, to assess nursing processes, rationing of care, that is, the partial or complete omission of care because of a lack of resources [19,20], has frequently been observed [19]. Higher proportions of rationing care are associated with lower staffing levels [21]. To date, the rationing of care has not been measured in psychiatric hospitals [20].

Patient Characteristics and Outcomes in Swiss Psychiatric Hospitals

In 2017, the most frequent diagnoses at admission to Swiss psychiatric hospitals were affective disorders (32.1%), schizophrenia (16.4%), and anxiety or dissociative disorders (13%) [13]. Of all the admissions, 19.7% were involuntary [22]. Involuntary admissions are only allowed if the treatment is absolutely indispensable, for example, in cases where patients pose a threat to themselves or others, and care cannot be provided in any other form, such as outpatient clinics [22]. In psychiatric inpatient facilities, the risk of patient violence is higher than that in other care settings [23]. Although this is mainly because of the acuity of patients' psychiatric symptoms, it also relates to the curtailment of patients' personal freedom in inpatient settings [24,25].

Patient outcome data were mandatorily collected for the Swiss National Association for Quality Development in Hospitals and Clinics. It included clinician-rated symptom burdens and self-rated symptom burdens at admission and discharge, as well as patient satisfaction and any coercive measures taken (ie, seclusion, restraints and coercive medication [26]). Aggregated and publicly reported at the hospital level, these patient outcomes serve as benchmarks for psychiatric institutions.

This purpose of this study is to describe the structure, processes, and nurse and patient outcomes in Swiss psychiatric hospitals. The results will deepen our understanding of the quality of care in psychiatric inpatient settings.

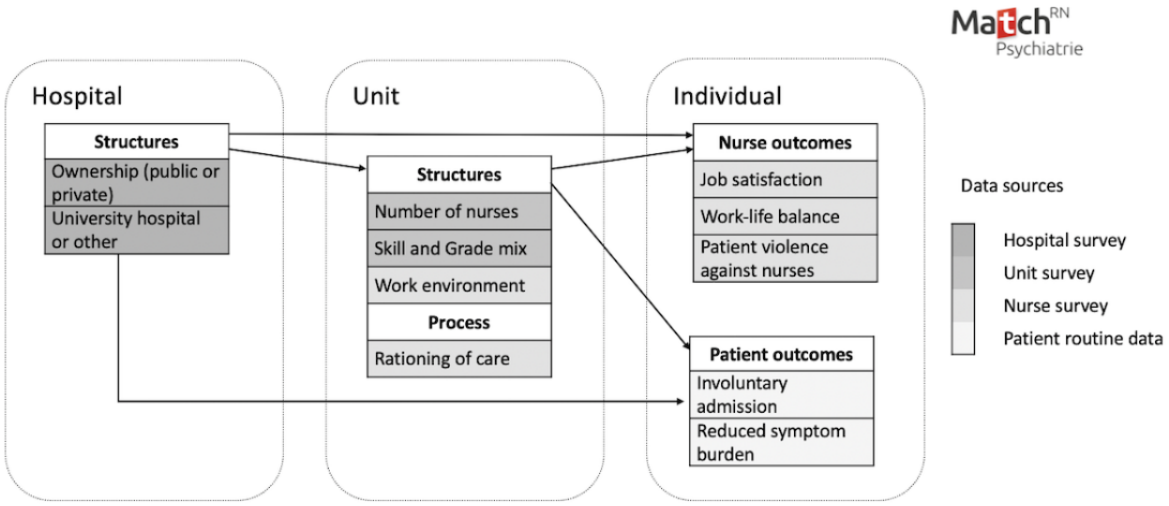
Aims

This study aims to (1) describe the structures and processes of nursing care, (2) describe patient outcomes at the unit level, and (3) explore possible associations between the nursing work environment and patient outcomes in psychiatric hospitals.

Framework

The Match[RN] Psychiatry framework deals with critical information collected at the hospital, unit, and individual levels (Figure 1). As a framework, it was adapted from the Match[RN] study, which was conducted for acute care hospitals [27], and was originally based both on the Donabedian SPO model [6] and Donaldson contingency theory [28].

Figure 1. The framework of Match[RN] Psychiatry.



According to Donabedian [6], quality of care can be evaluated in terms of structure (health care setting characteristics), processes (clinical processes in health care settings), and outcomes (eg, patient status after application of the process). The three SPO dimensions are interlinked, where structures provide the basis for the provision of a process that affects outcomes. Donaldson contingency theory assumes that organizations fit into their environment; for example, units fit into the hospital, and hospitals fit into the health care system. To achieve an appropriate fit, the organization must adapt to its environment [28]. A health care organization's fit is characterized by its performance, for example, quality of care (nurse and patient outcomes) and the efficiency of its services, for example, structure and process [29]. Combining the 2 models allows the mapping of the Donabedian quality criteria while highlighting interdependent and organizational dynamics at the hospital, unit, and individual (nurse and patient) levels (Figure 1).

Methods

Design

Match[RN] Psychiatry is a cross-sectional multicenter study of Swiss German psychiatric hospitals.

Setting and Sample

This study included psychiatric hospitals with units for adult inpatient care in the German-speaking part of Switzerland. All 40 institutions with membership in the Swiss Psychiatric Nursing Leaders Association (Vereinigung Pflegekader Psychiatrie Schweiz, 40/50, 80% of all Swiss psychiatric hospitals) were invited to participate. A total of 13 psychiatric hospitals decided to enroll in the study, leading to a convenience sample at the hospital level.

All units for adult inpatients were eligible; however, the hospitals decided which units to enroll, resulting in a convenience sample (units per hospital: range 3-17).

This study sample consisted of 115 inpatient units, including their nursing workforce, totaling approximately 1300 registered nurses and health care assistants. In addition, routine data from all inpatient cases treated in these units in 2019 will be included. Other inpatient areas, such as forensic units, were excluded.

Variables and Measurement

The Match[RN] Psychiatry variables and measurements include patient routine data and survey data at the hospital, unit, and individual nurses level based on the Match[RN] acute care survey [27].

Hospital Survey

The hospital-level survey asks for hospital characteristics: ownership status (private or public), hospital type (university or nonuniversity hospital), and hospital size (number of beds).

Unit Survey

On the basis of the Match[RN] acute care survey [27], the 57-item unit-level survey assesses each unit's staffing (eg, number of nurses and use of agency nurses), staff planning principles (eg, skill mix, nurse-to-patient ratio), and influence of the COVID-19 pandemic on the unit (Table 1). The unit managers will be asked to complete it.

Table 1. Variables and measurements in the units' survey.

Topic	Description	Measurements
Unit characteristics	5 items assessing the name, specialization, number of beds, average length of stay, and bed occupancy at the unit	2 text items, 3 number items
Workforce		
Numbers of FTEs[a]	2 items from the Match[RN] study [27] assessing the FTE of nurses according to educational background and function	Number of FTEs
Agency nurses	7 items from the Match[RN] study [27] assessing frequency, duration, and attitude for agency nurses' use	4 items: 10-point Likert-type scale from 1 (strongly disagree) to 3 (strongly agree); 3 items: 6-point Likert-type scale from 1 (never) to 6 (several times a week)
Organization of nurse service		
Resources allocation	20 items from the Match[RN] study [27] assessing resources allocation at the unit	4 items: 10-point Likert-type scale from 1 (very low) to 3 (very high); 16 items with various multiple answer options
Work schedule	16 items from the Match[RN] study [27] assessing the responsibility, influence, and flexibility in work schedules of nurses at the unit	4 items: 10-point Likert-type scale from 1 (strongly disagree) to 3 (strongly agree); 12 items with various multiple answer options
Influence of COVID-19 at the unit		
COVID-19 at the unit	4 investigator-developed items assessing whether patients with COVID-19 are at the unit; teaching and use of personal protection equipment	3 items: 2 answer options (yes or no); 1 open-text item
Career characteristics of the unit manager		
Career characteristics	5 items from the Match[RN] study [27] assessing qualification level, years in nursing, years in psychiatric care	N/A[b]

[a]FTE: full-time equivalent.

[b]N/A: not applicable.

Nurse Survey

On the basis of the Match[RN] acute care survey [27], the 164-item Match[RN] Psychiatry nurse survey captures variables of the psychiatric setting (Multimedia Appendix 1 [27,30-42]).

This survey fulfills 2 main objectives. First, it collects data on structural factors, such as the number of nurses present on the last shift, quality of the nurse work environment (measured via a modified version of the Practice Environment Scale of the Nursing Work Index [30]), and safety culture (measured via the Safety Attitude Questionnaire [31]). Second, it asks about work processes in the unit, including, for example, a version of the rationing of care [19] developed and modified by the Match[RN] Psychiatry study team that is fit for use in psychiatric inpatient settings. The modification process included a literature review and pilot test with experts from inpatient settings in psychiatric hospitals. In addition, it includes items on nurse outcomes such as job satisfaction, well-being, and experiences with patient violence against nurses [32], as well as on sociodemographics (eg, age and gender), and professional experience in nursing (eg, years in nursing and years in psychiatric care).

Patient Data

We will use 17 items from the Swiss National Association for Quality Development in Hospitals and Clinics questionnaire, which is mandatory for all psychiatric hospitals. This includes data on all inpatients who were hospitalized in participating units during 2019 (Table 2). In addition to demographic details (age and sex), clinical data will be included (medical diagnoses [with International Classification of Diseases-10 codes] and the reduction of symptom burden), along with symptom burden data taken at admission and discharge via the Health of the Nation Outcome Scale (HoNOS) [43].

Table 2. Variables and measurements for patient routine data.

Topic and variable	Measurement
Demographics	
Age	In years at admission
Gender	Female or male
Clinical data	
Length of stay	
• 1 item calculated from the date of admission and date of discharge	Number of days
Medical diagnosis	
• ICD-10[a] code	5-digit code
Symptom burden	

• All 12 items of the HoNOS[b] [44]
  • Overactive, aggressive, disruptive, or agitated behavior
  • Nonaccidental self-injury
  • Problem drinking or drug taking
  • Cognitive problems
  • Physical illness or disability problems
  • Problems with hallucinations and delusions
  • Problems with depressed mood
  • Other mental and behavioral problems
  • Problems with relationships
  • Problems with activities of daily living
  • Problems with living conditions
  • Problems with occupation and activities
	5-point Likert-type scale from 0 (no problem) to 4 (severe or very severe problem) measured at admission and discharge

[a]ICD-10: International Classification of Diseases-10.

[b]HoNOS: Health of the Nation Outcome Scale.

The HoNOS, which is to be completed by the responsible health professional, includes 12 items, such as *overactive, aggressive, disruptive, or agitated behavior*, *nonaccidental self-injury*, and *problems with activities of daily living*. The German-language version of the HoNOS showed satisfactory results for feasibility (range of missing values 1.3%-4.5% for 11 items) and satisfactory retest reliability (interclass correlation 0.80-0.91, for 9 items) [44]. Coercive measures will be assessed for each patient case using the number and duration of seclusion, restraint, and coercive medication occurrences, as well as admission status (ie, involuntary or voluntary).

Validity and Reliability

Except for the modified version of the rationing of care scales and the questions about COVID-19 in the unit survey, all data collection instruments have been tested for validity and reliability in previous international and national studies [33,34,45].

We used established or pretested German-language versions for the nurse survey to ensure the validity and reliability of the study instruments. In addition, the nurse survey items were pilot tested for content validity and comprehensibility in a group of 29 nurses from 5 psychiatric hospitals.

Data Collection

Data collection at the hospital, unit, and individual levels (nurses and patients) was initially planned for September 2019 to April 2020. However, because of the COVID-19 pandemic, only the nurse survey was completed within this period. Unit- and hospital-level data collection was completed in June 2021.

Each hospital can choose whether data are collected via a web-based survey or a paper-pencil questionnaire. At each participating hospital choosing the latter, a single point-of-contact person will be responsible for the onsite organization of the questionnaire distribution. Individual study participation is entirely voluntary. Informed consent will be obtained by filling out and submitting the questionnaire. The participating hospitals will provide patient routine data at the unit level. As these data include no information that could be used to identify individual patients or nurses, anonymity will be guaranteed. Data at all levels will be collected once.

Data Analysis

After checking the data quality for plausibility and missing data, we will conduct descriptive analyses for all variables using frequencies and percentages for categorical variables, with means and SDs reported for continuous variables. We will assess the dimensionality of the rationing of care items using a Mokken scale analysis [46]. To explore the relationship between nurse staffing, including the patient to nurse ratio and work

environment as exposure variables and patient's symptom burden or nurse outcomes such as work-life balance, we will use linear mixed models for normally distributed data and generalized linear mixed models for dichotomous outcomes. For the latter, we will calculate odds ratios and 95% CIs. For example, to assess work-life balance, a generic model would have the following structure:

where the outcome work-life balance is a normally distributed outcome, which is predicted by unit-level variables (eg, staffing and leadership), individual-level variables (eg, age, working time, and family status), and random intercepts for unit and hospital ID.

All statistical analyses will be performed using the software R (R Foundation for Statistical Computing), version 4.X for MacOS [47]. To minimize confounder bias and determine the robustness of the effects, we will conduct sensitivity analyses for all inferential regression analyses [48].

Ethical Considerations

The responsible ethics committee (Ethics Commission Northwest and Central Switzerland) ruled the status of the Match^{RN} Psychiatry as an exempt (project ID: Req-2019-00589).

The data collection procedure was approved by the data protection officer of the University of Basel.

The nurse questionnaire will be distributed with a cover letter explaining the study's purpose and data protection measures, assuring confidentiality and anonymity, and emphasizing that participation is voluntary.

Data protection and confidentiality will be ensured by using codes for each psychiatric hospital and unit so that only the research team at the University of Basel's Institute of Nursing Science will be able to identify study sites and units. Each individual nurse respondent will remain anonymous. The patient outcome routine data will be provided anonymously from participating psychiatric hospitals. The anonymized data will be deposited in the Zenodo open-access research data repository.

Dissemination of Findings

First, benchmark reports, including unit-level results, will be provided to the participating institutions, allowing the comparison of findings and interhospital learning. A national report with key descriptive results will be published, providing nonparticipating psychiatric hospitals access to the findings. To further support psychiatric hospitals, a congress will be held to promote and discuss the results with and between them. Furthermore, the study results will be communicated to the study sites on demand. We also envision the publication of study results via scientific journals and scientific conferences.

Results

The response rate from the nurse survey was 71.49% (1209/1691). All data are currently being checked for consistency and plausibility. The Match^{RN} Psychiatry study is funded by the participating psychiatric hospitals and the Swiss Psychiatric Nursing Leaders Association (Vereinigung Pflegekader Psychiatrie Schweiz).

Discussion

For the first time, the Match^{RN} Psychiatry study will assess the quality of care in Swiss psychiatric hospitals by considering all relevant structures, processes, and patient and nurse outcomes. On the basis of the relationships indicated between these variables, they can later be targeted to maintain or improve the quality of care in Swiss psychiatric hospitals in accordance with global initiatives, including the World Health Organization's Quality Rights Initiative [7,8,49,50]. The participating psychiatric hospitals will benefit from the planning and regulation of nurse staffing. By improving Swiss psychiatric hospitals' understanding of their nurse work environment factors' relationships with specific patient outcomes, Match^{RN} Psychiatry will allow and encourage Swiss psychiatric hospitals to target interventions that will improve both nurse and patient outcomes. Future research should also provide a foundation for cantonal, national, and international studies and comparisons.

Acknowledgments

Match^{RN} Psychiatry is supported by an advisory board of 4 experts with profound expertise in nursing and inpatient care in psychiatric hospitals. From the beginning of the project, its members have both raised the awareness of the study in mental health settings and provided invaluable advice on Match^{RN} Psychiatry's content and processes.

Authors' Contributions

All authors have agreed on the final version and meet at least one of the following criteria (as recommended by the International Committee of Medical Journal Editors): (1) substantial contributions to conception or design, the acquisition of data, or the analysis and interpretation of data and (2) drafting the article or revising it critically for significant intellectual content.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Variables and measurements in the nurses' survey.
[DOCX File , 22 KB - resprot_v10i8e26700_app1.docx]

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Abbreviations

HoNOS: Health of the Nation Outcome Scale
SPO: structure-process-outcome

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Original Paper

Mental Health Promotion and Stigma Reduction Among University Students Using the Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM) Framework: Protocol for a Mixed Methods Study

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Abstract

Background: Rapid urbanization, academic pressures, and developmental life transition stressors contribute to mental health stress for postsecondary students in China. Effective prevention, early identification, and timely intervention are challenged by stigma, a lack of mental health literacy, and inadequate mental health resources.

Objective: Our implementation science (IS) research project is aimed at evaluating the use of an evidence-informed mental health promotion intervention named Acceptance and Commitment to Empowerment – Linking Youth and 'Xin' (hearts) (ACE-LYNX) to promote university student mental health in Jinan, China.

Methods: We will engage and collaborate with Shandong Mental Health Center, the provincial mental health center, and six local universities in different regions of Jinan. The ACE-LYNX intervention aims to reduce social stigma against mental illness, enhance mental health literacy, and improve access to quality mental health care by increasing interdisciplinary collaboration and forming a mental health network. It is based on two evidence-based approaches, Acceptance and Commitment Therapy (ACT) and Group Empowerment Psychoeducation (GEP), and it will be delivered through online learning and in-person group training. The project will train 90 interdisciplinary professionals using the model. They will in turn train 15 professionals and 20 students at each university. The project will adopt the Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM) framework, which provides a structure to examine the process and outcomes of implementation using mixed methods comprising quantitative and qualitative approaches along five dimensions: reach, efficacy, adoption, implementation, and maintenance.

Results: Over the course of the project, 720 champions will be directly trained. They will contribute to developing a formal and informal mental health network, strengthened by student-led mental health initiatives and professional-led initiatives to promote collaborative care and facilitated care pathways. We anticipate that our project will reach out to 11,000 to 18,000 students.

Conclusions: This IS protocol will outline our unique intervention model and key steps to contextualize, implement, and evaluate community-based mental health intervention.

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KEYWORDS

China; implementation science; intervention; mental health; stigma reduction; university students

Introduction

In China, rapid urbanization and mass internal migration to big cities have led to increasing concerns about stress and mental health risks for people living in big cities [1]. Based on a national survey from 2013 to 2015, there is an estimated lifetime prevalence of 16.6% for all mental disorders excluding dementia, with the prevalence of most disorders being higher than that observed in the 2002 survey [2]. Youths constitute the age group particularly vulnerable to the first onset of major mental illness. The prevalence rate of anxiety disorders and depression among children and youths in China were 24% and 16%, respectively, in 2014 [3].

For university students in China, the prevalence rate of various mental disorders is as high as 20% to 30% [4,5]. This is particularly alarming as Chinese students make up one in five of the world's postsecondary student population [6]. Academic stress and performance requirements, high-pressure university majors or programs, minority status, family income, and ineffective coping were identified as factors contributing to university students' stress and mental disorders, including anxiety, depression, suicidal ideation, alcoholism, and self-harm [5,7-10]. As there is increasing evidence suggesting an association between the duration of untreated illness and clinical outcomes, it is of critical importance to implement effective prevention, early identification, and timely intervention initiatives [11].

Given the significant mental health needs, researchers, health care providers, and policy makers in China have called for higher prioritization of mental health promotion, prevention, and care [2]. A number of studies in China have found that the general public across different levels of education have limited knowledge about mental disorders, and mental disorders are often associated with stigma and misattributed to personality weaknesses or social skill deficits [12]. Mental health literacy strategies address this problem by increasing the ability of the target population to recognize common mental illnesses and learn how to seek mental health information or help [13]. At the systemic level, another factor is the shortage of trained mental health professionals and the lack of adequate mental health resources to match the population's growing needs [2]. Thus, strategies to promote mental health should address multiple barriers impeding help-seeking, including mental illness stigma, mental health literacy, and the capacity of service providers to respond to mental health needs [10,13].

Our implementation science (IS) research project named Acceptance and Commitment to Empowerment–Linking Youth and "Xin" (hearts) (ACE-LYNX) is a five-year Canada–China collaborative project aiming to promote the mental health and well-being of university students in Jinan, China. The project uses an evidence-informed multipronged approach to reduce stigma against mental illness, enhance mental health literacy, and improve access to quality mental health care by promoting interdisciplinary collaboration among service providers. The vision is to engage service providers and students to collaborate in developing formal and informal interdisciplinary mental health care networks to improve access to mental health services and peer support. As an IS project, it consists of two main phases: contextual analysis with service providers and students to inform the contextual adaptation of the ACE-LYNX intervention [14]; and the implementation phase of the ACE-LYNX intervention with service providers and university students, the focus of this protocol paper. Integrative knowledge translation (iKT) will be applied in all the stages of this study (paper under preparation) [15].

Methods

Project Location: Jinan, Shandong, China

Linking Hearts will take place in Jinan, a metropolis city with a population of over 7 million [1]. We will engage and collaborate with Shandong Mental Health Center, the provincial mental health center, and six local universities in different regions of Jinan, including Shandong University (63,185 students), University of Jinan (35,916 students), Shandong Jianzhu University (26,000 students), Shandong Youth University of Political Science (12,500 students), Shandong Normal University (36,456 students), and Shandong Women's University (11,410 students).

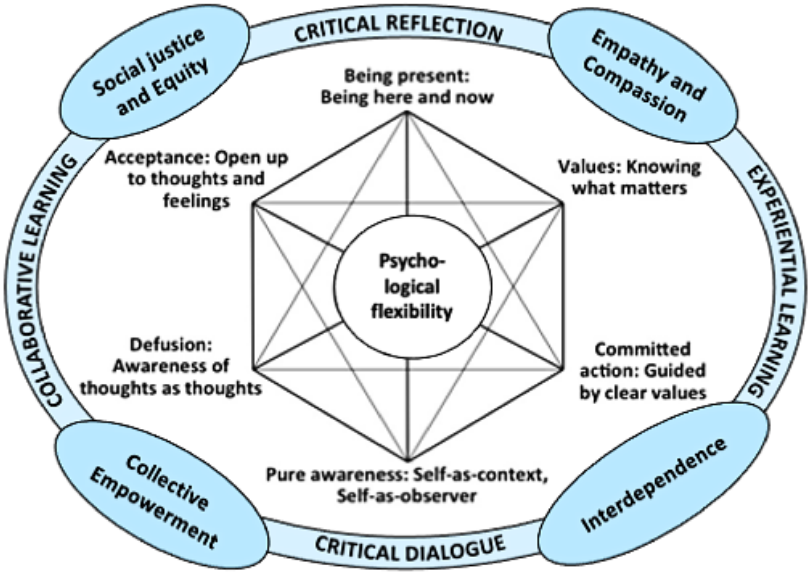
Project Intervention: The ACE-LYNX Intervention

ACE-LYNX is an integrated model of intervention based on two evidence-based approaches: Acceptance and Commitment Therapy (ACT) and Group Empowerment Psychoeducation (GEP) (Figure 1). The ACT model of psychological flexibility in the center of this diagram is adapted from Hayes et al [16] and the GEP model is based on the CHAMP intervention research project previously conducted by authors Li, Fung, and Wong [17-19].

ACT is a mindfulness-based cognitive behavioral intervention that has empirical support for its use in common mental disorders including mood and anxiety disorders, and psychosis [20-24]. ACT consists of six processes to increase psychological flexibility: defusion (observing thoughts as thoughts), acceptance (opening up to experiencing thoughts and feelings), contact with the present moment (attending to the present mindfully), self-as-context (being in touch with the "observer self" and increasing perspective-taking skills), values (being clear about what matters), and committed action (developing consistent patterns of behaviors based on one's chosen values). As ACT and the practice of mindfulness are congruent with Asian traditional self-care practices and Eastern philosophy, it is

especially suitable for the Chinese population. We have employed ACT clinically in the Canadian Chinese population with significant improvements in depressive symptoms as well as general functioning [25]. We have also successfully adapted it for nonclinical populations to reduce judgmental thoughts related to the stigma against HIV and mental illness in Chinese and other ethnoracial populations in Canada [26,27].

Figure 1. Acceptance and Commitment to Empowerment–Linking Youth and 'Xin' intervention presented as an integrated model of Acceptance and Commitment Therapy and Group Empowerment Psychotherapy.



The effectiveness of psychoeducation for stigma reduction and mental distress is well established [28-30]. The GEP component of our intervention is our refined model of psychoeducation underpinned by the principles of social justice and equity; empathy and compassion; interdependence; and collective empowerment. It aims to help participants improve their capacity for self-care and stress management, develop a critical understanding of health equity, and increase their readiness to proactively participate in mental health promotion activities. The knowledge-based content includes the following: holistic understanding of mental health; common signs, symptoms, and syndromes of mental illness; and current treatment approaches and local resources. It is supported by evidence from Canadian intervention studies with Chinese and other ethnoracial immigrant communities [31,32]. The delivery utilizes four empowerment processes: critical reflection, critical dialogue, collaborative learning, and experiential learning.

The integrated ACE-LYNX intervention will be operationalized and delivered via two complementary modalities: (1) an online self-study course named Mental Health 101(MH101) and (2) a 5-day experiential group training.

Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM) Project Implementation Framework

Our implementation project will be guided by the RE-AIM framework, which provides a structure to examine the processes and outcomes of implementing a public health intervention along five dimensions: reach, efficacy, adoption, implementation, and maintenance [33]. Reach measures participation at the individual level, including the risk characteristics and percentage of people who are affected by or receive a policy or program. Efficacy assesses the positive and negative outcomes, including changes in the quality of life, participant satisfaction, behavioral changes, and other clinical or nonclinical variables [33,34]. Adoption evaluates the proportion and representativeness of the settings that uptake and employ a given program or policy [35]. Implementation refers to the degree to which the intervention is conducted as intended in real-life settings, measured at the individual and program levels [33]. Finally, maintenance assesses the extent to which innovations become part of individuals' behavioral repertoire or system changes that are relatively stable and enduring [33].

