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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

James A Holdnack¹, PhD; Patricia Flatley Brennan¹, PhD, RN
National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, United States

Corresponding Author:
James A Holdnack, PhD
National Institute of Nursing Research
National Institutes of Health
BG 10 RM 2N110A
10 Center Drive
Bethesda, MD
United States
Phone: 1 301 402 8056
Email: jim.holdnack@nih.gov

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.

Trial Registration: ClinicalTrials.gov NCT04883359; http://clinicaltrials.gov/ct2/show/NCT04883359
International Registered Report Identifier (IRRID): PRR1-10.2196/28073

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 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
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 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.

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>
<thead>
<tr>
<th>Assessments</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>Virtual Reality Symptom Questionnaire</td>
<td>✓✓</td>
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<tr>
<td>Immersive VR b cognitive tests</td>
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<td>Immersive VR Visual Analog Scale–Fatigue</td>
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<td>Immersive VR NASA-TLX c</td>
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<tr>
<td>Presence Questionnaire</td>
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<tr>
<td>Shopping Values Questionnaire</td>
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<tr>
<td>Social Determinants of Health</td>
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<tr>
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<tr>
<td>Big Five Inventory</td>
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</tr>
<tr>
<td>National Institutes of Health Toolbox–Cognition Battery</td>
<td>✓</td>
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aAssessment is present.
bVR: virtual reality.
cNASA-TLX: National Aeronautics and Space Administration–task load index.
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 x 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 x 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 (e.g., blink rate, percent eye closure, gaze fixation length, and gaze shifts), and performance data for shopping and cognitive tasks (e.g., 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 (e.g., 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 eye strain. 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 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 (e.g., 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 (e.g., 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 (e.g., selecting objects using various techniques), legibility assessment of various product creation strategies, user testing by team members to identify potential sources of physical discomfort (e.g., effect of antialiasing on visual acuity and developing headache), comparison of movement modalities (e.g., walking vs sitting), ambient environmental factors (e.g., store sounds and signage), and sizing of store elements (e.g., 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.

**Acknowledgments**

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This protocol is funded by the Division of Intramural Research of the NINR/NIH Bethesda, Maryland, United States.
Conflicts of Interest

None declared.

References


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

Yuki Kawai¹,²*, MD; Akiko Sankoda¹*, MD, PhD; Kayo Waki¹,³, MD, MPH, PhD; Kana Miyake¹,³, MD, PhD; Aki Hayashi¹, MD, PhD; Makiko Mieno⁴, MHS, PhD; Hiromichi Waku², MD, PhD; Yuya Tsurutani⁵, MD, PhD; Jun Saito⁵, MD, PhD; Nobuhiyo Hirawa⁶, MD, PhD; Tadashi Yamakawa⁷, MD, PhD; Shiro Komiya², MD; Akihiro Isogawa⁸, MD, PhD; Shinobu Satoh⁹, MD, PhD; Taichi Minami¹⁰, MD, PhD; Uru Osada¹⁰, MD, PhD; Tamio Iwamoto¹¹, MD, PhD; Tatsuro Takano¹¹, MD, PhD; Yusuo Terauchi¹³, MD, PhD; Kouichi Tamura², MD, PhD; Toshimasa Yamauchi³, MD, PhD; Takashi Kadowaki¹⁴,¹⁵, MD, PhD; Masaomi Nangaku¹⁶, MD, PhD; Naoki Kashihara¹⁷, MD, PhD; Kazuhiho Ohe¹, MD, PhD

¹Department of Planning, Information and Management, University of Tokyo Hospital, Tokyo, Japan
²Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan
³Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
⁴Department of Medical Informatics, Center for Information, Jichi Medical University, Shimotsuke, Japan
⁵Endocrinology and Diabetes Center, Yokohama Rosai Hospital, Yokohama, Japan
⁶Department of Nephrology and Hypertension, Yokohama City University Medical Center, Yokohama, Japan
⁷Department of Endocrinology and Diabetes, Yokohama City University Medical Center, Yokohama, Japan
⁸Division of Diabetes, Mitsui Memorial Hospital, Tokyo, Japan
⁹Department of Endocrinology and Metabolism, Chigasaki Municipal Hospital, Chigasaki, Japan
¹⁰Department of Diabetes and Endocrinology, Saiseikai Yokohamashi Nanbu Hospital, Yokohama, Japan
¹¹Department of Nephrology and Hypertension, Saiseikai Yokohamashi Nanbu Hospital, Yokohama, Japan
¹²Department of Diabetes and Endocrinology, Fujisawa City Hospital, Fujisawa, Japan
¹³Department of Endocrinology and Metabolism, Yokohama City University Graduate School of Medicine, Yokohama, Japan
¹⁴Department of Prevention of Diabetes and Lifestyle-Related Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
¹⁵Toranomon Hospital, Tokyo, Japan
¹⁶Division of Nephrology and Endocrinology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
¹⁷Department of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Japan

* these authors contributed equally

Corresponding Author:
Kayo Waki, MD, MPH, PhD
Department of Planning, Information and Management, University of Tokyo Hospital
7-3-1 Hongo, Bunkyo-ku
Tokyo, 113-8655
Japan
Phone: 81 3 5800 9129
Fax: 81 3 5800 9129
Email: kwaki-tky@m.u-tokyo.ac.jp

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?reptno=R000037924](https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?reptno=R000037924)

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

**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

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**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 detectable clinical manifestations of kidney disease and is a potent risk factor for ESRD and all-cause death [3,4]. Renin-angiotensin blockade is 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 A1c (HbA1c) of 6.5% or more, and an estimated glomerular filtration rate (eGFR) of 45mL/min/1.73m² 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.
Inclusion and exclusion criteria.

