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# JMIR Research Protocols

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Impact Factor (2023): 1.4

Volume 10 (2021), Issue 1 ISSN 1929-0748 Editor in Chief: Xiaomeng (Simone) Ma, PhDc, MS, BS

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Protocol

# Effectiveness of the Use of Augmented Reality in Teaching the Management of Anaphylactic Shock at the Primary Care Level: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Augmented reality (AR) has benefits and feasibility in emergency medicine, especially in the clinical care of patients, in operating rooms and inpatient facilities, and in the education and training of emergency care providers, but current research on this topic is sparse.

**Objective:** The primary objective is to evaluate the short-term and long-term effectiveness of the use of AR in the treatment of patients with anaphylactic shock. The secondary objectives are to evaluate the safety in the treatment of patients with anaphylactic shock, evaluate the short-term and long-term effectiveness of stress management in this process, and determine the experiences and attitudes towards the use of AR in education.

**Methods:** The study will be conducted in 3 phases. In the first phase, we will develop and test the scenario for simulation of anaphylactic shock and the evaluation scale for assessing the effect of the intervention. In the second phase, a single-blinded, randomized controlled trial will be conducted. In the third phase, the use of AR in teaching the management of anaphylactic shock using focus groups will be evaluated qualitatively. All participants will participate in a 1-day training program consisting of a lecture on emergency care and anaphylactic shock as well as exercises in manual dexterity (aspiration, airway management, alternative airway management, artificial respiration, chest compressions, safe defibrillation, oxygen application, use of medication during emergency care). The test group will also focus on education about anaphylactic shock in AR (the intervention). The main outcome will be the evaluation of the participants' performance in coping with a simulated scenario of anaphylactic shock using a high-fidelity simulator (simulator with high levels of realism) and a standardized patient in an educational and clinical environment. The study will be conducted with primary care physicians.

**Results:** A scenario for the simulation with a high-fidelity simulator and standardized patient has already been developed. For the time being, we are developing an evaluation scale and starting to recruit participants. We plan to complete the recruitment of participants by the end of December 2020, start the randomized controlled trial in January 2021, and finish 1 year later. The first results are expected to be submitted for publication in 2021.

**Conclusions:** This will be the first study to evaluate the effectiveness of the use of AR in medical teaching. Specifically, it will be based on a clinical case of anaphylactic shock at the primary care level. With our study, we also want to evaluate the translation of these educational results into clinical practice and assess their long-term impact.

**Trial Registration:** ISRCTN Registry ISRCTN58047410; <http://www.isrctn.com/ISRCTN58047410>

**International Registered Report Identifier (IRRID):** PRR1-10.2196/22460

**KEYWORDS**

augmented reality; education; emergency medicine; primary health care

## Introduction

Augmented reality (AR) is a technology that enhances the user's reality with the help of digital information [1]. It maintains the user's connections with the real world and synthesizes the virtual with the real. It typically involves a headset through which one can view a physical reality that has been expanded or supplemented by computer-generated sensory inputs such as sound, video, and graphics [2]. AR differs significantly from virtual reality (VR), as the latter is completely immersive (ie, the real [external] world is completely blocked by the headsets) [2].

In the health care sector, AR is used in medical training [3-5], for surgical interventions [6,7], in nursing [8], in rehabilitation [1], in emergency medicine [2,9], and as a therapeutic aid [10]. In health education, it is used in a wide range of subjects (eg, surgery, forensic medicine, anatomy, clinical life support, cardiology) [4]. Educators use various devices, such as smart glasses, tablets, and smart watches [8]. Systematic reviews from the field of AR in medical education report that the subject is increasingly researched but still in the early stages. Studies have mainly focused on the development, usability, and first implementation of AR for learning. Perhaps the value of this teaching method lies in its motivational effect, the training of psychomotor skills, and the ability to make the invisible visible [5]. However, designed AR applications lack an explicit pedagogical framework [4], and there is no evidence that these applications are able to transmit information to the user [3]. There are also no clinical studies that support the effectiveness of the AR technologies used [1].

In emergency medicine, AR has benefits and feasibility in the clinical care of patients, in operating rooms and inpatient facilities, and in the education and training of emergency care providers, but current research on this topic is scarce [2]. Previous studies have shown that AR can enable reflection through experience [11] and can be useful in procedural learning [2]. It also appears that AR adds an extra level of realism to simulation learning, which improves learner self-confidence and teamwork [2].

Emergency management is an integral part of primary care. As a primary care provider, primary care workers can be confronted with any type of emergency that requires updated knowledge, communication and manual skills, trained personnel, appropriate equipment and practice organization, and necessary medication. The wide range of symptoms and the rarity of situations make it difficult for primary care staff to keep up to date and be competent in life support [12]. The use of new training methods, such as classroom simulations with 3-dimensional (3D), highly realistic simulators [13] or in situ simulations, can provide comprehensive training in handling medical emergencies and identifying potentially dangerous medical situations that are not

part of the daily work of primary care physicians and other health care workers [14].

Despite the growing body of evidence that AR is effective in medical education, some studies failed to confirm this, reporting no significant impact of the use of AR on learning and no differences according to device used (mobile or other) [15].

There are also several disadvantages of AR use for medical education that could be important, such as the possibility of deteriorating human connections; technical problems, which could affect the learning process; lack of privacy during learning; and questionable cost benefit.

The primary objective of this study is to evaluate the short-term and long-term effectiveness of the use of AR in the management of patients with anaphylactic shock. The secondary objectives are to assess the safety in the treatment of patients with anaphylactic shock, evaluate the short-term and long-term effectiveness of stress management in this process, and determine the experiences and viewpoints of participants regarding the use of AR in education.

## Methods

### Study Design and Settings

This is a mixed-methods study, incorporating quantitative and qualitative methodology and operating under a pragmatism paradigm.

The study will be conducted in 3 phases. In the first phase, we will develop and test the scenario for simulation of anaphylactic shock and the evaluation scale for assessing the effect of the intervention. In the second phase, a single-blinded, randomized controlled trial (RCT) will be conducted. In the third phase, a qualitative methodology with focus groups will be used to assess the attitudes and experience regarding AR use in participants.

The study will be conducted in a primary health care setting, partly in a classroom and partly in a clinical setting. The Slovenian Ethics Committee (No. 0120-67/2020/6) approved the protocol.

### Participants and Recruitment

#### Phase One

Up to 10 experts from the fields of family and general medicine, emergency medicine, and internal medicine will participate in the development of the scenario for the simulation with a high-fidelity simulator and for AR as well as the evaluation scale for assessing the effect of the intervention.

#### Phase Two

Family medicine physicians will participate in the study. We will send an invitation to all family physicians in Slovenia via the register of family medicine physicians at the Slovenian Medical Chamber. We plan to recruit 150 participants. They

will be randomly divided into test and control groups. Inclusion criteria will be a signed informed consent and willingness to participate. Exclusion criteria will be physical inability to participate in activities, previously experienced side effects of using AR, and heart disease.

**Phase Three**

For the focus groups, participants from the test group will participate. According to the guidance in previously reported studies, we expect to include a minimum of 4 participants and a maximum of 12 participants per group [16-19]. Qualitative data collection will be continued until data saturation is achieved. According to Guest et al [20], more than 80% of all themes are discovered by using 2-3 focus groups, and 90% are found by using 3-6 focus groups. For this reason, we anticipate having 3-6 focus groups; however, if the point of saturation is achieved sooner, fewer focus groups will be performed. If possible, focus groups will be stratified by work experiences (<10 years' experience, 10-20 years' experience, >20 years' experience). We feel that family physicians will be more open when in a group with physicians who have similar experience.

**Procedures and Data Collection**

**Phase One**

The simulation scenario (the simulation is presented with a high-fidelity simulator in a learning and clinical environment and for AR) is being developed by the researchers on the basis of the 2015 European Resuscitation Council guidelines and 2015 European Academy for Allergology and Clinical Immunology guidelines. The experts will validate the scenario and thus ensure its validity.

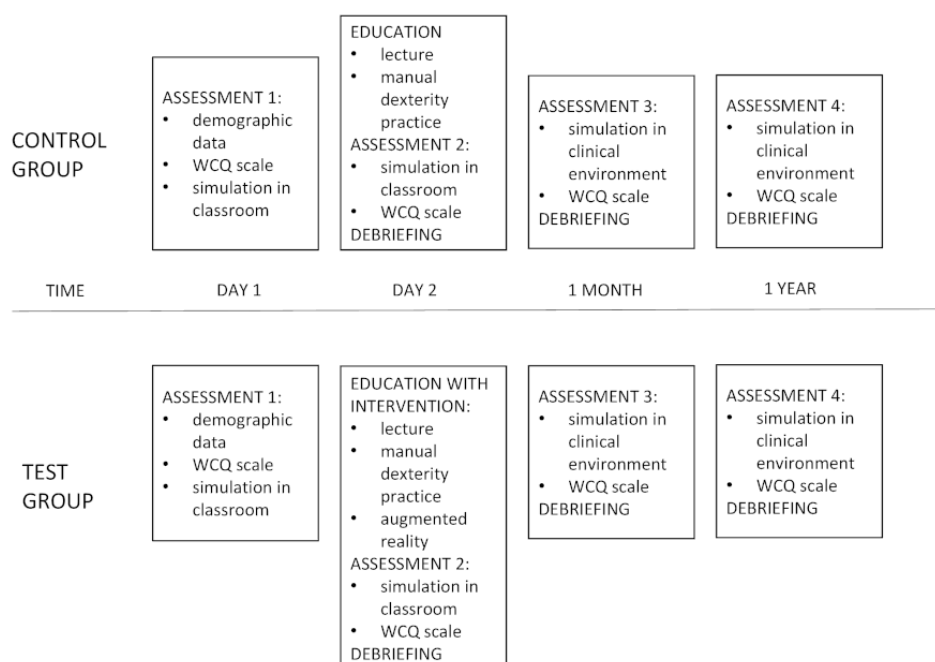
An evaluation scale will be developed to assess the impact of the intervention. The evaluation criteria will be developed based on the 2015 European Resuscitation Council guidelines and

2015 European Academy for Allergology and Clinical Immunology guidelines. These criteria are reviewed by the experts using a 2-step Delphi methodology. In the first step, the usefulness of items for assessment are assessed using grades 1 to 7, where 1 means that the criterion is not useful at all and 7 means completely useful. To be included in the evaluation scale, each criterion has to be given an average score of  $\geq 5$  points. In the second stage, the rating scale is re-evaluated by experts who express their agreement with the rating scale. We will aim for a consensus rate of 90%. Through this process, we will obtain the final version of the rating scale [21].

**Phase Two**

The flow of the study is presented in Figure 1. The study is expected to last for 1 year. Before the intervention, we will assess the baseline characteristics of the participants. All participants will complete the questionnaire on demographic and other data (see Measures). They will also complete the Folkman-Lazarus Ways of Coping Questionnaire (WCQ; please see Measures for more information) [22]. The baseline knowledge, skills, and competencies of the participants regarding the management of a patient with anaphylactic shock will be assessed through a simulation based on the developed scenario using a high-fidelity simulator in a learning environment (a classroom). The participants will perform the simulation in a group of 3; the other 2 members of the group will be educated trainers. They will follow the leadership of the individual participant and not engage in actions until instructed by the participant. The simulation will be video recorded. The recordings will be independently assessed by 3 experts that will not be aware of the participant's group allocation (blinded), based on the developed evaluation scale. They will harmonize their assessment and produce a single result. This will be in the form of a numeric outcome (primary outcome result) and in a binary form (successful/not successful).

**Figure 1.** Schematic presentation of the randomized controlled trial in phase two of the study. WCQ: Ways of Coping Questionnaire.





After the intervention (see Intervention), the participants will once again perform the simulation with a high-fidelity simulator and complete the WCQ, which will be followed by a debriefing. We will use a structured tool for debriefing called TALK (Target, Analysis, Learning Points, Key Actions), which is designed to guide structured team self-debriefing after any learning event in clinical environments. It promotes a supportive culture of learning and patient safety [23]. The simulations will be again video recorded, and the recordings will be assessed by experts as already described.

Both groups will be assessed again at 1 month and 1 year after the intervention, using the WCQ scale and simulation. This time, the simulation will be performed in the participant's workplace and with a standardized patient, followed by a debriefing. The scenario of the simulation will be the same as before. Again, simulations will be video recorded; experts, as already described, will assess the recordings.

The short-term effect will be measured using performance immediately and 1 month after the intervention, while the long-term effect will be measured 1 year after the intervention, which will also be our primary time point.

### **Phase Three**

Within 1 month after the intervention, the focus groups consisting of the test group members will be conducted according to qualitative methodology principles. The focus groups will be led by an experienced family physician who has extensive experience in conducting qualitative research and a family physician who will be observing and recording. Participants will be told that the focus groups' primary goal is to explore the experiences, beliefs, and views, providing a comprehensive understanding of the knowledge that participants had with AR in education.

Each focus group will last approximately an hour and will be audio-recorded. Participants will sign an agreement to be recorded. The recordings will be archived for 1 year, then destroyed. Participants will be seated at a round table so they can see each other. Before the group starts, each participant will be provided with a copy of the rules to respect other's opinions, listen to others, and speak in turn. Audio-recordings will be transcribed verbatim.

### **Measures**

We will record the following demographic and other characteristics of the participants: gender, age, workplace, work period, participation in previous training on anaphylactic shock, being a mentor or tutor, being a teacher, participation in emergency or off-duty care, and previous experience with patients with anaphylactic shock (number of cases).

The WCQ scale provides insight into the processes or strategies of stress management. It contains 66 statements measured on the following scale: 0: none at all; 1: partial; 2: extensive; 3: overwhelming. The statements measure 8 dimensions of stress management: confrontation, distance, self-control, seeking social support, taking responsibility, escape/avoidance, planned problem solving, and positive reassessment. The validity of the construct of the WCQ scale lies in the fact that the research

results are consistent with the following theoretical assumptions: (1) Coping involves both problem-oriented and emotionally regulating strategies, and (2) coping is a process. This means that the way stress is handled depends on the demands of the situation and the changes that occur over time [22].

The evaluation scale will consist of several criteria against which we will judge compliance with the guidelines for handling a patient with anaphylactic shock and the safe performance of the procedures. It will also include criteria for assessing the safety of the procedure. Each criterion will be rated as successfully completed or unsuccessfully completed, and the score on the evaluation scale will be the percentage of successfully completed criteria; this will be our primary outcome. Its dichotomous version (which will only be classified as successful if all criteria are successfully completed) will be our secondary outcome. In addition, we will analyze the criteria used to assess the safety of the procedures. Only those participants who meet all safety criteria will be classified as participants who treat the patient in a safe way.

### **Intervention**

All participants will participate in a 1-day training program consisting of a lecture on emergency care and anaphylactic shock as well as exercises in manual dexterity (aspiration, airway management, alternative airway management, artificial respiration, chest compressions, safe defibrillation, oxygen application, use of medication during emergency care). The test group will receive education on anaphylactic shock in AR. Training with AR is a scenario for the management of a patient with anaphylactic shock. When the head-mounted display is put on, a woman with symptoms of anaphylactic shock that gradually worsen can be seen. Her breathing becomes difficult, an urticarial rash appears, and she says she does not feel well and cannot breathe. When she is asked questions, she answers. The participant must then take the necessary steps to treat this patient correctly; otherwise, the augmented patient will die.

AR intervention represents a combination of standardized and evaluated medical procedures corresponding to a specific medical event (in our case, anaphylactic shock) and digital support id software. Development of an AR intervention consists of (1) defining a medical event, (2) analysis and documentation of crucial parameters (eg, patient type, symptoms, procedures, measurements, medication, equipment involved [eg, monitor, pulse oximeter], decision tree, execution process, and time perspective), (3) defining targeted users or user groups, (4) creation of the use case scenario, (5) defining the expected (un)wanted outcome in the form of standardized results (points achieved, success rate in percentages), (6) software development (environment creation including all 3D assets, animations, sounds, and user interactions), and (7) integration of all elements described into the most believable realistic, holistic experience producing adequate levels of stress in regards to the potential real case scenario. The AR intervention was developed by a group of medical experts (doctor, nurse, and instructor) and information technology experts (user experience engineers, 3D artists, designers, AR developers, and product specialists). The AR intervention will be delivered in the form of software as a service, meaning an application supporting available devices



for distributing AR content. Add-ons to the application will be web space for user management and tracking of participant success (pass rate). Trained instructors for emergency medicine education with simulations will deliver the intervention.

## Technical Information

### Hardware

The primary type of device used for the execution of an AR intervention now is HoloLens, a standalone computer supporting comprehensive 3D rendering, unlimited user movement, voice control, and hand tracking. Any additional controllers will be used. HoloLens supports communication with Internet of Things devices (id sensors or other supportive elements) and the cloud, offering additional computing resources for multiple user experiences (eg, debriefing).

### Software

The HoloLens uses a Windows Holographic platform. The device's interface uses gaze input (head tracking), gestures (bloom, air tap, air tap and hold), and voice commands. Three gestures are used to interact with the AR environment: (1) bloom: upward-facing palm, starting with fingertips together, then spreading fingers outward — used for application start-up and closure; (2) air tap (tap and release): with the dorsal aspect of the user's hand facing them, raising and flexing the index finger (ie, up, down, and up again) in a pinch-like fashion (press and release) — used for selecting an operation; (3) air tap and hold: raising and flexing the index finger to the thumb and motioning the pressed fingers together (press and hold) — used in the user's 3D space (ie, up, then down) for manipulation of selected objects.

## Ethical Considerations

In this study, we will determine the effectiveness of a new teaching method in a controlled environment without health risks. Possible side effects of using AR could be dizziness, headaches, and nausea. Therefore, participants with known similar reactions to similar environments will not be included in the study. Recordings from the study will be used for research purposes only and will be stored on a secure server. The use of a standardized patient in a clinical environment may cause stressful situations. To avoid this, participants are informed immediately before the start of the simulation with the standardized patient that this is a simulation and not a real situation. All participants will be offered a free 1-day training with AR at the end of the study.

## Statistical Analysis

### Power Calculation

Sufficient sample size to detect a difference between the test and control groups in the score of the evaluation scale (primary outcome) using a 2-tailed independent *t* test was determined using power analysis. For  $\alpha$  of .05 and 80% power to reject the null hypothesis of equal group means, when the population mean difference is 10 points (considered clinically relevant) and population SD of both groups is 20 points, a sample size of 128 (64 per group) is needed. The SD of 20 was used based on the results of a study on the use of case-based simulations

with high-fidelity mannequins in teaching and retention of emergency management team skills [18]. In that study, the SD of the evaluation scores was <20 for all scenarios. To account for dropouts, we plan to recruit 150 participants.