Project Objectives for Phase Two

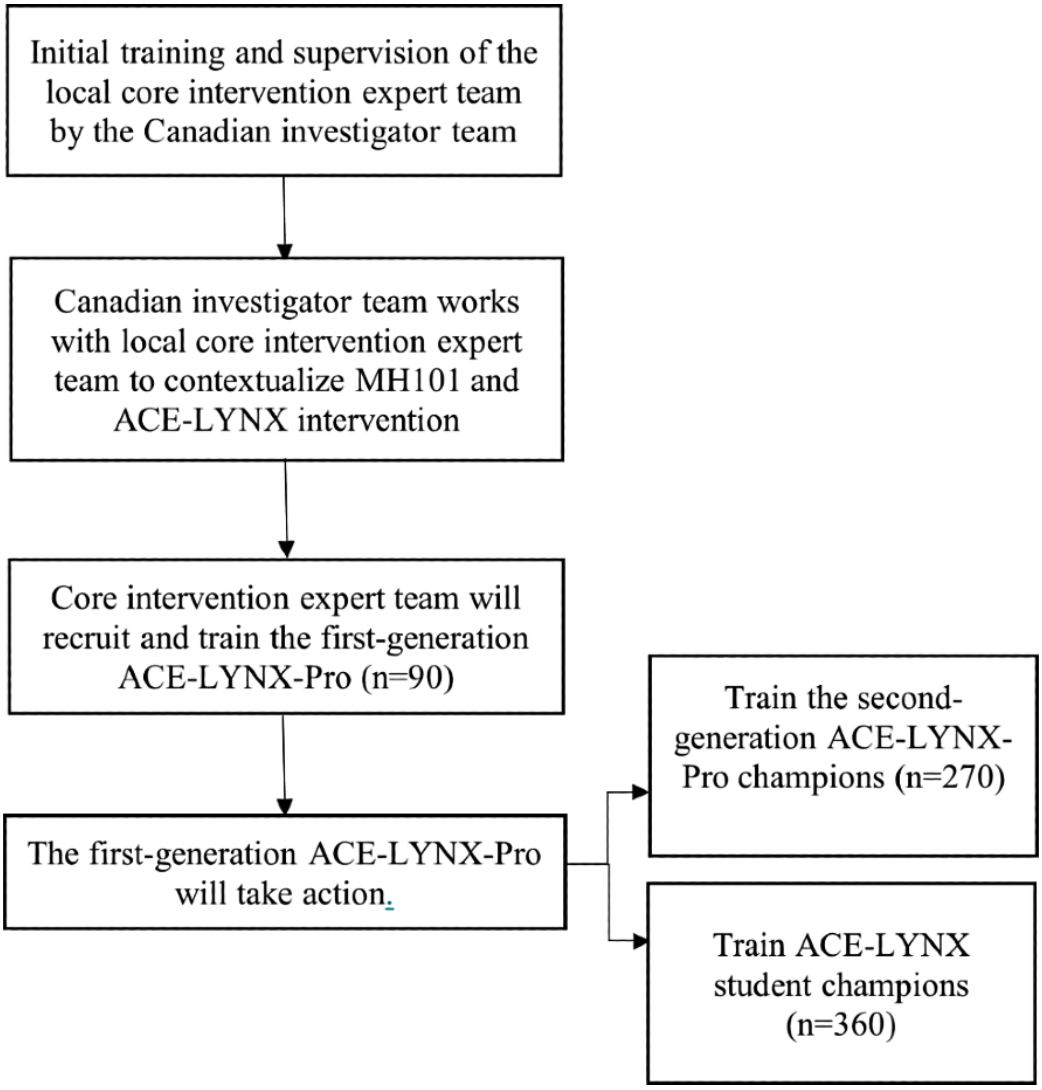
Guided by the RE-AIM framework, we will (1) examine the reach of the target populations by the intervention and an integrated mental health network, (2) evaluate their effectiveness, (3) gauge support for their adoption, (4) document the contextual adaptation and evaluate the fidelity in their implementation, and (5) track the maintenance and sustainability of individual behavioral changes and changes in the system processes [33].

Project Design: Key Stages of Implementation

Prior to the commencement of the project, research ethics approval was obtained from Canadian institutions, including Ryerson University, University of Toronto, University of Alberta, York University, and Chinese institutions including Shandong University, University of Jinan, Shandong Jianzhu University, Shandong Normal University, Shandong Women's University, Shandong Youth University of Political Science, and Shandong Mental Health Center. A contextual assessment will be conducted with local providers, students, and other stakeholders to evaluate the priority of needs, as detailed in our protocol paper (Wong et al, under review), to facilitate

implementation. The key phase two ACE-LYNX implementation steps are summarized in Figure 2 and detailed below.

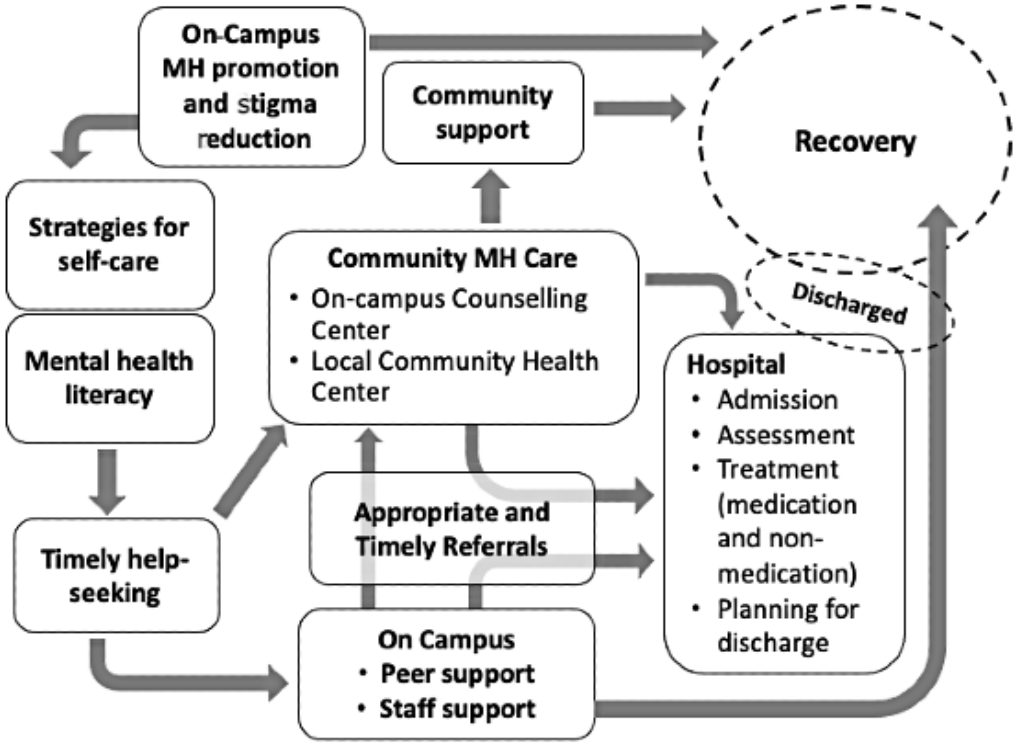
Figure 2. Key stages of Acceptance and Commitment to Empowerment – Linking Youth and 'Xin' implementation. ACE-LYNX: Acceptance and Commitment to Empowerment – Linking Youth and 'Xin' implementation; MH101: Mental Health 101.



Capacity Building: Local Core Intervention Expert Team

Effective implementation of evidence-based intervention is contingent on the appropriateness of the intervention approach and specific strategies for implementing the practice in the existing systems of care [36]. From the perspective of a multilevel model of change, middle-level practice changes within organizations and teams are influenced by the policy context within the system environment as well as the attitude, knowledge, and behavior of care providers and service users at the grassroots level [36]. Therefore, we will engage and build capacity among the local health and social care professionals within the existing systems of care allocated to health promotion, treatment, and recovery services already in place, as illustrated by the integrated pathways of mental health care (Figure 3). We will use a "train-the-trainer" capacity-building model to implement and evaluate the effectiveness of the ACE-LYNX intervention designed for professionals.

Figure 3. Integrated pathways of mental health care. MH: mental health.



A core team of 24 local interdisciplinary professionals, including psychiatrists, nurses, on-campus counselors, and social work university professors in Jinan, China will be recruited and trained by the Canadian investigator team to become the local ACE-LYNX expert team. They will serve as core intervention expert trainers for the project to deliver the intervention locally. After the initial 5-day in-person training, the core intervention expert trainers will engage in mock training and provide constructive peer feedback. The mock training will be video-recorded and reviewed by the Canadian team members for feedback via videoconferencing to ensure model fidelity. During implementation, the core intervention expert trainers will form training teams to deliver the intervention at the six universities with ongoing support from the Canadian team.

Contextualization of the ACE-LYNX-Pro Intervention

Mental Health Modules (MH101 Modules)

Key priorities and local mental health needs (Wong et al, under review) from contextual analysis will be used to locally adapt the MH101 online modules to ensure local relevance, efficacy, and acceptability. Module 1 will focus on key concepts regarding mental health and well-being drawing from positive psychology and holistic health. Module 2 will focus on factors that adversely affect mental health, including biological, psychological, sociocultural, and spiritual factors. Module 3 will introduce common mental disorders and addictions. Module 4 will discuss issues around suicide and suicide prevention, mental illness treatment and recovery, and local resources. All modules will be produced in Jinan, China, with active participation by local professors and students. The self-directed modules will be completed by all participants prior to joining the in-person group training.

ACE-LYNX-Pro In-Person Group Training

The ACE-LYNX-Pro group training is a 5-day intensive in-person experiential group training. During implementation, it can be flexibly scheduled as half-day (3-hour) sessions to accommodate participant needs. The first 3 days will focus on learning the core ACT and GEP processes through intense reflective and experiential group activities (see Table 1). The last 2 days will focus on the skills needed to become ACE-LYNX-Pro champions, namely delivering the training to others and taking steps toward forming a mental health network. Written informed consent will be obtained from all participants prior to the start of the training. Data from contextual analysis and inputs from the core intervention expert trainers will be used to contextualize the intervention. This includes the use of culturally appropriate translations of concepts and expressions; contextualized vignettes that reflect local experiences of stigma and mental illness; and local terms used in discussing life values.

Table 1. Acceptance and Commitment to Empowerment–Linking Youth and "Xin"-Pro group intervention training program.

Day	AM/PM	Session
1	AM	• Introduction to ACT[a] (theory) • Health continuum (GEP[b]) • Group rules/norms • How to get most out of it?

	PM	• Present moment I
		  • Leaves on a stream
		• Defusion
		  • Paired singing
		  • Stigma rules and stories

2	AM	• Acceptance
		  • Chair sculpture of suffering
		  • Exclusion circle

	PM	• Self-as-context
		  • Le'go exercise
		  • Three things you did today
		• Present moment II
		  • Loving kindness

3	AM	• Values
		  • Cultural and personal values exercise
		  • Your legacy

	PM	• Committed action
		  • Bull's-eye and bus driver
		  • Collective bull's-eye and committed group action project

4	AM	• ACEc communication skills • Group facilitation skills
	PM	• Facilitating and leading ACT and experiential exercises
5	AM	• Building a functional mental health network
	PM	• Next steps • Feedback

[a]ACT: Acceptance and Commitment Therapy.

[b]GEP: Group Empowerment Psychoeducation.

[c]ACE: Acceptance and Commitment to Empowerment

Selection and Eligibility of First Generation of ACE-LYNX-Pro

At each participating university, the Chinese core intervention expert team will recruit a group of 15 local psychiatric and nonpsychiatric professionals to take part in the ACE-LYNX-Pro intervention training. For each group, we aim to recruit counselors, dormitory counselors, social work professors, and psychiatrists or psychiatric nurses to promote interdisciplinary collaboration using interprofessional educational (IPE) principles [37]. After training, all participants will join a community of practice during a 3-month practicum period. They will be encouraged to post regular reflections on the impact of the intervention on their personal and professional lives. For their participation in the training program, participants will receive a certificate of completion. Effectiveness will be evaluated with psychometric scales, namely preintervention, immediately postintervention, and 3 months postintervention (see Table 2). Implementation evaluation will be guided by the RE-AIM framework (see Table 3). Participants will also be invited to join a 3-month postintervention focus group.

Table 2. Data collection tools.

Instrument name	Instrument description	Reliability statistics (from previous studies)
Demographics and Background Mental Health Questionnaire	This is a descriptive measure developed for the purpose of the project. Background information regarding family socio-economic status, health history, etc is collected to understand the profiles of participating individuals.	N/A[a]
Depression, Anxiety, and Stress Scale (DASS-21)	The DASS-21 is a 21-item measure of the emotional states of depression (D), anxiety (A), and stress (S) [38].	Cronbach α=.81(D),.89 (A), and.78 (S) [39]
Community Attitude toward the Mentally Ill (CAMI)	The CAMI is a 40-item self-reported inventory of attitudes and stigma toward mental illness [40].	Cronbach α=.6-.81 [41]
Mental Health Knowledge Questionnaire (MHKQ)	The MHKQ is a 20-item self-assessment to evaluate public knowledge and awareness of mental health concerns [42].	Cronbach α=.61 [42]
Acceptance and Action Questionnaire (AAQ-II)	The AAQ is a 7-item self-reported measure of experiential avoidance, psychological inflexibility, and cognitive fusion [43].	Cronbach α=.84 [43]
Bull's-Eye	The Bull's-Eye is an exercise to identify and measure personal values, value attainment, and persistence [44].	The test-retest reliability of the Bull's-Eye has been high; *r*=.85 [45].
Multi-System Model of Resilience Inventory (MSMR-I)	The MSMR-I is 27-item, self-reported multidimensional measure of individual resilience capacities across intraindividual, interpersonal, and sociostructural domains [45].	Cronbach α=.9-.91 [46]

[a]N/A: Not applicable.

Table 3. Implementation evaluation using the five dimensions of the Reach, Efficacy, Adoption, Implementation, and Maintenance framework.

Dimension	ACE-LYNX-Pro/ACE-LYNX[a] training	Integrated network
Reach	• % trained and % expressing interest / estimated eligible population • Comparisons: completers versus dropouts; completers versus population	• # of nodes in integrated "real" and "virtual" networks tracked by SNA[b] surveys, learning management system, and Weixin, including the # of professional champions, student champions, untrained professionals, and students
Effectiveness	Preintervention, postintervention, and 6-month follow-up: • Attitude: CAMI[c] • Knowledge: MHKQ[d] and localized questions • Empowerment/MH[e] Outcomes: DASS-21[f], AAQ-II[g], Bull's-Eye, and monthly activity logs (personal, peers, university, and community)	• Network structure: degree of interdisciplinary collaboration among professionals (SNA survey, learning management system); peer support and information exchange among students (Weixin); students to professional contacts (SNA survey, learning management system) • Service volumes: # of new cases; diagnoses; types of services delivered between preintervention and postintervention evaluations
Adoption	• Perceived feasibility, acceptability, and fit from contextual assessment (students and professional FG[h] and advisory committees) • Interest expressed for adoption by health, communities and educational organizations not involved in the project (advisory committees and iKT[i])	• Quarterly SNA survey to track programmatic, organizational, and institutional engagement by examining affiliations of champions and those that they are in contact with
Implementation	• Fidelity checklist to monitor adherence to protocols and manuals: (a) IA[j] training professionals; (b) ACE-LYNX-Pro training students; (c) ACE-LYNX-Pro training second- generation ACE-LYNX-Pro • Postsession forms filled by participants • Reflection forms filled by facilitators • Evaluation forms filled by participants of student-driven activities	• Quarterly SNA survey: density, degree centrality, centralization, and dynamic changes over time • Visualization with sociograms • Identification of "hubs" and "isolates"
Maintenance and sustainability	• Propagation of ACE-LYNX-Pro beyond the second generation • Online qualitative survey at 6 months • Uptake of ACE-LYNX-Pro training model by other organizations and other educational/health institutions through iKT	• Interdisciplinary consultation and support tracked through learning management system beyond 6-month practicum period • Quarterly SNA survey-document longitudinal activities • Dissemination of "MH101" and other mental health promotional messages through Weixin to untrained professionals and students • Monthly activity logs: activities / initiatives that sustain beyond the project (eg, starting new groups, websites, etc) • Uptake of network model by other educational/health setting through iKT

[a]ACE-LYNX: Acceptance and Commitment to Empowerment–Linking Youth and "Xin" implementation.

[b]SNA: Social Network Analysis

[c]CAMI: Community Attitude toward the Mentally Ill

[d]MHKQ: Mental Health Knowledge Questionnaire

[e]MH: mental health

[f]DASS21: Depression, Anxiety, and Stress Scale

[g]AAQ-II: Acceptance and Action Questionnaire

[h]FG: focus group

[i]iKT: integrative knowledge translation

[j]IA: intervention assistant

Recruitment and Eligibility of ACE-LYNX-Pro Champions

Over 3 months, the first-generation ACE-LYNX-Pro champions will (1) deliver the ACE-LYNX intervention (student version) to university students; (2) train interdisciplinary professionals at their university to become "second-generation" ACE-LYNX-Pro champions and provide ongoing mentorship; and (3) function as part of an integrated network to increase university students' access to mental health care.

Training University Students to Become ACE-LYNX Student Champions

At each university, the 15 trained ACE-LYNX-Pro champions will form 3 5-member teams. Each team will plan, recruit, and engage a group of 20 university students to take part in the ACE-LYNX intervention (student version), aimed at reducing stigma, increasing mental health literacy, and transforming the students to become ACE-LYNX student champions. For inclusion in the intervention, students should be actively enrolled in a Linking Hearts participating university, be aged 18-24 years, be interested in promoting the health and well-being of fellow students, and be committed to connecting with fellow students on campus.

Guided by the local contextual assessment at each university, the different teams may organize gender-specific or mixed-gender training groups. The student version will consist of the online MH101 modules and four face-to-face training sessions (3.5 hours per session, 14 hours in total). The student champions will add to the informal integrated network that facilitates and promotes student access to mental health care. The trained student champions will also attend two half-day workshops that help build their capacity to promote mental health among their peers (eg, leading group sessions on mindfulness, stigma reduction, and stress management workshops). The outcome measures among student participants will be evaluated preintervention, immediately postintervention, and 3 months postintervention, whereas implementation evaluations will be undertaken concurrently (see Table 2 and 3).

Each ACE-LYNX-Pro team will also recruit a group of 15 interdisciplinary professionals from their university to undergo training, including the online modules and group training, to become second-generation ACE-LYNX-Pro champions. The outcome measures (see Table 2) will be evaluated preintervention, immediately postintervention, and 3 months postintervention. The second-generation champions will also join the integrated network to facilitate and promote student access to mental health care.

Forming an Integrated Mental Health Network

All trained professionals and student champions will form formal and informal community mental health networks. Professional champions will be encouraged to increase interdisciplinary collaboration, facilitate student mental health care pathways, and develop integrated programs and services. Student champions will be encouraged to carry out student-led mental health initiatives and provide peer support on campus. The integrated collaborative practice will be supported by ongoing supervision and support through a learning management system and social media platforms. The ACE-LYNX implementation stages and processes are summarized in Figure 2.

Implementation Evaluation of ACE-LYNX

The RE-AIM framework will be used at two levels: ACE-LYNX training for professionals and students and the functioning of an integrated mental health network (see evaluation activities summarized in Table 3 and outline of project timelines in Table 4).

The reach of the ACE-LYNX training will be the proportion of professionals and students successfully trained compared to their corresponding eligible populations. The total number of eligible participants will be obtained based on the information from the advisory committees. We will examine this information for any significant differences in the demographics and other baseline variables between completers and noncompleters, and between the completers and student population data at each university. The reach of the integrated mental health care network will be determined by the parameters of the network, including the total number of trained and untrained professionals, and students who constitute and form part of the network.

Table 4. Overview of project activities over 5 years.

Year	Core project activities
1	Team infrastructure; capacity building: research and intervention training; training resource development
2	Contextual analysis of students and professionals; adaptation and production of online modules (MH101[a]); training, practice, and mentorship; outreach; iKT[b] forum
3	Recruitment; first-generation ACE-LYNX-Pro intervention @ six universities; data collection and analysis; iKT seminars and forum
4	Recruitment; second-generation ACE-LYNX-Pro and ACE-LYNX[c] student intervention @ six universities; data collection and analysis; iKT seminars and forums
5	Student support network building and student-led initiatives; final data analysis; iKT seminars, forum, and conferences

[a]MH101: Mental Health 101.

[b]iKT: integrative knowledge translation.

[c]ACE-LYNX: Acceptance and Commitment to Empowerment–Linking Youth and "Xin" implementation.

The effectiveness of the intervention will be evaluated with psychometric scales quantitatively preintervention, immediately postintervention, and 3 months postintervention, including mental illness stigma, empowerment, psychological flexibility, and other psychological self-reports (see Table 2). Behavioral outcomes will be measured using the following longitudinal data: (a) collaboration across disciplines to form networked pathways as measured by the number of connected nodes and frequency of contact using Social Network Analysis (SNA) [47]; and (b) monthly activity logs of mental health promotion

and stigma-reduction activities submitted online by ACE-LYNX-Pro and student champions. Participants will also be engaged in focus groups at 3 months postintervention to identify the facilitators and barriers to apply ACE-LYNX.

The effectiveness of the functional mental health care networks in improving access to care among students will be examined considering the (1) parameters of the network structure using SNA, including the degree of interdisciplinary collaboration among professionals; the degree of peer support and information exchange among students; and the degree of student-to-professional contacts; and (2) changes in service volumes, including the number of new cases, diagnoses, and types of services used at each university counseling center between the preintervention and postintervention evaluations.

Adoption will be assessed in terms of the perceived feasibility, acceptability, and fit, as reflected by the interest and actual uptake of the ACE-LYNX intervention by the participating universities (eg, student groups and departmental initiatives) and by other nonparticipating healthcare, educational, or community organizations. This will be tracked during dissemination through iKT strategies (manuscript in preparation).

Adoption of the integrated network at the organization level will be examined by the parameters of SNA, examining the numbers and types of programs, organizations, and institutions that are affiliated with the individuals participating in and reached by the network.

Implementation fidelity checklists will be used to evaluate the quality and adherence to the ACE-LYNX model by the core intervention expert team and by the first-generation professional champions. Intervention facilitators will complete a reflection form after each session to document implementation issues and group dynamics. Participants will be asked to complete a postsession feedback form after each training session to assess their satisfaction, knowledge gain, and confidence with specific skills.

SNA will be applied to evaluate the implementation of the integrated networks, including how the relationships between and among students and service providers shape individual practices related to accessing health services and information [48]. Each university will be defined as an integrated mental health care network. The structure and function of the network will be examined, including density, degree centrality, and centralization, and their changes over time. Sociograms will be produced to examine the structure of the networks and shared with the regional advisory committees to identify potential mental health promotion “hubs” of highly connected individuals or groups that can serve as links to others in the university community for optimal knowledge dissemination.

The maintenance and sustainability of the intervention and network will be measured at the individual and organizational levels over the follow-up period, especially with a focus on activities that can sustain beyond the project and uptake by stakeholders not directly involved in the study. This includes activities captured longitudinally by monthly activity logs, SNA surveys, the learning management system, and social media platforms. In addition, an online qualitative survey will be conducted 3 months postintervention with participants and stakeholders to evaluate the intervention’s acceptability, appropriateness, and feasibility; desire for widescale adoption; and personal, professional, and community impacts of ACE-LYNX.

Data Analysis

Quantitative data will be aggregated and descriptive. Preintervention and postintervention efficacy, and inferential analyzes will be conducted using the Statistical Package for Social Sciences (SPSS version 27.0, IBM Corp.). Trend analyses, mediation, moderation, and hierarchical modeling of data to examine the intervention mechanisms of change will be conducted using the Laavan (version 0.6-9) and Psych packages (version 2.1.6) (R-Studio). Qualitative data will be transcribed. N-Vivo will be used for data management and extraction of thematic clusters using inductive and deductive approaches.

Results

We will directly train 90 ACE-LYNX-Pro champions (first generation), who will further train 15 professionals and 20 university students at each of the 6 participating universities. The intervention is expected to directly benefit the participants, and all the champions (n=720) will contribute to the cause by forming a mental health network and engaging in mental health promotion activities, including student-led initiatives, and peer support and professional-led efforts to increase collaborative care and facilitated care pathways.

Discussion

The current paper outlines the key steps taken to contextualize and implement a multipronged intervention program to promote student mental health through cross-national collaboration. Based on our previous work, we anticipate that the impact of our intervention will reach 11,000 to 18,000 students through the train-the-trainer model, communities of support, and outreach activities on campus and via social media. Systemic and policy impacts are also expected through iKT strategies (paper under preparation).

The following are the unique and important elements that can substantively contribute to mental health promotion work locally and internationally: the train-the-trainer model; integrated models of individual well-being (ACT) and collective empowerment (GEP), sociocultural adaptation process; emphasis on interdisciplinary and professional–student collaboration; use of the RE-AIM framework to guide evaluation; and the examination of direct intervention impacts as well as the functioning of an emergent mental health network. The ACE-LYNX program will add to a growing body of literature in IS that identifies the strategies, challenges, and solutions for implementing evidence-based interventions to improve community mental well-being and drive system changes from the ground up.

Declarations

Ethics Approval and Consent to Participate

The study protocols of the current implementation project have been approved by the research ethics boards of all participating institutions in Canada (Ryerson University 2018-455; University of Toronto 37724; York University e2019-162; University of Alberta Pro00089364) and in China (Shandong University; Jinan University; Shandong Jianzhu University; Shandong Mental Health Center; Shandong Normal University; Shandong Women's University, and Shandong Youth University of Political Sciences). All participants will provide written informed consent before participating in the study.

Consent for Publication

The informed consent above includes consent for the recording and publication of anonymized information shared during individual participations.

Availability of Data and Materials

The data from this IS study will be made available upon study completion within the extent permitted and outlined by the data sharing agreement among the partnering institutions.

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Authors' Contributions

JPW and CXJ are NPIs of the collaborative grant. ATL, JG, SC, and KPF are co-PIs of the project. JJWL, CTH, and MY are coinvestigators of the project. NPIs, Co-PIs, and Is are responsible for the study protocol, whereas NPIs contributed to the allocation of resources and research materials. JPW, KPF, XN, and JJWL contributed to the initial draft. All the authors have approved the final submission.

Conflicts of Interest

None declared.

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Abbreviations

ACE-LYNX: Acceptance and Commitment to Empowerment–Linking Youth and “Xin” (hearts)
ACT: Acceptance and Commitment Therapy
GEP: Group Empowerment Psychoeducation
iKT: integrative knowledge translation
IPE: interprofessional education
IS: implementation science
RE-AIM: Reach, Efficacy, Adoption, Implementation, and Maintenance
SNA: Social Network Analysis
SPSS: Statistical Package for Social Sciences

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Protocol

A Study to Investigate the Prevalence of Device-Specific Errors in Inhaler Technique in Adults With Airway Disease (The SCORES Study): Protocol for a Single Visit Prevalence Study

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Abstract

Background: It is a recurring theme in clinical practice that patients using inhaled medications via an inhaler do not use their device to a standard that allows for optimum therapeutic effect, and some studies have shown that up to 90% of people do not use their inhalers properly. Observation and correction of the inhaler technique by health care professionals is advised by both national and international guidelines and should be performed at every opportunity to ensure that the optimum inhaler technique is achieved by the user. This study will provide a greater understanding of the most frequent technique errors made by people using 13 different inhaler types.