**Inclusion criteria**
- Diagnosed with T2DM
- HbA1c 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.
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 (HbA1c and fasting blood glucose), and lipid metabolism (high-density lipoprotein and triglyceride levels).
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>
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<th>Follow-up period</th>
<th>2 months</th>
<th>6 months</th>
<th>12 months</th>
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<td>●</td>
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<td>Composite cardiovascular outcome</td>
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<td>●</td>
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<tr>
<td>Composite renal endpoint</td>
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<td>Safety</td>
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<td>●</td>
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<td>●</td>
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<tr>
<td>DialBetesPlus usage frequency</td>
<td></td>
<td>●</td>
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</tbody>
</table>

*a*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, HbA1c, 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.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=130)</th>
<th>Control (n=61)</th>
<th>Intervention (n=69)</th>
<th>P value</th>
</tr>
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<tr>
<td>Age (years), mean (SD)</td>
<td>59.5 (9.4)</td>
<td>60.5 (8.7)</td>
<td>58.7 (10.0)</td>
<td>.28</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>.55</td>
</tr>
<tr>
<td>Male</td>
<td>96 (73.8)</td>
<td>47 (77.0)</td>
<td>49 (71.0)</td>
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<tr>
<td>Female</td>
<td>34 (26.2)</td>
<td>14 (23.0)</td>
<td>20 (29.0)</td>
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<tr>
<td>Physical parameters, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td>.67</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>28.5 (4.6)</td>
<td>28.3 (4.0)</td>
<td>28.6 (5.2)</td>
<td>.73</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>133.2 (16.7)</td>
<td>133.8 (17.2)</td>
<td>132.8 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>82.0 (10.7)</td>
<td>83.2 (10.2)</td>
<td>80.9 (11.0)</td>
<td>.23</td>
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<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>.79</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>53 (40.8)</td>
<td>23 (37.7)</td>
<td>30 (43.5)</td>
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<tr>
<td>Current smoker</td>
<td>29 (22.3)</td>
<td>14 (23.0)</td>
<td>15 (21.7)</td>
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<tr>
<td>Ex-smoker</td>
<td>48 (36.9)</td>
<td>24 (39.3)</td>
<td>24 (34.8)</td>
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<tr>
<td>Duration of diabetes (years), mean (SD)</td>
<td>13.1 (7.2)</td>
<td>12.5 (6.4)</td>
<td>13.7 (7.9)</td>
<td>.35</td>
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<td>Laboratory test, median (Q1-Q3)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>144.0 (124.0-174.0)</td>
<td>139.0 (124.0-159.0)</td>
<td>150.0 (123.0-185.0)</td>
<td>.37</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.5 (7.0-8.0)</td>
<td>7.4 (6.9-7.9)</td>
<td>7.5 (7.1-8.1)</td>
<td>.31</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>99.0 (78.0-117.0)</td>
<td>106.0 (78.0-117.0)</td>
<td>98.0 (83.0-112.0)</td>
<td>.55</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>49.5 (42.9-60.8)</td>
<td>49.0 (44.0-60.8)</td>
<td>50.0 (42.0-60.5)</td>
<td>.64</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>155.5 (100.0-261.0)</td>
<td>149.0 (100.0-261.0)</td>
<td>158.0 (100.0-252.0)</td>
<td>.64</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.78 (0.65-0.92)</td>
<td>0.82 (0.68-0.93)</td>
<td>0.78 (0.62-0.92)</td>
<td>.33</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>72.0 (61.8-85.3)</td>
<td>71.0 (63.8-83.0)</td>
<td>76.5 (59.5-85.5)</td>
<td>.29</td>
</tr>
<tr>
<td>UACR (mg/gCr)</td>
<td>36.4 (15.1-76.2)</td>
<td>32.3 (14.8-70.6)</td>
<td>41.0 (15.1-78.0)</td>
<td>.49</td>
</tr>
</tbody>
</table>

aBP: blood pressure.
bHbA1c: glycated hemoglobin.
cLDL-C: low-density lipoprotein cholesterol.
dHDL-C: high-density lipoprotein cholesterol.
eeGFR: estimated glomerular filtration rate.
fUACR: urine albumin-to-creatinine ratio.
gOne 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 HbA1c (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.

Acknowledgments

The MMAS-8 scoring and coding presented in the article were done using the electronic Morisky Widget MMAS-8 Software. Use of the Morisky Widget MMAS-8 software, copyright registration number TX 8-816-517, is protected by US copyright laws. Permission for the use of the Morisky Widget MMAS-8 software is required and was obtained for this research. A license agreement is available from MMAS Research LLC 14725 NE 20th St Bellevue, WA 98007, USA; strubow@morisky.org.

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

The author(s) disclose receipt of the external financial support for the research, authorship, and publication of this article: In addition to the AMED grant, this research was supported by NTT DOCOMO Inc. and Nihon Chouzai Co, Ltd. KM was a member of a cooperative program between the University of Tokyo and NTT DOCOMO.

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]

References


34. University Hospital Medical Information Network Clinical Trials Registry. URL: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000037924 [accessed 2021-08-15]


**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>DKD</td>
<td>diabetic kidney disease</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESRD</td>
<td>end-stage renal disease</td>
</tr>
<tr>
<td>HbA1c</td>
<td>hemoglobin A1c</td>
</tr>
<tr>
<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
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<td>JDS</td>
<td>Japan Diabetes Society</td>
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<td>JP-ADDQoL</td>
<td>Japanese version of the Audit of Diabetes-Dependent Quality of Life</td>
</tr>
<tr>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
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<td>mHealth</td>
<td>mobile health</td>
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<td>MMAS-8</td>
<td>8-item Morisky Adherence Scale</td>
</tr>
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<td>NFC</td>
<td>near field communication</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>J-SDSCA</td>
<td>Japanese version of the Summary of Diabetes Self-Care Activities Measure</td>
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<td>TG</td>
<td>triglycerides</td>
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<td>T2DM</td>
<td>type 2 diabetes mellitus</td>
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</table>
Protocol

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

Maria Soledad Arietaleanizbeaskoa1*, MD; Erreka Gil Rey2*, PhD; Nere Mendizabal Gallastegui1*, MD; Arturo García-Alvarez1*, MD; Ibon De La Fuente1, MD; Silvia Domínguez-Martínez1, MD; Susana Pablo1*, PhD; Aitor Coca2*, PhD; Borja Gutiérrez Santamaría2*, MD; Gonzalo Grandes1*, MD

1Biocruces Health Research Institute, Barakaldo, Spain
2Deusto University, Bilbao, Spain
*these authors contributed equally

Corresponding Author:
Nere Mendizabal Gallastegui, MD
Biocruces Health Research Institute
C/Plaza de Cruces, s/n.
Barakaldo, 48903
Spain
Phone: 34 946006637
Email: nere.mendizabalgallastegui@osakidetza.eus

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.

Trial Registration: ClinicalTrials.gov NCT03819595; http://clinicaltrials.gov/ct2/show/NCT03819595
International Registered Report Identifier (IRRID): DERR1-10.2196/24835 (JMIR Res Protoc 2021;10(8):e24835) doi:10.2196/24835

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<5000 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 (FACT-T-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 1-1½ 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).
Table 1. Definitions of exercise intensity categories.