For the secondary outcome (dichotomous version of the score of the evaluation scale), we performed power analysis using the planned sample size of 128 (64 per group). A chi-square test with  $\alpha$  of .05 achieves 80% power to reject the null hypothesis of equal group proportions of successful assessments if the population difference between the group proportions is 21%-25%, where the proportion of successful assessments in the control group is assumed to be between 15% and 40%.

Sample size calculations were conducted using PASS 2019 Power Analysis and Sample Size Software [24].

### Statistical Methods

We will summarize categorical variables with frequencies and percentages, and we will summarize numerical variables with means and SDs or medians and IQRs in the case of asymmetric distributions. To highlight the differences between the groups at baseline, we will use the chi-squared test or Fisher exact test (if more than 20% of the expected frequencies are below 5) for categorical variables and independent samples *t* test or Mann-Whitney U test (in the case of asymmetric distributions) for numerical variables.

For the comparison of groups after 1 year (primary time point), we plan to use a *t* test for independent samples (or Mann-Whitney U test) for the evaluation scale score (primary outcome) and a chi-squared test (or Fisher exact test) for its dichotomous version (secondary outcome) and for the safety criteria. To compare groups at all time points (right after the intervention, after 1 month, and after 1 year) efficiently in one model, we will use appropriate mixed-effects regression models, which are able to appropriately take into account repeated measurements of the same patient. The power for detecting differences between groups with these models is even higher than with independent *t* tests or chi-square tests that were used in the power analysis.

To evaluate the short-term and long-term effectiveness of coping with stress, only the following dimensions will be included in the analysis: confrontation, distance, self-control, seeking social support, taking responsibility, escape/avoidance, planned problem solving, and positive reassessment. We will sum items to provide each of these scales. For each scale, groups will be compared using a linear mixed-effects regression model.

A *P* value <.05 will be considered as statistically significant.

## Qualitative Analysis

We will perform a thematic analysis following a semantic approach. We intend to get the explicit opinions of the participants on their experiences with education using AR. We do not want to study the underlying assumptions and beliefs that are rooted in the context of the interviews we will perform. The thematic analysis is, according to Guest et al [25], the most useful data analysis technique in capturing the complexity of data within qualitative data and offers a valuable approach for applied research [26]. Thematic analysis is an "organic

approach” [27] to coding and generation of the themes that allow for in-depth exploration of the experiences, beliefs, and views, providing a comprehensive understanding of the knowledge that participants had with AR in education.

The inductive approach in this study will enable researchers to develop a thematic framework emerging from the data (“from the ground up”). A semantic approach will be used since our goal is to explore participants’ experiences, beliefs, and views.

The analysis will be comprised of 6 stages: (1) getting familiar with the data while reading the transcript, (2) generating initial codes, (3) generating themes based on the codes, (4) reviewing initial codes and re(combining) them into previous or new themes, (5) developing and defining names of the themes, and (6) reducing the number of themes into a more manageable set of important themes [27].

We will use NVivo Pro 11 software V.11, 2015 to code the data for the thematic analysis, generate codes and categories, and

**Textbox 1.** Scenario for simulation with a high-fidelity simulator and standardized patient.

The patient is an otherwise healthy 32-year-old woman with no known history of allergy who received an intramuscular injection of ketoprofen due to back pain. Within minutes, the patient showed signs and symptoms consistent with anaphylaxis, and the participant should quickly take a specific history and physical examination and begin treatment. If the correct diagnosis and treatment are made, the patient will improve. If the participant does not recognize that the patient is in anaphylaxis or is only administering second-line therapy without epinephrine, the patient deteriorates into respiratory arrest with pulseless electrical activity and requires resuscitation according to Advanced Cardiac Life Support (ACLS) guidelines.

## Discussion

### Expected Results

This will be the first study to evaluate the effect of using AR for teaching in an urgent primary health care situation. The main outcome of this study will be the short-term and long-term effectiveness of the use of AR in the training of primary care physicians. We expect that the participants who are trained with AR in addition to the standard training will achieve better results in the treatment of a patient with anaphylactic shock in the simulation compared to other participants.

Several systematic, scoping, and integrative reviews on the use of AR in medical education showed that, while AR technology is growing at a rapid rate, the current quality and breadth of AR research in medical training are insufficient to recommend its adoption into educational curricula [2-4,29]. Existing studies mainly focus on the evaluation of prototypes instead of long-term studies. There is a lack of evidence for the implementation of AR in medical education [8], including training in emergency care [9], even though some studies demonstrated its effectiveness [2,11]. Therefore, we expect that our study will fill the gap on the effectiveness of AR in medical training and provide new insights into its short-term and long-term effects.

Our additional outcome will be the evaluation of safety in the treatment of patients with anaphylactic shock. We expect that participants trained with AR will treat their patients more safely than participants who are not trained with AR. With the use of AR in teaching, we also reach participants who have never seen a patient with anaphylactic shock before. Training with AR enables comprehensive training in dealing with medical

increase the accuracy of the working methods and result [28]. We will treat data from every stage collaboratively and corroboratively. Multiple researchers from the team will code the data and confirm thematic analysis to ensure that the researcher’s perspective does not bias the data’s interpretation. This will ensure that the working methods are trustworthy and valid (investigator triangulation).

## Results

We developed a scenario for simulation with a high-fidelity simulator and standardized patient (Textbox 1). We are currently developing an evaluation scale and starting to recruit participants. We are planning to finish participant recruitment by the end of December 2020, while the main trial will start in January 2021 and finish a year later. The first results are expected to be submitted for publication in 2021.

emergencies on the one hand and in recognizing potentially dangerous medical situations on the other. This approach also enables us to determine the quality of work and identify potential safety risks in the treatment of patients. We will also evaluate the short-term and long-term effectiveness of stress management in dealing with patients with anaphylactic shock. Stress is widely present in medicine, particularly when dealing with urgent situations [10]. As stress hampers the ability to perform work safely and to achieve a high standard of quality [4], it is important that doctors are educated early on how to manage stress [10]. With AR simulations, we can replicate real patients to reflect real situations in the clinical environment [12] and compare the knowledge of different teams. This provides a safe way to learn how to deal with difficult, unusual, or serious clinical situations. The scenarios are standardized and at the same time flexible, which allows for adaptation to the level of competence of the trainees. The training process is uniform and standardized, which promotes a high quality of learning and does not require years of exposure at accident sites. Realistic, stressful scenarios using highly realistic simulations promote simulated learning, where primary health care teams can interact with patients. Participants learn how to deal with stress during a simulation and manage the patient independently. They can safely explore their feelings and fears and learn how to face and overcome them [13].

With the qualitative part of the study, we want to find out about the experiences with this kind of training, the attitudes toward this teaching method, and suggestions for improvement. We also expect to identify the strengths and limitations of this novel and innovative teaching approach.

## Methodology

The main methodology of this study will be a single-blinded RCT using the AR intervention. We chose AR technology over VR technology because AR allows virtual presence to be blended into the users' reality with minimal interference. Therefore, we will create a more realistic environment compared to VR, which will allow the training of users in their working environment.

In addition, we will use a qualitative methodology. With such a methodology, we want to prove the validity of our AR application for education or training of medical professionals. According to Barsom et al [3], it is important to focus on 5 levels of validity. Face validity (ie, the degree of similarity between the AR application and the training construct) will be evaluated with focus groups. Content validity (ie, the degree to which the content of the AR application covers the dimensions of the medical content) will also be evaluated with focus groups. The other 3 levels will be assessed through the RCT: (1) construct validity (ie, inherent differences in outcome between experts and novices on outcome parameters relevant to the educational construct), (2) concurrent validity (ie, concordance of the subject's outcome parameters using AR compared to the outcome parameters of an established instrument or method that is assumed to measure the same educational construct), and (3) predictive validity (ie, the degree of agreement between the outcome parameters of AR and the respondent's performance goals, which are supposed to be similar in reality). With the qualitative part of the study, we also want to address the possible downsides of the use of AR in medical education that have already been reported in previous studies [15].

The evaluation of performance will be conducted with a simulation, first in the training environment with a high-fidelity simulator and later in the clinical environment with a standardized patient. With such methodology, we will meet the criteria for translational research [5] using 3 stages: (1) evaluation of performance in the educational environment, (2) evaluation in the clinical environment, and (3) evaluation in health care, community involvement, and prevention services. This study will show the possibility of using AR education for actual clinical practice.

There are some drawbacks of simulation in health care. Simulation relies on space, time, equipment, and skilled human resources. Setting up and running the simulation can be expensive [30]. The simulation center where the study will be

conducted is an already established and active center with many simulation trainings conducted over previous years [14]. Therefore, we are certain that these drawbacks will be handled appropriately. Another problematic issue in simulation might be the need for an adaptation period for students to perform the simulation. It is mainly during the second simulation that a student will really start to be able to adapt and treat the patient simulator more realistically [30]. We are aware that this could affect the results of our study, but given the fact that all participants will have the same conditions, we think that this drawback will also be handled appropriately.

In education at all levels and in all fields, studies usually focus on short-term results, assessing the outcome during or immediately after the time when the education took place. Unfortunately, it is true that mastery demonstrated during or immediately after learning can easily be lost in the weeks and months that follow without continued practice [6]. Therefore, in this study, we have chosen to evaluate the short-term and long-term effects by assessing performance immediately after the intervention and 1 month after, given that short-term performance is a good predictor of performance over longer periods of time, and 1 year after the intervention (long-term effect). The long-term preservation of knowledge is the most important, as it is an indicator of permanent memory.

## Limitations

A limitation of this study could be a biased sample, as it is possible that only participants with a high level of interest and motivation will enroll in training courses. There could also be discontinuation of the study, as some participants might demonstrate poor performance results and may not want to participate anymore. To avoid this, the size of our initial sample will account for dropouts during the study. During the study (between the intervention and evaluations after 1 month and 1 year), participants may encounter a patient with anaphylactic shock in their clinical practice or attend training on the subject. This could affect their performance.

## Conclusions

This will be the first study to evaluate the effectiveness of the use of AR in teaching medicine based on a clinical case of anaphylactic shock at the primary care level. With this study, we will evaluate the implementation of AR-related educational results in clinical practice. We will also be able to assess their long-term impact. This study will also serve as a basis for other research in the field of training with AR.

## Acknowledgments

ZKK, APS, and UZ conceived the study. ZKK, ŠT, NG, PRS, and ŠM wrote the study protocol. UZ and ŠT will perform the data collection. NRG will analyze the quantitative data. APS and ŠT will analyze the qualitative data. ZKK, ŠT, NRG, ŠM, APS, PS, and UZ will interpret the data. ZKK wrote the first draft of the manuscript. ŠT, NG, ŠM, APS, PS, and UZ read the first draft and produced its final version. All authors approved the final version.

The Ljubljana Community Health Centre, Slovenia, financially supports the study. PS acknowledges partial financial support from the Slovenian Research Agency, research core funding Research in the Field of Public Health No. P3-0339.



## Conflicts of Interest

None declared.

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## Abbreviations

**3D:** 3-dimensional

**ACLS:** Advanced Cardiac Life Support

**AR:** augmented reality

**RCT:** randomized controlled trial

**TALK:** Target, Analysis, Learning Points, Key Actions

**VR:** virtual reality

**WCQ:** Ways of Coping Questionnaire

*Edited by G Eysenbach; submitted 13.07.20; peer-reviewed by R Lundin, HYC Wong; comments to author 15.08.20; revised version received 10.09.20; accepted 10.11.20; published 04.01.21.*

*Please cite as:*

*Klemenc-Ketis Z, Poplas Susič A, Ružić Gorenjec N, Mirošević Š, Zafošnik U, Selič P, Tevžič Š*

*Effectiveness of the Use of Augmented Reality in Teaching the Management of Anaphylactic Shock at the Primary Care Level: Protocol for a Randomized Controlled Trial*

*JMIR Res Protoc* 2021;10(1):e22460

URL: <https://www.researchprotocols.org/2021/1/e22460>

doi: [10.2196/22460](https://doi.org/10.2196/22460)

PMID: [33393927](https://pubmed.ncbi.nlm.nih.gov/33393927/)

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Original Paper

# Coaching While Waiting for Autism Spectrum Disorder Assessment: Protocol of a Pilot Feasibility Study for a Randomized Controlled Trial on Occupational Performance Coaching and Service Navigation Support

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## Abstract

**Background:** In Australia, the average time between a first concern of autism spectrum disorder (ASD) and diagnosis is over 2 years. After referral for assessment, families often wait 6-12 months before their appointment. This can be a time of uncertainty and stress for families. For some families, other forms of assistance are not accessible and thus timely intervention opportunities are missed. There is little evidence about how to provide the best support for children or caregivers while on assessment waiting lists.

**Objective:** The aim of this study is to determine whether use of a coaching intervention called Occupational Performance Coaching (OPC) combined with service navigation support is feasible for families waiting for ASD assessment, as a crucial first step in planning a randomized controlled trial.

**Methods:** A pilot and feasibility study will be conducted using recommended constructs and associated measures, which will be reported using CONSORT (Consolidated Standards or Reporting Trials) guidance. Participants will be child and caregiver dyads or triads, recruited within 4 months of their child (aged 1-7 years) being referred to one of two services for an ASD assessment in Victoria, Australia. A blinded randomization procedure will be used to allocate participants to one of three trial arms: (1) coaching and support intervention delivered face to face, (2) coaching and support intervention via videoconference, and (3) usual care. Descriptive statistics will be used to describe the sample characteristics of parents and children, inclusive of service access at baseline and follow up. Recruitment rates will be reported, and retention rates will be evaluated against a predicted rate of 70%-80% in each intervention arm. Goal attainment, using the Canadian Occupational Performance Measure, will indicate preliminary evidence for efficacy within the intervention arms, with an increase of 2 or more points on a 10-point performance and satisfaction scale considered clinically significant.

**Results:** The study was approved by The Royal Children's Hospital Research Ethics and Governance Department in September 2018. As of October 2020, 16 families have been recruited to the study. Data analysis is ongoing and results are expected to be published in 2021.

**Conclusions:** Study findings will support planning for a future randomized controlled trial to assess the efficacy of OPC and service navigation support for caregivers of children awaiting ASD assessment.

**Trial Registration:** Australian New Zealand Clinical Trials Registry ACTRN12620000164998; [www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378793&isReview=true](http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378793&isReview=true)

**International Registered Report Identifier (IRRID):** DERR1-10.2196/20011

(*JMIR Res Protoc* 2021;10(1):e20011) doi:[10.2196/20011](https://doi.org/10.2196/20011)

## KEYWORDS

coaching; Occupational Performance Coaching; feasibility; parents; caregivers; ASD; autism; waiting list; referral; service navigation

## Introduction

Autism spectrum disorder (ASD) is a wide-ranging developmental disorder defined by atypical social communication and behaviors [1]. In Australia, ASD can affect between 1% and 4% of children [2], and is typically diagnosed by pediatricians, psychologists, or psychiatrists, with or without the support of allied health clinicians such as speech pathologists and occupational therapists [3].

Despite the high prevalence and increased community awareness of ASD, there remains a paucity of assessment services to meet demand across Australia, including in Victoria [4,5]. Such challenges and service inequities have a significant impact on the early pathway for children and families [6]. Although a prompt diagnosis is made for some children after seamless recognition and assessment by service providers, many families wait years between identification of learning, social communication, and behavior differences and diagnostic assessment [7]. It is common for families to be referred to multiple service providers before an understanding of service needs is obtained, or to wait extended periods on waiting lists for assessment before accessing vital therapy services [8].

Australia, similar to other parts of the world, currently faces the challenge of balancing the need for comprehensive assessment against high demands for diagnostic services [9,10]. Alongside establishment of the Australia-wide, age-limited Helping Children with ASD Package (FACSIA funding) in 2008 [11], demand for early diagnosis has increased and placed notable pressure on assessment services [12]. In Australia, this funding model was recently replaced with the individualized, client-controlled National Disability Insurance Scheme, which oversees both early intervention and disability support services in the country. In the context of this changed funding model, publicly funded ASD assessment services remain under-resourced and overburdened [13]. This is likely due to recommended comprehensive diagnostic practices, as well as an ongoing emphasis on diagnosis as the entry point for further service access in some of Australia's disability and education systems [13,14]. Moreover, state-wide initiatives in Victoria have recently been funded to improve the identification of ASD risk in young children via early screening initiatives, but without a matched expansion of publicly funded diagnostic services

[15]. This is likely to increase the existing burden on assessment services in the coming years, further extending wait times and service access delays for children and families. The issues surrounding timely service delivery are not limited to either ASD assessment or to Australian settings, but rather represent an international health service issue in pediatrics; thus, calls for action to address these delays are continuing [16,17].

For families of children with an identified risk of ASD, emerging concerns are exacerbated by limited service availability and a lack of clarity regarding suitable interventions and support [13,18]. Outside of research focusing on siblings of children with ASD, who are known to have an elevated risk for the disorder, there is little research to date that addresses how a child's and family's needs are met, or not met, at this crucial stage when concerns first arise [19]. Despite this limitation, there is a general consensus among clinicians and researchers about the importance of timely access to needs-based services that have the potential to improve a child's long-term outcomes [20] and the outcomes for their family.

In particular, few studies have explored ways to support children and families while waiting for ASD assessment services [16]. Moreover, no study to date has provided a rigorous, methodological approach to reviewing what interventions, if any, best address caregiver-identified needs for their child and family at this stage.

Coaching interventions have been investigated for primary carers seeking support because their young child is experiencing developmental difficulties [21-23]. A recent systematic review highlighted their general acceptability, although only 5 randomized controlled trials (RCTs) have been reported [24]. Along with methodological flaws, the wide-ranging definitions for coaching and its subtypes were described. Coaching diversity and inconsistent outcome measurement were reported to have impeded efficacy conclusions. Occupation-orientated coaching, which has been delivered via face-to-face and videoconference modalities, is one coaching subtype [24,25] in which fidelity measures have been proposed and published as a way of addressing identified intervention inconsistencies [26,27].