Objective: This study aims to identify and compare inhaler technique errors and their prevalence in adults, using device-specific checklists in accordance with manufacturers' guidelines, for 13 specific inhaler types across all lung conditions and to correlate these errors with possible determinants of poor technique. It also aims to assess the error frequency at each step in the device-specific questionnaires and compare the error rates among device types.

Methods: In a single visit, participants using an inhaler included in the inclusion criteria will have their inhaler technique observed using an identical placebo device, which will be recorded using device-specific checklists, and technique-optimized, or switched to a suitable inhaler.

Results: The study is already underway, and it is anticipated that the results will be available by 2022.

Conclusions: The SCORES (Study to Investigate the Prevalence of Device-Specific Errors in Inhaler Technique in Adults With Airway Disease) study will ascertain the prevalence of device-specific inhaler technique errors at each step in the device-specific checklists, compare error rates among 13 device types, and correlate these errors with possible determinants of poor technique. Future work will involve the clarification and classification of these errors into *critical* and *noncritical* categories.

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International Registered Report Identifier (IRRID): DERR1-10.2196/26350

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KEYWORDS

inhaler; inhaler technique; inhaler technique error; asthma; COPD

Introduction

Background

Inhaled medications are the cornerstone of pharmacological treatment for many lung conditions, such as asthma and chronic obstructive pulmonary disease (COPD), and the amount spent by the National Health Service (NHS) on inhaled medication is considerable [1], with poor inhaler technique accounting for additional indirect costs [2].

It is a recurring theme in clinical practice that patients with asthma and COPD alike do not use their inhalers to a standard that allows optimum therapeutic effect [3-7]. Many patients continue to make critical errors when using their inhalers; therefore, they do not realize or enjoy the benefits of optimal inhaled treatment. Consequently, the NHS spends millions of pounds on high-cost yet subtherapeutic treatment [8]. In addition, there is now a burgeoning number of inhaler devices available for patient use, which causes additional confusion among health care professionals on how to reliably evaluate and quantify a good inhaler technique to a standard that allows quality assurance [9,10].

Both the Global Initiative for Asthma (GINA) [11] and Global Initiative for Chronic Obstructive Lung Disease (GOLD) [12] place great importance on correcting poor inhaler technique before escalating inhaled therapy. There is also a large body of evidence reporting that inhalation errors are associated with worse disease outcomes in patients with asthma and COPD and that the time invested by health care professionals to correct patients' inhaler technique is vital to improve health outcomes [13].

Other than device-specific checklists based on manufacturer's guidelines, which are often not used or shared in any standardized fashion, there is currently no formal way of assessing and quantifying the inhaler technique errors (ITE) made by patients in a way that can be translated between health care environments. Divergence and heterogeneity between checklists for the same device in previously published studies makes direct comparison of results difficult; thus, development of common checklists has been recommended [14].

Objectives

Overview

This study aims to identify ITE and their prevalence using device-specific checklists based on manufacturers' guidelines for 13 inhaler types across all lung conditions and to correlate these errors with possible determinants of poor technique. It also aims to assess the error frequency at each step in the device-specific questionnaires, compare error rates among device types, and determine which of these errors are deemed *critical* or *noncritical*.

Primary Objective

The primary objective of this study is to assess the prevalence of device-specific ITE in 13 different devices, using the manufacturers' guidelines.

Secondary Objectives

The secondary objectives are as follows:

1. To assess whether the frequency of ITE are associated with participant demographics, respiratory diagnosis, and comorbidities; disease control as measured by questionnaires, such as Asthma Control Questionnaire (ACQ) for asthma and COPD Assessment Tool (CAT) score for COPD, and participant clinical characteristics including exacerbation frequency within the past 12 months; length of time a participant has been using the observed inhaler, along with previous device-specific inhaler technique training (if and when previous training has taken place and given by whom); and levels of behavioral and adherence risk profile as measured by the social, psychographic, usage, and rational (SPUR) profiling tool (Observia).
2. To assess the user error frequency at each step in the device-specific guidelines.
3. To compare user error rates among device types.

Exploratory Objectives

The exploratory objectives are as follows:

1. To categorize ITE as *critical* or *noncritical* and prioritize the importance of these errors by conducting a further study outside the remit of this protocol and involves a Delphi consensus process. Owing to ongoing debate and variations in the definitions of critical and noncritical errors, final definitions will be based on the outcomes of the Delphi consensus process. The information from the Delphi process, along with the data from this prevalence study, will be collated to determine which ITE will be included in a subsequent study, in which a scoring system to quantify ITE will be developed.
2. To correlate severity of disease with ITE if a disease-specific tool is available. The GINA step will be used for asthma and GOLD stage for COPD with spirometry, whereas forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio measurements will be used if spirometry is performed as part of standard care.

Methods

Overview

This is a prevalence study and includes both descriptive and analytical methods, analyzing the prevalence of ITE in adults with airway disease across 13 different inhaled devices.

Eligibility Criteria

Participants will be drawn from a range of clinical conditions affecting adults that use an inhaler device. The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Participants must be aged ≥18 years.
- Participants should have been prescribed (by a doctor or health care professional) 1 of 13 inhaler device types for an airways condition (Accuhaler, Autohaler, Breezhaler, Easi-breathe, Easyhaler, Ellipta, Genuair, Handihaler, Nexthaler, pressurized metered-dose inhalers, pressurized metered-dose inhalers plus spacer [eg, Aerochamber or Volumatic], Respimat, and Turbohaler).
- Participants should be able to provide written informed consent.

Exclusion criteria

- Participants are currently on treatment with systemic steroids or antibiotics for an exacerbation of the participants' airway condition.
- In the opinion of the investigator, the participant will be unable to perform the study procedures.

Sampling and Sample Size

A minimum of 650 participants will be recruited for the study. To ensure an adequate sample size for each of the 13 different device types, a minimum of 50 participants will be recruited for each device group. Owing to the wide variety of devices involved in the study, it was not possible to conduct a power calculation because the device error frequency is known to be disparate among the inhalers involved. On the basis of existing recruitment numbers in published ITE trials [15], alongside the expert clinical opinion from within the protocol development team, a minimum of 50 participants using each device type was felt appropriate to provide a reasonable chance to identify a range of errors.

Potentially, participants may be using several different inhaler device types, so there could be a choice of device type to observe. Throughout the study, the study team will closely monitor the number of participants recruited using each of the 13 device types; therefore, to ensure that the risk of selection bias is distributed equally across all device types, the least commonly recruited device type will be observed in each participant.

Careful consideration has been afforded to ensure that adequate numbers of participants are recruited in all 13 device types included in the study. We will have access to more than 70,000 patients across the Wessex region using participant identification center ITE. Examination of primary care databases will identify those using the inhaler types included in this study, and invitations to participate will be sent to ensure recruitment across all device types.

Recruitment will last for up to 24 months and will not cease at the recruitment of 50 participants in each group, allowing sample sizes greater than this figure.

Recruitment

Participant recruitment into the study, undertaken by members of the research study team who are also part of the respiratory clinical care team at Queen Alexandra Hospital (Portsmouth Hospital University NHS Trust), will be via outpatient clinics, inpatient wards, research clinics in primary care, respiratory support groups, general practitioner (GP) practices as participant identification center ITE, social media feeds (Facebook and Twitter) of Portsmouth University Hospitals, staff and volunteers within the Trust, posters and flyers throughout the hospital, and the research database (in accordance with General Data Protection Regulation) compiled by the research department, which includes participants from previous research studies who have consented to be contacted for future studies.

Participants will be issued with a participant information sheet and will have adequate time to read this information before enrollment. Written consent will be obtained before undertaking any study-related activities.

Potential participants approached within clinical settings, who do not then consent to participate in the study, will be assured that nonparticipation will not affect their ongoing medical treatment, that their inhaler technique will be observed as per normal practice, and that they will be reeducated as necessary.

Study Assessments

This section describes the information that will be recorded in the participant's case report form (CRF), which will be anonymized using the participant's unique study number.

Participant Clinical Characteristics

This includes patient demographics, such as age and gender, diagnosis requiring inhaler use, and comorbidities.

Disease Control Questionnaires

Disease control will be assessed using the ACQ for participants with asthma and the CAT for participants with COPD. For participants with a respiratory diagnosis other than asthma or COPD, this will be assessed by recording the number of exacerbations of their respiratory condition in the previous 12 months. An exacerbation is defined as an acute worsening of symptoms requiring treatment with antibiotics or oral corticosteroids. The ACQ [16] is a validated questionnaire for assessing the level of asthma control over the preceding 7 days. The ACQ-6 will be recorded if spirometry is not recorded for the purpose of the study, otherwise the ACQ-7 will be used. The COPD Assessment Test [17] is a validated, 8-item unidimensional measure of health status impairment in COPD. It assists patients and their physicians in quantifying the impact

of COPD on the patient's health. Responses are given on a 5-point scale, with a maximum total score of 40. The higher the score, the greater the impact COPD has on the patient's health; scores of 0-9 are considered low impact; 10-20, medium; 21-30, high; and >30, very high.

Disease Severity

If possible, disease severity will be categorized. For participants with asthma, it will be step 1-5, as per the GINA guidelines. In patients with COPD, this will be categorized as A-D using the GOLD guidelines with the severity of airflow limitation based on current or last available spirometry results within the last 12 months combined with their CAT score and exacerbation history. For participants with respiratory conditions other than asthma and COPD, the number of exacerbations in the last 12 months and lung function, if available, will be used to determine disease severity.

Spirometry

Spirometry will be conducted using a spirometer conforming to American Thoracic Society/European Respiratory Society standards, as specified by the manufacturer's instructions. Participants will inhale rapidly and completely from functional residual capacity, then exhale in an initial forced exhalation and continue exhalation until the end of the breath. FEV_1 (L), FVC (L), and FEV_1/FVC ratio will be recorded. FEV_1 and FVC will be documented as both absolute values and as a percentage of the predicted value [18]. A minimum of 3 tests will be performed, with 2 tests within 100 mL or 5% of each other. Spirometry results taken within the last 12 months will be recorded if the current results are unavailable. Spirometry will only be performed and recorded in the CRF if it is required as part of the participant's routine care standard care (eg, as part of a clinical appointment). For participants recruited outside of the clinical setting, spirometry will not be performed as part of the study assessment.

Previous Inhaler Technique Training

The date of the participants' most recent inhaler technique assessment for the device being observed during the study visit will be recorded in the CRF, along with the cadre of the person by whom it was assessed (eg, nurse, pharmacist, physiotherapist, or doctor). We will also record which inhaler device the participant is observed using and how long they have been using this device for.

SPUR Profiling Tool

The SPUR profiling tool summarizes the understanding of patient behavior and their health beliefs into four drivers: social (ie, support from family and society), psychographic (ie, beliefs on identity and reactance to authority), usage (ie, financial or personal barriers), and rational (ie, decisions based on burdens to overcome and the gravity of their condition). It has been developed by the company Observia and is a comprehensive way of assessing an individual's level of behavioral and adherence profile. The tool is designed to be dynamic, so participants progress through the questions based on the responses to previous questions, which takes approximately 7 minutes to complete and is completed using an iPad, tablet, or smart phone with a user-friendly interface. Participants will be asked up to 17 questions, and the SPUR output will be calculated. The first 4 questions are not directly related to the participants' situation but are hypothetical situations of other patients, which is called the Vignette technique [19]. Responding to the circumstances of a third party (ie, other patients) not only allows for stronger reactions in a less threatening way but also elicits starting assumptions as a primer for the rest of the assessments. The results of the SPUR profile will not be disclosed to the patient and only be recorded in the CRF and stored by Observia, as this study does not intend to inform patient management decisions.

The data collected will be anonymized with the participants' unique study number and will only be collected for the purpose of the study. This profiling tool will be used for each participant in the presence of a member of the research team. Observia will host the data collected during the study by Avenir Télématique, an accredited health care data hoster based in France. Observia and Avenir Télématique both act in compliance with the General Data Protection Regulation requirements.

Device-Specific Error Frequency

Each of the device-specific checklists, devised from manufacturers' guidelines, includes steps to follow as recommended by manufacturers to achieve a good inhaler technique. Each step carried out by the participant will be recorded as a dichotomous yes or no answer. There will also be space on the checklist to record additional errors that may not have been recognized.

Error Rates

The error rates recorded for each device type will be compared with errors made in other devices in the statistical analysis.

Inhaler Technique Observation and Intervention

Once consent has been obtained, participants will be invited to a suitable clinic room to ensure privacy and a controlled environment with no time pressure. They will be accompanied by a member of the study research team, and the same person will both assess and correct any identified errors in the inhaler technique. The study team members will also record all relevant study data into the CRF. The participants will be asked to demonstrate their inhaler technique using a single-use placebo inhaler device. This is standard clinical practice, and placebo devices, which are identical to the inhaler, are available for all inhaler device types. The technique for using a placebo device is identical to how they would use their inhaler.

The member of the study team will first observe the participant's inhaler technique using the placebo device for the inhaler that the participant has been prescribed. Any errors in the inhaler technique will be recorded against the device-specific checklist formulated using the manufacturer's guidelines. This checklist, unique to each inhaler device, includes specific recommended steps to be followed to achieve an optimum inhaler technique, along with any errors in the technique that have been observed.

Participants who are observed to make errors with their inhaler technique will be given feedback by the study team member, and any errors will be highlighted and discussed. The correct

technique will be demonstrated by the study team member, with emphasis on correction of the errors, and the participant will then be asked to repeat the demonstration of the inhaler technique to ensure that the errors have been corrected. This method of inhaler technique correction is part of standard clinical practice. A written handout with the correct technique for that device will also be issued to the participant, so that they can refer to this to continue to implement the correct technique.

If a participant is observed making repeated errors using their device, despite inhaler technique correction, a more suitable inhaler device will be considered. If it is possible to obtain a prescription from a qualified health care professional for an alternative, more suitable device, then this device will be issued during the study visit. The participant will be taught how to use the new device and will be asked to demonstrate the correct technique as per standard clinical practice. Observations with ITE will be recorded in the participants' CRF for the initial device only. A letter will be sent to the participants' GP, informing them that a new inhaler device has been issued, with a request to add this to their future repeat prescriptions. If it is not possible to issue an alternative device, a letter will be sent to the participants' GP recommending a change to a more suitable device, and the participant will require training in the use of this new device. If a participant is participating in another research trial, they will be encouraged to communicate any change in device type or medication with the investigators of the other trial.

If a participant has been prescribed and uses more than 1 inhaler device type, observation and correction of only one device type will be carried out.

To ensure that each member of the study team involved in the inhaler technique observation has the necessary expertise and to ensure standardization across device technique assessment, all members of the study team will attend regular training sessions that will continue every 3 months throughout the study to ensure that competencies have been maintained. Study investigators will have to demonstrate the perfect inhaler technique for each device to be deemed competent. A standard operating procedure for the correct inhaler technique for each device will be produced, and records of competencies will be kept in the study site file.

Discontinuation or Withdrawal of Participants From the Study

Participants will be assured that they can withdraw from the study at any time and that they do not have to give reasons for their withdrawal. Participants who do not wish to have their inhaler technique observed and corrected will not be recruited into the study. Potential participants approached within the clinical setting of Queen Alexandra Hospital (Portsmouth), but who do not wish to be recruited into the study, will have their inhaler technique observed and will be reeducated as necessary as per normal clinical practice. They will be assured that withdrawing from the study will not affect their ongoing medical care in any way.

Procedures for Data Management

The observation and correction of inhaler technique is part of normal clinical practice, and enrollment in the study will not be documented in the participant's medical notes. Completed CRFs will be stored in a secure location at Queen Alexandra Hospital and can be accessed only by the research staff. All data will be recorded on paper CRFs.

The SPUR profiling tool will be administered using an iPad, tablet, or smart phone. The anonymized data will be hosted by Avenir Télématique, an accredited health care data hoster based in France. The data collected will only be collected for the purpose of this study. Observia and Avenir Télématique both act in compliance with the General Data Protection Regulation requirements.

Data Management

A bespoke database will be created for this study. Data will be entered, and 10% of records will subsequently be randomly checked against the original CRF. Further verification will be performed according to the frequency and pattern of the errors. The research team and the Portsmouth Technology Trials Unit will carry out all data verification.

Data Analysis

Overview

Errors made at each step in each specific device will be tabulated, so that errors and error frequencies can be recorded for each inhaler device against predefined checklists based on the manufacturers' guidelines. As a minimum of 50 participants are to be recruited for each inhaler device type, there may be a difference in the number of participants in each inhaler group. To reduce bias of over- or underselection, analysis will be restricted to 50 participants using each inhaler device, and participants will be randomly selected for the analysis.

Summary Statistics

Summary statistics will be presented for all the background characteristics. The proportion of participants for all background variables will be presented. The information will be available as described in the following sections.

Primary Analysis

The primary analysis will comprise a comparison of the number of errors made for each inhaler type. As the number of errors is unlikely to be normally distributed, both mean and median values will be presented in all cases. One-way analysis of variance (ANOVA) will be used to determine whether there is a significant difference between the number of errors per inhaler type. If this parametric test is inappropriate based on the distribution of the number of errors, the Kruskal–Wallis (ranked ANOVA) will be used instead.

Secondary Analysis

The secondary analysis will compare the error rates for different background measures. In all cases, the choice of test will depend on whether the number of events is normally distributed. Parametric tests will be used in the first instance, unless there

is evidence of nonnormality as assessed using a Shapiro–Wilk test, in which case a nonparametric alternative will be used.

CAT scores will be categorized for the purposes of analysis, with scores of 0-10, 11-20, 21-30, and 31-40 representing mild, moderate, severe, and very severe clinical impact, respectively. One-way ANOVA or Kruskal–Wallis tests will be used to assess whether there is any significant difference in the number of errors among CAT categories.

Exacerbation frequency within the last 12 months will similarly be categorized for the purposes of analysis, with the categories of xx-xx and yy-yy used. One-way ANOVA or Kruskal–Wallis tests will be used to assess whether there is any significant difference in the number of errors between CAT categories.

The association between the number of errors and continuous measures of FEV_1, FVC, and FEV_1/FVC ratio will be assessed using bivariate correlation. If the multivariate normality assumptions of the Pearson correlation are not met, logged values of the number of errors will be used to correct for this. If the logged values are still nonnormal, Spearman rank correlation coefficients will be used instead.

The severity of asthma will be measured using the GINA stepwise treatment guide. This measure will be categorized according to the GINA level, and comparisons between the number of errors will be assessed using a one-way ANOVA or Kruskal–Wallis test if the parametric assumptions of the former test are not met.

The severity of COPD will be categorized according to the GOLD stage, which is supplied in the form of categories. One-way ANOVA or Kruskal–Wallis tests will be used to assess whether there is any significant difference in the number of errors among GOLD levels.

Previous device training will be categorized on the basis of whether patients had received previous training. This will be classified as a binary yes or no contrast. Differences in the number of errors will be tested using an unpaired *t* test, or in the event of nonnormality, a Mann–Whitney *U* test.

Among the participants who had received previous inhaler technique training, the cadre of the person giving the training will be categorized as xx, yy, and zz. Differences in the number of errors will be tested using a one-way ANOVA test or a Kruskal–Wallis test if there is evidence of nonnormality.

Procedure for Missing, Unused, or Spurious Data

There are no plans for multiple imputation or other corrections for missing data.

Ethical Considerations

Statement of Compliance

All staff working on this study will hold evidence of good clinical practice training before undertaking any responsibilities, and all staff working within the research study team are also part of the respiratory clinical care team. Written informed consent will be obtained from all participants after an adequate explanation of the aims, methods, and anticipated benefit of the study using the participant information sheet. A signed copy of the consent form will be given to the participant, and copies will be filed in the study master file and the participants' medical notes.

Participants' anonymity will be maintained throughout by identification on a password-protected electronic database and CRFs only by initials and participant ID number. All documents will be stored securely and only accessible by study staff and authorized personnel; the study will comply with the Data Protection Act.

Potential Benefits or Risks of Study Participation

By participating in this study, participants who are observed making errors with their inhaler technique will have these errors highlighted and will be reeducated. This is a beneficial outcome for participants' self-care and management and ensures that they maximize drug delivery from their inhaler.

This study analyzes a wide variety of inhaler devices and will help provide a clear picture of the inhalers that are associated with the most errors. Understanding this information is important in the context of managing lung conditions, from treating patients in primary care through to feeding this information back to device manufacturers.

Any risks to the participants have been carefully considered. Participants found unable to use the inhaler device they have been prescribed will have an alternative device issued if possible, or a letter will be written to their GP with the recommended new device as per clinical practice.

Other Ethical Considerations

The study was approved by the Hampshire A Research Ethics Committee (REC; REC reference 19/SC/0286) in August 2019. They reviewed and approved the protocol and all relevant study materials. Any changes to the protocol or relevant study documents will be approved by the sponsor. If an amendment is made that requires REC approval, as defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received approval or favorable opinion from the REC and research and development departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided that the REC is notified as soon as possible and that an approval is requested. Minor amendments as defined by REC as a nonsubstantial amendment may be implemented immediately and the REC will be informed. All participants will have adequate time to consider participation in the study, as per the Good Clinical Practice guidelines.

Patients who are already enrolled in other research trials will be invited and allowed to participate in the study if they wish. This was discussed with our Patient Public Involvement representatives who felt that these patients should have the opportunity to participate in this study and should not be excluded.

Patient Public Involvement Process

Patient involvement in this study has been sought from patients with first-hand experience of living with chronic respiratory disease. Through face-to-face meetings, e-mail, and telephone

contact, we have discussed the concept, impact, and details of the study with our respiratory patient representatives from local British Lung Foundation groups. These people have lived with respiratory conditions and have been involved in previous research studies. They contributed to developing the key questions and setting our study objectives, ensuring that we answer the questions that are relevant to people suffering from airway diseases. Assistance was also sought with participant recruitment design and the implementation of the study within a standard clinical visit to minimize delays for patients who agreed to participate in the study. They also helped design the participant information sheet and coauthored the lay summary.

Results

Recruitment into the study has already commenced, with the study scheduled to be closed to recruitment by December 2021. It is anticipated that the results will be available by late 2022.

Discussion

The SCORES (Study to Investigate the Prevalence of Device-Specific Errors in Inhaler Technique in Adults With Airway Disease) study will provide valuable information on the frequency of ITE. These errors will enhance health care professionals' knowledge on this important subject, and by correcting their inhaler technique, participants will benefit from the study.

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Conflicts of Interest

TB reports personal grants and personal fees from Astra Zeneca, grants, personal fees and nonfinancial support from GlaxoSmithKline, personal fees and nonfinancial support from Teva, nonfinancial support from Napp Pharmaceuticals, and personal fees and nonfinancial support from Novartis, all of which are outside of the submitted work. HR reports honoraria and lecture fees from Astra Zeneca, Teva, Novartis, GlaxoSmithKline, and Chiesi, all of which are outside the submitted work. AJC reports honoraria and lecture fees from Teva, Astra Zeneca, and Sanofi and research grants from Airsonett, Novartis, and GlaxoSmithKline, all of which are outside of the submitted work. The other authors report no conflicts of interest.

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Abbreviations

ACQ: Asthma Control Questionnaire
ANOVA: analysis of variance
CAT: Chronic Obstructive Pulmonary Disease Assessment Test
COPD: chronic obstructive pulmonary disease
CRF: case report form
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GINA: Global Initiative for Asthma
GOLD: Global Initiative for Chronic Obstructive Lung Disease
GP: general practitioner
ITE: inhaler technique errors
NHS: National Health Service
REC: Research Ethics Committee
SCORES: Study to Investigate the Prevalence of Device-Specific Errors in Inhaler Technique in Adults With Airway Disease
SPUR: social, psychographic, usage, and rational

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Protocol

Variations in Patients' Overall Assessment of Their Health Across and Within Disease Groups Using the EQ-5D Questionnaire: Protocol for a Longitudinal Study in the Swedish National Quality Registers

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Abstract

Background: EQ-5D is one of the most commonly used questionnaires to measure health-related quality of life. It is included in many of the Swedish National Quality Registers (NQRs). EQ-5D health states are usually summarized using "values" obtained from members of the general public, a majority of whom are healthy. However, an alternative, which remains to be studied in detail, is the potential to use patients' self-reported overall health on the visual analog scale (VAS) as a means of capturing experience-based perspective.

Objective: The aim of this study is to assess EQ VAS as a valuation method with an experience-based perspective through comparison of its performance across and within patient groups, and with that of the general population in Sweden.

Methods: Data on nearly 700,000 patients from 12 NQRs covering a variety of diseases/conditions and nearly 50,000 individuals from the general population will be analyzed. The EQ-5D-3L data from the 12 registers and EQ-5D-5L data from 2 registers will be used in the analyses. Longitudinal studies of patient-reported outcomes among different patient groups will be conducted in the period from baseline to 1-year follow-up. Descriptive statistics and analyses comparing EQ-5D dimensions and observed self-assessed EQ VAS values across and within patient groups will be performed. Comparisons of the change in health state and observed EQ VAS values at 1-year follow-up will also be undertaken. Regression models will be used to assess whether EQ-5D dimensions predict observed EQ VAS values to investigate patient value sets in each patient group. These will be compared across the patient groups and with the existing Swedish experience-based VAS and time trade-off value sets obtained from the general population.

Results: Data retrieval started in May 2019 and data of patients in the 12 NQRs and from the survey conducted among the general population have been retrieved. Data analysis is ongoing on the retrieved data.

Conclusions: This research project will provide information on the differences across and within patient groups in terms of self-reported health status through EQ VAS and comparison with the general population. The findings of the study will contribute to the literature by exploring the potential of self-assessed EQ VAS values to develop value sets using an experience-based perspective.

Trial Registration: ClinicalTrials.gov NCT04359628; https://clinicaltrials.gov/ct2/show/NCT04359628.

International Registered Report Identifier (IRRID): DERR1-10.2196/27669

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KEYWORDS

EQ-5D; EQ VAS; experience-based values; health-related quality of life (HRQoL); hypothetical values; patient values; Swedish National Quality Registers; health state valuation

Introduction

Background

According to the US Food and Drug Administration, patient-reported outcomes (PROs) are defined as outcomes reported by patients without interpretation by anyone else [1]. They provide important information on outcomes that matter to patients [2], such as symptoms, functional outcomes, and health-related quality of life (HRQoL) [3,4]. PROs are increasingly used in health care [5,6] with applications in informing clinical practice and guidelines, informing health policy as well as supporting drug approval process among others [7]. In addition, PROs can be employed in different areas such as population surveillance, individual patient–clinician interaction, and research [8].