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

*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 IRM 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 specialties 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 IRM in the last 4 weeks of the program.

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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 differences of 5 points between groups as significant (α=0.05), 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=0.05).

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.

References


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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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

Shabina Ariff1*, MBBS, FCPS; Atif Habib2*, PhD; Zahid Memon3, MPH; Tayyaba Arshad2, MSc; Tariq Samejo2, MPH; Ikram Maznami2, MSc; Muhammad Umer2, MBA; Amjad Hussain2, MSc; Arjumand Rizvi2, MSc; Imran Ahmed2, MSc; Sajid Bashir Soofi1,2, MBBS, FCPS; Zulfiqar A Bhutta2, PhD

1Department of Paediatrics & Child Health, Aga Khan University, Karachi, Pakistan
2Center of Excellence in Women & Child Health, Aga Khan University, Karachi, Pakistan
*these authors contributed equally

Corresponding Author:
Zulfiqar A Bhutta, PhD
Center of Excellence in Women & Child Health
Aga Khan University
Stadium Road
P.O. Box 3500
Karachi, 74800
Pakistan
Phone: 92 2134864798
Email: zulfiqar.bhatta@aku.edu

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.

Trial Registration: clinicaltrials.gov NCT03545204; https://clinicaltrials.gov/ct2/show/NCT03545204
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).
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 co-champions (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 (i.e., 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.

References


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
Protocol

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

Amy B Petrinec1, PhD; Joel W Hughes2, PhD; Melissa D Zullo3, MA, MPH, PhD; Cindy Wilk1, MSN; Richard L George4, MD

1College of Nursing, Kent State University, Kent, OH, United States
2Department of Psychological Sciences, College of Arts and Sciences, Kent State University, Kent, OH, United States
3College of Public Health, Kent State University, Kent, OH, United States
4Department of Surgery, Summa Health, Akron, OH, United States

Corresponding Author:
Amy B Petrinec, PhD
College of Nursing
Kent State University
Henderson Hall
1375 University Esplanade
Kent, OH, 44242
United States
Phone: 1 3307152987
Email: apetrine@kent.edu

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.

Trial Registration: ClinicalTrials.gov NCT04316767; https://clinicaltrials.gov/ct2/show/NCT04316767
International Registered Report Identifier (IRRID): DERR1-10.2196/30813

(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 critically ill adult patients are at risk for developing clinically significant psychological distress. Such distress is called post-intensive 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.**

<table>
<thead>
<tr>
<th>Data collected</th>
<th>T1&lt;sup&gt;a&lt;/sup&gt; (Enrollment)</th>
<th>T2&lt;sup&gt;b&lt;/sup&gt; (30 days after enrollment)</th>
<th>T3&lt;sup&gt;c&lt;/sup&gt; (60 days after enrollment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale score</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>PCL-5&lt;sup&gt;d&lt;/sup&gt; score</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Mental Health Self-Efficacy Scale score</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>SF-12&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobile health app usage</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>T1: time point 1.  
<sup>b</sup>T2: time point 2.  
<sup>c</sup>T3: time point 3.  
<sup>d</sup>PCL-5: Posttraumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.  
<sup>e</sup>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.

References


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
Protocol

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

Russell Pine¹, MEd Psych, PGDipEPP; James Mbinta¹, MD, MPH; Lisa Te Morenga², PhD; Theresa Fleming¹, PhD

¹School of Health, Victoria University of Wellington, Wellington, New Zealand
²Research Centre for Hauora and Health, Massey University, Wellington, New Zealand

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 MatchEmoji 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 emojis to match. Each emoji has a unique level of difficulty and points awarded.

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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 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 GHSQ can also be used as a screening tool.

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.
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Abbreviations

- CAMM: Child and Adolescent Mindfulness Measure
- CVG: casual video game
- DMHI: digital mental health intervention
- FS: Flourishing Scale
- GHQ12: General Help-Seeking Questionnaire
- RCADS: Revised Children’s Anxiety and Depression Scale
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

Kathleen M Baggett¹, PhD; Betsy Davis², MEd, PhD; Lisa Sheeber², PhD; Katy Miller¹, MEd; Craig Leve³, MA; Elizabeth A Mosley¹, MPH, PhD; Susan H Landry³, PhD; Edward G Feil², PhD

¹Georgia State University, Atlanta, GA, United States
²Oregon Research Institute, Eugene, OR, United States
³University of Texas Health Sciences Center, Houston, TX, United States

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.
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. Refferred 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 2x2 analysis based on $\alpha=0.05$, 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], 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, multmethod 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 play 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 (i.e., 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 0.90.

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.**

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Enrollment</th>
<th>Allocation</th>
<th>Postallocation</th>
<th>Intervention (6-8 months)</th>
<th>T2 Postassessment (7-9 months)</th>
<th>T3 Follow-up assessment (13-15 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-T1</td>
<td>✓</td>
<td></td>
<td>T0</td>
<td>T1 Preassessment</td>
<td>S1</td>
<td>S4</td>
</tr>
</tbody>
</table>

**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 2x2 (group x 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) x 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 $\beta$ 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, MBN mothers with high dosage, when compared with low dosage MBN mothers and DDAS mothers, regardless of dosage level, would show higher positive change trajectories than those of DDAS mothers and infants.

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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.

Acknowledgments

The authors would like to acknowledge the support of this research by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant NIH R01HD086894).

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).

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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

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

Zahra Moussavi1,2, DPhil; Lisa Koski3*, DPhil; Paul B Fitzgerald4*, DPhil, MD; Colleen Millikan5*, DPhil; Brian Lithgow1*, MEngSc; Mohammad Jafari-Jozani6*, DPhil; Xikui Wang7*, DPhil

1Biomedical Engineering Program, Faculty of Engineering, University of Manitoba, Winnipeg, MB, Canada
2Department of Psychiatry, University of Manitoba, Winnipeg, MB, Canada
3McGill University, Montreal, QC, Canada
4Department of Psychiatry, Epworth Center for Innovation in Mental Health, Monash University, Melbourne, Australia
5Department of Clinical Health Psychology, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada
6Department of Statistics & Biomedical Engineering, Faculty of Science, University of Manitoba, Winnipeg, MB, Canada
7Warren Center for Actuarial Studies and Research, The Asper School of Business, University of Manitoba, Winnipeg, MB, Canada
*these authors contributed equally

Corresponding Author:
Zahra Moussavi, DPhil
Biomedical Engineering Program
Faculty of Engineering
University of Manitoba
75 Chancellor Circle
Winnipeg, MB, R3T5V6
Canada
Phone: 1 204 474 7023
Fax: 1 204 272 3773
Email: Zahra.Moussavi@umanitoba.ca

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.