Occupational Performance Coaching (OPC) is an occupation-informed intervention developed to address the functional support needs of children and families [23]. OPC is



theoretically informed by occupation and family-centered practice, along with ecological models of child health and well-being. This approach involves supporting families to generate goals relating to themselves, their child's functioning, or the functioning of their family as a whole. The therapist, through a series of interactive semistructured interview sessions, then provides opportunities for reflection, sharing of knowledge, and the development of attainable actions. Performance analysis, strategy generation, and resource identification take place collaboratively, and actions are reviewed in subsequent sessions until goals are reached. Effectiveness of this intervention holds promise and continues to be evaluated [28-30]. To date, OPC has been typically examined in face-to-face sessions around 60 minutes in length, with a range of dosages between 2 and 12 sessions [31]. However, OPC has not yet been tested specifically with families of children waiting for ASD assessment, nor have the modes of treatment delivery, including delivery via telehealth or videoconference modalities, been compared concurrently within the same study. These modalities require particular exploration given social distancing challenges brought about as a result of the COVID-19 pandemic.

In novel clinical trial applications, the importance of initial feasibility testing and reporting has been reiterated in recent years [32,33]. Therefore, the aim of this study is to assess whether a small number of coaching sessions is feasible for families and has potential to address family needs while waiting for ASD assessment. The intervention's acceptability, practicality, expandability, and demand, as well as the types of needs in the local context that require interventions [34] will be examined. Such explorations are essential to inform a future

randomized clinical trial protocol, with risk of bias minimization and appropriate methodological rigor.

The specific aims of this study are: (1) to assess the feasibility, including constructs of acceptability, practicality, and preliminary efficacy, of an RCT study design exploring goal-directed support for families of children waiting for ASD assessment; and (2) inform protocol planning for a future RCT to assess efficacy of short-phase coaching and family support via face-to-face and videoconference modalities.

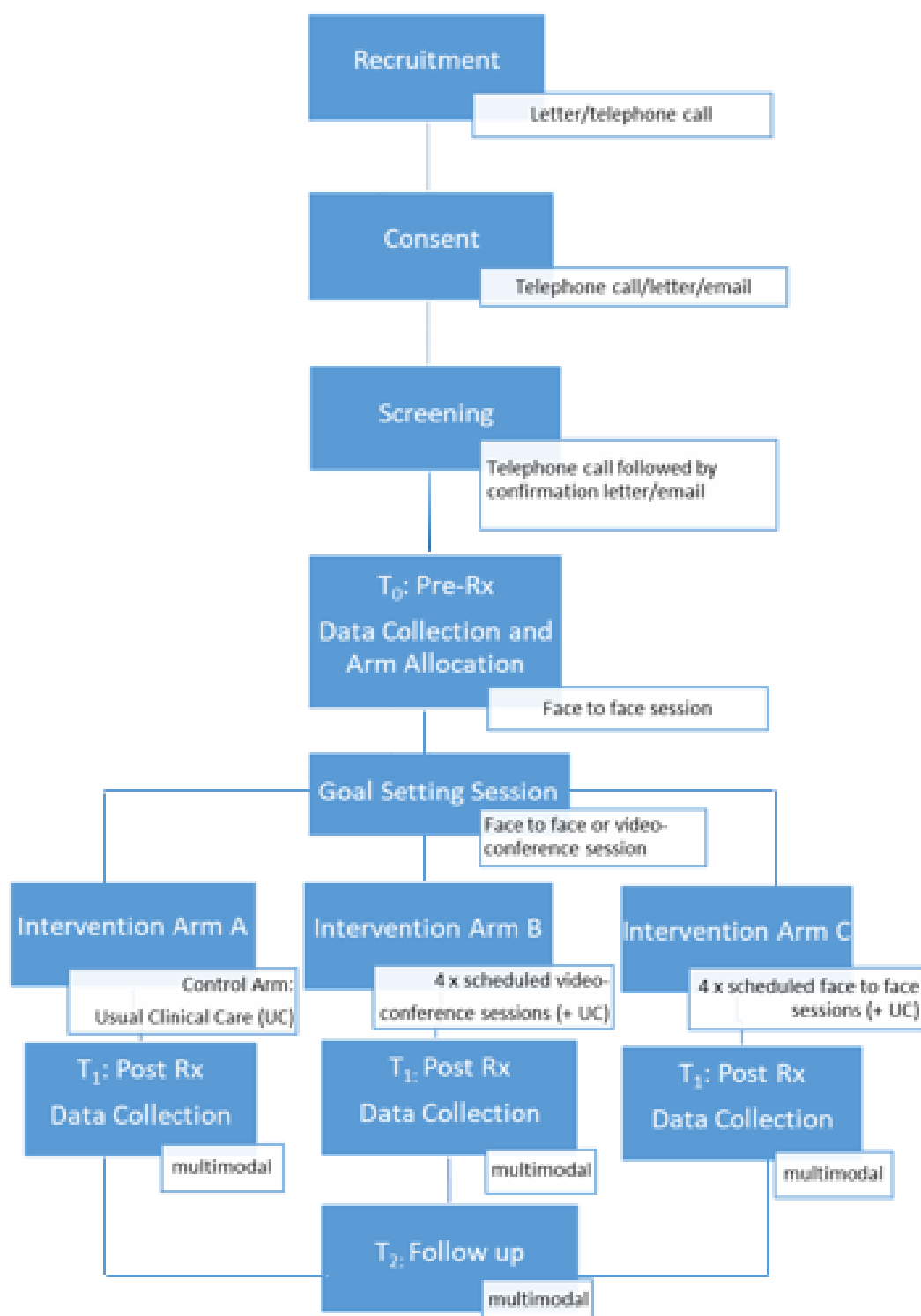
It is envisaged that the combined results from this feasibility study and a future RCT will inform service planning as well as service standards to address the needs of families with a child waiting for ASD assessment. The findings may also support new methods to eradicate wasteful waiting periods and prevent clinical practices that hinder access to needs-based interventions.

## Methods

### Trial Design

Trial design elements are described in line with CONSORT (Consolidated Standards of Reporting Trials) guidance for pilot and feasibility studies [35]. This study is a pilot RCT and feasibility study, with a focus on feasibility outcomes, following participant allocation to one of three parallel study arms inclusive of a usual care group. The study flow is detailed in [Figure 1](#).

Allocation ratios will be determined by the randomization process outlined below with an aim of obtaining an even number of participants allocated to each study arm.

**Figure 1.** Study procedures flow chart.

## Participants

Children below 7 years of age referred to the Royal Children's Hospital (RCH) in Melbourne for an autism assessment and their primary caregivers will be recruited for the study. Approximately 50 children per month are referred to the RCH by internal or external service providers for the specific purpose of ASD assessment. Referrals are typically received from all over the state of Victoria, although geography can be an

exclusion criterion for some of the assessment services. Additionally, Melton Health provides services for children and their families in the western suburbs of Melbourne, Victoria, and also receives high volumes of referrals per month. In both services, children are typically triaged centrally by a single, clinically trained ASD service coordinator. Referrals are screened for their appropriateness for services based on available clinical information, including demographic information such

as home address, identified referral concerns, previous service history, and referrer background.

The outcome of triage may be acceptance to a single professional group or multidisciplinary team for assessment to other developmental, medical, or behavioral services within the hospital, or redirection to an appropriate external service. Decision making occurs in line with specific service eligibility criteria, family resources, and service availability, and the nature of the presenting concerns.

The inclusion criteria are: (1) child up to the age of 6 years, 11 months with a recent (within the last 4 months) and active referral received querying ASD, who lives at home with primary caregivers; and (2) child and primary caregiver dyads or triads, which may include the child and up to two primary caregivers who live at home with the child. The exclusion criteria are: (1) child already diagnosed with ASD at the hospital or at an external service; (2) any participating primary caregiver who is unable to provide informed consent at the time of recruitment or at baseline ( $T_0$ ); (3) any participating primary caregiver who is currently accessing regular (weekly or biweekly) coaching or counseling support with a health professional relating to the care of their child or their individual mental health needs; and (4) child is aged 7 years or older at the time of referral.

### Recruitment and Consent

Following service allocation at the conclusion of referral triage at a tertiary hospital in Melbourne who accepts referrals for autism assessment, a study information leaflet will be sent by post to eligible families via the clinical service coordinator. Families who respond to the letter via telephone, email, or letter will proceed to the screening and consent stage. Families for whom no response is received will be telephoned by the triage clinician to enquire about the receipt of the leaflet and ascertain interest in the study. No more than two attempts will be made to contact nonresponding families.

For those who communicate interest in the study via telephone, email, or mail, screening will occur via a telephone-based interview conducted by the principal investigator. Eligibility will be determined by both the caregiver report, and information contained in the referral letter and the child's medical record. If inclusion criteria are met and no exclusions identified, participants will be sent the consent form and parent information statement to complete. Once a signed form is received, a face-to-face appointment to complete baseline study measures ( $T_0$ ) will be made.

### Interventions

In the first study arm (A), families will receive usual clinical care. Usual clinical care consists of telephone or email access to an ASD triage and service coordinator during the clinician's working hours 2 days per week. This clinician is based at a tertiary children's hospital for service direction and advice as needed, and has relevant expertise in ASD and developmental service delivery at a senior clinician level. Duties include answering service-related queries, offering advice regarding symptom presentation and management, and providing telephone-based counseling as required. Usual care also includes any local service provision that the child or parent may be

accessing to address previously identified developmental, behavioral, or health-related issues. These may include, but are not restricted to, access to a local pediatrician, speech pathologist, occupational therapist, or psychologist. Findings from the feasibility study will help to further inform community-based usual care provisions while children await autism diagnostic services.

In addition to usual care, OPC [31] will be carried out with participants in the other two study arms (B and C), differing only by mode of intervention delivery (videoconference vs face-to-face coaching). For the purpose of this study, videoconference is defined as an encounter between the intervention provider and study participants via a live video and audio link.

The intervention arms will be delivered by a clinician who is an experienced pediatric occupational therapist. Occupational therapists are increasingly part of child neurodevelopment assessment and intervention teams, supporting families to identify goals that will assist their child's functions and participation and improve family quality of life. They are well trained to support families to choose interventions, and to engage children and families in interventions that can help them achieve meaningful or functional goals [36].

In OPC, participants will initially be supported to identify goals using the Canadian Occupational Performance Measure (COPM) and additional questions that frame the vision of the goal. Goals identified in OPC are expressed as personally valued activities or routines in the contexts of daily life (ie, home, school, or community settings). For example, a parent's goal may be for the child and their family to collect groceries at the local grocery store once per week. Once goals are identified, the intervention provider will then use guiding questions and reflection techniques, including prompts or probes that help the caregiver to explore ideas and possible solutions. OPC will be subsequently delivered as per the approach's training manual [31].

Participants in arms B and C will be invited to attend 4 sessions of OPC. These will be 45-60-minute sessions, held between 1 and 5 weeks apart, depending on the participant's preference. This is to ensure there is adequate time between sessions to support strategy implementation outside of the intervention session itself, while meeting families' variable attendance needs. Participants allocated to the videoconference arm will be able to identify their preferred app for connecting with the intervention provider, which may include (but not be limited to) Zoom, WhatsApp, or Skype apps.

The delivery of OPC will be monitored using an established fidelity tool [37]. Intervention will be delivered by a clinician who has attended 24 hours of face-to-face training and further support hours relating to intervention fidelity, conducted by the original author of OPC. For every 3 participants that enroll in the study, all of the audio tapes from 1 participant will be submitted to the author of OPC for fidelity measurement. The first set of audio recordings will be used to develop familiarity with the fidelity measure and will not be included in the final fidelity analysis. Approximately 30% of the overall recordings in the study will be double-coded using the fidelity checklist

by the author or associates trained in use of the fidelity measure, in addition to the trained investigator delivering the intervention. This will occur until 80% or more fidelity constructs have occurred for 4 participants in a row.

## Outcomes

### Primary Feasibility Outcome Measures

Feasibility constructs adapted from Bowen et al [34] will be used to guide measures that will be reported following this

feasibility trial. These will be measured as described in Table 1. In particular, recruitment and retention rates will be explored and reported, as well as tolerance of randomization and feasibility of collection of the preliminary efficacy measures described in Table 1. Two standardized measures, the COPM [38] and the Measure of Processes of Care-20 [39], will also be used pre- and postintervention to assist with measurement of these feasibility constructs.

**Table 1.** Primary feasibility outcome measures.

Feasibility construct	Recruitment rate	Retention rate	Goal attainment (COPM <sup>a</sup> ) [38]	Measure of Processes of Care-20 [39]	Postintervention questionnaire	Time, resource, cost analyses (posthoc)
Acceptability	x	x		x	x	
Demand	x	x				
Implementation	x	x	x			x
Practicality			x	x		x
Adaptation					x	x
Integration	x	x		x		x
Expansion						
Limited-efficacy testing			x		x	

<sup>a</sup>COPM: Canadian Occupational Performance Measure.

All families will have goals set using the COPM. Although listed in Table 1 as an outcome, the process of goal setting and engagement in the COPM is additionally considered to be an intervention by some researchers and clinicians [40].

### Secondary and Preliminary Efficacy Outcome Measures

Characteristics of the participants, inclusive of the child and the caregiver(s), will be collected at baseline (T<sub>0</sub>). Secondary

measures will also be collected at T<sub>0</sub> and at follow up (T<sub>1</sub>) to assess participants' current priorities for the intervention, services accessed, and perspectives on service provision. Some measures will serve the dual purpose of measuring preliminary efficacy of the intervention (Table 2).

**Table 2.** Secondary preliminary efficacy measures.

Measure	Areas assessed and assessment duration	Psychometric properties and time points for measurement
Vineland Adaptive Behavior Scales 3 (VABS 3) [41]	Adaptive behavior and general functioning: child; 20 to 60 minutes	Validity and reliability established in children with developmental disabilities or ASD <sup>a</sup> [42]. To be administered at T <sub>0</sub> <sup>b</sup> and T <sub>1</sub> <sup>c</sup>
Social Responsiveness Scale (SRS) [43]	Child's social communication skills and ASD symptoms; 20 minutes (for children older than 2.5 years)	Reliability and validity established internationally [44,45]; good construct validity and internal consistency found. To be administered at T <sub>0</sub> and T <sub>1</sub>
Parenting Stress Index (Short) [46]	Caregiver stress as it relates to the child with presenting difficulties; 10 minutes	Well-established psychometric properties in various populations, including high-risk mothers and infants [47], and parents of toddlers in low-income areas [48]. To be administered at T <sub>0</sub> and T <sub>1</sub>
Beach Centre Family Quality of Life Scale [49]	Family quality of life; 5 minutes	Reliability and validity established in families of children with disabilities [50]. To be administered at T <sub>0</sub> and T <sub>1</sub>
Parent and Child History Questionnaire (self-designed)	Parent and child history; 10 minutes	Administered at baseline (T <sub>0</sub> ) with questions regarding current services accessed. To be administered at T <sub>0</sub> and T <sub>1</sub>

<sup>a</sup>ASD: autism spectrum disorder.

<sup>b</sup>T<sub>0</sub>: baseline.

<sup>c</sup>T<sub>1</sub>: follow up.

## Data Collection

All written forms completed by study participants, standardized and nonstandardized, will be explained in full to each participant prior to completion at  $T_0$  and  $T_1$ . They will be checked for accuracy and completeness, with any issues that emerge clarified, and managed by the principal investigator. Data collection during intervention sessions will be via direct audio recording using a dictaphone or equivalent recording device, or video recording.

In addition to source data collected at the first and last study visit, data will be collected directly from assessment teams regarding the diagnostic assessment, following signed permission from the study participant. Diagnostic assessment information will include clinical report and chart reviews, and are included in [Figure 1](#) as  $T_2$ .

Electronic study records will be stored on a password-protected, reidentifiable database in REDcap [51], backed up on a secure server. Paper records will be securely stored as per the study's ethics approval process.

## Sample Size

A pragmatic sample size of 18-24 families is sought to allow for 6-8 participants randomized to each intervention arm. These numbers are in line with similar pilot and feasibility studies in relation to coaching, including those delivered via videoconference or telehealth [25,52]. Based on clinical and research expertise across the team, this number was considered to be sufficient to inform protocol planning related to a future RCT, and to satisfactorily meet the requirements for obtaining all research aims. With a sample size of 24, we will be able to predict a participation rate of 20% to within a 95% CI of 16% [53].

## Randomization and Blinding

### Sequence Generation

Following initial recruitment actions carried out by the clinical service coordinator, the study's principal investigator will complete the consenting process described above for arm allocation. Participant dyads or triads will then be randomly allocated to an intervention arm A, B, or C, where arm A is usual care, arm B is face-to-face coaching, and arm C is coaching via videoconference ([Figure 1](#)). Randomization will occur using a random allocation sequence generated in Microsoft Excel for each reidentifiable participant number, allocated per participant dyad or triad at study enrollment. The sequence will be executed by a blinded research team member who is not directly involved in screening or intervention provision.

### Allocation Concealment Mechanism

Randomization and study arm allocation will occur prior to baseline measure commencement, and communicated via email or telephone to the participant and principal investigator (who is also the intervention provider) at the conclusion of baseline measure completion. It is not possible to conceal allocation to either party thereafter given that both the intervention provider and participant groups will be aware of either the absence or

mode of intervention delivery. Follow-up ( $T_1$ ) measures will be completed by the principal investigator.

## Statistical Methods

### Data Analysis

For the purpose of primary feasibility-related analyses, quantitative data will be analyzed with qualitative analyses relating to individual sessions and therapeutic progress conducted separately. Data analysis will occur according to the data measurement plan described above in [Table 1](#) and [Table 2](#). Descriptive statistics will be used to describe the sample characteristics of parents and children. Recruitment rates will be reported, and retention rates will be evaluated against a predicted rate of 70%-80% in each intervention arm [54]. Goal attainment, measured by performance and satisfaction ratings using the COPM, will provide preliminary evidence for efficacy within the intervention arms. An increase of 2 or more points on a 10-point performance and satisfaction scale in the COPM is considered clinically significant [55].

### Power

Data gathered from this feasibility study will be used to calculate recruitment and retention rates. Primary and secondary outcome measure data will be used to inform future power calculations, which are required to estimate appropriate recruitment numbers for a fully powered RCT aimed at gathering efficacy data.