Patients provide information on standardized questionnaires termed patient-reported outcome measures (PROMs) [9], which are categorized into generic and disease/condition-specific PROMs. Generic PROMs enable comparisons across different patient groups and allow overall evaluation of care and quality of life. EQ-5D and the 36-item Short-Form (SF-36) are among the most common generic questionnaires. Condition-specific PROMs are used to assess outcomes specific to particular diseases/conditions from the perspective of patients [9,10].

The EQ-5D is a generic questionnaire used to measure HRQoL worldwide for a range of conditions and treatments [11]. It has a descriptive system (a set of questions in an HRQoL questionnaire encompassing different dimensions of health, the answers to which form a profile of an individual's health) where respondents report their health in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each of the 5 dimensions is measured with 1 question on the descriptive system of the EQ-5D questionnaire. EQ-5D contains a visual analog scale (EQ VAS) component for recording the respondent's overall assessment of her/his health. There are 2 versions of the instrument for use in adults: one with 3 levels of severity (EQ-5D-3L) (1=no, 2=some/moderate, and 3=extreme problems/confined to bed/unable to), resulting in 243 (3^5) unique health states. The other version with 5 levels of severity (EQ-5D-5L) (1=no, 2=slight, 3=moderate, 4=severe, and 5=extreme problems/unable to), resulting in 3125 (5^5) unique health states. A health state is defined by combining the severity level from each of the 5 dimensions (e.g. for EQ-5D-3L health state 11223; no problem in the mobility [level 1] and self-care [level 1] dimensions, some problems with performing usual activities [level 2], moderate pain/discomfort [level 2], and extreme anxiety/depression [level 3]) [11].

An EQ-5D health state can be summarized into a single index (EQ-5D index) by applying a formula that attaches specific weights to each severity level in each dimension; this set of weights is termed a value set. The weights in a value set reflect the relative importance of the health dimensions and severity levels. The EQ-5D index enables the ranking of health states and can be used as the quality component in the adjustment of life years for calculation of quality-adjusted life years (QALYs) to be used in economic evaluation [12]. Commonly, EQ-5D indices are anchored at 1 (full health) and 0 (state as bad as being dead), with states considered worse than being dead given negative values [13].

A value set can be obtained using different health state valuation methods; for example, time trade-off (TTO), VAS, the standard gamble (SG) method, and the discrete choice experiments (DCEs) [12]. Choice-based health state valuation methods, which involve choosing between alternative scenarios, are crucial to produce health state utility used in the calculation of QALYs for use in cost-utility analyses. Such health state valuation methods are SG, TTO, and DCEs. SG is considered to have the strongest theoretical foundation on the basis of entailing the attributes of being choice based and incorporating an element of uncertainty. However, in terms of feasibility, TTO showed a better response rate [14] and is commonly employed in health state valuation. The VAS valuation method involves rating health states on the VAS scale. This leads to choice-based methods being preferred over it, as they are considered to allow choice/trade-off [15].

Currently, more than 30 countries have developed value sets for the EQ-5D-3L, predominantly using the TTO method. Some of the value sets have employed the VAS method, where respondents are asked to value described health states on the EQ-5D VAS. The EQ-5D VAS has a similar "thermometer"-like design as the EQ VAS, but when used for valuation purposes, respondents are given instructions to value a series of hypothetical EQ-5D health states by indicating where on the 0-100 line of the VAS they lie [12,13,16]. The EQ-5D-3L and EQ-5D-5L sample questionnaires containing the descriptive system and EQ VAS are presented in Multimedia Appendices 1 and 2 (Reproduced by permission of the EuroQol Research Foundation). In the development of value sets for the EQ-5D-5L,

the TTO method is currently used together with the DCE method based on the EuroQol Valuation Technology (EQ-VT) protocol [17,18] for about 30 countries.

Based on the perspective taken by respondents, valuation of health states could be performed through a hypothetical or experience-based perspective. While value sets have usually been based on members of the general population's values of health states described to them (hypothetical values), another approach involves individuals in the general population valuing their own current health state (experience-based values) [19-21]. There are also studies where patients valued hypothetical health states [22,23]. A large majority of the value sets have employed a hypothetical perspective [16,17]. Many valuation studies which used an experience-based perspective have also been conducted, including studies in Sweden [24-29]. According to the Dental and Pharmaceutical Benefits Agency in Sweden, the agency that determines state subsidization of a pharmaceutical product, experience-based values are given priority over hypothetical values [30,31]. There is a growing discussion and interest in experience-based perspective in health state valuation, based on general populations' and patient populations' valuation of health states globally as shown in different literature [19-21,32-41].

As a health state valuation method, the advantages and possible limitations of VAS have been discussed in comparison to other methods such as TTO and SG. The advantages include being quick to complete and relatively easy for self-administration [42]. However, the above discussed arguments of lack of theoretical basis and not being choice based have also been raised [42,43]. Besides, this idea has been challenged by questioning the need for valuation methods to be based on utility theory [44]. It was pointed out that empirical performance should be used to select the relevant valuation method and VAS valuation was regarded advantageous over other methods in this respect [44]. A recent paper discussed the issue of anchoring at "dead" (ie, to assign 0 to the state of being dead for the calculation of QALYs) and alternative approaches to remedy challenges associated with anchoring at "dead." The different alternative approaches provided in the paper indicate the potential of VAS to be used in economic evaluation [45].

Some studies comparing VAS with TTO and SG reported the advantage of VAS in terms of feasibility, whereas in other studies it was shown that VAS values differ considerably from TTO and SG values [14,46-52]. Specifically, in terms of feasibility, that is, response rate and cost of administration, findings indicated that VAS performed better than the other methods [14,46-48]. However, correlations of VAS values with those based on the TTO and SG methods were low to moderate, leading the authors to raise concerns regarding the use of VAS in health state valuation [14]. VAS values have also been compared with results from the TTO and DCE methods among patients, professionals, and laypersons. The decision to use VAS or TTO for individual patients and TTO or DCE for laypersons was recommended based on previous findings [49]. Transformation of VAS values to SG and TTO values through power functions has also been explored [50,51]. Concerning this, advise against transformation between VAS values and SG values through power function was expressed due to a lack of theoretical relationships [52]. In short, the studies explored the relationship of VAS with other valuation methods such as TTO and SG, indicating differences in valuations.

EQ VAS, as a component of the EQ-5D instrument, has been used to derive experience-based VAS value sets by using individuals' overall assessment of their health reported on the EQ VAS to summarize how good or bad the health state they report is. These value sets have been developed in countries such as Sweden, Germany, China, and Canada [24-28]. Applying such value sets, studies reporting population reference values (norms data) and those that compared problems reported on EQ-5D dimensions with EQ VAS values were conducted [53,54]. Furthermore, another study compared patient value sets with that of the general population [55]. In addition, comparisons involving experience-based values developed using patients' own EQ VAS values across 15 countries indicated significant differences in valuations of the same health states [32]. Similarly, EQ VAS values provided to the same health states by patients with 4 different medical conditions were also found to be different [56]. The cited studies showed the development of value sets based on EQ VAS and their application in addressing different questions in HRQoL research.

EQ VAS as a component of the EQ-5D has been in routine use with its validity and reliability demonstrated in different studies. Specifically, the EQ-5D questionnaire is employed in several Swedish National Quality Registers (NQRs) [57], making it possible to investigate the relationship between EQ-5D health states and self-reported EQ VAS values in different patient populations. As to the routine performance of EQ VAS in clinical settings, its significance as a possible diagnostic tool to predict frailty, the feasibility of its inclusion in daily patient diaries, and its performance in the National Health Service in the United Kingdom have been reported [58-60]. The validity, reliability, and responsiveness of EQ VAS values have also been shown by studies in different countries, including Sweden, in the general population, and in specific patient groups [26,47,61-66].

As shown above, TTO has been employed commonly for health state valuation, while VAS has also been employed in several studies [12,16]. While hypothetical perspectives were used commonly [16], increasing interest in experience-based perspectives was shown [19-21]. VAS has demonstrated advantages over other valuation methods in terms of feasibility [14,46-48]. However, arguments for and against the potential of VAS for use in health states valuation have been forwarded [42-44]. Studies employing EQ VAS in the valuation of health states and in reporting health have been conducted [24-29,53-55]. However, in the context of patient valuations of their own health, there is a knowledge gap in the literature regarding the relationship between the EQ-5D health states and self-assessed EQ VAS values across and within patient populations.

This research project will contribute to addressing the literature gap by adding to the current literature and international debate on the role of EQ VAS as a valuation method for experience-based health states. Addressing this issue will be facilitated through investigating large data sets containing PRO

records of different patient populations covering a wide variety of conditions within the 12 Swedish NQRs. Both the EQ-5D-3L and EQ-5D-5L health states will also be investigated.

Objective

The research project aims to assess EQ VAS as a valuation method with an experience-based perspective through a comparison of its performance across and within patient groups, and with that of the general population in Sweden. The following research questions will be investigated:

- How do EQ-5D health states and self-assessed EQ VAS values vary across and within patient groups, and at baseline and 1-year follow-up, and in comparison to the general population data?
- To what extent do EQ-5D dimensions predict EQ VAS values, and how do the resulting experience-based patient value sets differ when estimated from patients' data at baseline and 1-year follow-up and how do the EQ VAS values predicted from EQ-5D dimensions differ between different patient groups?
- How do these patient value sets modeled using data from the registers compare with the Swedish VAS and TTO experience-based EQ-5D value sets obtained from the general population?
- How do value sets for EQ-5D-3L, derived from EQ VAS, differ from value sets for EQ-5D-5L, derived from its EQ VAS?

Methods

Study Design

A longitudinal study involving analyses of data on different patient groups will be conducted by assessing PROs from baseline to 1-year follow-up. The data from patients will be compared with cross-sectional survey data from the general population.

Data Sources

Data from 12 NQRs on about 700,000 patients with PRO records will be included from the over 1.4 million patients in the registers. Clinical data (age, sex, BMI, diagnosis/es, and interventions) and PROs data (EQ-5D-3L, and EQ-5D-5L) will be retrieved from the registers. Data from cross-sectional population surveys in Sweden will be included for comparison; about 45,000 records were used in developing the Swedish experience-based VAS and TTO value sets [26]. The registers included in the project are described in Tables 1 and 2.

Table 1. General information on the 12 National Quality Registers [57,67].

Register	Diagnosis/condition	Intervention[a]	Start year	Unique patients[b]	New entries per year[b]
Better management of patients with Osteoarthritis (BOA)	Hip, knee, hand osteoarthritis	Supported Osteoarthritis Self-Management Programme (SOASP)	2008	110,000	18,000
Swedish Ankle Registry (Swedankle)	Osteoarthritis and inflammatory conditions in the ankle	Total ankle arthroplasty, ankle arthrodesis procedures	1997	4000	400
Swedish National Anterior Cruciate Ligament Register (xBase)	Cruciate ligament injuries	Cruciate ligament surgery	2005	46,000	4000
Swedish Fracture Register (SFR)	All types of fractures including vertebral/spinal fractures	Surgical and nonsurgical treatments	2011	430,000	82,000
Swedish Heart Failure Registry (SwedeHF)	Chronic heart failure	Pharmacological treatment, physical activity	2003	92,000	9500
Swedish Hip Arthroplasty Register (SHAR)	Hip osteoarthritis and other hip joint diagnoses	Hip replacement	1979	370,000	25,000
Swedish Knee Arthroplasty Register (SKAR)	Knee osteoarthritis and other knee joint diagnoses	Knee replacement	1975	220,000	16,000
Swedish National Quality Register for Bipolar Disorder (BipoläR)	Bipolar affective disorder	Pharmacological treatment, patient education	2004	21,000	1500
Swedish National Registry for Respiratory Failure (Swedevox)	Respiratory failure	Long-term oxygen therapy	1987	20,000	1200
Swedish Rheumatology Quality Register (SRQ)	Rheumatic diseases	Medical treatment, rehabilitation	1995	80,000	7000
Swedish Spine Register (Swespine)	Spinal stenosis, disk hernia, and other spinal diagnoses	Spine surgery	1993	130,000	10,000
Swedish Registry for Systematic Psoriasis Treatment (PsoReg)	Psoriasis	Systemic treatment for psoriasis	2007	6500	500

[a]An intervention refers to surgeries or other forms of treatments provided to patients in the registers.

[b]Information on the number of patients and new entries per year was received from registers.

Table 2. EQ-5D data collected at the 12 National Quality Registers [57,67].

Register	Follow-up times
Better management of patients with Osteoarthritis (BOA)	First visit, 3 and 12 months; 1, 2, 3, 4, 5, 6, and 7 years after (100 patients per year are randomized to continued follow-ups)
Swedish Ankle Registry (Swedankle)	Before surgery, 6 months, 1 and 2 years after
Swedish National Anterior Cruciate Ligament Register (xBase)	Before surgery, 1, 2, 5, and 10 years after
Swedish Fracture Register (SFR)[a]	A week before injury (recall) and 1 year after
Swedish Heart Failure Registry (SwedeHF)	At new visit, within 6 months and 1 year, once every year
Swedish Hip Arthroplasty Register (SHAR)	Before surgery, 1, 6, and 10 years after
Swedish Knee Arthroplasty Register (SKAR)	Before surgery, 1 year after
Swedish National Quality Register for Bipolar Disorder (BipoläR)	At visit
Swedish National Registry for Respiratory Failure (Swedevox)	At treatment start, 1 year after
Swedish Rheumatology Quality Register (SRQ)	At visit
Swedish Spine Register (Swespine)	Before surgery, 1, 2, 5, and 10 years after
Swedish Registry for Systematic Psoriasis Treatment (PsoReg)	At each revisit due to psoriasis/visit to the skin clinic/telephone conversation with a dermatologist

[a]Baseline data in SFR are collected by a recall of a few weeks after the occurrence of fracture.

Plan for Data Analyses

The analyses will focus on the 3 main data components coming from the EQ-5D instruments: data collected by the EQ-5D-3L (and EQ-5D-5L for some registers) descriptive systems on the 5 dimensions, the EQ VAS value self-assessed by patients, and indices resulting from transforming the EQ-5D-3L health states into a single index using the Swedish EQ-5D-3L experience-based VAS value sets.

The data from the NQRs will be pooled and diagnoses in each patient group will be used to identify the different subgroups. Records of patients with complete data on age, sex, diagnosis at baseline, and PROs at baseline and 1-year follow-up will be included in the analysis. Although different follow-up times are available in the registers as shown in Table 2, the baseline and 1-year follow-up data will be used in the comparison across the different patient groups. To make comparisons with findings from the patient data, demographic, BMI, and EQ-5D-3L data from the general population survey covering about 50,000 participants will be employed. Detailed information on the general population data is available elsewhere [26].

All analyses will be conducted using SAS version 9.4 (SAS Institute Inc.) and R version 3.6.2 (R Foundation for Statistical Computing).

EQ-5D Health States and Observed EQ VAS Values

In addressing the first research question, the proportion of problems (no problem [level 1], some problems [level 2], and severe problems [level 3]) for each dimension and observed EQ VAS values of patients, at baseline and 1-year follow-up, will be compared across and within the patient groups (as well as subgroups based on diagnosis groups) and with the general population data. These descriptive analyses will also be presented by age groups, sex, BMI, and American Society of Anesthesiologists (ASA) physical status classification system (for patient groups with data on ASA class; Tables 1 and 2). Comparison of EQ VAS values by sex in the different patient groups, controlling for age, will be performed using analysis of covariance. Cluster analysis will be performed to assess the distribution of the EQ VAS value in the different patient groups at both baseline and 1-year follow-up.

Furthermore, pooled data from all NQRs will be used to analyze EQ VAS and to explore the influence of both patient characteristics and the patient group (registers). This will be performed by accounting for the grouping of patients by register. Linear mixed effects models with the patient group, preoperative EQ VAS (for the analysis at 1 year and the change from baseline), intervention type, age, and sex as fixed effects, and the patient group as the random effect will be used. Age and sex have been shown to influence EQ VAS values in previous studies [68,69].

Change over time in terms of the proportions of problems reported in each dimension will be presented using the Paretian Classification of Health Change, introduced to apply the Pareto Principle to EQ-5D health states [70]. This analysis will be performed by calculating the proportions of changes in health states from baseline to 1-year follow-up. The changes will be categorized as “no problem” (health state 11111 at both baseline and 1-year follow-up), “no change” (same health state at both baseline and 1-year follow-up), “improved” (improvement in at least one dimension without worsening in any other), “worsened” (worsening in at least one dimension without improvement in any other), and “mixed” (a mix of improvement and worsening) [70]. These changes will be analyzed descriptively in different patient groups and subgroups. In addition, changes in EQ VAS in the Paretian Classification of Health Change categories will be analyzed.

Value Sets Based on Observed EQ VAS Values

In addressing the second research question, data on the EQ-5D health state and observed EQ VAS value at baseline and 1-year follow-up will be included in the respective analyses. To assess

how well the observed EQ VAS value reflects the EQ-5D health states, the EQ-5D-3L dimensions will be analyzed as possible predictors of the observed EQ VAS value through regression models, such as ordinary least squares and generalized linear models, in each patient group and the pooled data. Both unadjusted and adjusted (for age and sex) models will be used. Corresponding analyses will be performed for EQ-5D-5L dimensions.

Based on results from predictive performance measures of the models, such as mean absolute error and root mean square error, the most appropriate models will be selected. These models will be used to develop patient value sets based on observed EQ VAS values assessed by the respective patient groups and the pooled data. In this process, value sets will be created for both baseline and 1-year postoperative follow-up.

Comparison of Patient Value Sets With the Swedish Experience-Based VAS and TTO Value Sets

In addressing the third research question, value sets elicited for each patient group using EQ-5D-3L will then be compared with the Swedish experience-based VAS and TTO value sets for EQ-5D-3L, which are elicited from the general population [26]. This will be performed by comparing the regression coefficients (indicating the levels of decrement from full health) of the severity levels in each dimension across patient groups and the general population data. Furthermore, EQ-5D-3L indices calculated based on the value sets elicited from patients will be compared with those of the Swedish experience-based VAS (see model 4 in Table S4 of the supplementary material in Burström et al [26]) and TTO (see model 4 in Table 3 in Burström et al [26]) value sets to assess the levels of agreement. This will be performed using Lin's concordance correlation coefficients or intraclass correlation coefficient [71].

Comparison of EQ-5D-3L and EQ-5D-5L Value Sets From Patients in the BOA Register and Swedish Hip Arthroplasty Register

In addressing the fourth research question, a comparison of the value sets for the EQ-5D-3L and EQ-5D-5L versions modeled based on data from patients in the BOA and Swedish Hip Arthroplasty Register (SHAR) will be performed. The 2 patient groups were chosen because it is in these registers EQ-5D-5L data are available. Specifically, the comparisons will assess coefficients of the value sets for the 2 EQ-5D versions, EQ-5D index changes between adjacent health states, and the range of the indices (from minimum to maximum values in each index). Furthermore, analysis to compare the difference in EQ-5D index between comparable EQ-5D-3L and EQ-5D-5L health states will be performed through descriptive statistics using 243 health states from EQ-5D-3L and corresponding states from EQ-5D-5L. For a description of terms discussed in this paper, please see Textbox 1.

Textbox 1. Description of terms.

EQ-5D Dimensions

In both EQ-5D-3L and EQ-5D-5L versions, the 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) constituting the EQ-5D descriptive system [13].

EQ Visual Analog Scale (VAS)

A 20-cm vertical scale where respondents describe the overall rating of their health-related quality of life. It ranges from 0 (the worst imaginable health state) to 100 (the best imaginable health state) [13].

Health State

It is also described as an EQ-5D profile. It summarizes the severity of levels described in the 5 EQ-5D dimensions [13]. For example, health state 11111 describes no problems in all the 5 dimensions.

Value Set

An EQ-5D value set contains values for every possible EQ-5D health state. These values are calculated using algorithms providing weights to the level of problems reported on each EQ-5D dimension [13]. The algorithms are developed in valuation studies using different valuation methods.

EQ-5D Index

It is also known as EQ-5D value, score, or utility. It is a value that summarizes the value of a health state based on the set of weights assigned to the levels of severity for each dimension [13].

Standard Gamble

It measures preference under uncertainty. In this method, a respondent is presented with 2 alternatives. The comparison involves staying in a specific health state for a defined number of years (certain alternative) with that of a specific probability of being full health for the same period or a specific probability of immediate death (uncertain alternative) [72].

Time Trade-off

In time trade-off, respondents are asked to compare 2 certain alternatives. One alternative gives staying in a specific health state for a defined period. The alternative presents staying in full health for a specific duration, usually lower. The point at which the respondent becomes indifferent between the alternatives indicates his/her level of preference for the specific health state [72].

Discrete Choice Experiment

Respondents are presented with a choice between alternative hypothetical scenarios. The choices provided could vary across different levels of attributes or characteristics. Respondents choose from the alternative scenarios [73].

Ethics Approval and Consent to Participate

The study has been approved by the Regional Ethical Review Board, Gothenburg (1185-18/2019-00812). General population survey data, with approval from the Regional Ethical Review Board, Stockholm (2020-03090), will be used for comparison with patient data sets. The data on the patients will be pseudonymized and stored at the Centre for Registers in Västra Götaland before access is provided to members of the research team authorized to do so. All analyses of the data will be on an aggregate level and there will be no individual-level reporting of data.

Dissemination of Findings

Findings from studies in the project will be disseminated through publication in peer-reviewed scientific journals and presentations at national or international conferences.

Results

The study project involves data from 12 NQRs and the general population. Data retrieval started in May 2019. Data of patients from the 12 NQRs and the survey conducted among the general population have been retrieved. Data analysis on the retrieved data is ongoing.

Discussion

The project will provide information on the pattern of variation of EQ VAS value across patient groups and subgroups, and on how the pattern changes from baseline to 1-year follow-up. Information on the differences between experience-based values from patients and the general population in Sweden will also be provided. This could be an input to the discussion on the merits and characteristics of experience-based valuation.

This project is also expected to provide information on the level of importance of the different dimensions and levels of severity in the EQ-5D questionnaire to different patient groups. This will be assessed based on how a similar level of severity in one dimension (eg, pain/discomfort) is valued in different patient groups in terms of its impact on the EQ VAS value. Furthermore, the importance of different dimensions and severity levels to different patient groups will be assessed in comparison to the general population.

The project will also contribute to the discussion of valuation methods regarding the feasibility and appropriateness of EQ VAS as a valuation method. Based on the findings, the potential benefits of using experience-based EQ VAS values in clinical decisions—rather than values obtained from members of the general population valuing described health states—will be discussed. Furthermore, the potential role of value sets produced using EQ VAS values for use in resource allocation decisions will be discussed. If feasible value sets can be generated from patients' self-assessed EQ VAS data, this not only provides a means of building patients' views and experience into decision making, it also means not having to conduct separate, costly, and time-consuming stated preference studies.

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Authors' Contributions

FST, OR, ND, DP, and KB designed the study; FST drafted the manuscript of the study protocol; OR, ND, DP, EN, KB, and members of the SWEQR Study Group (AA, ME, MF, PF, ÅJ, ML, MM, MR, BR, MSE, JV, AWD) revised the draft manuscript for important intellectual content; all authors approved submission of the manuscript.

Conflicts of Interest

KB, ND, and DP are members of the EuroQol Group. The other authors have no conflicts to declare.

Multimedia Appendix 1
Sample EQ-5D-3L questionnaire, English.
[PDF File (Adobe PDF File), 83 KB - resprot_v10i8e27669_app1.pdf]

Multimedia Appendix 2
Sample EQ-5D-5L questionnaire, English.
[PDF File (Adobe PDF File), 93 KB - resprot_v10i8e27669_app2.pdf]

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Abbreviations

ANOVA: analysis of variance
ASA: American Society of Anesthesiologists
BipoläR: Swedish National Quality Register for Bipolar Disorder
BOA: Better management of patients with Osteoarthritis
DCE: discrete choice experiment
EQ VAS: EuroQol visual analog scale
EQ-VT: EuroQol Valuation Technology
HRQoL: health-related quality of life
NQRs: National Quality Registers
PRO: patient-reported outcome
PROM: patient-reported outcome measure
PsoReg: Swedish Registry for Systematic Psoriasis Treatment
QALYs: quality-adjusted life year
SF-36: 36-item Short-Form
SG: standard gamble
SHAR: Swedish Hip Arthroplasty Register
SKAR: Swedish Knee Arthroplasty Register
SRQ: Swedish Rheumatology Quality Register
Swedankle: Swedish Ankle Registry
SwedeHF: Swedish Heart Failure Registry
Swedevox: Swedish National Registry for Respiratory Failure
Swespine: Swedish Spine Register
TTO: time trade-off
VAS: visual analog scale
xBase: Swedish National Anterior Cruciate Ligament Register

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Protocol

Cross-Canada Release of the Post-Secondary Student Stressors Index (PSSI): Protocol for a Cross-sectional, Repeated Measures Study

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Abstract

Background: The prevalence of mental health–related problems, including stress, psychological distress, and symptoms of mental illnesses, continues to increase among Canadian postsecondary student populations. Excessive stress in this population has been linked to a number of negative academic and health outcomes. Despite attempts to improve mental health at postsecondary institutions, a persistent gap exists in the evaluation of the specific sources of stress for students within the postsecondary setting.

Objective: The purpose of this paper is to report the study protocol for a cross-Canada, multisite launch of the Post-Secondary Student Stressors Index (PSSI), which will engage postsecondary institutions across the country as partners and facilitate improved measurement of the sources of student stress, in addition to contributing toward improved tailoring of upstream mental health services and support.

Methods: Created in collaboration with students, the PSSI is a validated 46-item tool assessing stressors across five domains: academics, learning environment, campus culture, interpersonal, and personal stressors. The tool is designed to be applicable to students at all years, levels, and areas of study. Data will be collected longitudinally at multiple time points over the course of each academic year.

Results: We recruited 15 postsecondary institutions across Canada for the first year, inviting students to participate in an online survey including questions concerning sociodemographic characteristics, stress, mental health, and resiliency. Analyses, including appropriate data visualization, will be conducted to determine the impact of specific stressors on mental health, linking responses over time to allow for the observation of changes in trends.