Trial Registration: ClinicalTrials.gov NCT02908815; https://clinicaltrials.gov/ct2/show/NCT02908815

International Registered Report Identifier (IRRID): DERR1-10.2196/31183

https://www.researchprotocols.org/2021/8/e31183

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(page number not for citation purposes)
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
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. PPOsSs [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 uninformative 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(θ). 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].

### Table 1. Information on withdrawn patients.

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Became ineligible during the pandemic</td>
<td>2</td>
<td>They were enrolled before lockdown, but their cognitive function declined rapidly during the lockdown and they became ineligible.</td>
</tr>
<tr>
<td>Principal investigator withdrawal—noncompliant</td>
<td>3</td>
<td>One changed medication during the study and 2 developed an illness and were withdrawn by the principal investigator for safety concerns.</td>
</tr>
<tr>
<td>Participant withdrawal—changed mind before treatment</td>
<td>7</td>
<td>No particular reason was given.</td>
</tr>
<tr>
<td>Participant withdrawal—too much anxiety due to treatment</td>
<td>2</td>
<td>They found the pulses too painful to tolerate.</td>
</tr>
<tr>
<td>Unrelated health and family issues</td>
<td>8</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

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.

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.
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 and 12 have reported unexpected AE. The 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, i.e., 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.
References


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

Faheema Kimmie-Dhansay1*, BSc, BChD, MSc; Robert Barrie2*, BChD, MChD, PhD; Sudeshni Naidoo2*, BDS, LDS (RCS), MDPH, DDPH (RCS), MChD, PhD, DSC; Tina Sharon Roberts3*, BChD, MChD, PhD

1Division of Research and Postgraduate Studies, Faculty of Dentistry, University of the Western Cape, Cape Town, South Africa
2Department of Community Dentistry, University of the Western Cape, Cape Town, South Africa
3Diagnostics Cluster, University of the Western Cape, Cape Town, South Africa

*all authors contributed equally

Corresponding Author:
Faheema Kimmie-Dhansay, BSc, BChD, MSc
Division of Research and Postgraduate Studies
Faculty of Dentistry
University of the Western Cape
Private Bag X17
Bellville
Cape Town, 7535
South Africa
Phone: 27 0219373030
Email: fkimmiedhansay@uwc.ac.za

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

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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 of 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.

References


29. KIKAPU Research Data Repository. URL: https://kikapu.uwc.ac.za/ [accessed 2021-05-27]


Abbreviations
ECC: early childhood caries
WHO: World Health Organization
Protocol

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

Lisanne Kremer¹, MSc; Myriam Lipprandt², PhD; Rainer Röhrig², Prof Dr; Bernhard Breil¹, Prof Dr

¹Faculty of Health Care, Niederrhein University of Applied Sciences, Krefeld, Germany
²Institute of Medical Informatics, RWTH Aachen University, Aachen, Germany

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

International Registered Report Identifier (IRRID): DERR1-10.2196/29126

(JMIR Res Protoc 2021;10(8):e29126) doi:10.2196/29126

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.

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

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

<table>
<thead>
<tr>
<th>Theme</th>
<th>Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study identification</td>
<td>Author</td>
</tr>
<tr>
<td></td>
<td>Reference number</td>
</tr>
<tr>
<td>Setting of target</td>
<td>Eg, hospital, outpatient setting</td>
</tr>
<tr>
<td>Study design</td>
<td>Cross-sectional, longitudinal</td>
</tr>
<tr>
<td></td>
<td>Quantitative, qualitative, mixed methods</td>
</tr>
<tr>
<td>Sample characteristics</td>
<td>Sample size</td>
</tr>
<tr>
<td></td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
</tr>
<tr>
<td>Population type</td>
<td>Eg, physicians, nurses</td>
</tr>
</tbody>
</table>
Table 3. Systematic analyses of the main findings.

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

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.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Study 1</th>
<th>Study 2</th>
<th>...</th>
<th>Category %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicator 1</td>
<td>1</td>
<td>0</td>
<td>...</td>
<td>50%</td>
</tr>
<tr>
<td>Indicator 2</td>
<td>1</td>
<td>1</td>
<td>...</td>
<td>100%</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Indicator 1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Indicator 2</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Category Combinations</td>
<td>Combination 1</td>
<td>Study 1</td>
<td>Study 2</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Combination 2</td>
<td></td>
<td></td>
<td>...</td>
</tr>
</tbody>
</table>

...
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.

References


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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Protocol

A Technological-Based Platform for Risk Assessment, Detection, and Prevention of Falls Among Home-Dwelling Older Adults: Protocol for a Quasi-Experimental Study

Fátima Araújo1*, MSc, PhD; Maria Nilza Nogueira2*, MSc, PhD; Joana Silva2, MSc; Sílvia Rego2, MSc

1Escola Superior de Enfermagem do Porto (ESEP), Inovação e Desenvolvimento em Enfermagem, Centro de Investigação em Tecnologias e Serviços de Saúde, Porto, Portugal
2Fraunhofer Portugal Research, Center for Assistive Information and Communication Solutions, Porto, Portugal
*these authors contributed equally

Corresponding Author:
Fátima Araújo, MSc, PhD
Escola Superior de Enfermagem do Porto (ESEP)
Inovação e Desenvolvimento em Enfermagem
Centro de Investigação em Tecnologias e Serviços de Saúde
Rua Dr. António Bernardino, 830, 844, 856
Porto, 4200-072
Portugal
Phone: 351 00351 225 073 5
Email: araujo@esenf.pt

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.

**Trial Registration:** ISRCTN 15895163; [https://www.isrctn.com/ISRCTN15895163](https://www.isrctn.com/ISRCTN15895163)

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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 behaviors. 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 (Fervasive 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.

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### 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).
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 reported dependent in manual handling transfer, and individuals who complete the test in >30 seconds tend to depend on 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 (ICC2,1=0.999). Concurrent validity assessed using the activities-specific balance confidence (ABC) scale showed results indicative of good concurrent validity (r=-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.

**Figure 4. FallSensing Home App.**

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).
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 secure 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.