## Ethics Approval and Consent to Participate

All study attributes will be carried out in line with the National Health and Medical Research Council Act 1992, and following approval from the RCH Human Research Ethics Committee. Ethical approval was granted by The RCH Research Ethics and Governance Department in September 2018 (HREC 38154A), spanning all elements detailed in this protocol to take place across the campus organizations of The University of Melbourne, The Murdoch Children's Research Institute, and the RCH, Melbourne. Only families who provide explicit consent to participate with a signed consent form will be eligible for this study.

## Results

The trial has concluded recruiting families of children referred for an ASD assessment throughout 2019. It remains under ethical approval and will continue throughout 2020. As of October 2020, 16 families have been recruited to the study.

Results will be reported according to CONSORT guidance [56] following the conclusion of this study. Feasibility findings as described above will be reported as primary outcomes. Preliminary efficacy findings will be reported as primary and secondary outcomes, as described in [Tables 1](#) and [2](#).

## Discussion

To our knowledge, this is the first study measuring the feasibility of OPC via two different parallel modalities for families awaiting ASD assessment. Given the lag time between identification of concerns and assessment that many families



experience, identification of an intervention that addresses primary family concerns in this interim period is warranted

Uncertainty exists in relation to optimal feasibility study methodology when testing new interventions or existing treatments for alternative populations. In recent years, efforts have been made to make recommendations regarding pilot and feasibility studies; however, there remains no consistent approach as to how such studies should be conducted and measured [34,54]. As such, we have incorporated a diverse range of feasibility constructs and outcomes to ensure comprehensive evaluation that can inform future trial planning.

Additional strengths of this study include broad participant inclusion, consideration of alternative modes of service delivery in comparison with usual care, and incorporation of fidelity measures. Exclusion criteria have been kept to a minimum to allow the research team to have a broad sense of the nature of families who are interested in, and able to complete, the intervention. In particular, the availability of an interpreter service is aimed at encouraging participation of families for whom English is their second language. Moreover, the study will measure the feasibility of two different modes of service delivery in comparison with usual care, and explore the tolerance of randomization to these study arms. Finally, the fidelity of the intervention will be measured using a published tool as described previously [37].

In spite of these strengths, there are several limitations to consider during interpretation of the feasibility results. In line with suggested general pilot and feasibility methodologies, the sample size will be smaller than that used in full-scale clinical trials or efficacy studies. Preliminary efficacy findings will only be used as an aid to plan for a future RCT. Nevertheless, the planned sample size is consistent with similar studies that have focused on coaching, telehealth, or videoconference

interventions [25,52], and is appropriate to address the research aims.

Although a broad participant recruitment strategy has been formulated, occurring across two sites, data collection and face-to-face coaching sessions will be carried out at only one site (RCH). This may prove to be a limitation in either recruitment or retention. Additionally, given that these sites offer publicly funded services, the participant sample has the potential to be biased, likely excluding families for whom a prompt, private service for assessment was accessible. Such predictions are in line with previous research in publicly funded developmental assessment services in Australia [57], in which the researchers found that families accessing such services were more likely to have a lower sociodemographic status or have English as a second language when compared to the general population. Given our plan to include families who may require interpreting services, translation and tool validation-related issues will mean that the secondary feasibility measures will need to be interpreted with caution. A future RCT will likely require coaching to be delivered at multiple sites to maximize the recruitment and generalizability of results.

Finally, all families who are participating in the study, regardless of study arm allocation, will continue to receive usual care. This is likely to be highly variable given that service access depends on family resources, geographical location, and other factors not yet known to the research team. Usual care will be described and considered in relation to relevant findings.

This study is the first step toward addressing an evidence gap by exploring potential interventions that can support families when on an ASD assessment waiting list. Findings of this study could inform the best care for families and children on waiting lists for other presentations, catering to an ongoing issue in health systems internationally.

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## Acknowledgments

The research team would like to acknowledge the generous contribution of Sue and Leigh Clifford, whose funding through the Clifford Scholarship has enabled this research to take place within allocated time frames and at no cost to families. We would also like to acknowledge the support of the Department of Paediatrics at the University of Melbourne, the Murdoch Children's Research Institute, and The Royal Children's Hospital, particularly the Allied Health Department. Most importantly, we are grateful to the families who have donated their time to the project to date. This project has been funded through the Melbourne Research Scholarship, The Clifford Family Scholarship, and the Developmental Disabilities and Rehabilitation Research Top-up Scholarship.

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## Authors' Contributions

All authors contributed to the study design and manuscript revisions, following primary contributions by CB, TM, and KW. All authors read and approved the final manuscript. The corresponding author can provide further study details upon request.

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## Conflicts of Interest

None declared.

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Multimedia Appendix 1

CONSORT 2010 checklist.

[PDF File (Adobe PDF File), 279 KB - [resprot\\_v10i1e20011\\_app1.pdf](#) ]

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## Abbreviations

**ASD:** autism spectrum disorder

**CONSORT:** Consolidated Standards of Reporting Trials

**COPM:** Canadian Occupational Performance Measure

**OPC:** Occupational Performance Coaching

**RCH:** The Royal Children's Hospital, Melbourne, Australia

**RCT:** randomized controlled trial

*Edited by G Eysenbach; submitted 09.05.20; peer-reviewed by L Oppenheimer, S Fazio; comments to author 21.08.20; revised version received 14.10.20; accepted 03.11.20; published 07.01.21.*

*Please cite as:*

*Bernie C, Williams K, Graham F, May T*

*Coaching While Waiting for Autism Spectrum Disorder Assessment: Protocol of a Pilot Feasibility Study for a Randomized Controlled Trial on Occupational Performance Coaching and Service Navigation Support*

*JMIR Res Protoc* 2021;10(1):e20011

URL: <https://www.researchprotocols.org/2021/1/e20011>

doi: [10.2196/20011](https://doi.org/10.2196/20011)

PMID: [33410761](https://pubmed.ncbi.nlm.nih.gov/33410761/)

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Protocol

# Assessing the Effectiveness and Acceptability of a Personalized Mobile Phone App in Improving Adherence to Oral Hygiene Advice in Orthodontic Patients: Protocol for a Feasibility Study and a Randomized Controlled Trial

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## Abstract

**Background:** Orthodontic treatment is a common health care intervention; treatment duration can be lengthy (2-3 years on average), and adherence to treatment advice is therefore essential for successful outcomes. It has been reported that up to 43% of patients fail to complete treatment, and there are currently no useful predictors of noncompletion. Given that the National Health Service England annual expenditure on primary-care orthodontic treatment is in excess of £200 million (US \$267 million), noncompletion of treatment represents a significant inefficient use of public resources. Improving adherence to treatment is therefore essential. This necessitates behavior change, and interventions that improve adherence and are designed to elicit behavioral change must address an individual's capability, opportunity, and motivation. Mobile phones are potentially an invaluable tool in this regard, as they are readily available and can be used in a number of ways to address an individual's capability, opportunity, and motivation.

**Objective:** This study will assess the effectiveness and acceptability of a personalized mobile phone app in improving adherence to orthodontic treatment advice by way of a randomized controlled trial.

**Methods:** This study will be conducted in 2 phases at the Eastman Dental Hospital, University College London Hospitals Foundation Trust. Phase 1 is feasibility testing of the My Braces app. Participants will be asked to complete the user version of the Mobile Application Rating Scale. The app will be amended following analysis of the responses, if appropriate. Phase 2 is a randomized controlled trial to test the effectiveness and acceptability of the My Braces app.

**Results:** This study was approved by the London – Bloomsbury Research Ethics Committee on November 5, 2019 (reference 19/LO/1555). No patients have been recruited to date. The anticipated start date for recruitment to phase 1 is October 2020.

**Conclusions:** Given the availability, affordability, and versatility of mobile phones, it is proposed that they will aid in improving adherence to treatment advice and hence improve treatment completion rates. If effective, the applicability of this methodology to developing behavior change/modification interventions and improving adherence to treatment across health care provides an exciting opportunity.

**Trial Registration:** ClinicalTrials.gov NCT04184739; <https://clinicaltrials.gov/ct2/show/NCT04184739>

**International Registered Report Identifier (IRRID):** PRR1-10.2196/18021

(*JMIR Res Protoc* 2021;10(1):e18021) doi:[10.2196/18021](https://doi.org/10.2196/18021)

**KEYWORDS**

orthodontics; adherence; smartphone apps; mobile phone apps; personalized health care; information provision

## Introduction

### Overview

Orthodontic treatment is a common health care intervention; the most recent National Child Dental Health Survey (England, Wales, and Northern Ireland) indicated that 9% of 12-year-old children are receiving orthodontic treatment, and a further 37% have an unmet need [1]. Treatment duration can be lengthy (2-3 years on average), and adherence to treatment advice is therefore essential for successful outcomes [2]. Failure to adhere to treatment advice can mean that treatment objectives are not met, and there may be detrimental effects on dental health. For example, failing to adhere to dietary advice may result in breakage of the braces and increased overall treatment time, and nonadherence to dietary and oral hygiene advice during treatment can lead to avoidable tooth decay and gum disease.

The National Health Service (NHS) experiences significant costs as a result of nonadherence to treatment [3], and orthodontics is no exception to this. One multicenter study found that 43% of patients failed to complete treatment, and there were no useful predictors for this [4]. To put this into perspective, the NHS England annual expenditure on primary-care orthodontic treatment alone is in excess of £200 million (US \$267 million) [5]; noncompletion of treatment therefore represents a significant inefficient use of public resources.

Improving adherence is complex and necessitates a change or modification of existing behavior. A contemporary and widely accepted framework based on multiple models of behavior change developed by Michie et al [6] is the behavior change wheel (BCW). The COM-B model forms the core of the BCW and proposes that individuals need capability (C), opportunity (O), and motivation (M) to perform or adapt a particular behavior (B).

Attempts to improve adherence to treatment advice in orthodontics have included utilizing mind maps and multimedia-assisted methods of providing information. Although these methods have been shown to significantly increase knowledge [7-9], this does not necessarily equate to better adherence to treatment advice or better outcomes [8]. A recent systematic review considered techniques including the use of motivational tests, the Hawthorne effect, and the use of awards and rewards, concluding that there is insufficient evidence to recommend a single method to improve patient adherence to treatment and that more research is required in this area [10].

Mobile phones are potentially an invaluable tool in improving adherence; they are capable of delivering both generic and personalized treatment information (for example, appointment and toothbrushing reminders) in a variety of formats (eg, visual, text, video). Ultimately, several methods for improving adherence can be delivered with a single resource. In orthodontics, mobile phones could serve to improve adherence to treatment advice, in particular adherence to oral hygiene

advice, as this has been shown to be problematic in orthodontic patients. Previous research has highlighted that plaque levels in patients with fixed orthodontic appliances are 2 to 3 times higher than plaque levels in nonorthodontic patients [11]; it is crucial to optimize oral hygiene as poor oral hygiene can result in gingivitis and demineralization.

In 2019, a paper summarizing the availability of orthodontic-related apps found that 305 apps were available on the Apple App Store and Google Play Store in the United Kingdom [12]. However, to date there are very few studies assessing the effectiveness of apps for orthodontic patients. A recent systematic review that aimed to assess the effectiveness of interventions delivered by mobile phones (including apps) in improving adherence to oral hygiene advice for children and adolescents concluded that mobile phones were found to be effective [13]. However, the generalizability of these results is limited due to the small number of trials included (n=2) and the unclear risk of bias of the included studies [13]. Additionally, none of the included studies assessed the effectiveness of personalized information provision, despite evidence that personalized communication in health care is more effective than nonpersonalized communication in relation to changing health-related behaviors [14]. More recently, a pilot study demonstrated the potential effectiveness of a chat room via a mobile phone app in improving appointment attendance and reducing relapse in patients wearing retaining braces [15]. Furthermore, a randomized controlled trial assessing the effectiveness of a personalized mobile phone app in supporting orthodontic patients during fixed appliance treatment demonstrated the potential for improvement in oral hygiene at 3 months into treatment, with the app group demonstrating a greater reduction in gingival bleeding and plaque scores [16].

To date, there have been no randomized controlled trials published in orthodontics assessing the effectiveness of behavior change interventions designed using the BCW. In light of this, an app called “My Braces”, which is grounded in behavior change theory, has been developed by the research team in order to provide generic and personalized orthodontic treatment information. The personalized element allows patients to input their own treatment information (including progress photographs), set goals, and develop plans for achieving these goals and provides the patient and clinicians with appropriate dashboards to monitor progress. Ultimately, this app aims to improve adherence to orthodontic treatment advice. For the purposes of this study, the My Braces app has been designed to allow three different levels of access and functionality:

Version 1 includes a toothbrushing timer only.

Version 2 includes a toothbrushing timer and generic treatment information (a combination of images and text).

Version 3 includes a toothbrushing timer; generic treatment information; access to input patient-specific personalized treatment information (including progress photographs), set goals, and develop plans for achieving these goals; and



appropriate dashboards for the patient and clinicians to monitor progress.

The longitudinal nature of orthodontic treatment makes this an ideal opportunity to assess the effectiveness of new ways to provide information in order to improve adherence to treatment advice. If found effective, the applicability of this methodology to improve adherence across health care provides an exciting opportunity.

### **Aims**

This study will assess the quality, effectiveness, and acceptability of the My Braces app and test the following primary hypothesis:

Using the full functionality of the My Braces app improves adherence to oral hygiene advice in patients undertaking fixed brace treatment.

The secondary hypothesis is as follows:

Using the full functionality of the My Braces app improves adherence to orthodontic treatment advice (reduction in fixed appliance breakages, missed and rescheduled appointments, treatment duration, number of appointments, and enamel demineralization).

## **Methods**

This study will be conducted in 2 phases at the Eastman Dental Hospital (EDH), University College London Hospitals (UCLH) Foundation Trust, London, United Kingdom.

### **Consent Process**

A member of the direct care team (the clinician undertaking treatment) will ask eligible patients if they would be prepared to consider involvement in the study. Children younger than 16 years will only be approached if accompanied by a parent/legal guardian. All prospective participants will be provided with patient information leaflets and will be given ample opportunity to ask questions about the study before enrolling. Participants will be required to provide written informed consent to participate in the study. For participants younger than 16 years, parents/legal guardians will also be required to provide written informed consent for their child to participate in this study. Contact details for a designated member of the research team will be provided, and patients will be informed that they may withdraw from the study at any point if they wish to do so. If this happens and participants give a reason for doing so, that reason will be recorded. Withdrawing from the trial will not affect treatment in any way. Signed consent and assent for inclusion will be obtained by a member of the research team. All members of the team have undertaken training in research ethics, including completion of Good Clinical Practice in Secondary Care. Example consent forms can be obtained by contacting the corresponding author.

### **Phase 1**

Phase 1 is a feasibility study with a convenience sample of patients at different stages of treatment. The purpose of this phase is to assess whether the app is deemed to be of high quality by end users.

### **Inclusion Criteria**

The study will include patients already accepted for fixed orthodontic appliance treatment (“train track”-type braces) at the EDH. Patients at all stages of treatment will be recruited. Patients must also be 10-18 years of age (inclusive), be familiar with and have daily access to a smartphone or tablet, and be able to read and communicate in English, as the app is currently available only in English.

### **Exclusion Criteria**

Patients with severe hypodontia (developmental absence of teeth) and craniofacial/orthognathic patients will be excluded from this study. These patients require complex multidisciplinary treatment; the information needs for these patients are therefore different. Treatment involves input from specialties other than orthodontics, and this may therefore influence adherence to treatment advice.

Patients with communication difficulties (for example, severe autism or learning difficulties) will also be excluded from the study.

### **Recruitment**

A convenience sample will be recruited for phase 1. Patients meeting the inclusion criteria and willing to participate in the feasibility study will be enrolled. Patients at different stages of treatment will be recruited as follows: 20 patients who have been accepted for fixed orthodontic appliance treatment but who have not yet started treatment, 20 patients who are currently in fixed appliance treatment, and 20 patients who have completed treatment and are wearing retainers.

The reason for allocating patients in this manner is that the app is designed to support the whole treatment journey (before, during, and after active treatment). Recruiting patients at different stages of this journey therefore ensures that all relevant components of the app are experienced and assessed by an appropriate patient group.

### **Data Collection**

The app will be assessed by current orthodontic patients and tested for quality using the user version of the Mobile Application Rating Scale (uMARS) [17]. The uMARS is a reliable tool for assessing app quality and consists of sections relating to app engagement, functionality, aesthetics, and information [15]. The uMARS quality score can range from 1 (“Inadequate”) to 5 (“Excellent”). Additionally, there is a free text section for patients to provide comments.

It is estimated that the total duration of this phase for each participant will be around 8-12 weeks. Patients will be provided with access to the app and asked to complete the uMARS questionnaire prior to, or at, the next appointment. Patients will be prompted by the My Braces app to complete the uMARS form online using UCL Opinio. After this point, no further data will be collected.

The following baseline details will also be obtained: age, gender, and stage of treatment.

### Planned Analyses

The Kruskal-Wallis test will be used to compare the uMARS scores across the three groups and the scores across different sections of the uMARS form.

Any changes felt to be appropriate based on feedback from the uMARS questionnaire will be implemented in the app prior to using it in phase 2.

**Table 1.** Schedule of enrolment and assessments (groups A, B, and C will receive different versions of the intervention, the My Braces app).

Characteristic	Screening	Intervention phase		Final visit
	Visit 1	Visit 2	Visit 3	Visit 4
Visit timing	Baseline	3 months	12 months	End of treatment
Window of flexibility for timing of visits	N/A <sup>a</sup>	1 month	2 months	1 month
<b>Assessment</b>				
Informed consent	✓	N/A	N/A	N/A
Medical history	✓	✓	✓	✓
Eligibility confirmation	✓	✓	N/A	N/A
Taking photographs	✓	N/A	N/A	✓
Type of dental bite and whether teeth were removed	✓	N/A	N/A	N/A
Randomization	✓	N/A	N/A	N/A
Bleeding scores	✓	✓	✓	✓
Plaque scores	✓	✓	✓	✓
App subjective quality assessment	N/A	✓	N/A	✓
Adverse events review	✓	✓	✓	✓

<sup>a</sup>N/A: not applicable.

### Inclusion Criteria

The study will include patients who have been accepted for fixed orthodontic appliance treatment (“train track”-type braces) at the UCLH NHS Foundation Trust EDH but who have not yet commenced treatment. Patients must also be 10-18 years of age (inclusive) at the start of treatment, have a sufficient number of permanent teeth erupted to allow outcome assessment, be familiar with and have daily access to a smartphone or tablet, and be able to read and communicate in English.