Conclusions: The PSSI is an intuitive and evidence-informed tool that can aid postsecondary institutions in evaluating the sources of student stress on their campuses. This multisite project will make a substantial contribution to the current literature regarding postsecondary student stress and allow institutions across the country to improve the tailoring of upstream mental health services in order to directly support the unique needs of their student body. Opportunities for knowledge translation and exchange are discussed.

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KEYWORDS

stress; mental health; health promotion; postsecondary; higher education; measurement tool; study protocol

Introduction

Over the past decade, the mental health of postsecondary students has increasingly been identified as a major public health concern. The majority of those attending postsecondary education in Canada belong to the 18-to-25-year age group, referred to as "emerging adulthood" [1]. As a result of increased autonomy, and a lack of permanent roles and responsibilities, emerging adults tend toward engaging in risk behaviors as maladaptive methods of coping with the stressors they commonly face in the postsecondary setting. Simultaneously, emerging adulthood encapsulates a period of substantial brain and psychosocial development, where individuals are at increased sensitivity to risk factors for the development of mental illnesses, including substance use and sleep disruption [2]. Excessive stress among postsecondary student populations has been linked to languishing mental health, which, in turn, is associated with a number of negative outcomes, including the development of mental illnesses [3,4], poor academic performance [5], dropout [6], burnout [7], and, in extreme cases, self-injury and suicidal ideation [5,8]. Canadian postsecondary students reported a substantial prevalence of both stress and common mental illnesses, such as anxiety and depression (formally diagnosed or self-reported through the use of screening tools), through the National College Health Assessment II (NCHA II) survey [9]. In 2019, over 60% of students who responded reported experiencing above-average stress within the past 12 months (on an adjectival five-point scale ranging from "no stress" to "tremendous stress"), while 69% reported "overwhelming anxiety" and 52% reported feeling "so depressed it was difficult to function" [10]. Notably, prevalence estimates for self-reported symptoms of anxiety and depression, stress, and help seeking for mental health–related problems significantly increased between the 2013 and 2019 iterations of the survey [11].

Although many postsecondary institutions have attempted to ameliorate mental health–related issues by increasing on-campus treatment options, few have developed effective upstream services and support, such as mental health promotion and mental illness prevention [12,13]. In fact, a survey-based review of mental health and well-being services offered on postsecondary campuses across Canada revealed that only 70% of the institutional representatives who responded believe that students are well informed about mental health issues and available services on campus [14]. Additionally, almost all representatives indicated that their campuses could benefit from expanding upstream services, such as mental health promotion and outreach activities [14]. Better targeting of the main stressors students face may improve existing mental health promotion and mental illness prevention activities, but the ability to do so hinges on an improved understanding of student-specific stress.

Previous instruments designed to assess postsecondary student stress demonstrate substantial measurement weaknesses. Few involved a diverse sample of students in the development process (eg, engaging students only in a particular year, level, or program of study [15-18]), while others are too narrow (eg, items based solely on the literature or with little consideration for student input [19]) or too broad (eg, including stress-related items not relevant to the postsecondary setting [20]). In other cases, the process of development has not been disclosed at all, making it difficult to judge the validity of the instrument [15]. Additionally, the majority of existing instruments demonstrate weak validity and reliability [16,18,21] or have not been psychometrically assessed [19]. Finally, the majority of these instruments assess only a single element of stress, either the severity or the frequency of occurrence but not both. As a result of these measurement weaknesses, holistic data on the sources of postsecondary student stress are currently lacking.

In response to this gap, the Post-Secondary Student Stressors Index (PSSI) was developed, which evaluates 46 stressors by both severity and frequency of occurrence across five domains of stress: academics, learning environment, campus culture, interpersonal, and personal stressors [22]. The purpose of this paper is to report the study protocol for a cross-Canada, multisite, longitudinal release of the PSSI that will evaluate the sources of postsecondary student stress on diverse campuses across Canada. An improved understanding of student stressors will enable postsecondary institutions to better align their upstream campus mental health services with the needs of their student population. The key objectives of the study include the following:

1. Confirm the validity of the PSSI by conducting an additional psychometric evaluation of the tool using a large, varied sample of students from across Canada.
2. Partner with postsecondary institutions across Canada to evaluate the sources of postsecondary student stress and develop recommendations regarding improved tailoring of upstream mental health services.
3. Determine whether patterns of stress exist across various demographic factors of interest (ie, region, sex, level of study, area of study) and over time.

Methods

Project Overview

The PSSI was developed and validated through extensive collaboration with diverse samples of students over a 2-year period. To develop a tool that was specific enough to evaluate stress and individual experiences within the social context of being a student yet broad enough to be holistically applicable to a varied student body (and therefore useful to a variety of postsecondary institutions), students who varied in age, gender, area, level, and year of study participated in the development and refinement of the tool. Per the *Standards for Educational and Psychological Testing* [23], the authors collected four types of evidence for validity throughout the development and validation of the tool using a three-phase mixed methods sequential exploratory study design. Overall, the PSSI demonstrated strong psychometric properties, including test–retest reliability, relationships to like constructs, and an internal structure consistent with the expectations for an index. The complete development and psychometric analysis of the PSSI is detailed elsewhere [24].

The cross-Canada, multisite release of the PSSI is a cross-sectional, repeated measures study. Data is collected via online surveys at multiple time points over the course of the academic year. Responses are linked via a unique identifier, facilitating longitudinal data analysis. In addition to the PSSI, the survey includes additional measures to facilitate a thorough analysis of the relationship between student stress and mental health. The survey consists of three sections: (1) sociodemographic characteristics, (2) stress [24,25], and (3) mental health measures evaluating psychological distress [26] and resiliency [27] (Textbox 1). In the wake of COVID-19, additional items were added to the stress section of the survey in 2020 to capture students' experiences of stress specific to the pandemic, drawing on items developed by the American College Health Association [28] and the Mental Health Research Canada [29]. Qualtrics survey software is used as the electronic platform for the survey.

Textbox 1. Survey measures.

Section I: Sociodemographics

- Age
- Sex
- Relationship/marital status
- Children (yes/no)
- Living arrangement
- Year of study
- Level of study (undergraduate/graduate/professional)
- Area of study
- Student status (part-time/full-time)
- International student status (international/domestic)
- First-generation student (yes/no)
- Grade point average

Section II: Stress

- Post-Secondary Student Stressors Index (PSSI)
- COVID-19-related stress scales
- Perceived Stress Scale (PSS-10)

Section III: Mental Health Measures

- Psychological Distress Scale (K10)
- Mental Health Diagnosis History
- Connor–Davidson Resiliency Scale (CD-RISC 10)

This multisite study received ethics clearance from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (TRAQ #6029173).

Procedure

Sampling and Participants

Recruitment of students at each participating site is flexible, allowing for each institution to determine its own desired sample size and method of recruitment. Options for recruitment used to date include (1) drawing a sample of students through the Office of Institutional Research and Planning (or equivalent), (2) sending a recruitment notice via institutional student email listservs, (3) posting the recruitment notice to an institution-based posting service for research, and (4) posting the recruitment notice through institution-based social media channels, such as those run by student unions. Regardless of the method of recruitment, an anonymous URL is made available to prospective participants. As incentive to participate in the 2020-2021 launch of the survey, students who completed the survey were offered an opportunity to enter a raffle for a chance to win one of several US $20-$50 gift cards. Students are eligible to submit one raffle entry for each completed survey at each time point of data collection. A similar incentive is planned to be used moving forward with future iterations of the study.

Survey Dissemination

Participants receive the letter of information (LOI) for the study and the URL to the online survey in the recruitment notice. The LOI communicates the participants' rights with respect to withdrawals, refusal to answer questions, and data confidentiality. The first item on the online survey asks prospective participants to provide their free and informed consent after reading the LOI. Participants must provide consent in order to progress in the survey. The survey consists of 30

questions (some of which are multi-item questions) and takes about 20 minutes to complete.

Data Collection and Processing

This study is cross-sectional and longitudinal in nature, with multiple data collection time points facilitating the analysis of changes and trends in stressors over the course of the academic year. Data collection time points are intentionally selected to avoid periods of time where stress levels might be artificially skewed (eg, assessing stress levels at final exam time is likely to result in an overestimation of usual mean stress levels). As a result, slight differences may occur between participating institutions on the basis of the timing of exam periods, reading weeks, etc. Data will be collected between September and April, with analysis conducted during spring.

Risk Mitigation

Although the risk is low, to mitigate any feelings of elevated stress or emotional distress that participants may feel after completing the survey, contact information for Student Wellness Services at each participating site and national mental health crisis lines (eg, Good2Talk and Canada Crisis Services) are provided at the end of the survey.

Statistical Analysis

Descriptive statistics (frequencies, measures of central tendency, and dispersion, where appropriate) will be calculated for all demographic variables to evaluate the nature of the sample.

To evaluate the validity of the PSSI, correlational analyses with like constructs will be conducted, in addition to exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). Scores on the PSSI will be correlated with those on the Perceived Stress Scale [25,30], the Kessler Psychological Distress Scale [26], and the Connor–Davidson Resiliency Scale [27] in order to assess relationships to other variables as evidence for construct validity. Results of the EFA using the multisite data will be compared to those of the EFA using the pilot data. The CFA will be used to evaluate model fit and further assess the internal structure of the tool. As the PSSI is designed as an index, not a scale, there is no prior assumption for correlation between groups of stressors [31]. Further details on the analytical implications of this concerning the validation of the PSSI are detailed elsewhere [24].

Means for severity and frequency will be calculated for all stressor variables on the PSSI, with results plotted on a quadrant graph, color-coded by domain of stress (Figure 1). Results will also be plotted by individual domain of stress and can be stratified by demographics of interest, color-coded by demographic category (Figure 2). This depiction of stressors by mean severity (y-axis) and mean frequency (x-axis) will facilitate an intuitive understanding of the most severe and frequently occurring sources of stress (Figure 2, upper right-hand quadrant). Appropriate statistical tests will be conducted to determine whether the mean severity and frequency ratings for stressors are statistically significantly different. *T* tests for differences in means will be performed across demographic groups of interest, with corresponding 95% confidence intervals. Cumulative link mixed-effects regression analyses will be conducted to evaluate whether the mean severity for stressors has significantly changed over time (ie, over the course of the academic year across data collection time points) and across regions of Canada. Regression analyses will also be conducted to evaluate the impact of stressors on psychological distress. All statistical analyses will be conducted using R statistical software (R Foundation for Statistical Computing).

Figure 1. Post-Secondary Student Stressors Index (PSSI) stressors—all domains. Data (n=4954) are derived from the first timepoint of the 2020-2021 release of the PSSI. Comm: communication, Env: environment, Expec: expectations, GPA: grade point average, Heavy Assign: heavy assignment load, Mult Assign: multiple assignments, Multi Exams: multiple exams, XCs: extracurriculars.

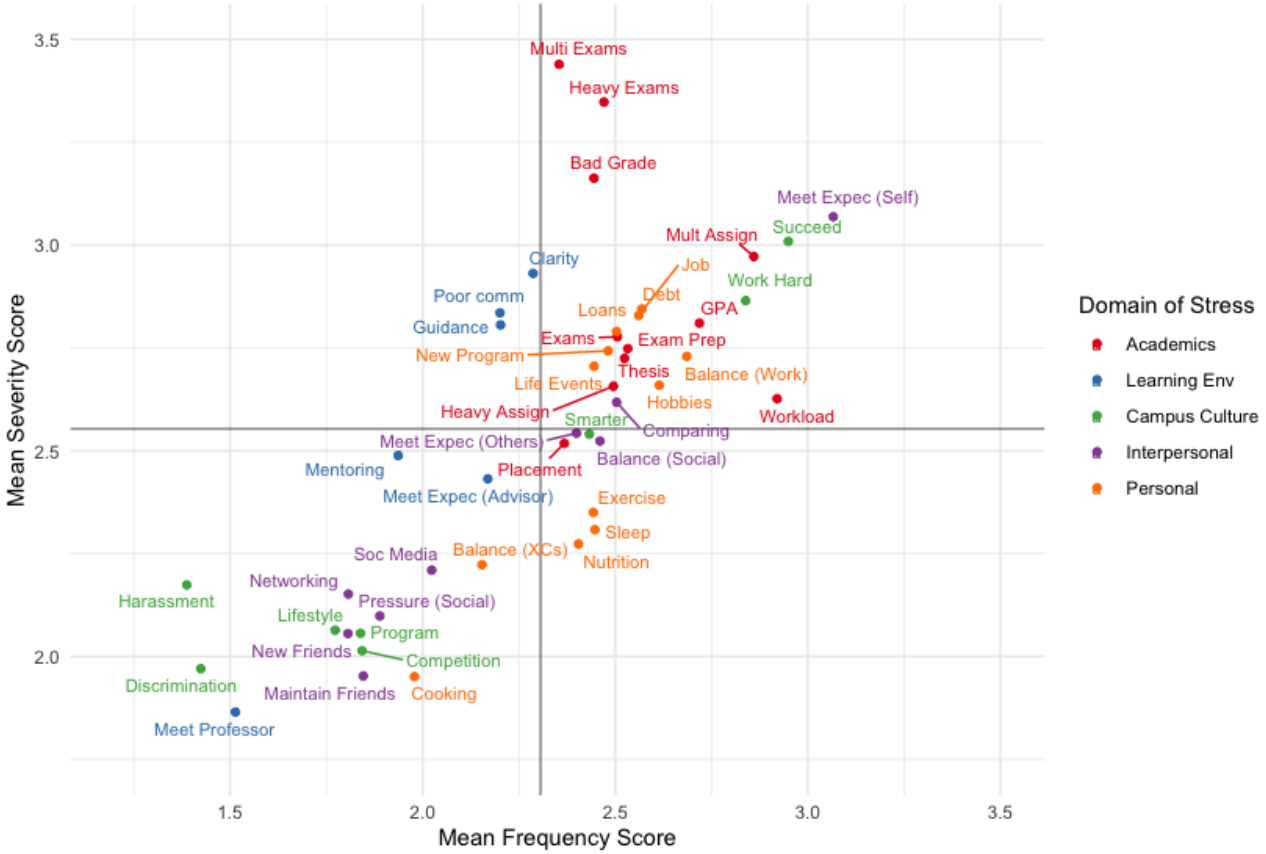

Figure 2. Academic stressors, stratified by sex. Data (n=535) are derived from the pilot test evaluation of the Post-Secondary Student Stressors Index [22]. GPA: grade point average.

Dissemination of Results

Following the completion of the study, institutional partners (coinvestigators) will get an opportunity to receive their own institution's anonymized data for their own use. This data use agreement will create a positive community impact by allowing institutions to use the results of the PSSI for their campuses to inform improvements to their Student Wellness Services, facilitating knowledge exchange. Opportunities for knowledge translation will also be created. At the end of the survey, participants will be invited to add their names to an email list to receive a technical report of the findings of the study at the end of the study period. Several scholarly papers will be submitted to open access academic journals to ensure wide distribution of the study findings. Findings will also be disseminated through academic conferences via oral, poster, and workshop-style presentations. In addition, opportunities will be available for use of the anonymized data in student research and thesis projects.

Results

The goal of this research is to survey a wide variety of students enrolled at public postsecondary institutions across Canada. In 2020-2021, 15 universities were successfully recruited for the first year of the project, representing all but 1 province, in addition to 1 territory (Figure 3); this suggests that the institutional uptake of and response to the tool are positive. There are no inclusion or exclusion criteria for participation, aside from enrolment at a participating institution at the time of survey completion. Moving forward, additional institutions (including additional universities and colleges) will be added with each subsequent iteration of the survey.

Figure 3. Participating institutions for project year 1 (2020-2021): (1) Aurora College (Northwest Territories); (2) University of British Columbia, Okanagan (British Columbia); (3) University of Calgary (Alberta); (4) University of Alberta (Alberta); (5) University of Saskatchewan (Saskatchewan); (6) University of Regina (Saskatchewan); (7) University of Manitoba (Manitoba); (8) Lakehead University (Ontario); (9) Western University (Ontario); (10) Queen's University (Ontario); (11) University of New Brunswick (New Brunswick); (12) University of Prince Edward Island (Prince Edward Island); (13) Dalhousie University (Nova Scotia); (14) St. Francis Xavier University (Nova Scotia); and (15) Memorial University of Newfoundland (Newfoundland and Labrador). PSSI: Post-Secondary Student Stressors Index.

Discussion

Aims and Strengths of the PSSI

Improved measurement of student stress will facilitate the improved targeting and alignment of mental health promotion and mental illness prevention services and support to best meet the needs of the student population. Enhancing upstream approaches targeting mental health promotion and stress reduction will help reduce not only the burden of mental health problems among the student population but also the demand currently placed on overburdened campus treatment services (eg, counseling). Available to Canadian postsecondary institutions at no cost in both English and French, the PSSI is an efficient and effective tool that provides a straightforward method of gathering data on the most severe and frequently occurring sources of stress on campus in order to support evidence-informed tailoring of campus mental health support. Implementation of the tool is flexible, with the ability to accommodate the timing of data collection in alignment with individual institution scheduling (exam periods, reading weeks, etc). The tool can also be used on its own or as an additional measure added to an existing or ongoing student mental health survey. Although the instrument's current length may present a challenge in the latter option, a brief version of the PSSI is currently under development to facilitate easier addition onto existing survey tools.

The flexibility of this tool is a major strength. Given what we know about the impact of contextual factors and individual institutional cultures, it is not advisable to make blanket recommendations for student wellness services and mental health initiatives at the provincial or national level. Increasingly, governing bodies and leading organizations in this field (eg, the Mental Health Commission of Canada) are recommending the adoption of individualized, whole-campus approaches to student mental health and well-being that take into account the unique needs of each campus, using broad guidelines, such as those laid out in Canada's Standard for Mental Health and Well-Being for Post-Secondary Students, as a guiding framework. The PSSI is an ideal tool for use alongside this framework; it provides institutions with an opportunity to obtain a clear road map of the most severe and frequently occurring stressors unique to their campuses and take appropriate, targeted action. As a result, gaining a representative sample of Canadian students to make generalizable recommendations is not the goal of the PSSI study. However, moving forward, making the best efforts to gain a representative sample of students at each participating institution will be a priority, as this will enable researchers to make recommendations that are more likely to have an impact on the mental health and well-being of the majority of students at an institution.

Limitations

This research is subject to some practical and operational challenges. Many postsecondary institutions, particularly those that regularly participate in large-scale surveys, such as the NCHA II survey and, more recently, the Canadian Campus Well-Being Survey (CCWS) [32], are wary of oversurveying their students. Additionally, institutions that are already participating in these large-scale surveys feel they are already evaluating their students' mental health, which can make it challenging to obtain buy-in.

While the NCHA II survey and the CCWS are valuable resources for broadly surveilling student mental health and well-being, the PSSI more specifically facilitates an in-depth analysis of potentially modifiable sources of student stress and is aimed at a tangible outcome: improving the tailoring of upstream mental health services and support to best serve students on campus. Additionally, when institutions opt for a repeated-measures longitudinal study design, the PSSI facilitates a more in-depth understanding of the timing of the need for services. Finally, our project team is open to working with institutions to avoid oversaturation of survey invitations by (1) finding survey time points throughout the academic year that do not conflict with other surveys and (2) selectively sampling students on the basis of a number of survey invitations received to date in the academic year.

Another challenge with respect to recruitment is related to the sharing of student information. Many institutions are restricted in their ability to share student contact information (eg, institutional emails) with outside investigators, while others have policies in place that restrict or prevent the recruitment of students via direct email contact. In cases like these, institutions should explore different approaches to recruiting, including (1) requesting an administrative staff member to send the recruitment notice to students via an institutional listserv or a newsletter; (2) posting through internal channels, such as campus notices and institutional research advertisement systems; and (3) reaching out to the student population through other channels, such as institutional-affiliated social media (eg, student unions). Although this flexibility in study design with respect to recruitment and sampling presents its own limitations, mainly with respect to determining representativeness of institutional samples, it is also a strength, in that it allows institutions with a variety of limitations associated with student access to participate in the project. However, the ability to make evidence-informed recommendations regarding the tailoring of campus mental health support is greatly improved by the institutions' ability to secure a representative student sample.

Conclusions

The PSSI is an intuitive and evidence-informed tool that can aid postsecondary institutions in evaluating the sources of student stress and tailoring upstream mental health services to directly support the unique needs of their campuses. The cross-Canada, multisite release of the PSSI is designed to be a long-term project, with the potential to observe whether improved tailoring of upstream services and support can produce changes in the patterns of student stress. Following each project year, additional institutions will be approached to participate in the project, with the goal of reaching as many postsecondary institutions across Canada as possible. To date, only universities have been engaged. Moving forward, we will also test the PSSI for efficacy among college populations to determine whether it needs an adaptation, acknowledging that potential item adjustment and additional validation work may be warranted among this unique population of students. A brief version of

the PSSI is currently under development, in addition to an adaptation of the tool to explore its use as a student-facing self-assessment, with responses to the tool mapped to useful resources for students on the basis of stressors they find to be the most severe and frequently occurring. For example, if students find exam- and assignment-related stressors to be most severe, they might be directed to studying or time management resources the institution offers.

The PSSI is available upon request to institutions at no cost in both English and French.

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Conflicts of Interest

BL is the creator of the Post-Secondary Student Stressors Index (PSSI) tool, and declares a nonfinancial conflict of interest.

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Abbreviations

CCWS: Canadian Campus Well-Being Survey
CFA: confirmatory factor analysis
EFA: exploratory factor analysis
GPA: grade point average
LOI: letter of information
NCHA II: National College Health Assessment II
PSSI: Post-Secondary Student Stressors Index

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Protocol

Mucopolysaccharidosis Type I Disease Prevalence Among Patients With Idiopathic Short Stature in Saudi Arabia: Protocol for a Multicenter Cross-sectional Study

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Abstract

Background: Since the underlying cause of idiopathic short stature can indeed be undiagnosed mucopolysaccharidosis type I, it is critical to identify patients with mucopolysaccharidosis type I among screened patients with idiopathic short stature.

Objective: The primary objective of this study is to determine the prevalence of mucopolysaccharidosis type I disease in a high-risk group (ie, patients with idiopathic short stature).

Methods: We plan to perform a multicenter, cross-sectional screening study to primarily assess the prevalence of mucopolysaccharidosis type I disease in patients with idiopathic short stature. All eligible patients will be tested after obtaining written informed consent from their parents and guardians. Eligible patients will be recruited over 18 months from specialty care centers for pediatrics and genetics.

Results: This protocol was approved by the Institutional Review Board of King Fahd Medical City and funded by Sanofi Genzyme Saudi Arabia. We expect to collect data from ≥800 patients, as determined by our sample size calculation.

Conclusions: Saudi Arabia is the largest country in the Arabian Peninsula; it has a population of more than 28 million people. To date, there are no reliable data regarding the incidence and prevalence of mucopolysaccharidosis type I in Saudi Arabia; therefore, future multicenter studies will be needed. Further, the prevalence of an attenuated form of mucopolysaccharidosis type I is largely underestimated in Saudi Arabia due to the absence of an effective newborn screening program. Therefore, the implementation of a nationwide newborn screening program is essential for the accurate estimation of the burden of mucopolysaccharidosis and the early diagnosis of patients.

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KEYWORDS

mucopolysaccharidosis; lysosomal storage disorders; epidemiology; Saudi Arabia

Introduction

Mucopolysaccharidoses are a group of chronic progressive disorders with multisystem affection and a fatal disease course; each disorder results from the significant deficiency of 1 of the 10 known enzymes that contribute to the lysosomal degradation of glycosaminoglycans [1]. Mucopolysaccharidosis type I is a common form of mucopolysaccharidosis; it accounts for nearly 15% of all mucopolysaccharidosis cases and occurs secondarily to a deficiency in α-L-iduronidase enzyme activity and the subsequent intracellular accumulation of dermatan and heparan sulfate [2]. Mucopolysaccharidosis type I is an autosomal recessive disorder with a progressive course and multisystem involvement [3]. The condition is associated with a wide range of phenotypic and clinical features. However, there are three distinct phenotypes of mucopolysaccharidosis type I—the Hurler, Hurler-Scheie, and Scheie syndromes (Scheie syndrome is the most severe form of mucopolysaccharidosis type I) [4]. Patients with mucopolysaccharidosis type I can present with characteristic facial features, cognitive and neurological impairments, hearing impairments, eye problems, cardiomyopathy, heart failure, recurrent respiratory infections, acute and chronic liver failure, joint contractures, and cervical instability, and spinal stenosis [2]. Further, patients with mucopolysaccharidosis type I are at higher risk of morbidity and mortality during anesthesia and surgical interventions [5].

The diagnosis of mucopolysaccharidosis type I depends on the detection of glycosaminoglycans in urine and a significant deficiency in the activity of the α-L-iduronidase enzyme. Alongside biochemical analysis, molecular tests play a critical role in the identification of the genotype of mucopolysaccharidosis; knowing the genotype can aid in the identification of the phenotype, genetic counseling, and prenatal diagnosis [6]. With regard to mucopolysaccharidosis diagnosis, different methods are available for the early diagnosis of mucopolysaccharidosis type I. These methods are based on the detection of deficient enzyme activity via dried blood spot (DBS) punches. DBS punching is a blood sampling technique in which a drop of blood is dried and placed on filter paper (a DBS card) [7]. These blood samples can be shipped to central laboratories—those in the same country or those from abroad—to be analyzed by using different methods such as enzymatic assays and confirmatory molecular testing, as in our study. Conventional fluorometric methods are widely available techniques for the detection of enzymatic activity; however, they have limited value due to their inability to test multiple enzymes simultaneously [8]. Tandem mass spectrometry (MS/MS) methods, which quantify lysosomal enzyme activity, have exhibited high diagnostic accuracy for the detection of lysosomal storage disorders (LSDs) and have a high capacity for multiplex testing [9]. Recent reports have also introduced new, cheap, and feasible MS/MS-based methods for the mass detection of mucopolysaccharidosis type I [10,11].

All mucopolysaccharidosis types are characterized by musculoskeletal manifestations in the form of joint stiffness, reduced joint mobility, carpal tunnel syndrome, and bone abnormalities [12]. Idiopathic short stature is widely considered as the main feature of mucopolysaccharidosis type I [13]; in previous studies, children with mucopolysaccharidosis type I constantly had growth measure values that were below the normal percentiles for age and sex and independent of disease severity and the age of onset [14,15]. Since the underlying cause of idiopathic short stature can indeed be undiagnosed mucopolysaccharidosis type I, it is critical to identify patients with mucopolysaccharidosis type I among screened patients with idiopathic short stature. Therefore, the primary objective of our study is to determine the prevalence of mucopolysaccharidosis type I disease in a high-risk group (ie, patients with idiopathic short stature). The secondary objectives are to describe the demographic profiles and clinical characteristics of patients with mucopolysaccharidosis type I and to describe other comorbid conditions in patients with mucopolysaccharidosis type I.