References


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

Maxime Morsa¹*, PhD; Amélie Perrin²*, CRN; Valérie David²*, MD; Gilles Rault¹*, MD; Enora Le Roux³,⁴*, PhD; Corinne Alberti³,⁴*, PU-PH; Rémi Gagnayre¹*, PU; Dominique Pougheon Bertrand¹*, PhD

1The Health Education and Practices Laboratory (LEPS UR 3412), Sorbonne Paris North University, Bobigny, France
2Pediatric Cystic Fibrosis Center, Nantes University Hospital, Nantes, France
3Unité Mixte de Recherche 1123 Épidémiologie Clinique et Évaluation Économique appliquées aux populations vulnérables, Université de Paris, Institut National de la Santé et de la Recherche Médicale, Paris, France
4Centre d’Investigation Clinique 1426 Unit of Clinical Epidemiology, Hôpital Universitaire R Debré, Assistance Publique des Hôpitaux de Paris, Institut National de la Santé et de la Recherche Médicale, Paris, France

*all authors contributed equally

Corresponding Author:
Maxime Morsa, PhD
The Health Education and Practices Laboratory (LEPS UR 3412)
Sorbonne Paris North University
74 rue Marcel Cachin
Bobigny, 93017
France
Phone: 33 177 194 691
Fax: 33 177 194 691
Email: maxime.morsa@univ-paris13.fr

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.

**Trial Registration:** ClinicalTrials.gov NCT03304028; https://clinicaltrials.gov/ct2/show/results/NCT03304028

**International Registered Report Identifier (IRRID):** DERR1-10.2196/14552

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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. 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. 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.

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. West et al 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. 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. 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, 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.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Score, mean (SD)</th>
<th>Rank order</th>
</tr>
</thead>
<tbody>
<tr>
<td>A large decrease in lung function (greater than 10% FEV1&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>9.33 (0.784)</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Feeling more short of breath than usual</td>
<td>8.52 (1.087)</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>8.52 (1.805)</td>
<td>2</td>
</tr>
<tr>
<td>Feeling the need to do more airway clearance than usual</td>
<td>8.37 (1.115)</td>
<td>4</td>
</tr>
<tr>
<td>An increase in symptoms at night</td>
<td>8.22 (1.450)</td>
<td>5</td>
</tr>
<tr>
<td>Producing more sputum</td>
<td>8.19 (1.388)</td>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Finding it harder than normal to do usual exercise</td>
<td>7.96 (1.581)</td>
<td>7</td>
</tr>
<tr>
<td>Finding it harder than normal to do usual activities</td>
<td>7.93 (1.838)</td>
<td>8</td>
</tr>
<tr>
<td>Feeling more exhausted than usual</td>
<td>7.85 (1.703)</td>
<td>9</td>
</tr>
<tr>
<td>More coughing than usual</td>
<td>7.85 (1.610)</td>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>FEV1: forced expiratory volume in 1 second.

<sup>b</sup>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].

<table>
<thead>
<tr>
<th>Statement</th>
<th>Score, mean (SD)</th>
<th>Rank order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased sputum</td>
<td>8.84 (1.027)</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>A large decrease in lung function (greater than 10% FEV&lt;sub&gt;1&lt;/sub&gt;)&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>8.84 (1.263)</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>More shortness of breath than usual</td>
<td>8.32 (1.141)</td>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Increased inflammatory markers (for example CRP&lt;sup&gt;c&lt;/sup&gt; and white cell count)</td>
<td>7.92 (1.124)</td>
<td>4</td>
</tr>
<tr>
<td>Fever or increased temperature</td>
<td>7.89 (1.269)</td>
<td>5</td>
</tr>
<tr>
<td>Increased respiratory rate at rest</td>
<td>7.82 (1.557)</td>
<td>6</td>
</tr>
<tr>
<td>Decreased oxygen saturation</td>
<td>7.79 (1.510)</td>
<td>7</td>
</tr>
<tr>
<td>Hypoxia/hypoxemia</td>
<td>7.76 (1.807)</td>
<td>8</td>
</tr>
<tr>
<td>Change in the color of sputum</td>
<td>7.61 (1.636)</td>
<td>9</td>
</tr>
<tr>
<td>New changes on chest x-ray</td>
<td>7.47 (1.767)</td>
<td>10</td>
</tr>
<tr>
<td>Increased coughing</td>
<td>7.47 (1.466)</td>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Also ranked in the top 10 by adults with cystic fibrosis.

<sup>b</sup>FEV<sub>1</sub>: forced expiratory volume in 1 second.

<sup>c</sup>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: non-usage, 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.](image)

**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 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 patient-like 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.

<table>
<thead>
<tr>
<th>CF&lt;sup&gt;a&lt;/sup&gt; center investigator</th>
<th>Patients included (n=36), n</th>
<th>Patients educated (n=24), n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric centers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Versailles</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Paris R. Debré</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Nantes</td>
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<sup>a</sup> 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.

Funding was provided by FRM to the entire project entitled “Use of home-based connected devices in the early detection and treatment of pulmonary exacerbations: Feasibility and clinical validity in cystic fibrosis patients” (“Évaluation de l’utilisation des objets connectés pour la détection précoce et le traitement des exacerbations respiratoires des patients Mucoviscidose”) in the framework of the call for Project “Évaluation de l’impact des objets connectés sur la santé” (FRM decision for funding was delivered on November 18, 2016).

This research benefited from additional funding from Vertex Pharmaceuticals in the form of a Circle of Care charitable grant attributed in 2016 to a project entitled “A pilot experience to assess the feasibility of the use of electronic devices to allow educated adults with CF to get more involved in their own health care”.

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 ]

References


https://www.researchprotocols.org/2021/8/e14552 JMIR Res Protoc 2021 | vol. 10 | iss. 8 | e14552 | p.123 (page number not for citation purposes)


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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Muscular Assessment in Patients With Severe Obstructive Sleep Apnea Syndrome: Protocol for a Case-Control Study

Paz Francisca Borrmann1*, BSc; Carlos O'Connor-Reina2,3*, MD, PhD; Jose M Ignacio4,5*, MD, PhD; Elisa Rodriguez Ruiz4,5*, RNC; Laura Rodriguez Alcala2,3*, MD, PhD; Florencia Dzembrovsky1*, BSc; Peter Baptista6, MD, PhD; Maria T Garcia Iriarte7, MD, PhD; Carlos Casado Alba8*, MDS; Guillermo Plaza9,10,11*, MD, PhD