### Exclusion Criteria

Patients with severe hypodontia (developmental absence of teeth) and craniofacial/orthognathic patients will be excluded from this study. These patients require complex multidisciplinary treatment; the information needs for these patients are therefore different, and treatment involves input from specialties other than orthodontics, and this may therefore influence adherence to treatment advice.

Patients with communication difficulties (for example, severe autism or learning difficulties) will also be excluded from the study.

Patients who are aware that a family member or friend is enrolled in the study (phase 1 or phase 2) will be excluded from the study because it is possible that these patients may become

## Phase 2

### Overview

Phase 2 is a randomized controlled trial. The purpose of this phase is to assess the effectiveness of the My Braces app in improving adherence to oral hygiene advice in orthodontic patients. [Table 1](#) is the schedule of enrolment and assessments.

aware of details of the app that may not be relevant to the group that they are randomized to.

### Recruitment

It is anticipated that recruitment will take approximately 18 months. Patients meeting the inclusion criteria and willing to participate in the trial will be randomized to one of the three study groups:

Group A will act as the control group and will be provided with standard treatment information (verbal and written) and access to the basic version 1 of the app with just a toothbrushing timer. The timer is necessary as the health behavior outcome is toothbrushing duration.

Group B will be provided with standard treatment information (verbal and written) and access to version 2 of the app, which has a toothbrushing timer and provides generic treatment information (a combination of images and text).

Group C will be provided with standard treatment information (verbal and written), and patients will have access to version 3 of the app; this group will have access to the full functionality of the app, which will allow patients to input their own personalized treatment information (including progress photographs), set goals, and develop plans for achieving these goals and will provide the patient and clinicians with appropriate dashboards to monitor progress.

It is important to include Group B, as this will allow the team to ascertain whether it is the personalization of the app content that confers any benefit over and above providing generic information via an app if a difference is found between Groups A and C.

### ***Randomization and Allocation Concealment***

Randomization will be undertaken using computer-generated random number sequences; block randomization (blocks of 6) will be used to help ensure balance in the allocation of participants to each arm of the trial. Sealed opaque envelopes will be used to ensure allocation concealment. This aspect of the study will be carried out by a member of the research team not involved in recruitment/data collection; this team member will also hold the randomization list and maintain a trial subject enrolment log.

### ***Data Collection***

A complete data set will be collected at baseline, 3 months into treatment, 12 months into treatment, and at the end of treatment when the orthodontic appliances have been removed.

Two primary outcome measures have been selected, a health behavior outcome and a clinical outcome, as both are felt to be important. The outcome measures are timed toothbrush use and gingival bleeding scores (these scores indicate the amount of bleeding from the gums, where bleeding is an indicator of inadequate toothbrushing).

The secondary outcomes of interest are as follows: plaque scores, which indicate the amount of plaque on the teeth, where retention of plaque is an indicator of inadequate toothbrushing; number of fixed appliance breakages; number of missed and rescheduled appointments; treatment duration, number of appointments (including emergency appointments for appliance breakages); enamel demineralization (early tooth decay) on the upper anterior six teeth (using standardized photographs), as demineralization is a further indicator of inadequate toothbrushing and nonadherence to the appropriate diet; subjective quality of the app (sections E and F of the uMARS questionnaire); and app engagement.

The following baseline measurements and details will be obtained prior to treatment commencing: age, gender, malocclusion (type of dental bite), whether or not extractions (removal of teeth) are required for treatment, clinical photographs of the teeth (these will be compared with completion of treatment photographs to assess for enamel demineralization), bleeding score, and plaque score.

### ***Methods of Outcome Assessment***

#### **Timed Toothbrush Use**

Timed toothbrush use will be determined via the information stored on the app. It is anticipated that participants will not remember to time every brushing episode; therefore, the duration and number of brushing sessions stored within the app will allow for the average brushing duration to be determined. The unit of measurement will be seconds.

#### **Gingival (Gum) Bleeding**

A periodontal probe (specialized probe to test gum health) will be used; the presence of bleeding within 10 to 30 seconds of probing is indicative of inflammation of the gingivae (gums). Scores will be recorded for all teeth anterior to the molars (incisors, canines, and premolars) and will be recorded as the percentage of the total number of tooth surfaces (6 surfaces per tooth). A binary score will be assigned to each surface (1 for bleeding present, 0 for no bleeding).

A calibration exercise will be conducted prior to commencing the study. The key factors affecting consistency of probing technique are probe position and pressure applied (ideally 20 to 25 grams). The bleeding assessment technique will therefore be reviewed and observed in a volunteer subject by a gold standard examiner following training performed on models. It is not possible to do duplicate bleeding assessments as the act of repeated probing can cause bleeding; therefore, it is essential that this aspect of the study is well controlled for.

#### **Plaque Scores**

Plaque scores will be recorded for all teeth anterior to the molars (incisors, canines, and premolars) as the percentage of total surfaces (6 surfaces per tooth). A plaque disclosing agent (a temporary dye that is retained on the plaque to make it visible) will be used for the plaque assessment. A binary score will be assigned to each surface (1 for plaque present, 0 for no plaque present) [18].

Prior to the initiation of the study, 10 non-study subjects with similar characteristics to those who will be included in the study will be recruited for an examiner calibration exercise. A request for volunteers will be made from current patients within the orthodontic department. The designated examiner (MOS) will measure full mouth plaque scores in the manner described for all 10. This will be repeated on the same day (at least 15 minutes apart to reduce memory bias); the examiner will evaluate the same subjects for a second time with no brushing undertaken in between. Subjects will be redisclosed for the second plaque scoring.

Intra-examiner repeatability for plaque measurement will then be assessed.

#### **Enamel Demineralization**

Before placing the orthodontic braces, teeth will be polished with a rubber cup and fluoride-free pumice paste and dried with air, and standardized digital photos will be taken under identical lighting conditions and with the same camera settings. These will be used to assess for enamel demineralization [19]. Three photographs will be obtained (front, right, and left with the teeth biting together) and stored securely.

At the end of treatment, the brace and the adhesive used to secure it to the teeth will be removed, and the teeth will be polished with a rubber cup and fluoride-free pumice paste and dried with air. A further series of standardized photographs will be obtained.

For the evaluation of demineralization, photographs will be assessed, and the severity of enamel demineralization will be recorded. The labial surfaces of the upper incisors and canines



will be scored as follows [20]: (1) no white spot formation, (2) slight white spot formation (thin rim), (3) excessive white spot formation (thicker bands), or (4) white spot formation with cavitation.

A random sample of photographs will be re-examined after 1 month to check reliability.

These photographs are an essential part of routine orthodontic records for all patients, and therefore no additional patient appointments or increase in appointment time will be needed.

### Other Outcomes

Information relating to treatment duration and the number of breakages (for example, detachment of the brace from the tooth, displacement of the brace wire), missed or rescheduled appointments, and emergency appointments will be obtained from the patient's medical records. Data relating to the subjective quality score for the app will be obtained by way of patient-completed paper questionnaires (sections E and F of the uMARS form). Furthermore, app engagement will be determined via the data available on Google's Firebase system.

### Blinding

The outcome assessor will be blinded; however, given the nature of the intervention, it is not possible to blind the patient.

### Sample Size

The following assumptions have been made in the sample size calculation:

Data are normally distributed and initial comparison of the 3 groups would use an analysis of variance (ANOVA), followed by 2-sample *t* tests for A versus B, B versus C, and A versus C if any statistical significance is found.

The significance level is  $P < .05$  with 80% power.

### Timed Toothbrush Use

Using a clinically relevant difference of 20 seconds between groups and a SD of 23.6 seconds from a paper by Tesini and

Perlman [21] (standardized difference=0.85) and accounting for multiple testing, 29 patients are required in each group ( $n=87$ ). Assuming a dropout of 20%, the sample size is 35 per group.

### Gingival Bleeding

An estimated clinically relevant difference of 15% and a SD of 20% (standardized difference=0.75) was used, based on advice from Dr Jeanie Suvan (clinical trials coordinator, Restorative Dental Sciences, UCL Eastman Dental Institute, Faculty of Medical Sciences, UCL), who has experience in commercial trials using these outcome measures. The same assumptions were followed as described above, and this indicated a sample size of 38 per group. With the 20% dropout factored in, the sample size calculation is 46 per group ( $n=138$ ).

Therefore, 138 patients will be recruited. There are a number of assumptions in these calculations; therefore, an internal pilot will be conducted, and the calculations will be repeated using 3-month data for the first 15 patients recruited to each group.

### Planned Analyses

Proposed outcome analyses are summarized in [Table 2](#).

For each of the main outcome measures, it is anticipated that regression analysis will be undertaken. The main factor of interest (group allocation) and confounding variables (eg, age, gender, ethnicity) will be entered into univariable regression analyses to determine the level of significance and to limit the number of variables entered into the multivariable analysis. Any factors with  $P \leq .10$  will be considered for inclusion in the multivariable analysis. Factors with  $P < .05$  in the multivariable analysis will be considered as having a significant effect on toothbrushing time or gingival bleeding. Secondary outcomes will be explored in a similar manner.

If necessary, an intention to treat analysis will be performed; all enrolled and randomized patients will be included in the analysis and analyzed in the groups to which they were randomized.

**Table 2.** A summary of proposed statistics for outcome analysis.

Outcomes	Method of analysis
Toothbrushing duration	Comparison of the 3 groups using an ANOVA, followed by 2-sample <i>t</i> tests (A vs B, B vs C, and A vs C) if any statistical significance is found
Bleeding score	Chi-square test
Plaque scores	Comparison of the 3 groups using an ANOVA, followed by 2-sample <i>t</i> tests (A vs B, B vs C, and A vs C) if any statistical significance is found
Number of breakages	Kruskal-Wallis test, followed by Mann-Whitney test (A vs B, B vs C, and A vs C) if any statistical significance is found
Number of missed appointments	Kruskal-Wallis test, followed by Mann-Whitney test (A vs B, B vs C, and A vs C) if any statistical significance is found
Total number of appointments	Kruskal-Wallis test, followed by Mann-Whitney test (A vs B, B vs C, and A vs C) if any statistical significance is found
Treatment duration	Comparison of the 3 groups using an ANOVA, followed by 2-sample <i>t</i> tests (A vs B, B vs C, and A vs C) if any statistical significance is found
Enamel demineralization	Chi-square test
App subjective quality	Comparison of the 3 groups and different section of the uMARS form by using the Kruskal-Wallis test.
App engagement	Comparison of the 3 groups using an ANOVA, followed by 2-sample <i>t</i> tests (A vs B, B vs C, and A vs C) if any statistical significance is found

### Data Handling and Confidentiality

For phase 1, all responses to the uMARS questionnaire will be received anonymously. For phase 2, the researchers will receive a complete list of the random user log-in codes (randomly generated using letters and numbers only) from the app developers; these log-in codes will divide participants into the three groups (A, B, and C). These codes will be used to randomly assign patients. Details relating to toothbrushing duration and app engagement will be logged against these codes; however, it will not be possible to identify individuals from these codes alone. A separate document linking the log-in codes to an individual's unique trial ID will be held on secure storage devices (mobile devices will have Advanced Encryption Standard 256-bit encryption, which has been made a security standard within the NHS). Only members of the research team or those regulatory bodies that are involved in monitoring research studies will have access to this data, and it will only be used for the purposes of analysis or if unblinding is required.

The app has been developed in such a manner that the researchers will not be able to access progress photographs (these will be stored on the patients' camera rolls), location data, other apps on the patients' mobile devices, or contacts.

### Study Monitoring

Given that there is no morbidity or mortality risk, an independent data monitoring committee will not be established. However, an interim data analysis will be conducted using 3-month data for the first 15 participants in each group, and the research team will meet to review these and take any action if necessary.

The research team will meet on a regular basis to ensure the research is progressing with no difficulties; this will include

reviewing of recruitment rates. It is intended that the Research Ethics Committee and study sponsor will be updated if a substantial amendment is made to the conduct of this research.

### Results

This study was approved by the London – Bloomsbury Research Ethics Committee on November 5, 2019 (reference 19/LO/1555). No patients have been recruited to date. The anticipated start date for recruitment is October 2020.

### Discussion

Improving adherence to treatment advice in orthodontics necessitates a change/modification of existing behaviors. High noncompletion rates [4] and poor plaque control among orthodontic patients [11] support the notion that nonadherence to treatment advice is a significant issue for orthodontic patients. Given the availability, affordability, and versatility of mobile phones, it is proposed that using this technology will aid in improving adherence to treatment advice and hence treatment completion. Furthermore, several methods for improving adherence could be delivered within a single app, and the experience can be made personal for each patient. In this study, the effectiveness of a personalized mobile phone app in improving adherence to orthodontic treatment advice will be investigated.

If effective, the applicability of this methodology to developing behavior change/modification interventions and improving adherence to treatment across health care provides an exciting opportunity.

## Acknowledgments

The authors wish to thank Dr Elinor Jones (senior teaching fellow, Statistical Science, UCL, London) and Dr Jeanie Suvan (clinical trials coordinator, Restorative Dental Sciences, UCL Eastman Dental Institute, Faculty of Medical Sciences, UCL, London), for their advice on the statistical aspects of this research and outcome measures, respectively.

MOS was awarded the Royal College of Surgeons of England Faculty of Dental Surgery 70th Anniversary Research Fellowship in 2017 and the Royal College of Surgeons of England Faculty of Dental Surgery Research Fellowship in 2019. This funding has supported the development of the My Braces app and will support the feasibility study and randomized controlled trial proposed in this protocol.

## Authors' Contributions

MOS, JTN, and SJC conceived the study, assisted in its design, and developed the original protocol.

## Conflicts of Interest

None declared.

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## Abbreviations

**ANOVA:** analysis of variance

**BCW:** behavior change wheel

**EDH:** Eastman Dental Hospital

**NHS:** National Health Service

**SPIRIT:** Standard Protocol Items: Recommendations for Interventional Trials

**UCLH:** University College London Hospitals

**uMARS:** user version of the Mobile Application Rating Scale

*Edited by G Eysenbach; submitted 29.01.20; peer-reviewed by F Zotti, G Capocasale; comments to author 06.04.20; revised version received 17.08.20; accepted 04.09.20; published 13.01.21.*

*Please cite as:*

*Sharif MO, Newton JT, Cunningham SJ*

*Assessing the Effectiveness and Acceptability of a Personalized Mobile Phone App in Improving Adherence to Oral Hygiene Advice in Orthodontic Patients: Protocol for a Feasibility Study and a Randomized Controlled Trial*

*JMIR Res Protoc* 2021;10(1):e18021

URL: <http://www.researchprotocols.org/2021/1/e18021/>

doi: [10.2196/18021](https://doi.org/10.2196/18021)

PMID: [33439142](https://pubmed.ncbi.nlm.nih.gov/33439142/)

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Protocol

# A Text Messaging Intervention for Coping With Social Distancing During COVID-19 (StayWell at Home): Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Social distancing is a crucial intervention to slow down person-to-person transmission of COVID-19. However, social distancing has negative consequences, including increases in depression and anxiety. Digital interventions, such as text messaging, can provide accessible support on a population-wide scale. We developed text messages in English and Spanish to help individuals manage their depressive mood and anxiety during the COVID-19 pandemic.

**Objective:** In a two-arm randomized controlled trial, we aim to examine the effect of our 60-day text messaging intervention. Additionally, we aim to assess whether the use of machine learning to adapt the messaging frequency and content improves the effectiveness of the intervention. Finally, we will examine the differences in daily mood ratings between the message categories and time windows.

**Methods:** The messages were designed within two different categories: behavioral activation and coping skills. Participants will be randomized into (1) a random messaging arm, where message category and timing will be chosen with equal probabilities, and (2) a reinforcement learning arm, with a learned decision mechanism for choosing the messages. Participants in both arms will receive one message per day within three different time windows and will be asked to provide their mood rating 3 hours later. We will compare self-reported daily mood ratings; self-reported depression, using the 8-item Patient Health Questionnaire; and self-reported anxiety, using the 7-item Generalized Anxiety Disorder scale at baseline and at intervention completion.

**Results:** The Committee for the Protection of Human Subjects at the University of California Berkeley approved this study in April 2020 (No. 2020-04-13162). Data collection began in April 2020 and will run to April 2021. As of August 24, 2020, we have enrolled 229 participants. We plan to submit manuscripts describing the main results of the trial and results from the microrandomized trial for publication in peer-reviewed journals and for presentations at national and international scientific meetings.



**Conclusions:** Results will contribute to our knowledge of effective psychological tools to alleviate the negative effects of social distancing and the benefit of using machine learning to personalize digital mental health interventions.

**Trial Registration:** ClinicalTrials.gov NCT04473599; <https://clinicaltrials.gov/ct2/show/NCT04473599>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/23592

(*JMIR Res Protoc* 2021;10(1):e23592) doi:[10.2196/23592](https://doi.org/10.2196/23592)

## KEYWORDS

COVID-19; mental health; depression; reinforcement learning; microrandomized trial

## Introduction

### Background

The current COVID-19 pandemic not only poses a large threat to physical health but also has detrimental consequences for mental health. Social distancing is a crucial intervention to slow down person-to-person transmission of this infectious disease. However, culminating research shows that it also has unintended consequences for large groups of the population: increased anxiety, depression, and stress [1,2]; decreased physical activity [3,4]; and lower sleep quality [5]. In the United States, vulnerable populations from low-income backgrounds, people of color, and Spanish speakers are more likely to work in jobs where they are at higher risk of contracting COVID-19 [6]. In part because of this, these groups experience disproportionately worse mental health outcomes [6,7].

The current situation calls for new and innovative digital methods to reach vulnerable populations [8]. Text-messaging interventions, which can be implemented during social distancing, have previously demonstrated effectiveness in behavioral health promotion and disease management [9]. They are also suitable for low-digital literacy populations and underserved groups [10]. For instance, our own Health Insurance Portability and Accountability Act (HIPAA)-approved texting platform, HealthySMS, has shown high acceptability and engagement among low-income English and Spanish speakers in California [11-13].

We developed text messages based on cognitive behavioral therapy to help people cope with the stress and anxiety of COVID-19 social distancing. Messages are developed within two different categories: behavioral activation (BA) [14] and other skills, more typical of psychoeducation for improving mood [15]. BA messages include prompts to increase BA and decrease avoidance of anxiety-inducing situations. Other skills focused on changing thinking patterns and tips about sleep, self-care, and breathing exercises; see examples of messages in Table 1. We will distribute this text messaging system to a wide group of individuals in the United States via social media advertisements. Further, we designed these messages both in English and in Spanish, enabling the program to reach a diverse group of people. Mobile health interventions are less often designed for Spanish speakers.