Methods

Study Design and Participants

We plan to perform a national, multicenter, cross-sectional screening study in which an interventional diagnostic procedure (DBS enzymatic assays followed by confirmatory molecular testing) will be conducted for each patient who meets the inclusion criteria in the outpatient setting. The study will be noninterventional in terms of the therapeutic strategy. The primary aim is to assess the prevalence of mucopolysaccharidosis type I disease in patients with idiopathic short stature.

Inclusion Criteria

Patients will be deemed eligible for the study if they meet the following criteria:

- Male and female children aged between 2 and 15 years with idiopathic short stature if the treating physician believes that the underlying cause of idiopathic short stature could be undiagnosed mucopolysaccharidosis type I
- Patients who are confirmed to have at least 1 symptom of mucopolysaccharidosis type I, including growth impairment, hepatosplenomegaly, claw hand, carpal tunnel syndrome, and skeletal involvement (eg, kyphoscoliosis, joint stiffness, joint limitation, hernia, or scoliosis or corneal clouding)

Idiopathic short stature will be defined as a height of more than 2 SDs below the corresponding average height for a given age and sex.

Exclusion Criteria

Patients will be deemed ineligible for the study if they meet the following criteria:

- Patients who are already known to have mucopolysaccharidosis disease
- Patients with a confirmed growth hormone deficiency
- Patients with other known causes of short stature, such as endocrine, genetic, and organ system disorders
- Patients who have already undergone DBS enzymatic assay tests

All eligible patients will be tested after obtaining written informed consent from their parents and guardians.

Eligible patients will be recruited over 18 months from specialty care centers for pediatrics and genetics, which have a fair amount of experience with managing patients with idiopathic short stature and may have experience with clinical research.

Evaluation Criteria

Main Evaluation Criteria

The main evaluation criterion will be the percentage of subjects with confirmed (low enzymatic activity based on the enzyme assay and positive molecular tests; ie, "genetic pathogenic mutation detected") mucopolysaccharidosis type I disease.

Secondary Evaluation Criteria

The description of demographic profiles and patient characteristics will include age, gender, risk factors (eg, a family history of mucopolysaccharidosis disease and the ethnicity of patients with mucopolysaccharidosis I disease; risk factors will be compared to those of the rest of the screened population), and the frequency of comorbid conditions in patients with mucopolysaccharidosis type I disease.

Sample Size Calculation and Sampling Technique

The primary objective of this study is to evaluate mucopolysaccharidosis type I prevalence in the high-risk group (patients with idiopathic short stature). According to the Saudi Arabia Demographics Profile 2018, about 26.1% of the Saudi population are aged under 15 years [16]. Moreover, El Mouzan et al [17] reported that the prevalence of moderate and severe short stature in Saudi male and female children is 24.8%, as shown in Table 1.

Table 1. The prevalence of short stature among children in Saudi Arabia.

Sex	Children with moderate short stature, %	Children with severe short stature, %
Male	11.3	1.8
Female	10.5	1.2

The expected number of people with short stature aged under 15 years in Saudi Arabia is about 2,193,698. According to Pedicelli et al [18], about 80% of short children have no history of low birth weight and length and no detectable pathologies (ie, idiopathic short stature). Therefore, we expected to find 1,754,958 patients with idiopathic short stature aged under 15 years in Saudi Arabia, given that the overall Saudi population size is 33,891,021 (based on the latest United Nations estimates).

The expected prevalence of mucopolysaccharidosis type I disease worldwide is 3.5 to 4.5 patients per 100,000 people among the overall population [3]. On the other hand, the expected prevalence of mucopolysaccharidosis type I in Saudi Arabia is 3.31 patients per 100,000 people (0.003%) [19]. We calculated a sample size of 720 patients with idiopathic short stature aged under 15 years and an acceptable absolute deviation (95% CI) of 0.04% between the sample rate and the population rate (precision rate) in Saudi Arabia. We expect to have a 10% dropout rate resulting from a lack of data. Therefore, 800 patients will be required for this study. The sample size was calculated by using StatsDirect Statistical Analysis Software (version 3.1.17; StatsDirect Ltd).

Data Collection

Following an initial screening test, all potentially eligible patients will undergo anthropometric examinations to confirm the diagnosis of short stature. The following equations will be used:

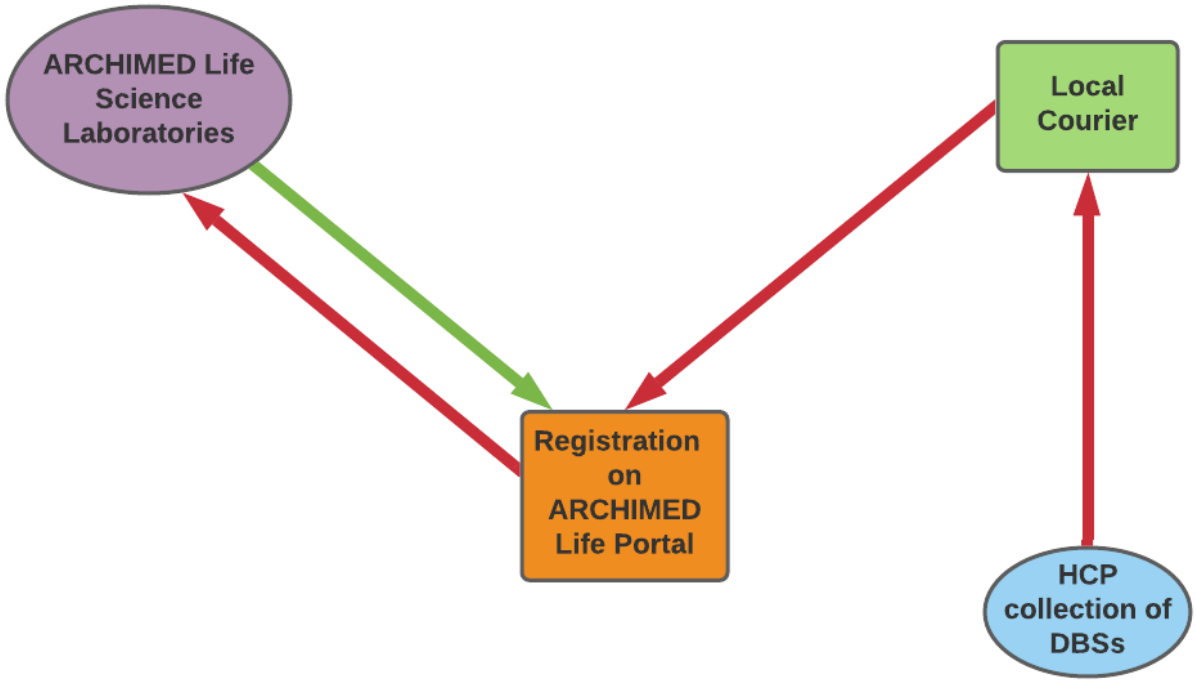
Stature of females = (maternal stature + paternal stature – 12.5 cm)/2 **(1)**

Stature of males = (maternal stature + paternal stature + 12.5 cm)/2 **(2)**

The following data will be collected from each patient: sociodemographic profiles; findings from the physical examination; anthropometric examination findings, including height, weight, BMI, and body circumference (waist, hip, and limb circumferences); a history of comorbidities; a history of previous surgeries; a family history of inborn errors of metabolism; presenting symptoms; findings from routine laboratory investigations; a history of mucopolysaccharidosis treatment; and findings from enzymatic assay screening.

A central laboratory will provide ARCHIMED Life Science Laboratories DBS and genetic test services to all sites participating in the study. All patient data (except the results of the investigation) will be collected during a single visit. Each enrolled patient will visit the investigators for a baseline visit. The investigators will complete the electronic case report form (eCRF) soon after the baseline visit. Upon receiving the test results, investigators will be required to report in the eCRF (within 5 days) that the results that will be provided to their respective patients. The general logistic aspects of the study are presented in Figure 1.

Figure 1. A flowchart depicting the logistic aspects of the study. Lab results will be uploaded on Arvado (ARCHIMED Life Sciences Laboratories) by the lab and will be available on each HCP account. DBS: dried blood spot; HCP: health care personnel.



An independent contract research organization (CRO) will provide the study centers with the proper levels of access, grants, and privileges for the eCRFs, which will be filled by the investigators or the authorized designees according to the complete guidelines. Data entry screen development, validation rules programming, and the maintenance of the study database will be the responsibility of the independent CRO. The computerized handling of the data by the CRO may generate additional queries, which will be automatically identified via preprogrammed and tested validation rules. Validation rules will be detailed in the data validation plan. In addition to automatic validation rules, a manual and medical review of data may generate further queries; these will be uploaded to the system as well. Site staff will be responsible for resolving automatic and manual queries by confirming or modifying the data, which will be collected with the electronic data capture system. The data collection and validation procedures will be detailed in the operational study manual.

Study End Points

The primary end point is the prevalence of mucopolysaccharidosis type I in the high-risk group (patients with idiopathic short stature), which will be confirmed by enzyme activity DBS testing. Other end points include a description of demographic profiles and patient characteristics and the frequency of comorbid conditions in patients with mucopolysaccharidosis type I.

Statistical Methods

All data collected during the study will be analyzed with the appropriate descriptive analysis. Statistical analyses will be performed by using SPSS version 18 or higher (IBM Corporation). The prevalence of mucopolysaccharidosis type I will be described by using counts and percentages with 95% CIs. Other variables will be described by using means and SDs (for continuous variables) or counts (for categorical variables). Patients' variables will be compared by using Mann-Whitney-Wilcoxon tests for continuous parameters and Chi-square tests for categorical parameters. A *P* value of less than .05 will be considered significant.

Ethics Approval and Consent to Participate

The study's protocol was approved by the ethics committee of King Fahd Medical City for participant hospitals (Aseer Central Hospital and Abha and Yamamah General Hospital in Riyadh). The study protocol was registered by the Institutional Review Board (IRB) of King Abdulaziz City for Science and Technology.

Written informed consent will be obtained from every eligible patient prior to the sample withdrawal.

This study will be conducted in accordance with the principles laid out by the 18th World Medical Assembly (1964 Helsinki Declaration) and all their subsequent amendments.

The study will be conducted in accordance with the US and European guidelines for Good Epidemiology Practice. All necessary regulatory submissions (eg, IRB and independent ethics committee) were performed in accordance with Saudi Arabia's local regulations, including the local data protection regulations.

Consent for Publication

If case reports are presented in the study, consent for publication will be obtained from the subject of the case report. If children

are the subject of the case report, consent for publication will be obtained from their parents and legal guardians.

Availability of Data and Materials

Data sharing does not apply to this paper, as no data sets were generated or analyzed in this manuscript.

Results

Our protocol was reviewed and approved by the IRB of King Fahd Medical City and funded by Sanofi Genzyme Saudi Arabia. According to our sample size calculation, we expect that at least 800 patients from different sites in Saudi Arabia will be enrolled in our study.

Discussion

The early diagnosis of mucopolysaccharidosis followed by early treatment can have a huge impact on patients' quality of life; previous reports have demonstrated that the early initiation of treatment is the most important factor for slowing the progression of the disease [2]. Enzyme replacement therapy, when delivered early in the disease process, has alleviated many systematic signs and symptoms of mucopolysaccharidosis. This is possibly due to the prevention of permanent tissue damage resulting from excessive substrate deposition [20]. Since many mucopolysaccharidosis type I symptoms are often unspecific, many patients, especially those with undiagnosed mucopolysaccharidosis type I or an attenuated form of the disease, are either misdiagnosed or diagnosed later in the course of the disease (ie, after precious time has been lost due to inappropriate treatment and after irreplaceable organ damage has occurred) [21]. At some point during the course of the disease, patients with mucopolysaccharidosis consult rheumatologists. As such, rheumatologists should be aware of clinical manifestations that raise the suspicion of a mucopolysaccharidosis diagnosis. Thus, we found it imperative to assess the prevalence of mucopolysaccharidosis type I among high-risk patients, such as pediatric patients with idiopathic short stature.

The added values of our screening program include (1) the determination of the actual prevalence of mucopolysaccharidosis type I among children with idiopathic short stature, (2) the early detection of potentially disabling conditions among Saudi children (these data will provide a chance for early treatment and better prognoses), and (3) the increased awareness of Saudi pediatricians and primary care physicians with regard to how and when to suspect a mucopolysaccharidosis diagnosis in children.

We chose to conduct this epidemiological study in Saudi Arabia due to the peculiar characteristics of this country, which is located in the Arabian Peninsula and has a population of more than 28 million people. Recent reports have noted a trend toward a higher incidence of genetic disorders among Arab countries when compared to those of other parts of the world. These incidence rates also apply to the incidence of mucopolysaccharidosis type I. Recent global data show that the overall birth prevalence rate of mucopolysaccharidosis ranges from 1.04 to 4.8 infants per 100,000 live births. Additionally, reports from Europe show that the incidence rate of mucopolysaccharidosis is 1.56 infants per 100,000 live births [3]. This incidence rate is quite similar to the mucopolysaccharidosis incidence rates of Japan and other East Asian countries that were reported during the same period [22-24]. On the other hand, reports from Saudi Arabia show that the country has a higher incidence of mucopolysaccharidosis compared to those in the abovementioned reports. The first retrospective study from Saudi Arabia on this topic reported that the combined incidence rate of mucopolysaccharidosis type I and mucopolysaccharidosis type IV was 3.62 infants per 100,000 live births, and each disease type accounted for 21% of all mucopolysaccharidosis cases. Moreover, the birth prevalence of mucopolysaccharidosis III is 1.8 infants per 100,000 live births (11% of total cases) [25]. In addition, Al-Sannaa and colleagues [19] reported that the incidence rate of mucopolysaccharidosis diseases was 14 infants per 100,000 live births; with mucopolysaccharidosis type VI accounted for most of the mucopolysaccharidosis cases. A 13-year retrospective chart review reported an incidence rate of 14 infants per 100,000 live birth [26]. The incidence of mucopolysaccharidosis in Saudi Arabia appears to be even higher than those reported by other Arab countries; a previous report from Tunisia reported a mucopolysaccharidosis birth prevalence of 2.27 infants per 100,000 live births [27]. These high figures were postulated to stem from the higher incidence of congenital and genetic diseases in Arab countries compared to those of other parts of the world [28]; high consanguinity rates, which reach up to 60% in some regions; the high prevalence of hemoglobinopathies and metabolic disorders; relatively high maternal and parental ages; and the lack of proper genetic screening [28-30].

With regard to mucopolysaccharidosis diagnosis, different methods are available for the early diagnosis of mucopolysaccharidosis type I. These methods are based on the detection of deficient enzyme activity via DBS punches. Conventional fluorometric methods are widely available techniques for the detection of enzymatic activity; however, they have limited value due to their inability to test multiple enzymes simultaneously [8]. MS/MS methods, which quantify lysosomal enzyme activity, have exhibited high diagnostic accuracy for the detection of LSDs and have a high capacity for multiplex testing [9]. Recent reports have also introduced new, cheap, and feasible MS/MS-based methods for the mass detection of mucopolysaccharidosis type I [10,11]. Such advances in the diagnostic methods have encouraged other researchers to conduct several mucopolysaccharidosis type I neonatal screening programs; these researchers aim to evaluate the utility of mucopolysaccharidosis type I neonatal screening to determine whether such screening should be included in primary screening programs. From 2008 to 2013, a pilot screening program for mucopolysaccharidosis type I was conducted for 35,286 newborns from Taiwan. Only 2 neonates had a confirmed diagnosis of mucopolysaccharidosis type I. The rate of mucopolysaccharidosis type I incidence in Taiwan that was estimated from the results of this program was about 1:17,643 [31]. In the United States, several states have conducted pilot mucopolysaccharidosis screening programs. In a comprehensive program for LSDs that was conducted in

Missouri, a multiplexing digital microfluidic fluorometric enzymatic assay was used to detect Pompe disease, Fabry disease, Gaucher disease, and mucopolysaccharidosis type I in 2013. Of the 43,701 screened newborns, 3 had a confirmed diagnosis of mucopolysaccharidosis type I, and 7 had pseudodeficiencies. In this Missouri program, the rate of mucopolysaccharidosis type I incidence (1:14,567) was similar to the incidence rate reported in a previous pilot study conducted in Taiwan (1:17,643) [32]. In Saudi Arabia, a national newborn screening program was established in 2005. This program covers inborn errors of metabolism, endocrine disorders, congenital heart defects, and hearing loss [33]. A recent 7-year retrospective study of 139 hospitals reported a higher rate of inborn errors of metabolism in Saudi Arabia compared to those in other parts of the world [34]. However, the inclusion of LSDs, including mucopolysaccharidosis type I, in Saudi Arabia's newborn screening program has not yet been discussed.

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Conflicts of Interest

AE, MEB, SR, and YA are employees of Sanofi Genzyme. The study has been funded by Sanofi Genzyme Saudi Arabia.

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Abbreviations

CRO: contract research organization
DBS: dried blood spot
eCRF: electronic case report form
IRB: Institutional Review Board
LSD: lysosomal storage disorder
MS/MS: Tandem mass spectrometry

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Protocol

Advancing Intersectional Discrimination Measures for Health Disparities Research: Protocol for a Bilingual Mixed Methods Measurement Study

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Abstract

Background: Guided by intersectionality frameworks, researchers have documented health disparities at the intersection of multiple axes of social status and position, particularly race and ethnicity, gender, and sexual orientation. To advance from identifying to intervening in such intersectional health disparities, studies that examine the underlying mechanisms are required. Although much research demonstrates the negative health impacts of perceived discrimination along single axes, quantitative approaches to assessing the role of discrimination in generating intersectional health disparities remain in their infancy. Members of our team recently introduced the Intersectional Discrimination Index (InDI) to address this gap. The InDI comprises three measures of enacted (day-to-day and major) and anticipated discrimination. These attribution-free measures ask about experiences of mistreatment *because of who you are*. These measures show promise for intersectional health disparities research but require further validation across intersectional groups and languages. In addition, the proposal to remove attributions is controversial, and no direct comparison has ever been conducted.

Objective: This study aims to cognitively and psychometrically evaluate the InDI in English and Spanish and determine whether attributions should be included.

Methods: The study will draw on a preliminary validation data set and three original sequentially collected sources of data: qualitative cognitive interviews in English and Spanish with a sample purposively recruited across intersecting social status and position (gender, sexual orientation, race and ethnicity, socioeconomic status, age, and nativity); a Spanish quantitative survey (n=500; 250/500, 50% sexual and gender minorities); and an English quantitative survey (n=3000), with quota sampling by race and ethnicity (Black, Latino/a/x, and White), sexual or gender minority status, and gender.

Results: The study was funded by the National Institute on Minority Health and Health Disparities in May 2021, and data collection began in July 2021.

Conclusions: The key deliverables of the study will be bilingual measures of anticipated, day-to-day, and major discrimination validated for multiple health disparity populations using qualitative, quantitative, and mixed methods.

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KEYWORDS

stigma; discrimination; racism; measurement; health disparities; survey research; psychometrics

Introduction

Health Disparities

Disparities in health status and access to care along single axes of social status and position (SSP), such as race and ethnicity, gender, and sexual orientation, are well documented in the United States [1,2]. Informed by intersectionality frameworks, recent research has emphasized disparities at the intersection of multiple axes of SSP. Intersectionality is rooted in Black feminist scholarship [3-5] and has become a central framework for public health efforts to understand and intervene in multiple, interacting, and context-dependent forms of social and health advantage and disadvantage [6,7]. Intersectional health disparities research allows for independent estimation of outcomes across intersections, acknowledging that groups at particular SSP intersections may experience better or poorer health than that predicted by nonintersectionally combining the effects of individual SSP. Examples include HIV infection among Black sexual minority men and transgender women [8], smoking among Asian or Pacific Islander sexual minority women [9], opioid misuse among high-income Black women [10], and hypertension among Black and Latina women [11].

Health Impacts of Perceived Discrimination

A robust literature demonstrates that perceived, self-reported discrimination is associated with poorer mental and physical health, with most studies focusing on the health impacts of racial and ethnic discrimination among people of color and, to a lesser extent, sexuality- and gender-based discrimination among lesbian, gay, bisexual, and transgender people [12-15]. Perceived discrimination, including acute *major* events, chronic *day-to-day* discrimination, and anticipated discrimination, are thought to primarily impact health through (1) stress processes resulting in distress or health-harming coping strategies, and (2) physiological reactions such as elevated blood pressure and dysregulated hypothalamic-pituitary-adrenal axis function, which elevate cardiovascular disease risks [16-20]. Although not amenable to self-reporting and thus beyond the scope of this project, structural forms of oppression, such as residential segregation and lack of legal protection, set the context for perceived discrimination and drive poor health [21,22].

Need for Intersectional Discrimination Measures

Quantitative intersectionality studies have burgeoned in the last decade and have largely focused on describing inequalities across groups cross stratified by SSP, taking an intercategorical [6] approach by examining outcomes across multiple intersecting SSPs [23,24]. In contrast, intersectional studies of the mechanisms potentially underlying health disparities have largely been intracategorical studies, focusing on experiences at a particular intersection [25,26]. Recognizing the conceptual bias inherent in using within-group analyses to make inferences about between-group differences [27,28], we and others have called for analytic approaches to *intercategorical* intersectionality to identify modifiable processes, including discrimination, that lead to health disparities [27-30]. Such studies require discrimination measures whose estimates are meaningfully comparable across intersectional groups. Previous intercategorical studies have adopted measures of racial and ethnic discrimination [31-36] that may not have content validity for other types of discrimination, or even for diverse racial and ethnic groups [37,38]. In fact, recent evidence shows that traditional scales of discrimination may not provide meaningful estimates of perceived general or racial and ethnic discrimination across diverse groups in the United States [39].

Intersectional Discrimination Index

The Intersectional Discrimination Index (InDI) is a set of three measures of anticipated (InDI-A) and enacted (day-to-day [InDI-D] and major [InDI-M]) discrimination, originally designed for cross-group use. Notably, although anticipated discrimination is associated with mental health and cardiovascular stress responses [40,41], it is rarely measured [42]; the InDI-A is the first scale to measure this construct across multiple SSP. The InDI asks about discrimination *because of who you are* but without requesting attributions to specific SSP. Rather, these measures can be analyzed using cross-stratified demographic data. In 2019, our team published a binational study that provided preliminary evidence of the measures' construct validity and test-retest reliability. Among participants in the United States (n=1518) and Canada (n=1065), as hypothesized, people of color and sexual and gender minorities (SGMs) reported higher levels of perceived discrimination, lifetime and past-year discrimination were associated with psychological distress, and enacted discrimination was correlated with the Everyday and Major Discrimination scales [43,44]. Test-retest reliability at 6 weeks was 0.70-0.72, similar to or higher than comparable measures [45,46].

The preliminary InDI study was published alongside four invited commentaries that identified the strengths of the InDI as well as areas requiring further study to clarify its utility for intersectional health disparities research [25,47-49]. Qualitative research using cognitive interviewing would reveal how respondents understand and respond to items in relation to multiple SSPs, identifying items that may require revision [48]. Psychometric analyses are needed to further validate the InDI measures across intersectional groups, including the assessment of configural, metric, and scalar properties (eg, factor structure, item loadings, and item intercepts) and measurement equivalence [26,47]. The preliminary InDI study was ethnically and racially diverse but had small sample sizes at specific intersections (eg, 50 Black SGM in the combined US and Canada sample), precluding intersectional validation analyses. In addition, Spanish measures are essential for health disparities research in the United States but need to be assessed for conceptual, semantic, and measurement equivalence to allow valid data pooling and comparison [50,51]. This is critically important given evidence of systematic response differences to discrimination measures by survey language and acculturation among Latino/a/x persons [52,53].

Asking for Attribution in Intersectional Discrimination Measures

To date, intercategorical, intersectional discrimination studies have adapted extant measures to permit multiple attributions [31-36]. Research has highlighted attributional ambiguity among individuals situated at the intersection of marginalized SSP [54-56]. Allowing multiple attributions may not reduce cognitive

burden or improve measurement validity; for example, conceptual slippage between SSPs may make participant selections arbitrary [56]. Options for quantitatively modeling attributions are limited because they are not tied to frequencies; this has resulted in analyses that either dichotomize discrimination or count attributions [31-36,57], representing losses of information on dose-response relationships [58] and on the complexity of experiences at particular intersections [26]. Therefore, the InDI was designed to be attribution free. This decision rests on a lack of evidence that the health impacts of discrimination depend on attribution. Some researchers have argued that a different construct underlies measures of discrimination that include attributions to perceived discrimination compared with those that do not [59], but no study has empirically tested the validity of this claim. Indeed, a 2015 review noted that the few studies comparing attributed and unattributed (racial and ethnic) discrimination measures have compared *apples and oranges* (ie, measures that reflect different constructs); the authors called for direct comparisons, including cognitive interviewing [18]. Further, some research participants reported the ability to unambiguously attribute discrimination to one or more SSP, and health disparities researchers remain interested in the burden and consequences of specific discrimination types [47,56]. Thus, we will conduct an evaluation inclusive of participant perspectives, examination of the degree to which SSP and attributions overlap, and direct comparison of correlations with health outcomes.

Objectives

The primary aims of the study are to (1) assess the content and wording of the InDI measures (InDI-A, InDI-D, InDI-M) in English and Spanish; (2) evaluate the InDI measures' configural, metric, and scalar structures, as well as their measurement equivalence across language and intersecting SSP; and (3) determine whether attributions should be included in the InDI measures.

Methods

Overview of Study Design

As described in Table 1, the study will draw on the preliminary validation data set and three original data sources.

Table 1. Overview of approach.

Method	Sample	Aims	Analysis
Cognitive interviews (n=50)	• 25 (50% per language) sampled for maximum diversity	1: Cognitive evaluation and InDI[a] revisions 2: Participant perspectives on attributions	1: Within- and between-interview analysis using Q-Notes 2: Qualitative analysis using grounded theory techniques
Previously collected validation data set (n=2583)	• 1518 (58.77%) in the United States • 1065 (41.23%) in Canada	2: Intersectional psychometric evaluation	2: Exploratory factor analysis, exploratory structural equation modeling, and CFA[b]
Quantitative surveys	• 500 in Spanish[c] • 3000 in English[c]	2: Intersectional psychometric evaluation 3: Determine analytic utility of attributions	2: Multiple indicator multiple cause models and multigroup CFA 3: Descriptive statistics and multivariable regression models

[a]InDI: Intersectional Discrimination Index.