1Phonoaudiology Section, Otorhinolaryngology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
2Otorhinolaryngology Department, Hospital Quironsalud Marbella, Marbella (Malaga), Spain
3Otorhinolaryngology Department, Hospital Quironsalud Campo de Gibraltar, Palmones, Cadiz, Spain
4Pulmonology Department, Hospital Quironsalud Marbella, Malaga, Spain
5Pulmonology Department, Hospital Quironsalud Campo de Gibraltar, Palmones, Cadiz, Spain
6Otorhinolaryngology Department, Clinica Universitaria de Navarra, Pamplona, Spain
7Otorhinolaryngology Department, Hospital Universitario Virgen de Valme, Sevilla, Spain
8School of Medicine, Clinica Universitaria de Navarra, Pamplona, Spain
9Otorhinolaryngology Department, Hospital Universitario Sanitas la Zarzuela, Madrid, Spain
10Otorhinolaryngology Department, Hospital Universitario Fuenlabrada, Madrid, Spain
11School of Medicine, Universidad Rey Juan Carlos I, Madrid, Spain

* these authors contributed equally

Corresponding Author:
Carlos O'Connor-Reina, MD, PhD
Otorhinolaryngology Department
Hospital Quironsalud Marbella
Avda Severo Ochoa 22
Marbella (Malaga)
Spain
Phone: 34 952774200
Email: coconnor@us.es

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.

Trial Registration: ISRCTN Registry ISRCTN12596010; https://www.isrctn.com/ISRCTN12596010

International Registered Report Identifier (IRRID): PRR1-10.2196/30500
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, CO₂ 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-cm² 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 \( \chi^2 \) 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 inter-rater 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.

**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 phon奥迪ologists and requires considerable time. In most countries, there is a lack of phonaudiologists 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]

References


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
Health Impacts of Perchlorate and Pesticide Exposure: Protocol for Community-Engaged Research to Evaluate Environmental Toxicants in a US Border Community

Robert Trotter II*, BA, MA, PhD; Julie Baldwin*, BA, MA, PhD; Charles Loren Buck*, BA, MA, PhD; Mark Remiker*, BA, MA; Amanda Aguirre*, MA; Trudie Milner*, BA, MA, PhD; Emma Torres*, MSW; Frank Arthur von Hippel*, AB, PhD

* these authors contributed equally

Corresponding Author:
Robert Trotter II, BA, MA, PhD
Department of Anthropology
Northern Arizona University
1395 Knoles Drive
Flagstaff, AZ, 86011
United States
Phone: 1 9283808684
Email: robert.trotter@nau.edu

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.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/15864

**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.

**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%).

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).

<table>
<thead>
<tr>
<th>Sex</th>
<th>All, n (%)</th>
<th>Clinical, n (%)</th>
<th>Community, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>68 (21)</td>
<td>22 (15)</td>
<td>46 (26)</td>
</tr>
<tr>
<td>Female</td>
<td>255 (79)</td>
<td>123 (85)</td>
<td>132 (74)</td>
</tr>
<tr>
<td>Total</td>
<td>323</td>
<td>145</td>
<td>178</td>
</tr>
</tbody>
</table>
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 2. Clinical and community sample numbers by residence time in Yuma County.

<table>
<thead>
<tr>
<th>Sample</th>
<th>&lt;6 months, n (%)</th>
<th>6 months to 1 year, n (%)</th>
<th>1 to 3 years, n (%)</th>
<th>3 to 5 years, n (%)</th>
<th>&gt;5 years, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community (N=178)</td>
<td>1 (0.6)</td>
<td>2 (1.1)</td>
<td>8 (4.5)</td>
<td>6 (3.4)</td>
<td>161 (90.4)</td>
</tr>
<tr>
<td>Clinical (N=145)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>3 (2.1)</td>
<td>4 (2.8)</td>
<td>136 (93.8)</td>
</tr>
</tbody>
</table>
Table 3. Key elements of successful engagement with community partners.

<table>
<thead>
<tr>
<th>Key element</th>
<th>Illustrative quotes from community partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community priorities and salience of health issues –</td>
<td>-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.</td>
</tr>
<tr>
<td>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.</td>
<td>Partnership length and trust –</td>
</tr>
<tr>
<td>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.</td>
<td>Shared responsibility -</td>
</tr>
<tr>
<td>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.</td>
<td>Partnership synergy –</td>
</tr>
<tr>
<td>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.</td>
<td>Capacity to create desired community changes –</td>
</tr>
</tbody>
</table>

\textsuperscript{a}NAU: Northern Arizona University. \textsuperscript{b}ABRC: Arizona Biomedical Research Commission. \textsuperscript{c}CSF: Campesinos Sin Fronteras. \textsuperscript{d}YRMC: Yuma Regional Medical Center. \textsuperscript{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.

Acknowledgments

We would like to acknowledge the collaboration and continuing participation of the Regional Center for Border Health, Inc., Campesinos sin Fronteras, and the Yuma Regional Medical Center. Their counsel, assistance in data collection, and advocacy have been invaluable for the project. The authors would also like to thank Dr. Francisco Villa, Professor of Biological Sciences at Northern Arizona University, Yuma, and his students Ashley Menard, Kevin Hurtado, and Melissa Cabrera Bernal for their assistance with study coordination; Joseph Espinosa for his help with medical record audits; and Danielle Dillion, Jonathan Credo, and Amy Chandos for laboratory analyses. This study was funded by The Flinn Foundation (grant numbers 2102 and 2187), 1802 N. Central Avenue, Phoenix AZ 85004-1506; Center for Health Equity Research, Northern Arizona University; and Southwest Health Equity Research Collaborative (National Institutes of Health grant U54MD012388).

Conflicts of Interest

None declared.

References

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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
Cyberbullying Among Traditional and Complementary Medicine Practitioners in the Workplace: Protocol for a Cross-sectional Descriptive Study

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

(JMIR Res Protoc 2021;10(8):e29582) doi:10.2196/29582
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 role 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

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.

![Snowball Sampling Diagram](https://example.com/snowball.png)

**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.](image)

**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).

<table>
<thead>
<tr>
<th>Topic/parameter and measure</th>
<th>Source</th>
<th>Number of items</th>
<th>Assessing objectivesa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, age group, and current relationship status</td>
<td>N/Ab</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td>N/A</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household income</td>
<td>N/A</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Health status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td>Pattern of Substance and Drug Misuse Among Youth in Malaysia [36]</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Geography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working sector, location (city)</td>
<td>N/A</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Working status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community participant work, current job level, practice area</td>
<td>Official Portal of Traditional and Complementary Medicine Division [37]</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Cyberbullying Behavior Questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work-related bullying, person-related bullying</td>
<td>Negative Acts Questionnaire-Revised [35]</td>
<td>11</td>
<td>1 and 3</td>
</tr>
<tr>
<td>Aggressively worded messages, distortion of messages</td>
<td>The Measurement and Impact of Workplace Cyberbullying [34]</td>
<td>2</td>
<td>1 and 3</td>
</tr>
<tr>
<td>Posted offensive photos/videos, hacking computer or sending virus or rude message, attaching or threatening messages about personal life or family</td>
<td>Forssell Cyberbullying Behavior Questionnaire [8]</td>
<td>7</td>
<td>1 and 3</td>
</tr>
</tbody>
</table>

aObjective 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.

bN/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.