### Objective

The main purpose of this study, which is called the StayWell at Home study, is to examine whether automated text messages will improve depression and anxiety symptoms and enhance

positive mood. Additionally, we will compare the effectiveness of sending messages on a random schedule using a microrandomized trial (MRT) design [16], further referred to as *uniform random* (UR), or sending messages via a *reinforcement learning* (RL) algorithm on the overall change in depression and anxiety symptoms and daily mood during the 60-day study. Finally, within the microrandomized group, we will examine which types of text messages are more effective in helping people increase their positive mood. We will examine the hypotheses discussed in the following two sections.

### Primary Analysis

We hypothesize that participants will show improvements in depression symptoms, measured using the 8-item Patient Health Questionnaire (PHQ-8); anxiety symptoms, measured using the 7-item Generalized Anxiety Disorder (GAD-7) scale; and daily mood during the 60-day study. We will conduct a pre-post comparison among all participants.

We hypothesize that the participants in the group receiving RL will have a greater decrease in depressive symptoms and anxiety and a greater daily increase in mood ratings during the 60-day study than participants in the UR group (ie, randomized design).

### Secondary Analysis

We hypothesize that we will find differential effects on mood ratings for the two categories of messages and different timings (ie, microrandomized design).

## Methods

### Design

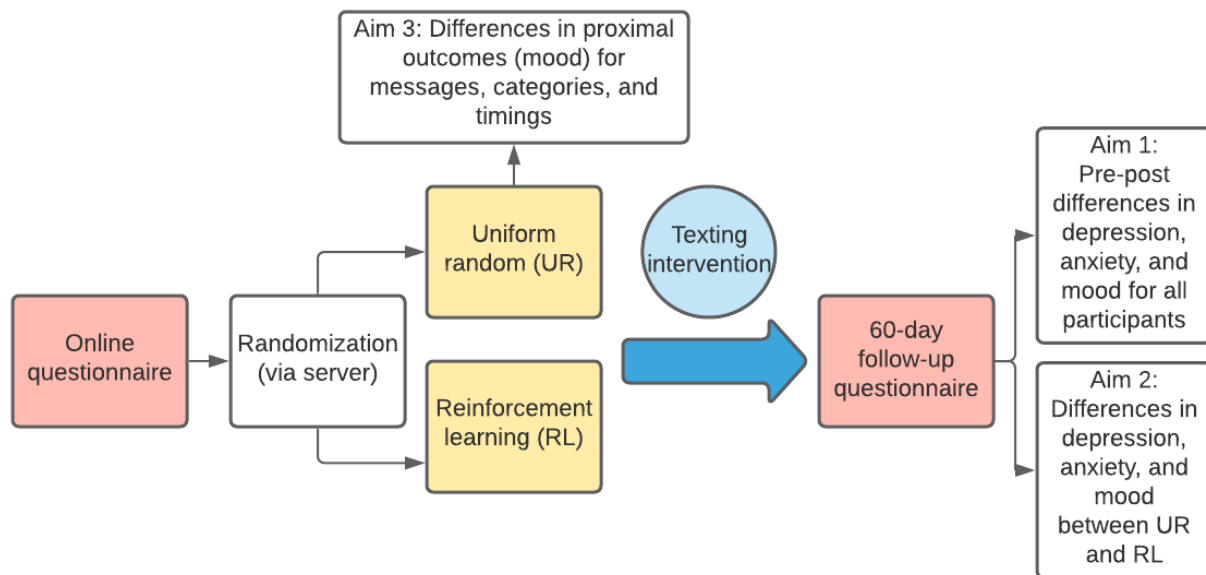
This study has various designs: (1) a pre-post comparison, in which we assess changes in depression and anxiety for all patients before and after the intervention; (2) a randomized controlled trial with two groups, RL and UR; and (3) an MRT, only within the UR group.

Randomization will be performed as block randomization with a 1:1 allocation. Participants will be automatically randomized into groups through our secure server during onboarding of the study, ensuring allocation concealment. Participants will be informed of the nature and frequency of the messages they will be receiving. They will be blinded to their group randomization. Further, if messages are not sent out appropriately, research assistants will contact the developer to address errors (eg, when individuals do not receive messages, or they receive messages out of the specific time bounds). Throughout the study, the researchers will check whether the randomization of messages is functioning adequately approximately once every two months.

The necessity of these steps makes it infeasible to blind the researchers. Microrandomization will happen automatically on a daily basis through our secure server. We used the SPIRIT

(Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing this protocol [17]. Figure 1 shows our study design.

**Figure 1.** StayWell at Home study design.



## Recruitment

This is a fully remote trial. We will recruit on social media platforms, such as Facebook, Twitter, and Craigslist, and through university websites (ie, University of California [UC] Berkeley and UC San Francisco). Our posts and ads will be designed by the research team to target low-income, vulnerable populations across the United States. We will utilize the *detailed targeting* feature on Facebook to select the group of people to whom we want to show our ads. We will recruit in both English and Spanish.

The Facebook posts and ads will be informed by user-centered design (UCD) methods, including implementation of user personas in recruitment efforts. User personas, a common UCD tool [18], consist of fictional characters that represent our target populations. The user personas will include English speakers and Spanish speakers of various demographic groups. Each ad will contain a title and picture, followed by a reason for participating in the study and enrollment details. We will rely on Facebook's built-in algorithms to present the most relevant ad version to each viewer.

## Inclusion Criteria

We will include adults 18 years or over who have a functioning mobile phone and who speak English and/or Spanish. We will

exclude participants who use an online text messaging app, as this is more prone to online scams and fraud (eg, individuals creating fake accounts to receive reimbursements). Through targeted ads, we will make concerted efforts to recruit vulnerable populations, such as low-income individuals and people of color, who are disproportionately impacted by COVID-19 in the United States.

## Measures

For our primary outcomes, we will administer a survey at baseline and at 60-day follow-up, which includes the PHQ-8 [19] and GAD-7 [20]. In addition to these questionnaires, we will also ask open-ended questions to assess how participants are impacted by COVID-19. Questionnaire data will be stored on UC Berkeley's Qualtrics platform. Our secondary outcome, daily mood ratings, will be collected via text message on a daily basis and stored on the HealthySMS platform. The project coordinator and research assistants will be responsible for managing patient data collection. Once data from all participants are collected, they will be stored on UC Berkeley's Secure Box, a secure cloud-hosted platform. See Table 1 [21,22] for all included questionnaires and timing of their administration.

**Table 1.** Questionnaires included in the StayWell at Home study and timing of administration.

Questionnaire <sup>a</sup>	Baseline	Follow-up
PHQ-8 (8-item Patient Health Questionnaire) <sup>b</sup>	X <sup>c</sup>	X
GAD-7 (7-item Generalized Anxiety Disorder) scale <sup>b</sup>	X	X
COVID-19 questions	X	X
System Usability Scale <sup>d</sup>	N/A <sup>e</sup>	X

<sup>a</sup>The measures were taken from validated questionnaires in English and Spanish.

<sup>b</sup>The PHQ-8 depression scale and the GAD-7 anxiety scale were not modified.

<sup>c</sup>X indicates that the measure was administered at this time point.

<sup>d</sup>The System Usability Scale [21] was modified to decrease literacy levels, using the Flesch-Kincaid readability test [22].

<sup>e</sup>N/A: not applicable; the measure was not administered at this time point.

## Procedure

### Baseline Assessment

Interested subjects will be sent to the designated Qualtrics platform to verify that their mobile phone number and ZIP Code are based in the United States. We will also determine human identity using a built-in CAPTCHA.

The project coordinator and/or research assistants will email each subject a one-time use personalized link. Subjects will click on the designated link taking them to a Qualtrics questionnaire. Here, they will give their informed consent and indicate whether they are over 18 years old. Thereafter, we will collect all baseline survey measures of interest as well as patient demographics. Upon survey completion, participants will be automatically enrolled onto the text messaging platform.

## Intervention

### Text Messages

We will send participants supportive text messages for a period of 60 days. These text messages include tips about BA and other coping skills to deal with worries and stress. The text messages used in this effort were based on core principles of evidence-based interventions for depression and anxiety and focus on rapid adoption of new behavior change strategies. Messages are balanced so that half the messages are related to BA and half are framed around other skills (see Table 2). Participants will receive one of these messages within three different time windows per day, between 9 AM and 6 PM. Participants will be sent a message asking them to rate their mood on a scale of 1 to 9, with 9 being the best mood, 3 hours after receiving the BA or skills message. These text messages were based on previous work conducted by SD and AA [23,24] and were edited by the study team members. Examples of BA and skill-based text messages are shown in Table 2.

**Table 2.** Examples of StayWell at Home text messages.

Message category	Example text messages
Behavioral activation	“Make a list of people that make you happy. Commit to reaching out to at least one of them each day this week.” “If there is something you have always wanted to do, like learning to play the guitar or painting, try a YouTube video today for learning a new skill.”
Other skills and coping	“Ugh. Sheltering in place is hard. Take some time to feel angry or sad or whatever you are feeling.” “If you are feeling a bit more sad or stressed right now, you are not alone. This is a hard time, but you can do this!”

## Messaging Platform

We will use a text messaging platform, HealthySMS, developed by AA, to send text messages and manage participant responses back to our system. HealthySMS has been successfully used with various low-income, adult populations in English and Spanish [11-13].

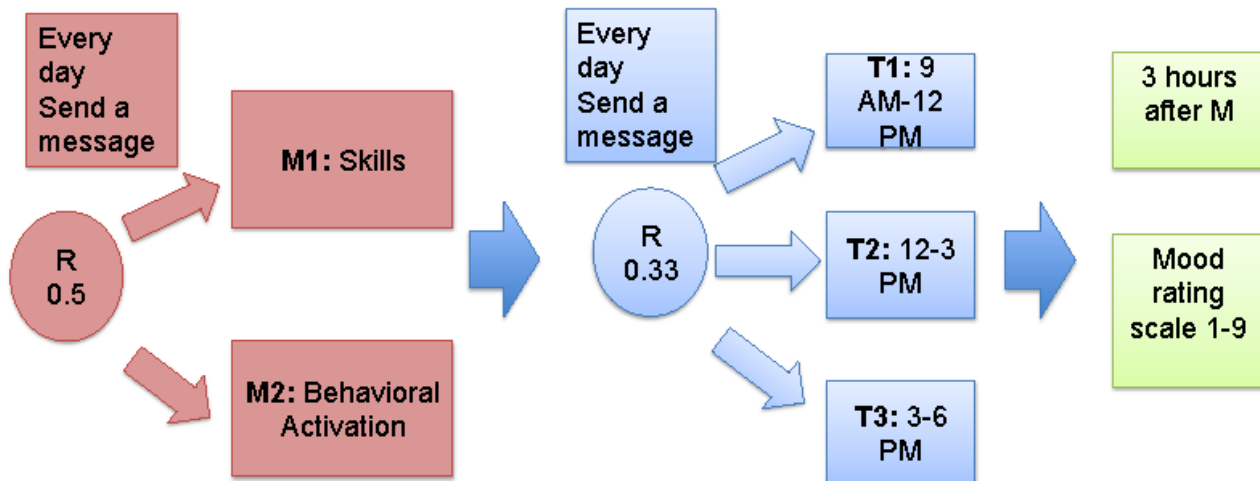
### Uniform Random Policy

This study design is an MRT [16], where every day during the study treatment, allocation is characterized by a full factorial design with a total of two factors representing supportive *messages* and the *time frame* when the message was sent. The *messages* factor has two levels, and the *time frame* factor has three levels (ie, 9 AM-12 PM, 12 PM-3 PM, and 3 PM-6 PM).

Each participant will be rerandomized to a new combination of *messages* and *time frame* every day. The study is set up so that each day participants will be randomized to receive one message out of the message categories (ie, BA vs other skills), constituting a multilevel MRT design with probabilities of 0.5 for the message categories and 0.33 for the timing. Thus, every participant will receive one BA or skill message per day and one mood check-in message.

This design allows us to understand the type and timings of text messages that most improve participants' mood, which is a secondary aim of this study. MRTs enable the testing of specific intervention components, while still allowing for the evaluation of a causal, average treatment effect of the intervention [16]. Figure 2 shows our MRT design.

**Figure 2.** Microrandomized trial design of the StayWell at Home study. M: message; T: time point.



### Reinforcement Learning Policy

We employ a learned decision mechanism for the timing and type of text message. The RL algorithm learns from previous data to maximize an increase in participants' mood using a linear regression model that is updated every morning, comparable to previous work in mobile health [25]. The learning data include which message category was previously sent and at what time, days since messages were sent, participants' mood after the messages, and the day of the week (ie, Monday-Sunday). We employ two different learned decision mechanisms—one for the type of message and one for the timing of the message—using two separate linear regression models.

Both groups (ie, UR and RL) will receive the same messages. However, for the UR group, the type and timing of text messages will be randomly selected, whereas for the RL group, they will be selected by a learning algorithm. We will compare the effect of sending text messages by a random schedule with sending text messages chosen by the RL algorithm. This allows us to assess whether using RL to adapt the messaging scheme is more effective than a random messaging schedule. Additionally, we will be able to evaluate the effect of the individual intervention components over time, within an MRT design.

Participants in both groups can reply “STOP” or “PARAR” if they wish to stop receiving messages at any time during the study within 60 days.

### Statistical Analysis Plan

#### Primary Analysis

Paired *t* tests will be used to detect the improvement in depression score (ie, PHQ-8) and anxiety score (ie, GAD-7) from baseline to follow-up measured 60 days later. Two-sample *t* tests will be used to examine the difference in improvements between the UR and RL groups. The mood ratings of each participant will be collected each day over the 60-day study period. We will also compare the average of daily mood rating improvements compared to baseline (ie, each consecutive daily measure minus the baseline measure) between these two groups using a longitudinal data analysis approach (eg, generalized estimating equation [GEE]). We will not compare the baseline characteristics between the samples in each arm. This practice

could potentially be misleading because any differences would be due to chance [26-28].

#### Secondary Analysis

For the UR intervention group, the differences in proximal outcome (ie, daily mood rating assessed 3 hours after the message sent) between both message categories (ie, BA versus coping skills) or among the time windows (ie, reference level versus the other three levels) will be examined using the weighted and centered least-squares (WCLS) method for longitudinal data analysis under the multilevel MRT design proposed by Xu et al [24]. This method is similar to the GEE approach. The independent working correlation matrix will be adopted. The covariates include days in study (ie, from 1 to 60 days), day of the week (ie, Monday-Sunday), intervention component (ie, message or time window), and the interaction term between days and intervention component. The trend of the intervention effect over days can be constant, linear, or quadratic. The message or the time window component categories will be converted to dummy variables, and each of these will be centered by the corresponding randomization probabilities (ie, 0.5 and 0.33 for each level of the message and time components, respectively).

The mood rating changes from baseline will be categorized into binary outcomes (ie, high [greater or equal to the median of the whole sample] or low [less than the median]). The WCLS estimator under the MRT design for binary outcome proposed by Qian et al [29] can be applied to the message component (ie, two-level intervention). For the timing (ie, three-level) component, we will propose the novel WCLS method by combining the ideas of both Xu et al [24] and Qian et al [29]. This method can also be extended to model the mood ratings as ordinal outcome variables.

#### Sensitivity Analysis

The following sensitivity analyses will be or can be performed:

1. Both the primary and secondary analyses will be repeated based on the participants with at least 45 out of 60 (75%) days of data.



2. The change of the secondary outcome will be imputed using the last-observation-carried-forward method if either the corresponding pretest or posttest value is missing.
3. We will conduct the secondary analyses—the effects of message categories and timings—in the RL group.
4. An interaction between the components of the message and time window can be considered in the GEE model for the secondary hypothesis. This interaction term allows us to examine what type of message, sent at what time of the day, leads to the highest increase in daily mood ratings.

### ***Normality Assumption Check***

The normality assumptions for both primary and secondary outcomes will be checked by quantile-quantile plots. If normality fails, then the outcome variable will be taken as logarithm transformation (ie, log). We will add 0.5 to the zero-change value for either the depression or anxiety score, or the mood rating before applying the log transformation.

### **Power Analysis**

We will perform sample size calculation at the usual 80% power at 5% level of significance.

### ***Primary Analysis***

The Cohen methods [30] were used to calculate sample sizes for primary hypotheses. At a medium standardized effect size (ie, Cohen  $d=0.5$ ), a total sample size of 64 is required to detect an improvement of either the depression or anxiety score from baseline to 60-day follow-up, and a sample size of 128 to detect differences between the UR and RL groups.

### ***Secondary Analyses***

Using the GEE-based sample size calculation method [31,32] with a small standardized effect size (ie, Cohen  $d=0.2$ ), with the correlation coefficients of 0.2 and 0.4 among the daily mood rating improvements compared to baseline, sample sizes of 84 and 161 are required to detect a group effect for either the UR or RL group, respectively, randomly allocated at baseline. Assuming 15% of the participants will drop out before the end of the study, a sample size of 190 is required for each group.

At a small standardized effect size (ie, Cohen  $d=0.1$ ), with a constant trend of intervention effect over days, sample sizes of 55 and 76 are required to detect the average daily causal effects of message and time window, respectively, for the UR intervention group, using the WCLS-based sample size calculation method proposed by Xu et al under the multilevel MRT design [33]. Assuming each participant has an expected 70% response rate to the sent messages and 15% of the participants are expected drop off before the end of the study, a sample size of 126 is recommended for the UR group.

Since our primary aim is to detect differences between the UR and RL groups for depression and anxiety scores, we aimed to include at least 128 participants. However, since our goal is also to provide a service during this unprecedented COVID-19 pandemic, we will continue to make the program available and recruit participants until at least April 2021 or for as long as funding allows.

### **Engagement Measures**

In addition to the measures mentioned above, we will also explore measures of engagement, such as response rates to the mood messages and the BA and skills messages as well as usability data, assessed by the System Usability Scale. This will help us to improve future iterations of the texting program.

### **Compensation**

Participants will receive no compensation for participation in the baseline part of the study. They will receive US \$20 for completion of the 60-day follow-up questionnaire.