[b]CFA: confirmatory factor analysis.

[c]Quota sampling by race and ethnicity and sexual or gender minority status.

Participants

Eligible participants will be aged ≥18 years and residing in the United States. For cognitive interviews (25/50, 50% English; 25/50, 50% Spanish), participants will be of any race and ethnicity and purposively sampled to achieve maximum diversity in gender, sexual orientation, race and ethnicity, socioeconomic status, age, and nativity. Quota sampling will be used for the quantitative surveys. The Spanish survey (n=500) will include 250 SGM and 250 non-SGM. The English survey (n=3000) will include non-Hispanic Black (1000/3000, 33%), non-Hispanic White (1000/3000, 33%), and Hispanic or Latino/a/x persons of any race (1000/3000, 33%), with 50% (250/500 for Spanish and 1500/3000 for English) of each group being composed of SGM. We will further stratify recruitment by gender to generate sample sizes of approximately 250 at each race and ethnicity *SGM* gender intersection (eg, White non-SGM women). Transgender and gender nonbinary respondents will be grouped by gender identity (eg, transgender men and transmasculine persons with men).

Recruitment

Participants will be recruited using Facebook and Google advertisements in English and Spanish. Advertisements will also be placed on Black-, Latino/a/x-, and SGM-focused websites and circulated through relevant organizations. For the cognitive interviews, ads will link to the study information website. Interested individuals will complete a demographic screener and provide contact information. The bilingual study staff will contact selected participants to schedule an interview. For the quantitative survey, the ad will link to an eligibility screener with programmed quotas; individuals who meet eligibility criteria and whose recruitment category is open will be invited to participate and directed to the consent page. Multiple evidence-based strategies will be used to prevent and detect fraudulent respondents, including nondisclosure of eligibility criteria in ads, modest incentives, blocking responses

from the same IP address, CAPTCHA (Completely Automated Public Turing test to tell Computers and Humans Apart), consistency and attention checks, and exclusion of records with implausible response times [60-62]. Using Qualtrics (SAP Inc) software, the English and Spanish surveys will be programmed as a single bilingual survey to prevent duplicate participation. Cognitive interview and survey participants will receive US $50 and US $15 electronic Amazon gift cards, respectively.

Cognitive Interviews

Interviews will be conducted by trained research assistants using Health Insurance Portability and Accountability Act—compliant videoconferencing software (Zoom Health Insurance Portability and Accountability Act Private Mode). Verbal probing will be used to assess potential problems in the cognitive processes of question comprehension, information retrieval, judgment and estimation, and response [63]. At the start of the interview, participants will be sent a weblink to a questionnaire containing the unattributed InDI. Participants will respond to each item, and then the interviewer will ask them how they answered the question and why. Following best practices for cognitive interviewing, subsequent probes will ask the respondent to paraphrase the question, judge their confidence in the response, reflect on the accuracy of their recall, and indicate whether they had difficulty answering [64].

After completing the unattributed measures, participants will be presented with one of two attributed versions, one that requests either item-level attributions or overall attributions for each of the InDI measures (Multimedia Appendix 1). The interviewer will ask the respondent to complete the attribution items and then probe their responses as above. In addition, participants will be asked to share their perspectives on the importance of attributions (eg, “Did you prefer answering these questions with or without being asked for reasons why others mistreated you?”).

Interviewers will take notes directly into Q-Notes software, developed by the National Center for Health Statistics for the analysis of cognitive interviewing data [65]. Q-Notes is designed to facilitate real-time cross-site collaborations to evaluate instruments in multiple languages. This will facilitate the rapid analysis of data for aim 1 and subsequent revisions to improve the clarity and completeness of the InDI items. Interviews will also be recorded, transcribed verbatim, and translated into English if needed.

Quantitative Surveys

The self-administered survey will take approximately 20 minutes to complete.

Intersectional Discrimination Index

All Spanish-language participants will receive the unattributed InDI (Multimedia Appendix 1), with potential modifications based on cognitive interview findings. For the English survey, we will use the block-randomization feature in Qualtrics to implement a split-ballot design: 1000 participants will receive each of the unattributed, item-level attributed, or overall attributed versions of the InDI.

Demographics

Age, sex assigned at birth, current gender identity, race, ethnicity, immigration history, education, income, sexual orientation, geographic region, and community size (eg, urban and rural) data will be collected.

Health Outcomes

To permit psychometric evaluation of these novel instruments (aim 2) and comparisons between attribution methods (aim 3), analyses in the current proposal will focus on two of the most well-established health consequences of perceived discrimination: psychological distress and self-rated general health [15]. Psychological distress will be measured using the 6-item K6 measure developed by Kessler et al [66]. The K6 was developed to estimate the prevalence of serious mental illness and has shown good sensitivity and excellent specificity in US population samples when dichotomized at a score of 13/24 or above and compared with Diagnostic and Statistical Manual of Mental Disorders-IV diagnoses via structured clinical interviews [66,67]. Self-rated general health, a robust predictor of morbidity and mortality [68], will be assessed using a standard question from the Behavioral Risk Factor Surveillance System and other federal surveys (“Would you say in general that your health is—excellent, very good, good, fair, or poor?”). To facilitate secondary analyses of these data focused on a wider range of health outcomes, the survey will also collect data on substance use (nicotine, alcohol, and illicit drugs), hypertension, and diabetes.

Analysis Plan

Aim 1: Cognitive Evaluation of the InDI Measures in English and Spanish

Using sorting features in the Q-Notes software, we will first analyze detailed interview notes at the within-interview level (to capture response errors). Next, we will compare data on each survey item across interviews to evaluate consistency in understanding what the question intends to capture. Finally, we will sort data by participant subgroups (eg, by language, race and ethnicity, and SGM status individually) to identify potential response biases. Two analysts will complete each of these steps independently, meeting to compare analysis notes and generate a list of potential modifications at the end of each stage. Potential modifications to address identified problems with instructions, items, or response options will be reviewed by all team members; if modifications are made, the revised measures will be evaluated with five new cognitive interviews in each language.

Aim 2: Psychometric Evaluation of the InDI Measures Across Languages and Intersecting SSPs

Analyses will be conducted in MPlus (Muthén & Muthén) and Stata (StataCorp LLC). As a first step, we will conduct exploratory factor analysis, exploratory structural equation modeling, and confirmatory factor analysis (CFA) of the InDI-D and InDI-M in our previously collected data, using split-halves of the sample by country (n=1065 and n=1518). These analyses will help us establish the configural and metric structures of the two enacted discrimination measures. We previously used this

approach to assess the psychometric properties of the InDI-A, finding support for its hypothesized unidimensionality. At that time, we opted not to conduct factor analyses of the enacted discrimination measures, with the rationale that their items are causal-formative indicators that aggregate to form a construct, rather than items that reflect the level of an underlying construct and should necessarily correlate [69]. Nevertheless, existing research demonstrates that discrimination scales do show strong interitem correlations and factor structures [47], likely reflecting both respondent characteristics that determine perception and self-reporting of discrimination, as well as the social clustering of discrimination. Furthermore, the assessment of configural, metric, and scalar structures of the InDI measures should precede the evaluation of measurement equivalence across intersectional groups, thereby determining whether the discrimination burdens they estimate can be meaningfully compared across groups [47]. We will evaluate the goodness of fit for CFA with parsimony, incremental, and absolute indices [70]. If substantive changes are made to the InDI items in aim 1, we will instead conduct the exploratory factor analysis, exploratory/confirmatory factor analysis, and CFA using randomly selected samples of the new survey data (n=200 each).

Once the configural and metric structures of the InDI measures are established, we will assess their scalar structures. We will estimate the Loevinger H coefficient to determine whether scales reflect the Mokken model (ie, those endorsing severe items are more likely to endorse less severe items) [71]. This will be followed by the estimation of item response theory models [72]; item discrimination and item difficulty will be estimated to assess how well the InDI measures tap their underlying traits. The results will be graphically displayed in a Wright map, item characteristic curves, a test information function plot, and a test characteristic curve graph.

Next, we will use originally collected survey data to assess differential item functioning and measurement equivalence, using Multiple Indicator Multiple Cause (MIMIC) models and multigroup CFA (mCFA), respectively. These approaches are complementary: mCFA compares the full measurement model across groups, whereas MIMIC is generally limited to testing for differences in item difficulty (thresholds for endorsement). However, mCFA estimates parameters separately for groups defined by a single categorical variable and requires a sufficient sample size for each group, whereas MIMIC uses a single model for the full sample, making it more efficient and permitting isolation of reasons for differential item functioning [73,74]. Therefore, we will use the MIMIC methods across a range of SSPs of interest and the mCFA methods across the intersectional quota-sampled strata. We will include gender, sexual orientation, race and ethnicity, socioeconomic status, age, and nativity as covariates in the MIMIC model for each measure.

We will use mCFA to determine whether the configural, metric, and scalar structures of the InDI measures are equivalent across (1) language (English vs Spanish) and (2) the 12 intersectional race and ethnicity*SGM*gender sample strata. Achieving equivalence across all these scale structures is necessary for the InDI measures to generate meaningful cross-group comparisons. After estimating the baseline models for each group, we will test configural equivalence across language and intersectional strata. We will then assess the metric equivalence of the scales by examining whether factor loadings vary across these groups by comparing the fit of the metric models with those of the configural models. To assess scalar equivalence, item thresholds will be tested for their equivalence among the same groups. Formal comparisons will be carried out by comparing the fit of the scalar models with those of the metric models. To compare less (eg, configural) and more restrictive (eg, metric and scalar) models, we will use a reduction ≥0.002 in the value of the comparative fit index as an unbiased indication of lack of equivalence, given the sensitivity of *P* values to large sample sizes [75]. We will also assess the partial invariance of the InDI measures. If needed (eg, because of numerous large modification indices), the alignment method will be used as an alternative to assess measurement equivalence [76].

Aim 3: Determine Whether Attributions Should Be Included in the InDI Measures

Overview

Aim 3 will use a convergent mixed methods design; quantitative and qualitative data analyses will be conducted separately and then the findings will be integrated to identify areas of convergence and divergence [77], following the National Institutes of Health Best Practices guidelines for mixed methods research [78].

Qualitative Analysis

Transcripts will be uploaded to Dedoose cloud-based software for analysis, facilitating remote collaboration. We will code the portion of the interview in which participants reflect on attribution items as well as any other portions relevant to attribution (eg, if raised by a participant earlier in the interview). The analysis will use techniques adapted from grounded theory [79,80]. Inductive coding to identify emergent themes will follow the constant comparative method of going back and forth between the data and coding to identify patterns and regularities. Two analysts will read all transcripts. Each analyst will code 5 transcripts independently, at which point discrepancies will be resolved through discussion before the remaining transcripts are coded. We will compare codes and themes by age, race, ethnicity, nativity, urban or rural residence, gender, and sexual orientation. To establish credibility, we will maintain an audit trail of coding decisions.

Quantitative Analysis

As a first step, we will compare discrimination burden (mean or median score on each of the InDI-A, InDI-D, and InDI-M) across the three conditions for each measure (unattributed, item-level attribution, and overall attribution) to determine whether the presence of attributions influences reporting. We will use appropriate parametric and nonparametric statistics (eg, chi-square and Mann-Whitney U test) to test for statistically significant differences between conditions. Next, we will estimate concordance between intersectional SSPs and discrimination attributions to determine the extent to which attributions align with SSPs. Among those reporting any discrimination in both the item-level and overall attribution conditions, we will calculate the proportion of (1) Black or Latino/a/x individuals who report racial and/or ethnic

discrimination, (2) SGM individuals who report sexuality and/or gender identity–related discrimination, and (3) Black or Latino/a/x SGM who report both types of discrimination. In the item-level attribution condition, we will further calculate the proportion of items for which the aforementioned groups endorsed the respective attributions.

Finally, we will compare the magnitude of effect on psychological distress (continuous) and fair or poor (vs good or excellent) self-rated general health of reporting each discrimination type (InDI-A, InDI-D, and InDI-M), (1) based on sexuality and/or gender identity, (2) based on race and/or ethnicity, or (3) based on both (1) and (2). Using data from the attributed conditions, we will fit linear regression models to separately estimate the association between a categorical indicator of discrimination attributions (race and/or ethnicity, sexuality and/or gender, both, or other attributions only) and psychological distress, adjusting for total discrimination burden. These analyses will be conducted separately among Black and Latino/a/x SGM reporting any discrimination for each measure (InDI-A, InDI-D, and InDI-M). Parallel analyses focused on attributions to race and/or ethnicity, gender, both, or other attributions will be conducted among Black and Latino/a/x women. For self-rated health, we will use a similar approach with logistic regression.

Mixed Method Integration

We will merge qualitative and quantitative databases for analysis and interpretation. Specifically, we will use a joint display of data to visually represent and compare findings from each data set as they relate to key concepts [77,78,81]. We will be attentive to differences in the ethnoracial composition of the data sets to identify any themes that are unique to non-Black, non-Latino/a/x people of color. Implications for the measurement of divergent or inconsistent findings will be identified, with particular attention to how optimal measurement strategies might differ across intersectional groups and research foci.

Sample Size

For cognitive interviews, our sample size exceeds qualitative research guidelines for achieving data saturation—the number of interviews by which no new relevant themes are identified (eg, up to 25 participants) [82,83]. The quantitative survey sample sizes were determined based on sample size requirements for multigroup CFA, which has the greatest sample size requirement among the planned analyses. Simulation studies show that 200 respondents per group is the minimum number required to have ≥80% power to detect measurement invariance via changes of ≥0.002 in the comparative fit index [75]. Therefore, we will recruit 250 per race and ethnicity*SGM*gender stratum in English (n=3000); the Spanish-language sample (n=500) will allow for mCFA by language as well as by SGM status, race, or gender. All other planned quantitative analyses have smaller sample size requirements.

Results

The study was funded by the National Institute on Minority Health and Health Disparities from May 6, 2021, to January 31, 2023 (Multimedia Appendix 2). The study was approved by the institutional review board of Drexel University in May 2021 (IRB # 2006007889). Cognitive interview data collection began in July 2021. The publication of study results is expected to begin in early 2023.

Discussion

Study Importance

This study offers multiple innovations. It aligns with the National Institute on Minority Health and Health Disparities priorities for promoting the advancement of health disparities science by “strengthen[ing] the understanding of how racism and discrimination are conceptualized and measured, and how they contribute to health disparities” [84]. The key deliverables of this study will be bilingual measures of anticipated, day-to-day, and major discrimination validated for multiple health disparity populations using rigorous qualitative, quantitative, and mixed methods. Despite the high cognitive burden posed by discrimination measures, few studies have combined cognitive interviewing and psychometric approaches to validate them [85]. By subjecting these novel measures to a comprehensive and early evaluation of measurement equivalence, we will identify and be able to revise potentially problematic items before widespread use. Multiple studies have uncovered differential item functioning across diverse social groups among measures, such as the widely used Everyday Discrimination Scale [39,85,86], but only after they had been used in hundreds of studies [87] and were thus unlikely to be modified. The study will further advance measurement methods for health disparities research by determining the utility of including attributions in intersectional discrimination measures. If an attribution-free approach is viable, it will be possible to briefly assess discrimination experiences across a range of individual SSPs and their intersections in broad population surveys, enabling health disparities researchers to answer a much wider range of questions than with single-attribution measures.

Limitations, Challenges, and Future Directions

Our 2-year study timeline is feasible because we have developed a two-stage analysis plan for cognitive interview data to ensure that any InDI revisions can be made rapidly, facilitating a timely launch of the quantitative survey. Our web-based recruitment and data collection plan will not be affected by social distancing requirements related to the COVID-19 pandemic. Nonrandom sampling will limit generalizability, but quota sampling will allow for the evaluation of InDI measures in intersectional strata that are typically small in representative surveys. The quantitative survey focuses on the largest racial and ethnic groups in the United States in which most health research on discrimination is conducted; as the design requires 1000 participants per racial or ethnic group, this restriction is necessary given finite resources. However, cognitive interviews will include all ethnoracial groups to ensure that revisions are made inclusively, and the qualitative findings will provide pilot data for future assessment of the InDI measures in other ethnoracial groups. Other future directions for this research include secondary use of the data (to be made publicly available)

for intersectional analyses of relationships between discrimination and health among SGM persons of color, for whom large publicly available data sets are scarce.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Intersectional Discrimination Index test measures.
[DOCX File , 61 KB - resprot_v10i8e30987_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from the Health Disparities and Equity Promotion Study Section, National Institutes of Health.
[PDF File (Adobe PDF File), 135 KB - resprot_v10i8e30987_app2.pdf]

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Abbreviations

CAPTCHA: Completely Automated Public Turing test to tell Computers and Humans Apart
CFA: confirmatory factor analysis
InDI: Intersectional Discrimination Index
InDI-A: Intersectional Discrimination Index-anticipated
InDI-D: Intersectional Discrimination Index-day-to-day
InDI-M: Intersectional Discrimination Index-major
mCFA: multigroup confirmatory factor analysis
MIMIC: Multiple Indicator Multiple Cause
SGM: sexual and gender minority
SSP: social status and position

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Protocol

The COVID-19 Citizen Science Study: Protocol for a Longitudinal Digital Health Cohort Study

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Abstract

Background: The COVID-19 pandemic has catalyzed a global public response and innovation in clinical study methods.

Objective: The COVID-19 Citizen Science study was designed to generate knowledge about participant-reported COVID-19 symptoms, behaviors, and disease occurrence.

Methods: COVID-19 Citizen Science is a longitudinal cohort study launched on March 26, 2020, on the Eureka Research Platform. This study illustrates important advances in digital clinical studies, including entirely digital study participation, targeted recruitment strategies, electronic consent, recurrent and time-updated assessments, integration with smartphone-based measurements, analytics for recruitment and engagement, connection with partner studies, novel engagement strategies such as participant-proposed questions, and feedback in the form of real-time results to participants.

Results: As of February 2021, the study has enrolled over 50,000 participants. Study enrollment and participation are ongoing. Over the lifetime of the study, an average of 59% of participants have completed at least one survey in the past 4 weeks.

Conclusions: Insights about COVID-19 symptoms, behaviors, and disease occurrence can be drawn through digital clinical studies. Continued innovation in digital clinical study methods represents the future of clinical research.

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KEYWORDS

COVID-19; digital technology; participant engagement; electronic health records; mobile app; mHealth; digital health

Introduction

The ubiquity of the internet, computers, and smartphones has enabled new ways for people to participate in clinical studies [1]. Traditional research methods involve direct interaction between research staff and participants with laborious and costly efforts to recruit, enroll, consent, and follow participants [2]. The creation of digital tools for conducting clinical studies has made it possible to engage large numbers of people in research studies, collect data beyond the clinical setting, avoid constraints related to geographic location or proximity to a research center, collect frequent participant-reported outcomes, collect data from connected devices such as smartphones and wearables, and rapidly generate results to inform advances in health and science [1,3].

In 2014, University of California, San Francisco (UCSF) researchers launched the Health eHeart Study [4], a ground-breaking cohort study conducted using web- and mobile-based recruitment, enrollment, consent, and participation [5-8]. Recognizing the potential of this approach to facilitate clinical research more broadly, the infrastructure of the Health

eHeart Study was expanded to develop the NIH-supported Eureka Research Platform [9] for developing and hosting digital clinical studies [10-12]. The platform enables studies to be conducted entirely through web and mobile interactions, as well as studies with digital interaction as a complement to traditional clinical research methods. The Eureka Research Platform has hosted over 40 studies.

The COVID-19 pandemic has catalyzed innovation in clinical investigation and especially digital methods for clinical studies [3]. The risk of virus transmission has created a need to limit face-to-face interactions between study participants and research staff, highlighting the need for digital approaches [13]. Despite the challenges, researchers have rapidly innovated to solve an urgent global health crisis, and citizens of the world have been inspired to contribute to research studies in unprecedented numbers [3,14-17].

Here, we describe the methods of the COVID-19 Citizen Science (CCS) study, an entirely digital clinical study on the Eureka Research Platform. The objectives of the study are to generate knowledge about participant-reported COVID-19 symptoms, behaviors, and disease occurrence to facilitate the public health response to COVID-19. These methods highlight clinical study innovations and future directions for advancing science using digital clinical study methods.

Methods

Study Design, Setting, and Participants

This report of an observational study is consistent with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. CCS is a cohort study on the Eureka Research Platform conducted through the Eureka mobile app (Figure 1) [18]. The CCS study was launched on March 26, 2020, after 8 days of intensive scientific and technical development utilizing established Eureka workflows (Figure 2). Participant enrollment and follow-up are ongoing and are expected to continue for years to investigate the long-term consequences of the COVID-19 pandemic. There are no prespecified enrollment targets or end dates for enrollment or completion. Participants must be 18 years of age or older, register for a Eureka account, have an iOS or Android smartphone, have a cell phone number, agree to participate in English, and be able to provide consent to participate in the study. After providing electronic consent to participate in the study, participants are asked to complete a baseline survey about demographics, medical conditions, medications, and behaviors through the study app. Participants can voluntarily provide permission to collect additional data from their smartphones, including geolocation and, among iOS users, HealthKit data (providing this data is optional and does not otherwise preclude study participation). Participants then complete daily, weekly, and monthly surveys through the study app. Surveys are written in lay language meeting Flesch-Kincaid criteria for an eighth-grade reading level [19]. The study does not currently include any interventions. On January 21, 2021, we also launched a web version of the study to enable participation options for people without a mobile phone or with concerns about downloading an app. The study is only available in English.

CCS is an entirely digital study that is hosted on the Eureka Research Platform, which has standard elements for electronic consent, surveys, and feedback that can be customized for individual studies. Studies on the Eureka Research Platform follow rapid development cycles that enable swift progression through study concept, user-centered design, programming, software quality assurance, and deployment to production. Additionally, study design and content are not static, but undergo iterative revisions in response to participant feedback, research collaborations, new scientific or public health findings, and newly developed research questions arising in the course of the research. Within the participant study app, questions are presented as one question per screen. The participant has the opportunity to go back and change responses within a survey, but they cannot change responses within the app after submitting the survey.

The Eureka platform and the CCS study were reviewed and approved by the UCSF Institutional Review Board (IRB) (#17-21879). Due to pre-existing Eureka IRB protocols and institutional prioritization of COVID-19 research, we received CCS study-specific IRB approval in under 3 days. All participants provide electronic consent to participate in the study. Some partner studies also include additional consent through Docusign. There were no monetary incentives for participation in the main study. Some partner studies include monetary incentives for participation to enhance participation in underrepresented groups.

Figure 1. Screenshot of the COVID-19 Citizen Science study app on the Eureka Research Platform.

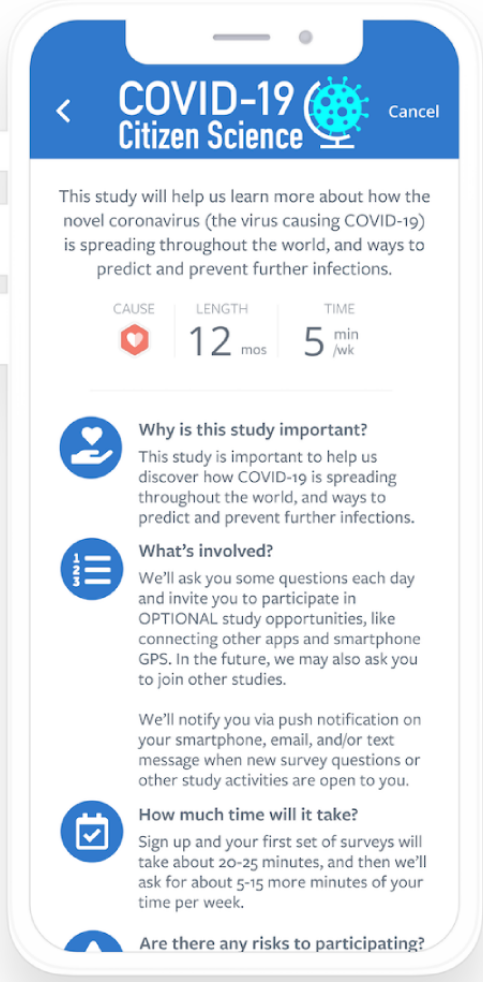
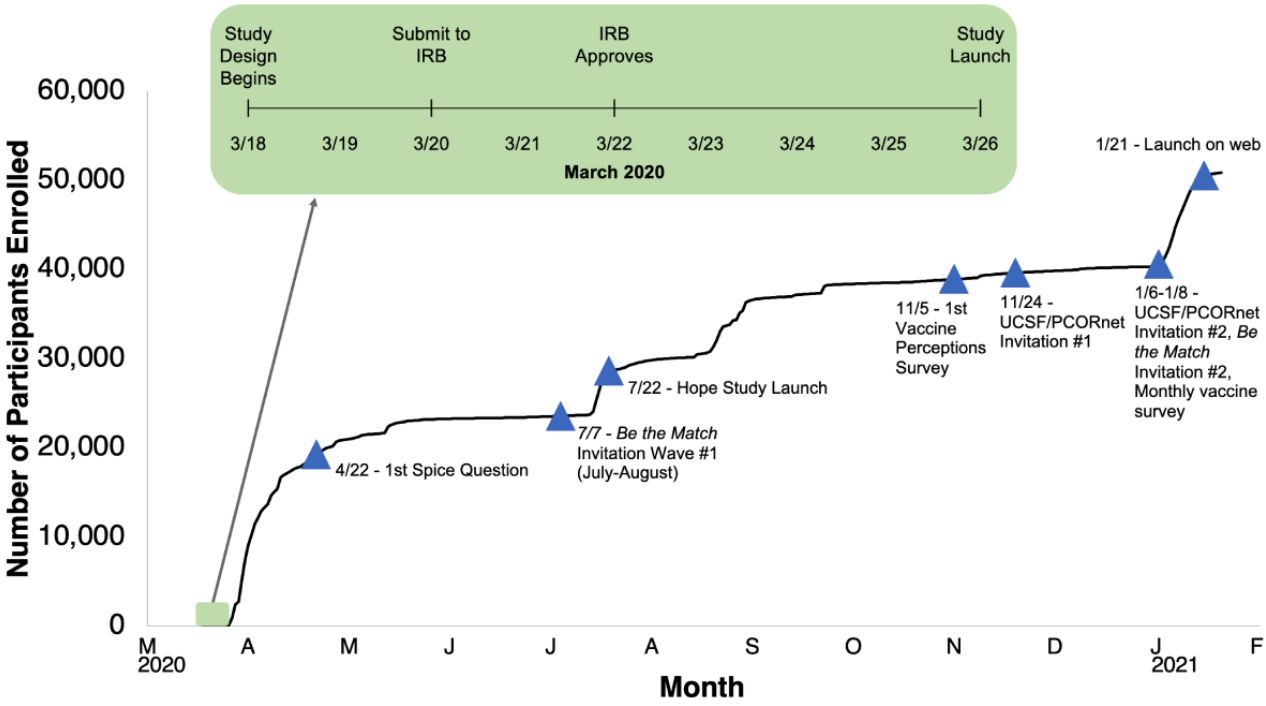


Figure 2. COVID-19 Citizen Science study development, enrollment, and iteration. IRB: institutional review board; PCORnet: National Patient-Centered Clinical Research Network; UCSF: University of California, San Francisco.