Acknowledgments

The authors gratefully acknowledge Xiamen University Malaysia for their support and guidance. This work is supported by the Xiamen University Malaysia Research Fund (Grant No: XMUMRF/2020-C6/ITCM/0005). The funding body had no role in the design and conduct of this study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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.

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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

Anita Abd Rahman1*, MD, MPH; Rosliza Abdul Manaf2*, MBBS, MPH, PhD; Poh Ying Lim1*, BSc, MSc, PhD; Subapriya Suppiah2*, MD, MMed; Muhammad Hanafiah Juni1*, MD, MPH

1Department of Community Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Seri Kembangan, Malaysia
2Department of Radiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Seri Kembangan, Malaysia
*all authors contributed equally

Corresponding Author:
Anita Abd Rahman, MD, MPH
Department of Community Health
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
Seri Kembangan, 43400
Malaysia
Phone: 60 123180272
Fax: 60 389450151
Email: anitaar@upm.edu.my

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.

International Registered Report Identifier (IRRID): DERR1-10.2196/25877

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KEYWORDS
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.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quantitative research</th>
<th>Qualitative research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>Provide an understanding of the research questions</td>
<td>Proves research hypothesis</td>
</tr>
<tr>
<td>Design</td>
<td>Cross-sectional study</td>
<td>Case study approach</td>
</tr>
<tr>
<td>Extension</td>
<td>Breath view</td>
<td>In-depth view</td>
</tr>
<tr>
<td>Sample size</td>
<td>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.</td>
<td>Generally smaller; until achieving a saturation point</td>
</tr>
<tr>
<td>Sample selection</td>
<td>Simple random sampling</td>
<td>Purposely involving the 7 governmental agencies</td>
</tr>
<tr>
<td>Instrumentation</td>
<td>Standard questionnaire</td>
<td>In-depth interview</td>
</tr>
<tr>
<td>Analysis and interpretation</td>
<td>Through statistical analysis including bivariate analysis as well as correlation and prediction using multiple logistic regression analysis</td>
<td>Identify research themes</td>
</tr>
<tr>
<td>Reporting guidelines or protocol</td>
<td>Strengthening the Reporting of Observational Studies in Epidemiology checklist</td>
<td>Consolidated criteria for reporting qualitative research checklist</td>
</tr>
</tbody>
</table>

The qualitative approach used an in-depth interview technique through a semi-structured 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 audi-taped, 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.
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
Proposal

Effect of Preconception Care Intervention on Maternal Nutritional Status and Birth Outcome in a Low-Resource Setting: Proposal for a Nonrandomized Controlled Trial

Dharitri Swain1, MSc; Jasmina Begum2, MD; Swayam Prangnan Parida3, MD

1College of Nursing, All India Institute of Medical Sciences, Bhubaneswar, India
2Department of Obstetrics & Gynecology, All India Institute of Medical Sciences, Bhubaneswar, India
3Department of Community Medicine and Family Medicine, All India Institute of Medical Sciences, Bhubaneswar, India

Corresponding Author:
Dharitri Swain, MSc
College of Nursing
All India Institute of Medical Sciences
Sijua, Dumduma
Bhubaneswar, 751019
India
Phone: 91 94 38884272
Email: dhari79@yahoo.co.in

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&EncId=&userName=CTRI/2021/04/032836
International Registered Report Identifier (IRRID): PRR1-10.2196/28148

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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 MCH 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.
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. Preconception service package includes:
- Screening of cases
- Nutritional supplementation of iron and folic acid along with multivitamins.
- Vaccination if needed
- Contraceptive education and distribution.
- Sex education
- Individual and group counseling

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.

<table>
<thead>
<tr>
<th>Service</th>
<th>Screening activities</th>
<th>Plan of action</th>
</tr>
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| Reproductive history and contraception | Inquire about previous pregnancies:  
• Preterm birth, preeclampsia  
• Congenital anomalies, stillbirth/miscarriage  
• Gestational diabetes  
• Cesarean birth, uterine anomalies, high/low birth weight  
Inquire about contraception:  
• Interventions to delay age at first pregnancy and inter-pregnancy 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. |
Some of the prepregnancy health conditions such as which in turn influences health status throughout the lifetime. Preconception health is associated with infant birth outcomes, providing preconception service will begin in August 2021, and of participants to phase 1 began in April 2021, phase 2 of

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.

References


Abbreviations

LMICs: low- and middle-income countries
MHC: maternal health care
Protocol

Association of Postoperative Clinical Outcomes With Sarcopenia, Frailty, and Nutritional Status in Older Patients With Colorectal Cancer: Protocol for a Prospective Cohort Study

Nia Angharad Humphry¹, MBBS, BSc, MSc; Thomas Wilson², BSc, MSc, PhD; Michael Christian Cox³, MD; Ben Carter⁴, BSc, MSc, PhD; Marco Arkesteijn², BSc, MSc, PhD; Nicola Laura Reeves⁵, MBChB; Scott Brakenridge⁶, MS, MD; Kathryn McCarthy⁷, MBBS, MD; John Bunni⁸, MBChB, DipLapSurg; John Draper², BSc, PhD; Jonathan Hewitt⁹, MBBS, PhD

¹School of Medicine, Cardiff University, Cardiff, United Kingdom
²Institute of Biological, Environmental & Rural Sciences, Aberystwyth University, Aberystwyth, United Kingdom
³Department of Surgery, College of Medicine, University of Florida, Gainesville, FL, United States
⁴Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King’s College, London, United Kingdom
⁵Department of Surgery, Cardiff and Vale University Health Board, Cardiff, United Kingdom
⁶Department of Surgery, Harborview Medical Center, University of Washington, Seattle, WA, United States
⁷North Bristol National Health Service Trust, Bristol, United Kingdom
⁸Royal United Hospitals Bath National Health Service Foundation Trust, Bath, United Kingdom
⁹Division of Population Medicine, Cardiff University, Cardiff, United Kingdom

Corresponding Author:
Nia Angharad Humphry, MBBS, BSc, MSc
School of Medicine
Cardiff University
9th Floor Neuadd Meirionydd
University Hospital of Wales
Cardiff, CF14 4XW
United Kingdom
Phone: 44 7815913222
Email: HumphryNA1@cardiff.ac.uk

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 computed 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 (cm²), 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 (cm²/m²) 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 (cm²/m²).