### **Data Statement**

We will submit study results for publication in peer-reviewed journals and for presentations at national and international meetings. We will aim to publish all findings in open access journals when possible or in other journals with a concurrent uploading of the manuscript content into PubMed Central for public access. Curated technical appendices, statistical code, and anonymized data will become freely available from the corresponding author upon request.

### **Potential Harms**

Participants will be instructed to contact the researchers if their phones are lost or stolen to ensure that we stop sending messages to them. Our study website will serve as the way to control which participants receive messages and when. The server receiving data from participants (ie, text responses) is hosted behind a UC San Francisco firewall in a secure location subject to health care–grade security measures, including strict firewalls, intrusion detection, and active monitoring by study and university staff.

### **Ethics and Dissemination**

The informed consent form for this study can be found in [Multimedia Appendix 1](#). All protocol amendments will be communicated for approval to the UC Berkeley Committee for the Protection of Human Subjects (CPHS). We will ensure that our text messaging content is publicly available through a Creative Commons licensing agreement. The HealthySMS system is available for use upon request.

## **Results**

The UC Berkeley CPHS approved this protocol in April 2020 (No. 2020-04-13162) and the trial was registered at ClinicalTrials.gov (NCT04473599). Our enrollment started on April 17, 2020, and will continue to April 2021. As of August 24, 2020, we have enrolled 229 participants, of whom 218 were English speaking and 11 were Spanish speaking.

## **Discussion**

### **Overview**

The COVID-19 pandemic and the measures taken to combat it, such as social distancing, can take a large toll on mental health, exacerbating stress and symptoms of anxiety and depression. This study aims to assess the effect of a text messaging tool for improving mental health by providing daily text messages based



on BA and skill building. We expect the text messages sent to all participants in this study to improve participant well-being, as measured by depression, anxiety symptoms, and daily mood ratings, by encouraging healthy behaviors and improving coping skills.

The COVID-19 pandemic has demonstrated the need for affordable, scalable, and effective digital mental health tools [8]. Here, we provide such a tool to a wide group of individuals and examine its effectiveness.

In addition to the primary study outcome of mental health, we will also be able to assess the feasibility and challenges of deploying a large-scale public health text messaging intervention completely remotely. The COVID-19 pandemic and measures to combat the spread of the virus led to the necessity to conduct many operations online, including research. Online surveys, online consent forms, virtual online recruitment strategies, and mobile or internet interventions and programs are crucial during this time.

This study will provide important insights and practical tools on remote recruitment with English and Spanish speakers in the United States. This will also allow us to write and disseminate guidelines for other researchers in this space. Knowledge on the careful implementation of user-centered programs is now more important than ever.

Of note, our recruitment up to this point has been significantly slower for Spanish-speaking participants. Previous work also reported that recruiting Hispanics or Latinxs who speak little or no English into randomized trials is challenging [34], and online recruitment may be even more difficult because of digital literacy issues. We hope to increase the recruitment rate of our monolingual Spanish-speaking population by continuously improving the personalization of our ads on websites, such as Facebook, which has been identified as an effective strategy for online recruitment with Spanish speakers [35].

One advantage of text messaging-based interventions is the ability to easily incorporate machine learning algorithms into the research design and test whether this approach improves effectiveness. RL algorithms have the potential to greatly contribute to the effectiveness of digital mental health studies as well as to the personalization and tailoring of these studies [36,37].

Though there is a tremendous interest in the use of machine learning techniques to improve mobile health interventions, not many studies have examined the feasibility and effectiveness of these approaches. Our unique design allows us to assess the added benefit of using RL on participant outcomes, as opposed to a random messaging schedule. While the microrandomized UR group facilitates the estimation of causal effects, the participants of that group do not benefit from that knowledge. In contrast, the participants of the RL arm get allocated to

empirically better-performing messages with higher probabilities as the trial progresses and new knowledge accrues. Thus, the RL arm is an outcome-adaptive MRT design, which learns online, with the randomization probability of the intervention messages being adjusted according to the participant's responses. This design is more participant-centric than the standard MRT, which learns offline, with equal and fixed randomization probabilities over the study period. Thus, a comparison of UR versus RL arms is a comparison between these two design approaches.

Additionally, MRTs are a novel and currently underutilized study design. Typical MRTs consider binary-level components (ie, control versus intervention); however, in this study, we instead use a unique multilevel MRT design, where there are more than two levels for the intervention [33]. This study will, thus, also provide various methodological contributions, especially to the digital health literature. Results from the MRT design will allow us to optimize our text messaging intervention and serve as preliminary evidence for a just-in-time adaptive intervention (JITAI). A JITAI is a type of personalized intervention that aims to provide the right type and amount of support at the right time and is adapted to an individual's state [38]. This will be relevant information for optimizing this text messaging stress prevention app.

### Limitations

There are disadvantages to fully online recruitment. For instance, participants may perceive a lack of connection to the research without contact with the researcher and, therefore, show lower engagement [39]. Furthermore, online recruitment comes with risks of fraudulent activity. In addition, our monetary incentive may lead to a selection of a sample mostly motivated by financial incentives. We aimed to minimize this potential bias by only providing the reimbursement at the end of the study. We also aimed to design a messaging bank with content relevant for a broad demographic group. Thus, the content might not be adequately tailored toward specific subgroups (eg, people with chronic physical diseases or severe mental illness). Finally, we use a multilevel MRT design as opposed to contrasting sending a message with not sending a message, which is a more common design. However, by using this design, we will not be able to assess the pooled effectiveness of sending any message versus no message.

### Conclusions

This study will examine whether automated supportive text messages will improve depression, anxiety, and mood of a broad community sample in a fully remote trial. In addition, we will assess whether using an RL algorithm to personalize messages is more effective than randomly selected messages. Overall, results will contribute to our knowledge of effective psychological tools to alleviate the negative effects of social distancing.

### Acknowledgments

We would like to thank Chris Karr for helping to develop and support the HealthySMS platform. We would also like to thank Lizbeth Ortiz-Pivaral for contributing to the design of, and recruitment for, the StayWell at Home study. This study is funded by

a Health Resources and Services Administration grant to the Latinx Center of Excellence at the School of Social Welfare, UC Berkeley.

## Conflicts of Interest

None declared.

Multimedia Appendix 1

Informed consent form.

[[DOCX File, 28 KB](#) - [resprot\\_v10i1e23592\\_app1.docx](#) ]

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## Abbreviations

- BA:** behavioral activation
- CPHS:** Committee for the Protection of Human Subjects
- GAD-7:** 7-item Generalized Anxiety Disorder
- GEE:** generalized estimating equation
- HIPAA:** Health Insurance Portability and Accountability Act
- JITAI:** just-in-time adaptive intervention
- MRT:** microrandomized trial
- PHQ-8:** 8-item Patient Health Questionnaire

**RL:** reinforcement learning

**SPiRiT:** Standard Protocol Items: Recommendations for Interventional Trials

**UC:** University of California

**UCD:** user-centered design

**UR:** uniform random

**WCLS:** weighted and centered least squares

*Edited by G Eysenbach; submitted 25.08.20; peer-reviewed by S Guo, L Bell; comments to author 11.09.20; revised version received 24.09.20; accepted 10.11.20; published 14.01.21.*

*Please cite as:*

*Figuroa CA, Hernandez-Ramos R, Boone CE, Gómez-Pathak L, Yip V, Luo T, Sierra V, Xu J, Chakraborty B, Darrow S, Aguilera A*

*A Text Messaging Intervention for Coping With Social Distancing During COVID-19 (StayWell at Home): Protocol for a Randomized Controlled Trial*

*JMIR Res Protoc 2021;10(1):e23592*

*URL: <http://www.researchprotocols.org/2021/1/e23592/>*

*doi: [10.2196/23592](https://doi.org/10.2196/23592)*

*PMID: [33370721](https://pubmed.ncbi.nlm.nih.gov/33370721/)*

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Protocol

# Optimizing an Obesity Treatment Using the Multiphase Optimization Strategy Framework: Protocol for a Randomized Factorial Trial

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## Abstract

**Background:** Effective weight loss interventions exist, yet few can be scaled up for wide dissemination. Further, none has been fully delivered via text message. We used the multiphase optimization strategy (MOST) to develop multicomponent interventions that consist only of active components, those that have been experimentally determined to impact the chosen outcome.

**Objective:** The goal of this study is to optimize a standalone text messaging obesity intervention, Charge, using the MOST framework to experimentally determine which text messaging components produce a meaningful contribution to weight change at 6 months.

**Methods:** We designed a 6-month, weight loss texting intervention based on our interactive obesity treatment approach (iOTA). Participants are randomized to one of 32 experimental conditions to test which standalone text messaging intervention components produce a meaningful contribution to weight change at 6 months.

**Results:** The project was funded in February 2017; enrollment began in January 2018 and data collection was completed in June 2019. Data analysis is in progress and first results are expected to be submitted for publication in 2021.

**Conclusions:** Full factorial trials are particularly efficient in terms of cost and logistics when leveraged for standalone digital treatments. Accordingly, MOST has the potential to promote the rapid advancement of digital health treatments. Subject to positive findings, the intervention will be low cost, immediately scalable, and ready for dissemination. This will be of great potential use to the millions of Americans with obesity and the providers who treat them.

**Trial Registration:** ClinicalTrials.gov NCT03254940; <https://clinicaltrials.gov/ct2/show/NCT03254940>

**International Registered Report Identifier (IRRID):** RR1-10.2196/19506

(*JMIR Res Protoc* 2021;10(1):e19506) doi:[10.2196/19506](https://doi.org/10.2196/19506)

**KEYWORDS**

text message; digital health; weight loss; personalized



## Introduction

The obesity epidemic continues, currently affecting more than one-third of all Americans [1,2], with dire consequences, including chronic disease, premature mortality, and significant costs to the US health care system. Efforts to reduce obesity include successful behavioral weight loss treatments with frequent interactions with a trained counselor and regular self-monitoring of diet and/or exercise [3-5]. These treatments produce 7% to 10% weight loss after 6 to 12 months [6,7]. However, the intensity of these treatments limits their widespread dissemination. A rapidly emerging evidence base supports the use of digital interventions for obesity treatment. Through a wide variety of intervention designs, digital interventions can produce clinically meaningful weight loss and reach a large range of populations [8].

Texting, one of the most long-standing mobile health (mHealth) approaches, is the most frequently performed activity on mobile phones and has nearly 90% population penetration, particularly among racial and ethnic minorities [9-11]. Despite these advantages, few studies have investigated the effectiveness of standalone texting interventions for weight loss and what components of text messaging enhance engagement. Rather, texting is often used as one of several intervention delivery channels in obesity treatments [12], combined with web and/or email delivery [13,14], paper materials and monthly coaching calls [15,16], mobile apps [17], social media support groups [18], and interactions with a dietitian or physician provider [19]. We know little about how to design texting interventions in a manner that maximizes both engagement and dissemination potential [20].

Moreover, texting has been used in a myriad of ways, making it challenging to extract best practices. For example, some interventions text participants bidirectionally [21] to facilitate self-monitoring, while others text unilaterally to deliver tips and/or feedback. Interventions use a variety of frequencies, sending texts weekly, daily, or even multiple times a day [13]. Similarly, when tailored feedback is provided via text, it has been variably designed as a summary score of participant progress, links to graphical figures, or as text describing weight loss progress. These design choices are not trivial and may differentially affect intervention engagement, the most important predictor of weight loss outcomes [20].

Standalone digital interventions (eg, without human counseling) have the potential for substantial population-level impact, given their broad reach and low marginal costs of operation [22]. However, relatively few trials have tested digital interventions that are deployed in a fully standalone manner; most evidence-based digital treatments include support from a human interventionist [8]. There is limited evidence detailing the efficacy of standalone digital treatments, but they most often suffer from low user engagement and high rates of nonuse attrition [23]. Thus, a key challenge for standalone digital interventions is designing technologies that people will use long enough to experience positive benefits. Standalone interventions do not benefit from the type of accountability that a human interventionist can produce [24,25].

We sought to design a standalone, 6-month texting intervention that would retain maximal dissemination potential. Given the limited consensus in the empirical literature regarding how to best design a texting intervention, we leveraged the multiphase optimization strategy (MOST) [26] to aid in developing an optimized digital treatment package. Behavioral interventions are usually *packages* of intervention components. However, traditional trial designs (eg, two-arm randomized controlled trials) cannot determine which intervention components contribute most to weight loss, which might have limited effects or even detrimental effects. This limits our ability to create lean, cost-efficient interventions that can optimally affect clinical outcomes.

MOST offers a framework to help build efficient multicomponent treatment packages that contain only meaningful intervention components. Its first phase involves using theory to identify tenable intervention components. While behavioral science theory can help us develop interventions that produce weight loss, it is less useful in informing the design of technologies that individuals will want to use daily for the months needed to produce weight loss. Thus, we leveraged the Technology Acceptance Model (TAM), a dominant information services theory [27,28], which argues that people will be more likely to use technologies that help them achieve their goals (ie, perceived usefulness) and are easy to use. One tenet of the TAM is that if these two conditions are met, people will have positive attitudes toward use, which can increase technology use intentions. TAM argues that when technologies are easy to use, people will have higher self-efficacy for their use. Though this model is widely studied, few studies have used it to inform mHealth intervention design. The second phase of the MOST framework—the basis of this study—involves implementing an experimental trial to identify active intervention components that might be included in an optimized treatment package. The third phase of the MOST framework involves testing the optimized treatment package in a fully powered randomized clinical trial.

The aim of this paper is to present the design of our MOST optimization trial, Charge. The goal of the trial is to identify intervention components and levels that might be included in a 6-month, standalone texting treatment aimed at physical activity and diet changes that result in clinically meaningful weight loss (ie, >5% from baseline) at 6 months and weight loss maintenance at 12 months. We will also explore associations of engagement and nonuse attrition with weight change. The following section describes the study design and intervention.

## Methods

### Overview

From our comprehensive review of intervention trials utilizing text messaging for weight loss, we abstracted intervention design details. There was great similarity in the core interventions utilized; most used social cognitive theoretical approaches with an emphasis on self-efficacy as a primary mediator [12,14,15,17-19]. From an intervention design perspective, most interventions involved sending texts bidirectionally, using texting for self-monitoring, and providing tailored feedback.

Thus, we did not test these components experimentally, but built them into our core intervention. However, there was marked variability in most other design components: frequency of texting, whether self-monitoring data were collected, referent tracking day, timing of monitoring, feedback scheduling, and use of skills training. From this group of components and guided by the TAM, we identified components that would heighten the perceived usefulness and perceived ease of use of our texting intervention. MOST also recommends that we design our intervention for real-world implementation. For example, the ongoing MOST trial by Bonnie Spring and Linda Collins is designed to find the most effective weight loss intervention that can be delivered for US \$500 per person [29]. They acknowledge that they might not be able to achieve maximal

weight loss at this cost, but they view US \$500 as an optimal target for dissemination.

In selecting experimental conditions, we did not include components that might maximize weight loss (eg, individual or group counseling) or components that cannot be delivered via texting (eg, web-based materials, email feedback, automated phone calls, and apps). We recognize that these design choices might limit the magnitude of our treatment outcomes, relative to gold-standard treatments. However, we think these concessions will help us achieve the goal of creating a standalone texting intervention that can be optimally disseminated. Based on preliminary data collected as part of Phase 1 of this trial, we identified five intervention components (see Table 1) that can enhance perceived usefulness or ease of use.

**Table 1.** Reference and comparator levels for intervention components.

Intervention component	Reference level	Comparator level
Motivational message source	Expert-generated	Self-generated
Texting frequency	Weekly	Daily
Reminder timing	One	Multiple
Feedback level	Individual goal	Summary score
Performance comparison	Self	Others (group)

### Motivational Messaging Source: Self-Generated Versus Expert-Generated

Interventions frequently use text messages to enhance and sustain participant motivation. For these messages to enhance participant efficacy, they must be perceived as salient to the individual, be relevant to one's personal circumstances, and incorporate familiar social norms, otherwise there is a risk of undermining efficacy [30]. Presently, most motivational messages are developed by content experts, who are guided by theory, evidence, and experience [14-19,31-34]. One possible way to increase the potency of motivational messaging is to change the source of the messages. Self-generated text messages may result in greater attitudinal and behavioral change because they (1) exemplify *optimal* tailoring (ie, one knows oneself best), (2) are seen as highly self-relevant, (3) are viewed as credible, (4) are more often remembered (ie, self-referring effect), and (5) generate less resistance to persuasive attempts than messages originated by others. This is consistent with Self-Determination Theory's emphasis on increasing autonomous self-regulation and perceived competence [35]. Participants randomized to the self-generated condition will create text messages in two areas at baseline: reasons and competence for weight loss. The former will target autonomous self-regulation (ie, change stems from within), while the latter will target efficacy for weight-related behavior change. We will send texts from these pools randomly. We hypothesize that receipt of self-generated motivational messages, compared to expert-generated messages, will enhance intervention engagement, resulting in larger weight loss outcomes.

### Texting Frequency: Daily Versus Weekly

There is substantial variability in the number of days that texting interventions request self-monitoring data. Some studies have participants self-monitor daily [13-16,33], 3 to 5 times per week [18,19], and weekly [32,33]. Regular self-monitoring is believed to activate self-regulatory processes that result in energy restriction and increased physical activity. For optimal self-regulation, self-monitoring should be routine and feedback should be provided. Although daily self-monitoring might appear to be optimal, if the texts are perceived as burdensome, there is potential for nonuse attrition. Indeed, in one of our previous texting interventions, we found that engagement with our daily self-monitoring texts was high through 6 weeks but subsequently decreased [13]. By trial end, 49% of the participants texted daily. A somewhat less regular, but still routine, frequency (eg, weekly) might minimize perceived burden. Ours will be the first study to look at this question experimentally. We hypothesize that daily self-monitoring will be superior to once-weekly self-monitoring for maximizing intervention engagement and weight loss.

### One Reminder Versus Multiple Reminders

As noted, sustained intervention engagement is a key goal for standalone digital interventions. Thus, reminders might serve as a powerful aid to promote regular self-monitoring, the primary participant engagement in this study's intervention. However, as with texting frequency, there may be concern that sending multiple self-monitoring reminders might promote user burden and intervention fatigue, thus negatively impacting engagement behaviors. The impact of reminder notifications on user behavior is largely unclear. There is limited empirical evidence that multiple reminders produce user burden; in fact, frequent notifications are often used in commercial digital

interventions to enhance engagement. We randomized participants to receive either a single reminder or multiple reminders if they fail to self-monitor on their assigned day. We hypothesize that receiving multiple reminders will result in superior intervention engagement and weight loss outcomes.