Recruitment

Study participants are recruited through multiple mechanisms, which not only allows broad study recruitment but also enables answering targeted research questions in specific populations through collaboration with research partners.

The Eureka app is publicly available on the Apple App Store and Google Play Store; anyone who downloads and installs the Eureka app and meets the CCS study enrollment criteria can participate. No payment is required, and no monetary incentives are provided. The Eureka app hosts many studies; some studies (such as CCS) are visible to anyone with the app and other studies are only visible with specific deep links. The CCS study is broadly advertised through press releases and articles in print and digital media, including social media. To date, advertisement has been conducted organically without paid or targeted ads, but rather by word of mouth, social media sharing, coverage by news outlets or other external content creators, and outreach to interested organizations. Digital advertisements include deep links that take participants directly to the app store to download and then open the Eureka app to specifically enroll in the CCS study. Participants may see opportunities to join other studies, but only after they finish their CCS-related study activities. Advertisements can also include "text backs" wherein a word (such as "COVID") is texted to a 5-digit SMS short code (such as 41411), resulting in an immediate text that provides the deep link. A similar mechanism also supports QR-code mediated recruitment. Referral codes also support tracking the recruitment source, such as from a specific article or video, allowing optimization of recruitment methods. Lastly, Eureka users who have previously downloaded the app may discover the CCS study in the app without external prompting.

We are also able to recruit study participants from other Eureka platform studies. For example, we sent emails to Health eHeart participants to invite them to participate in the CCS study. Recruitment email versions were tested, with two versions of emails sent to 71,669 prospective participants (randomized 1:1) over 2 days in the first phase of recruitment. We then selected the more successful email version, defined by the number of consented participants who received each, to send to later phases of recruitment to increase the likelihood of participation.

CCS also employs a partner study model for recruitment. Through this model, an individual in a selected population is invited to participate in the CCS study using a unique participant code. This code enables the data that are collected through the CCS to be linked with the participant's data from another program, registry, or research study, with data sharing under the auspices of a partner-specific consent that is presented during study onboarding prior to the general CCS consent. Each partner maintains its own IRB approval distinct from the core CCS study and Eureka platform approvals. One example of partner study recruitment is the invitation of *Be The Match* registry participants to join the CCS study. *Be The Match* registry participants, who have registered as potential bone marrow donors and undergone HLA antigen typing [20], were emailed a unique link to enroll in the CCS study. Researchers will then be able to study whether HLA antigen types are related to COVID-19 risk. A second example of partner study recruitment is through health systems willing to deliver invitations to their patients [21]. Health systems email participants an invitation to participate with a unique link. The participant first provides partner consent to link their standardized electronic health record data to their CCS data before proceeding to CCS enrollment and consent. Researchers will then be able to link patient-reported data from the CCS study with electronic health record data (eg, from health systems participating in the National Patient-Centered Clinical Research Network [PCORnet]) [22].

Recruitment can also occur with partner studies through two-way recruitment and data-sharing. The CCS study partnered with the HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID-19) study investigating the impact of the COVID-19 pandemic on pregnancy [23]. CCS study participants who may be eligible are sent invitations to participate in the HOPE COVID-19 study, and participants in the HOPE COVID-19 study are sent invitations to participate in the CCS study. Each study can link data for mutual participants to generate richer data in a specific topic area and limit duplication of study questions. Through this IRB-approved process, participants can provide consent to data sharing across studies.

Engagement

Enhancing engagement in digital clinical studies is a challenge, and we have employed several engagement approaches to date. Since the study includes daily surveys, we send a push notification to participants on a daily basis at the time the survey becomes available. In order to address various time zones as well as work schedules, the most convenient time of day for each participant is automatically inferred by sending subsequent notifications at 24-hour intervals following completion of the baseline set of surveys. For weekly and monthly surveys, we send both a push notification and a delayed SMS text message (which is not sent if the activities are completed before the delay) with a link to the Eureka app. The SMS text message is deliberately utilized less frequently than the mobile app-based notification because it is more intrusive, potentially resulting in heightened response rates and incurring greater participant burden. These surveys are sent at 7-day intervals from the completion of the baseline survey.

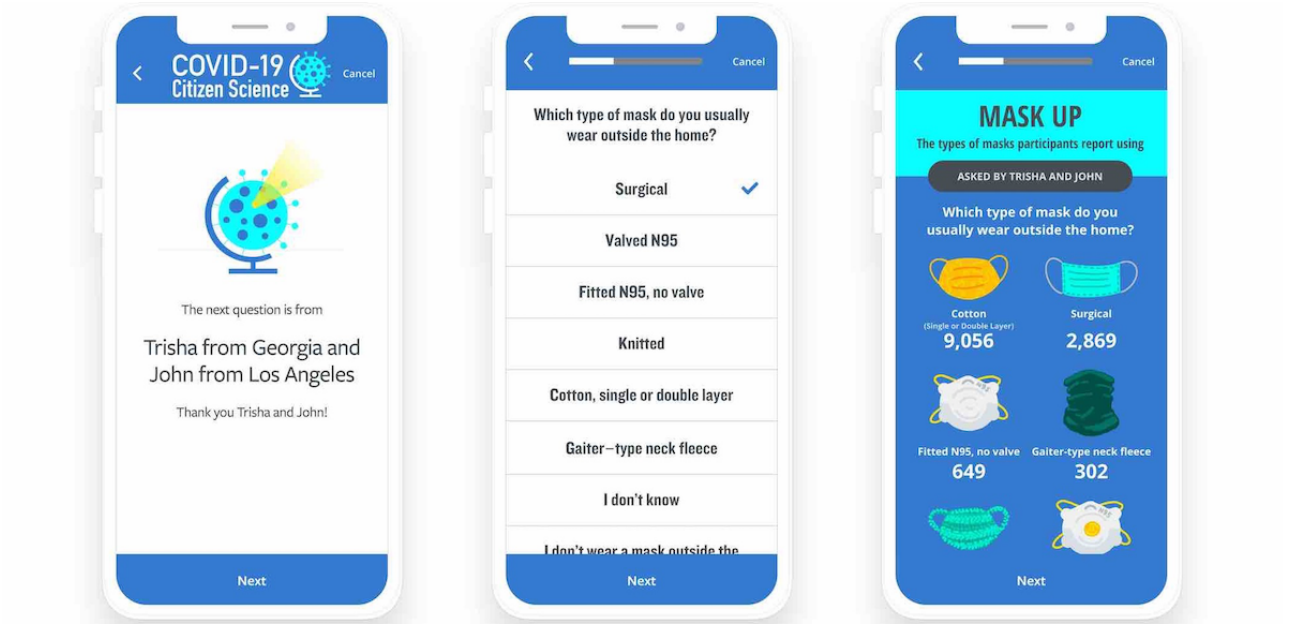
Additionally, because one motivation for this study is citizen participation in science, we actively promote feedback of study information to participants. We post study updates to a public website [24] that is linked within the study app and periodically send participants messages with study updates (approximately quarterly).

A novel engagement technique in this study is the *Spice Question* (Figure 3). Because the study includes repetitive daily surveys, we instituted a Spice Question that is added to the survey approximately once a week. The day-of-week that a Spice Question is sent is intentionally variable to avoid predictability to invoke intermittent reinforcement, potentially employing similar psychological engagement as a random slot machine [25]. This is also a mechanism to rapidly incorporate research questions posed to the entire cohort at one point in time that may be addressed with a single question. To promote the *citizen science* aspect of the study, we asked study

participants to submit suggestions for Spice Questions through a survey mechanism. After review and edits as needed to avoid replication, limit questions to those that are answerable via survey, and to assure the question is delivered in easily understandable language, we then present the participant-proposed Spice Question to study participants. For these questions, we indicate that the question originated from a study participant, and we include the following details of the participant that contributed the question: first name and town or city of residence along with the state or country (if outside the US) name (Figure 3). Spice Questions are often the topic of website update posts to further emphasize citizen science engagement in research questions, participation, and sharing of results

Study participants are also able to request support or submit suggestions for study improvement through the app or email to the study staff. These messages are managed through Zendesk, which allows us to rapidly triage and respond to participant messages (median response time is 14.3 hours). Participant suggestions are routinely used to refine survey questions and identify technical bugs.

Figure 3. Example of participant-proposed "spice question" engagement method on the COVID-19 Citizen Science study app. Screenshots depict an introductory screen, a survey question, and a subsequent report of results delivered to the survey participants.



Data Collection and Management

Study data can be collected from participant-reported responses within the study app, smartphone data, connected devices and services, and partner data such as electronic health record data. Additionally, these data can be supplemented by information from public sources, including data on regional health care policies, and public data on COVID-19 cases and deaths, such as data through the New York Times GitHub server. Study data are stored on private, secure, HIPAA (Health Insurance Portability and Accountability Act)–compliant cloud-based servers with access restricted only to authorized study personnel.

Surveys include baseline, daily, weekly, and monthly surveys (Table 1 and Multimedia Appendix 1). At baseline, participants are asked about their past COVID-19 test results, demographics, medical history, medications, and behaviors. Daily surveys ask about symptoms and interactions outside of the household. These questions were asked daily to enable the study team to capture rapidly changing symptoms. Weekly surveys ask about new COVID-19 test results and community behaviors to promote response while the test results and behaviors are fresh in the participant's mind. Monthly surveys ask about depressive symptoms and anxiety symptoms in validated questionnaires that are designed to capture symptoms experienced by the participants over the past 2 weeks. Through the course of the study, additional surveys have been added, such as surveys about vaccine perceptions and receipt of a COVID-19 vaccine. Surveys were designed to ask participants about known COVID-19–related symptoms, risk mitigation behaviors, disease occurrence, and potential demographic characteristics and medical conditions that may confound associations between exposures and outcomes. When possible, the study uses validated questionnaires to enhance the validity and interpretation of results.

Table 1. COVID-19 Citizen Science study survey schedule.

Survey item	Baseline	Daily	Weekly	Monthly	One-time
Demographics	✓				
Medical history	✓				
Medications	✓		✓		
MacArthur Scale of Subjective Social Status [26]	✓				
Patient Health Questionnaire–8 (omits suicidal ideation) [27]				✓	
General Anxiety Disorder Questionnaire–7 [28]				✓	
COVID-19 symptoms, interactions outside of household	✓	✓			
Community behaviors eg, (large events, restaurants, bars, gyms)			✓		
COVID-19 testing and results	✓		✓		
Vaccine perceptions					✓
Vaccine receipt	✓			✓	
Spice questions					✓

Smartphone and device data include data collected through Apple HealthKit, as authorized by the participant to be shared with the CCS study team (Multimedia Appendix 2). We also collect geolocation data to allow us to identify and measure time spent at places of interest. Through a partnership with COVIDSEEKER [29], a novel tool being tested at UCSF, we invite CCS participants to contribute retrospective geolocation data to identify locations of possible COVID-19 exposures.

Statistical Analysis

Due to the rapidly changing nature of the COVID-19 pandemic, we did not prespecify a sample size or statistical analyses for the study. Each research project that researchers wish to conduct using data from the CCS study will formulate a statistical analysis plan prior to analyzing data and register that analysis with the CCS study team. Examples include the following studies: (1) “Characteristics and behaviors associated with prevalent SARS-CoV-2 infection” [30], (2) “Factors associated with access to and timing of coronavirus testing among US adults after onset of febrile illness” [31], and (3) “Predictors of incident viral symptoms ascertained in the era of COVID-19” [32].

Results

Participants from every state in the USA and 99 countries have enrolled in the CCS study (Multimedia Appendix 3). Baseline characteristics of participants enrolled as of January 14, 2021, are presented in Table 2. Geolocation data were contributed by 78.3% (36,116/46,106) of participants, and HealthKit data were contributed by 34.8% (16,044/46,106) of all participants. Although the percentage of participants completing surveys decreases over time since enrollment (Figure 4), over the lifetime of the study, an average of 59% of participants have completed at least 1 survey in the past 4 weeks. The study publishes real-time results on a public website [24] that is linked from the participant study app. These results include updates on numbers of participants, interactive maps of worldwide participation, and patient-reported symptoms (Figure 5; Multimedia Appendix 4) [33], and blog posts with charts illustrating participant responses to study questions. Ongoing efforts include creating a dashboard to display historic and real-time results and future predictions about COVID-19 trends based on data contributed by CCS participants and publicly available data.

Table 2. Baseline characteristics of participants in the COVID-19 Citizen Science study as of January 14, 2021 (N=46,106).

Characteristic[a]	Value
Age at consent (years), n (%) (n=46,106)	
18-39	20,897 (45.3)
40-64	21,475 (46.6)
≥65	3734 (8.1)
Sex at birth, n (%) (n=42,902)	
Male	13,437 (31.3)
Female	29,391 (68.5)
Decline	74 (0.2)
Gender identity, n (%) (n=42,890)	
Male	13,289 (31)
Female	28,904 (67.4)
Transgender woman	53 (0.1)
Transgender man	92 (0.2)
Genderqueer	327 (0.8)
Other	137 (0.3)
Decline	98 (0.2)
Race, n (%) (n=42,418)	
Black or African American	875 (2.1)
White	38,086 (89.8)
Asian	3150 (7.4)
Native Hawaiian or Pacific Islander	131 (0.3)
American Indian or Alaska Native	569 (1.3)
Other or don’t know	1516 (3.6)
Hispanic ethnicity, n (%) (n=42,902)	3305 (7.7)
Subjective social status, median (IQR) (n=42,898)	7 (6-8)
Educational attainment, n (%) (n=42,885)	
High school or less	1951 (4.5)
Some college	6864 (16)
Bachelor’s	15,394 (35.9)
Postgraduate	18,140 (42.3)
Other, don’t know, or prefer not to state	536 (1.2)
Residence in USA, n (%) (n=43,905)	41,058 (93.5)
Residence: USA region, n (%) (n=40,943)	
West	20,146 (49.2)
Midwest	6662 (16.3)
Northeast	5723 (14)
South	8412 (20.5)
Exercise, n (%) (n=43,819)	
Never	2775 (6.3)
Less than once per month	4146 (9.4)
Once per month to once per week	5857 (13.3)

Characteristic[a]	Value
Once per week	5792 (13.2)
1 to 4 times per week	13,275 (30.2)
4 or more times per week	11,900 (27.1)
Other	146 (0.3)
Alcohol consumption (drinks/week), median (IQR) (n=27,649)	2 (0-5)
Current smoking, n (%) (n=41,604)	2385 (5.7)
Current e-cigarette use, n (%) (n=41,682)	1408 (3.4)
Medical condition, n (%)	
Hypertension (n=42,783)	7969 (18.6)
Diabetes (n=42,780)	1676 (3.9)
Coronary artery disease (n=42,781)	979 (2.3)
Myocardial infarction (n=42,781)	402 (0.9)
Congestive heart failure (n=42,781)	266 (0.6)
Stroke or transient ischemic attack (n=42,783)	520 (1.2)
Atrial fibrillation (n=42,780)	1128 (2.6)
Sleep apnea (n=42,781)	4226 (9.8)
Chronic obstructive pulmonary disease (n=42,782)	682 (1.6)
Asthma (n=42,780)	4414 (10.3)
Cancer (active) (n=42,779)	1272 (2.9)
Immunodeficiency (n=42,783)	867 (2)
HIV (n=42,783)	179 (0.4)
Anemia (n=42,780)	4530 (10.6)
Pregnant (n=42,781)	515 (1.2)
Tested positive for COVID-19 before baseline, n (%) (n=43,905)	1214 (2.8)

[a]Not all participants provided responses to all survey questions, so the denominator for each characteristic differs.

Figure 4. Survey completion metrics in the COVID-19 Citizen Science study.

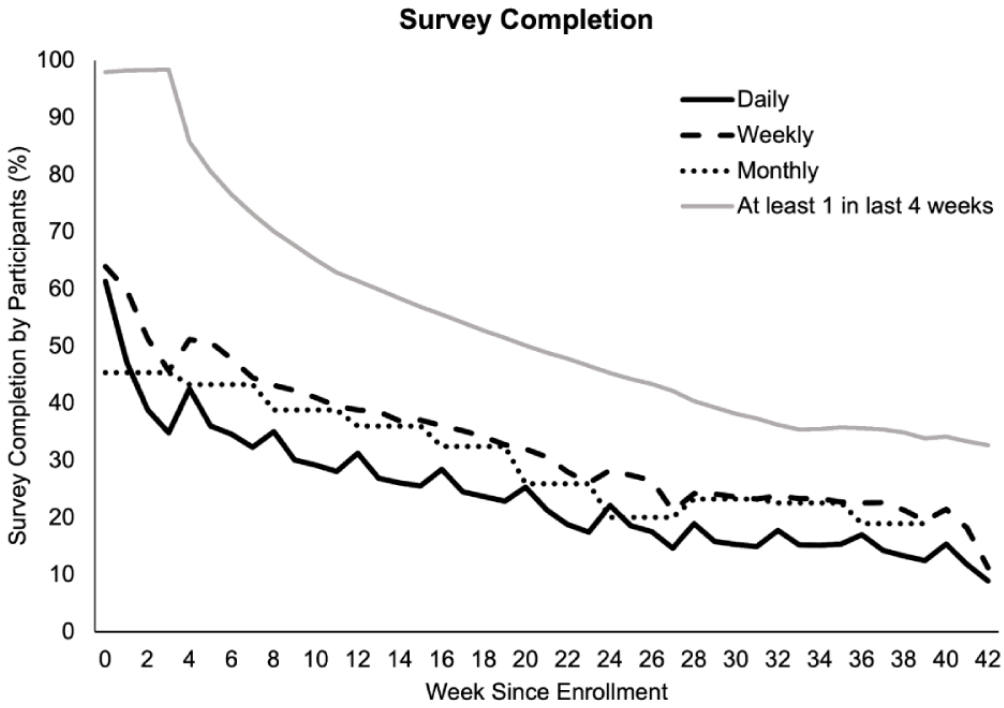
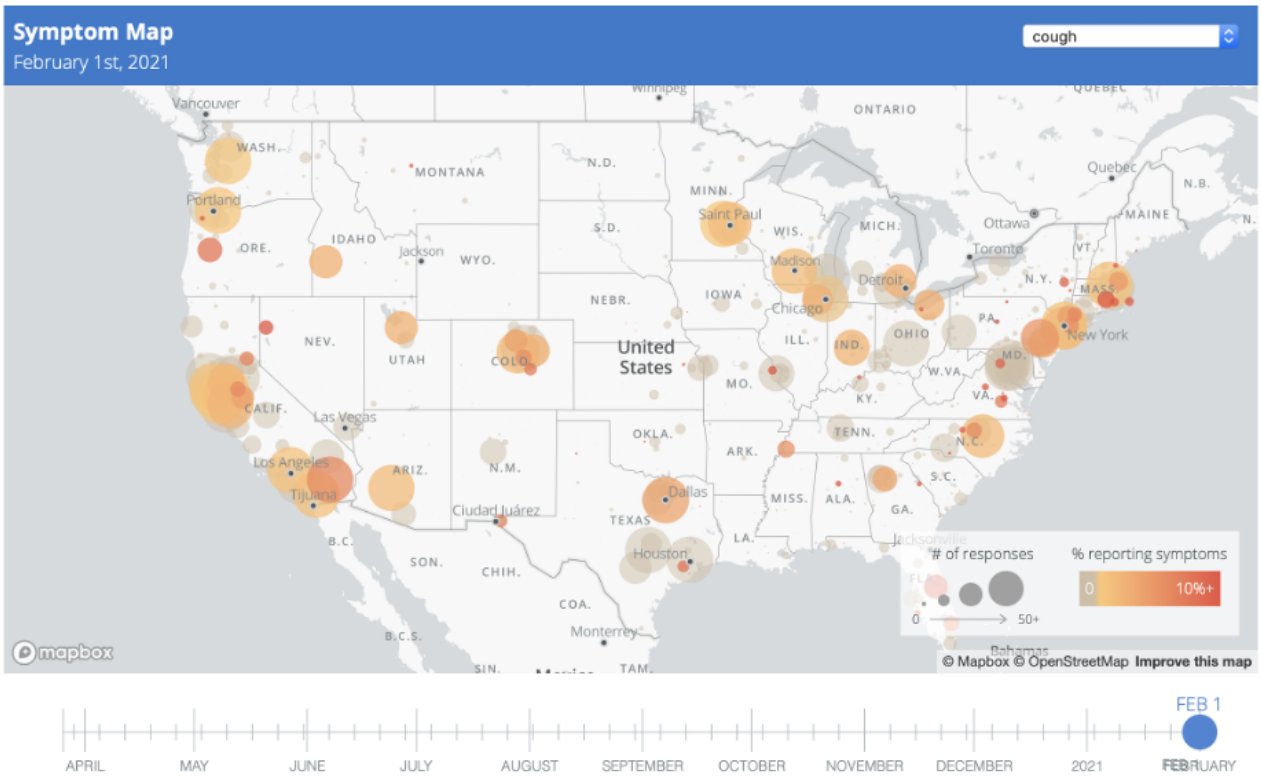


Figure 5. COVID-19 Citizen Science study symptom map (see Multimedia Appendix 4 for details).



Discussion

The CCS study was rapidly designed and launched, facilitated by the existing infrastructure, workflows, and approvals of the NIH-funded Eureka Research Platform. Consequently, the CCS study team was able to rapidly enroll and engage large numbers of participants to generate real-time research results.

Other digital cohort studies have been launched during the pandemic to track symptoms and disease occurrence. The COVID Symptom Study has enrolled millions of participants, primarily in the United Kingdom and the United States to track symptoms of COVID-19. The COVID Symptom Study cohort has a similar proportion of female participants and less racial and ethnic diversity, with 92.5% of the cohort identifying as

White and only 0.5% identifying as Hispanic [3,34]. COVIDENTIFY is a digital cohort study that aims to determine whether smartphone and smartwatch data can predict COVID-19. The study reported similar demographic and gender representation in early study participants [35].

The strengths of our study include the incorporation of real-time feedback data to participants through our study website and engagement with participants through novel engagement methods, such as *Spice Question*s. Additionally, our partnerships with other studies will have implications for studying the association of HLA antigen types with COVID-19 and analysis of the combination of patient-reported and device data with electronic health record data. These studies may yield new knowledge about the biology of COVID-19 and improve our understanding of COVID-19 symptoms, risk mitigation behaviors, and disease occurrence within communities.

Studies relying on digital methods for recruitment and participation often raise concerns about diverse, inclusive, and equitable participation [5]. Indeed, this study has limitations with regard to nonrandom geographic distribution and low participation among traditionally underrepresented research populations. Although approaching design with user-centered design methods can reduce potential barriers, additional efforts are needed to promote digital clinical studies that are diverse, inclusive, and equitable. Ongoing work on the Eureka Research Platform will enable a Spanish-language version of the CCS study. Additionally, we anticipate generating insights from targeted recruitment at clinical sites with connected electronic health records that will seek to recruit participants identifying as racial or ethnic minorities, since these groups have been disproportionately affected by the COVID-19 pandemic. Recruitment methods will include additional outreach through letters, phone calls, and incentives for enrollment and participation [22]. Prior research on engagement of diverse communities has also demonstrated that individual outreach at community events may also facilitate participation in digital studies [12]. Beyond individual outreach, providing technology training may also be a strategy to enable participation among individuals with limited digital literacy or other barriers related to social determinants of health [8]. Future research is needed to better understand how to recruit, enroll, and engage participants in digital clinical studies to promote diverse, inclusive, and equitable health care and research.

The findings from this study will be subject to potential limitations. Although the study has recruited participants from 99 countries, because of the low levels of participation outside of the United States, the ability to conduct analyses based on country-specific characteristics such as development, income, and education levels may be limited. Because this is an observational study, we may not be able to make causal statements about associations between exposures and outcomes. We are collecting an array of participant-reported measures that may help to address potential confounding bias, but we will not be able to eliminate potential confounding from unmeasured factors. Measurement bias may be observed in participant-reported outcomes. When possible, the study uses validated questionnaires to limit bias. Bias may also occur from potentially differential loss to follow-up of participants. The CCS study has an average of 59% continued participation in surveys, which is similar to a digital follow-up on surveys that have been observed in other digital cohort studies, even in well-established cohorts such as the Framingham Heart Study [2]. Nevertheless, the CCS study team will continue to make efforts to engage participants through real-time updates and novel engagement strategies, such as participant-proposed *Spice Questions*.

This study illustrates important advances in digital clinical studies, including an entirely digital study participation, targeted recruitment strategies, electronic consent, analytics for recruitment and engagement, recurrent and time-updated assessments, integration with smartphone-based measurements, connection with partner studies, novel engagement strategies such as participant-proposed questions, and feedback in the form of real-time results to participants. Continued innovation in digital clinical study methods represents the future of clinical research.

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Conflicts of Interest

ALB was formerly employed by Apple Inc. (2018-2019) and holds stock in Apple Inc. Other authors have no conflicts of interest to declare.

Multimedia Appendix 1
COVID-19 Citizen Science study surveys.
[PDF File (Adobe PDF File), 2066 KB - resprot_v10i8e28169_app1.pdf]

Multimedia Appendix 2
HealthKit data types used in the COVID-19 Citizen Science study.

[DOC File , 79 KB - resprot_v10i8e28169_app2.doc]

Multimedia Appendix 3
Countries represented by study participants.
[DOC File , 120 KB - resprot_v10i8e28169_app3.doc]

Multimedia Appendix 4
Video of patient-reported symptoms in the COVID-19 Citizen Science study.
[MP4 File (MP4 Video), 6264 KB - resprot_v10i8e28169_app4.mp4]

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Abbreviations

CCS: COVID-19 Citizen Science
HIPAA: Health Insurance Portability and Accountability Act
HOPE COVID-19: Health Outcome Predictive Evaluation for COVID-19
IRB: institutional review board
PCORI: Patient-Centered Outcomes Research Institute
PCORnet: National Patient-Centered Clinical Research Network
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UCSF: University of California, San Francisco

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