**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].

Urinary 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 intra-individual 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 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)

**Acknowledgments**

We offer many thanks to Cardiff University for acting as the study sponsor and Professor John Draper and the team at the High Resolution Metabolomics Laboratory of the Institute of Biological, Environmental & Rural Sciences at Aberystwyth University for supplying urine collection kits and hand dynamometers as well as performing the metabolomics analysis of urine samples. NAH was awarded with an external, peer-reviewed grant by the British Geriatrics Society.

**Conflicts of Interest**

None declared.

**References**


20. Older Person Surgical Outcomes Collaborative. OPSOC. URL: https://www.opsoc.eu/ [accessed 2021-06-21]


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)

Beatrice Gehri¹,², MSc; Stefanie Bachnick¹,³, PhD; René Schwendimann¹,⁴, PhD; Michael Simon¹,⁵, PhD

¹Institute of Nursing Science, University of Basel, Basel, Switzerland
²Department of Psychiatry, University of Basel, Basel, Switzerland
³Department of Nursing Science, University of Applied Sciences (hsg Bochum), Bochum, Germany
⁴University Hospital Basel, Basel, Switzerland
⁵Nursing Research Unit, Inselspital Bern University Hospital, Bern, Switzerland

Corresponding Author:
Michael Simon, PhD
Institute of Nursing Science
University of Basel
Bernoullistrasse 28
Basel, 4056
Switzerland
Phone: 41 41 61 207 0912
Email: m.simon@unibas.ch

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: MatchRN 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 MatchRN 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 MatchRN 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.

International Registered Report Identifier (IRRID): DERR1-10.2196/26700
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 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\textsuperscript{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\textsuperscript{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\textsuperscript{RN} Psychiatry.](image)

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\textsuperscript{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\textsuperscript{RN} Psychiatry variables and measurements include patient routine data and survey data at the hospital, unit, and individual nurses level based on the Match\textsuperscript{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\textsuperscript{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.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unit characteristics</strong></td>
<td>5 items assessing the name, specialization, number of beds, average length of stay, and bed occupancy at the unit</td>
<td>2 text items, 3 number items</td>
</tr>
<tr>
<td><strong>Workforce</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbers of FTEs(^a)</td>
<td>2 items from the Match(^{RN}) study [27] assessing the FTE of nurses according to educational background and function</td>
<td>Number of FTEs</td>
</tr>
<tr>
<td>Agency nurses</td>
<td>7 items from the Match(^{RN}) study [27] assessing frequency, duration, and attitude for agency nurses’ use</td>
<td>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)</td>
</tr>
<tr>
<td><strong>Organization of nurse service</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resources allocation</td>
<td>20 items from the Match(^{RN}) study [27] assessing resources allocation at the unit</td>
<td>4 items: 10-point Likert-type scale from 1 (very low) to 3 (very high); 16 items with various multiple answer options</td>
</tr>
<tr>
<td>Work schedule</td>
<td>16 items from the Match(^{RN}) study [27] assessing the responsibility, influence, and flexibility in work schedules of nurses at the unit</td>
<td>4 items: 10-point Likert-type scale from 1 (strongly disagree) to 3 (strongly agree); 12 items with various multiple answer options</td>
</tr>
<tr>
<td><strong>Influence of COVID-19 at the unit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19 at the unit</td>
<td>4 investigator-developed items assessing whether patients with COVID-19 are at the unit; teaching and use of personal protection equipment</td>
<td>3 items: 2 answer options (yes or no); 1 open-text item</td>
</tr>
<tr>
<td><strong>Career characteristics of the unit manager</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Career characteristics</td>
<td>5 items from the Match(^{RN}) study [27] assessing qualification level, years in nursing, years in psychiatric care</td>
<td>N/A(^b)</td>
</tr>
</tbody>
</table>

\(^a\)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.

<table>
<thead>
<tr>
<th>Topic and variable</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>In years at admission</td>
</tr>
<tr>
<td>Gender</td>
<td>Female or male</td>
</tr>
<tr>
<td>Clinical data</td>
<td>Number of days</td>
</tr>
<tr>
<td>Length of stay</td>
<td>1 item calculated from the date of admission and date of discharge</td>
</tr>
<tr>
<td>Medical diagnosis</td>
<td>5-digit code</td>
</tr>
<tr>
<td>ICD-10(^a) code</td>
<td>5-point Likert-type scale from 0 (no problem) to 4 (severe or very severe problem) measured at admission and discharge</td>
</tr>
<tr>
<td>Symptom burden</td>
<td>All 12 items of the HoNOS(^b) [44]</td>
</tr>
<tr>
<td></td>
<td>• Overactive, aggressive, disruptive, or agitated behavior</td>
</tr>
<tr>
<td></td>
<td>• Nonaccidental self-injury</td>
</tr>
<tr>
<td></td>
<td>• Problem drinking or drug taking</td>
</tr>
<tr>
<td></td>
<td>• Cognitive problems</td>
</tr>
<tr>
<td></td>
<td>• Physical illness or disability problems</td>
</tr>
<tr>
<td></td>
<td>• Problems with hallucinations and delusions</td>
</tr>
<tr>
<td></td>
<td>• Problems with depressed mood</td>
</tr>
<tr>
<td></td>
<td>• Other mental and behavioral problems</td>
</tr>
<tr>
<td></td>
<td>• Problems with relationships</td>
</tr>
<tr>
<td></td>
<td>• Problems with activities of daily living</td>
</tr>
<tr>
<td></td>
<td>• Problems with living conditions</td>
</tr>
<tr>
<td></td>
<td>• Problems with occupation and activities</td>
</tr>
</tbody>
</table>

\(^a\)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:

\[ \text{work-life balance} = \beta_0 + \beta_1 \times \text{staffing} + \beta_2 \times \text{age} + \beta_3 \times \text{working time} + \beta_4 \times \text{family status} + \epsilon \]

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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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**

https://www.researchprotocols.org/2021/8/e26700
Variables and measurements in the nurses’ survey.

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Abbreviations

HoNOS: Health of the Nation Outcome Scale
SPO: structure-process-outcome