### Feedback From Summary Scores Versus Individual Goals

Weight loss interventions in general, and our intervention specifically, implicitly seek to promote change in multiple behaviors simultaneously. Accordingly, self-monitoring interfaces, like ours, are designed to allow participants to track multiple behaviors in a given self-monitoring session. A challenge emerges when deciding how to provide feedback in response to self-monitoring. Feedback might describe performance singly for each tracked goal. Doing so best allows feedback to be tailored to a specific goal, which might be important given the potential for variability in user adherence to their assigned goals. In contrast, one might leverage recommendations from the risk communication literature, which describes the potentially superior performance of a single summary score that collapses across the variability in an individual's assigned goals. Such a summary score might minimize the literacy and numeracy challenges in interpreting feedback, perhaps at the expense of offering the detailed feedback that might be necessary to promote change in discrete behaviors. We randomized participants to either the summary score group or the individual goal feedback group. We hypothesize that the summary score approach will facilitate easier processing and comprehension, thus improving engagement and weight loss outcomes.

### Self-Performance Versus Group Performance Comparison

Tailored feedback often benchmarks a participant's performance against one's own prior performance. An alternative is to use principles of gamification, comparing a user's behavior change progress against that of other participants [36]. Such a *leaderboard* strategy can amplify competition and promote positive engagement and behavior change outcomes [37]. However, a potential risk of the leaderboard approach is that it seems to perform best when there are small relative differences between users; when users significantly underperform compared to their peers, the leaderboard approach might be demotivational [38]. We randomized participants to receive either comparison to themselves or comparison to their peers. We hypothesize that those who receive feedback benchmarked relative to their peers will have significantly better weight loss outcomes than those whose behaviors are compared to their own performance.

### Intervention Design

All participants will receive a core, 6-month, weight loss texting intervention built on a theory-based approach. Participants will be assigned an individualized set of routine lifestyle behavior change goals and directed to make small behavioral changes to create an energy deficit sufficient to produce weight change. We developed this approach and named it the interactive obesity treatment approach (iOTA). We designed iOTA specifically for delivery via digital health methods, such as texting, where sustained intervention engagement is critical. Individuals expect their digital health experience to be straightforward and highly personalized with minimal effort. Accordingly, iOTA does not require expert knowledge or expensive resources [13,39]. From the participants' perspective, they simply take a short survey and are immediately assigned a set of personally tailored behavior change goals. Participants use text messaging to self-monitor their adherence to these goals. They receive tailored feedback based on their progress, skills-training videos, and motivational texts.

All core iOTA intervention components are designed to target self-efficacy, which we selected from Social Cognitive Theory [40,41], given its consistent association with weight loss outcomes [42-44]. Bandura identified four primary factors [45] that influence self-efficacy: mastery experiences, social modeling, social persuasion, and somatic and emotional reactions. Our text messages will cover all of these domains. Social Cognitive Theory also indicates that behavior change can be facilitated through a number of self-regulatory processes, including self-monitoring [46-48], goal setting [24,44], and social support [49,50].

### Obesogenic Behavior Change Goals

Each participant will track four behavior change goals that produce an energy deficit sufficient to produce weight loss. We have a library containing obesogenic behavior change goals that have been selected based on their (1) empirical support, (2) population relevance, and (3) ease of self-monitoring. We adapted the goal library that was deemed efficacious in our previous studies [22,31]. All participants take a short survey—the iOTA survey—and are immediately assigned a set of personally tailored behavior change goals. Our prescription algorithm assigns three tailored behavior change goals and one universal goal for each 8-week goal cycle (see [Textbox 1](#)). The prescription algorithm prioritizes behaviors based on highest need of change, those for which the participant has high self-efficacy and readiness, and those that achieve the intended caloric deficit.

**Textbox 1.** Behavior change goals.**Universal goal assignment:**

- Cycle 1: no red zone foods
- Cycle 2: portion control
- Cycle 3: walk 10,000 steps per day

**Goal list (in cycle date order):**

- Goal 1: no sugary drinks
- Goal 2: no sweet snacks
- Goal 3: no fast food
- Goal 4: no fried food
- Goal 5: 5+ fruits and vegetables
- Goal 6: no salty snacks
- Goal 7: fast between 7 PM and 7 AM
- Goal 8: eat grains and starches <1× per day
- Goal 9: no red meat
- Goal 10: restaurants ≤1× per week
- Goal 11: ≤2 hours of TV per day
- Goal 12: ≤1 alcoholic drink per day
- Goal 13: get brisk activity
- Goal 14: do strength training 2× per week
- Goal 15: no high-fat seasoning

**Self-Monitoring and Tailored Feedback**

Regular self-monitoring is a robust predictor of weight loss, although adherence typically wanes over time [46,48,51]. Disengagement likely results from usability limitations, cognitive complexity, and lack of immediate feedback. As a result, our trials have involved extensive testing to ensure that our texting self-monitoring tools are engaging. Our text messaging system is fully automated, currently operational, uses open source technologies, and is designed for scalability.

Depending on their randomization status, we will contact participants either daily or weekly. An outbound text will request self-monitoring data (ie, a prompt) based on a participant's behavior change goals. For example, the system may ask if an individual walked 10,000 steps yesterday. Participants will then respond by text to the prompt with their self-monitoring data. We immediately provide tailored, real-time feedback on participants' progress via text. The feedback an individual receives depends on their randomization: whether they are being compared to themselves or the group and whether they receive feedback from summary scores or from each individual goal. We will also provide skills-training tips, tailored to each participant's assigned goals.

**Tailored Skills-Training Videos**

We have skills-training videos, 2 to 5 minutes in length, for each of the goals in our library. For example, for those assigned a fast food–reduction goal, we will provide skills-training materials on eating out, social eating, and lunch packing. We

will also have a larger library of general behavior change skills (eg, stimulus control, problem solving, social cues, and stress management). Our materials include tailored narratives and information about cost and community resources. We sent links to videos at the beginning of each goal period that correspond to participants' goals that are assigned as discussed in the *Obesogenic Behavior Change Goals* section above.

**Participants**

Participants are adult men and women, aged 18 to 65 years, who have English-language proficiency and a BMI above 25 kg/m<sup>2</sup>. We aim to recruit a sample of 448 participants that is 30% male and 40% racial or ethnic minority, similar to the demographics of Durham, North Carolina, United States. Participants are required to own a smartphone and be willing to receive multiple text messages daily. Exclusion criteria include the following: prior or planned bariatric surgery; psychiatric hospitalization in the past 12 months; pregnant, nursing, or planned pregnancy; history of a cardiovascular event; history of an eating disorder; history of a health condition (eg, end-stage renal disease, cancer, or schizophrenia) or use of medications (eg, lithium, steroids, or antipsychotics) that would affect weight measurement, for which weight loss is contraindicated, or might promote weight change; current participation in a weight loss trial and/or recent weight loss of more than 10%; and investigator discretion, for safety reasons.



## Recruitment and Screening

Participants were recruited using the following multipronged strategy: (1) direct marketing, (2) local media, (3) social media, (4) snowball recruitment, and (5) community organizations. We have used these methods successfully in many of our team's previous studies. The geographically targeted postings were placed on Nextdoor, Facebook, and Reddit.

Those who responded to initial study marketing were directed to a preliminary eligibility screening assessment via a Qualtrics online survey. If deemed eligible via the screening assessment, participants were then invited to complete the study's online informed consent process and baseline surveys. Those who completed all surveys were then invited for an in-person visit to confirm participant eligibility. At the baseline visit, study staff collected written informed consent and confirmed participant eligibility by taking anthropometric measurements. After randomization, each participant received an individual orientation to the intervention.

## Procedures

All study procedures were registered at ClinicalTrials.gov (NCT03254940). After confirming eligibility, participants were randomized to one of 32 experimental conditions (see [Multimedia Appendix 1](#)) to test the intervention components, including frequency (weekly vs daily), motivational messaging (self- vs expert-generated), reminders (one vs multiple), feedback type (summary score vs individual score), and comparison unit (self vs group). We randomized participants using a permuted block method with stratification for gender. A computer algorithm sorted each participant into three self-reported gender categories—male, female, or any other self-description—and then assigned them accordingly into blocks of the 32 groups, randomly ordered by the computer. The computer algorithm, developed by a software engineer as directed by a biostatistician, minimized selection bias by generating the blocks ad hoc, thereby preventing prediction of the assignment order. Due to the logistics of enrollment and quality control of the intervention, it was impossible to completely blind the data collection staff to treatment assignment. However, all possible steps were taken to reduce unnecessary awareness of treatment assignment and to limit opportunities for the introduction of bias into the data by our data collection staff. We will analyze outcomes while blinded to allocation status.

## Data Collection

### Survey Data

Data were collected at four study visits: baseline and 3, 6, and 12 months postbaseline. A protocol window for follow-up assessments was defined as 2 weeks before to 4 weeks after the 3-, 6-, and 12-month dates, relative to the baseline visit. Every reasonable effort was made to complete an in-person follow-up visit within the protocol window, including multiple rescheduling attempts and reminders. During the last week of the protocol window, we approached participants who refused or were unable to attend an in-person follow-up visit using a secondary data collection protocol. We emailed participants a link allowing them to access the online survey assessments on

their own and asked them to provide a weight photograph or self-reported weight.

Surveys were administered in English via computer using an online survey tool where questions required responses to ensure completeness. Demographic variables collected at baseline included age, gender, race or ethnicity, marital status, parity, height and weight, socioeconomic status, insurance status, occupational status, and educational attainment.

### Primary Outcome

The primary outcome is weight in kilograms. During in-person visits, participants removed shoes and items from pockets prior to height and weight measurements. Height was measured to the nearest 0.1 cm using a calibrated wall-mounted stadiometer [52]. Body weight was measured to the nearest 0.1 kg using a portable electronic scale [52]. BMI was calculated using participant height collected at baseline and weights collected at sequential in-person visits or self-reported weights if the participant was unable to come in person.

### Secondary Outcomes

#### Physical Activity Outcomes

Physical activity was measured using the Global Physical Activity Questionnaire version 2 (GPAQ 2) at baseline and at 6 months postrandomization [53]. The GPAQ 2 was developed by the World Health Organization to measure physical activity participation as well as sedentary behavior. Participants were asked to report the frequency and duration of moderate to vigorous physical activity participation at work, travel to and from places and recreational activities, as well as the time spent being sedentary, in a typical week.

#### 12-Item Short Form Health Survey Outcomes

Adapted from the 36-item Short Form Health Survey (SF-36) [54], the 12-item Short Form Health Survey (SF-12) [55] has been operationalized for large-scale health measurement and monitoring efforts for all age groups. Participants were asked to complete the survey at baseline and at 6 and 12 months postrandomization to understand mental (ie, mental health, role emotional, and social functioning scales) and physical (ie, physical functioning, role physical, or bodily pain scales) performance and overall health-related quality of life. The age-specific mean difference score will be calculated from a participant's physical and mental health composite score to compare participants to their age group's mean score.

#### Engagement Outcomes

Intervention engagement is defined as successful self-monitoring during an expected window of time after a self-monitoring prompt was sent to the participant via text message. The window of time and frequency of the prompts delivered is determined by participant allocation to the five components of the intervention across the 6-month intervention period. Self-monitoring is considered complete if the participant texted back a properly formatted response with self-monitoring data for their four behavior change goals. For each participant, we will calculate a rate of completed responses out of the number expected.



## Statistics

### Overview

Using the FactorialPowerPlan macro from SAS 9.4 (SAS Institute) [56], developed by the Penn State Methodology Center, University Park, Pennsylvania, we computed the sample size needed for a full 2<sup>5</sup> factorial design. We determined that a total sample size of 282 participants would be required to achieve an overall power of 80% to detect a 0.75-kg difference in weight loss. We conservatively assumed 30% dropout at 6 months, so we inflated the sample size to 403. To obtain an equal number of participants in each treatment combination (ie, condition), we further inflated this sample size to 448, which would give a final sample of 14 participants in each of the 32 conditions. To achieve greater gender and racial diversity consistent with our recruitment goals, enrollment may be amended to perform additional targeted recruitment.

### Statistical Analysis

For each of the five components, participants' weights and demographics will be summarized by levels of the component. Continuous variables will be summarized using means, standard deviations, medians, quartiles, and ranges, and categorical variables will be summarized using counts and percentages.

In the primary analysis, those whose data were collected outside of the study window or who sent in weight measured at home, rather than having weight measured in person, will be treated as missing for that time point. Sensitivity analyses will be performed including such data.

The primary outcome is absolute change in weight from baseline to 6 months. We will estimate the main effects of each intervention component on the primary outcome and of all pairwise, three-way, four-way, and five-way interactions of those components at each follow-up time point using a linear mixed-effects model. In order to estimate effects on weight change, we will model all four weights for each individual (ie, baseline and 3-, 6-, and 12-month follow-ups) in the same model. The model will include fixed effects for time point (ie, 3 months, 6 months, and 12 months); the time × component, time × pairwise, time × three-way, time × four-way, and time × five-way interactions; up to five-way interactions; and gender, the variable by which the randomization was stratified. We will not include the effects of the components and their interactions at baseline. This constrains the baseline comparisons to be equal, which is appropriate in a randomized trial and increases power [57,58]. We will model the correlation between repeated measures on the same individual using an unstructured residual covariance matrix. The model will allow us to estimate weight change and percentage weight change at the interim time point (ie, month 3) and final follow-up time point (ie, month 12), but the main estimates of interest will be the interaction of the five treatment indicators by month 6.

After examining the model, we will assemble a multicomponent intervention package. If a component has a main effect on weight loss at 6 months that is greater than or equal to 0.7 kg (1.5 lbs) and no significant interaction with another component, then the superior level of the component will be retained for the intervention package. Otherwise, if there is no significant

main effect or interaction, the default (ie, reference) level of the component will be retained (see Table 1). We will reconsider inclusions based on the presence of large (ie, effect ≥0.7 kg) interactions. This decision making is based on the approach outlined in an article by Collins et al [59]. Although the 3- and 12-month weight will not be used in the primary decision-making process, we may reconsider our inclusions if there is a large change in effect between 6 and 12 months, or if there are larger effects at 3 months. Given the factorial design, we will use effect coding, rather than dummy coding, for analyzing the effects of the intervention components. If the sample size is equal per condition, all of the tests of main effects and interactions are uncorrelated; that is, the main effect of a condition is the same even if other treatment conditions and interactions are included in the statistical model. Even with unequal sample sizes across conditions, as may occur with differential dropout by condition, if the imbalance is minor, the correlations between effects should be small [26].

Missing outcome data due to dropout or missing intermediate visits are expected to be, at most, 30%. Since the mixed model will be fit using a full maximum likelihood method, we will be able to account for predictors of missingness in the model in order to obtain valid estimates of the main component effects, thanks to the property that the response can be missing at random [60]. In practice, we will compare baseline characteristics of completers and noncompleters. If we find that any covariates predict missingness, we will adjust for these variables in a sensitivity analysis model.

In addition, we will examine gender as a potential moderator of the intervention effects. We acknowledge that the study is not powered to detect moderators, but these results may be used to guide future studies.

## Results

The project was funded in February 2017; enrollment began in January 2018 and data collection was completed in June 2019. Data analysis is in progress and first results are expected to be submitted for publication in 2021.

## Discussion

### Overview

The intensive nature of most traditional weight loss interventions constrains their dissemination. To make a population-level impact in addressing the obesity epidemic, we need treatments that are novel, easy to disseminate, and sustainable. The overarching goal of Charge is to develop an efficacious, standalone, text messaging obesity intervention. We focus on standalone approaches—treatments that can be delivered solely via text messaging—because of their dissemination potential. Standalone treatments are scalable, affordable, and can achieve population reach. They can reach into broad, diverse, and geographically dispersed populations that do not have stable access to other approaches (eg, counseling, web, email, and video) frequently employed in digital weight loss trials. However, these interventions are also modular; they can be delivered independently to maximize cost-effectiveness or

combined with other approaches (eg, provider counseling) to maximize outcomes.

### Comparison to Prior Work

Despite their translational potential, few trials have tested a standalone texting intervention for weight loss [8]. While the widespread availability of mHealth apps has been an undeniable boon for Americans who are seeking easy access to strategies to help them manage their health, very few of the commercially available digital solutions have any evidentiary basis. Further, engagement with apps wanes over time, making them a potentially less appealing approach [25,61]. Also, apps require data plans that are prohibitive for those on limited incomes [39]. In contrast, it has been extremely difficult to promote the translation of evidence-based treatments, both because of the latency in the process and because few research-tested digital treatments match the needs of the broader marketplace. Our interest is in developing an intervention solution that would be suitable for population distribution; accordingly, we designed it to match the conventions of the most widely accessible digital tools.

Charge is one of the first trials to apply the MOST framework to the development of a digital health intervention. For several reasons, MOST is particularly well suited to this task. There are myriad ways to design digital treatments, particularly those that are standalone. Indeed, design considerations and their impact on user behavior receive considerable attention in commercial software design. In contrast, the empirical literature provides little guidance on optimal intervention designs, and the extant evidence is replete with interventions with designs that vary considerably. This is problematic because even minor changes to the design of digital components can markedly impact user engagement, the most important predictor of weight loss outcomes. MOST allows us to isolate the weight loss effects of discrete texting intervention components and to then assemble an efficacious standalone texting treatment package. Of note, MOST encourages optimization for a specific purpose. Here we have chosen to optimize a standalone treatment for broad public health delivery, similar to the text4baby intervention [62]. What MOST describes as the continuous optimization principle could also be described as iteration, a concept that is fundamental to modern software design. In principle, when

Charge is complete, one might continue the optimization process to continue refining our interventions for optimal effectiveness. Indeed, our group has plans to do this at the conclusion of the Charge trial.

### Limitations

There are some study limitations. One limitation is whether we selected the appropriate components, component levels, and number of components. As mentioned previously, we understand that these design choices might constrain the magnitude of our treatment outcomes, relative to gold-standard treatments. However, our goal is to create a standalone texting intervention that can be optimally disseminated. Additionally, lack of diversity in sampling could be a limitation. It is important for our sample to be diverse, particularly considering evidence that racial and ethnic minorities both experience the health effects of obesity at disproportionately high rates, and that the use of text messaging in these groups is almost ubiquitous [10]. We also acknowledge that we have made design decisions that may constrain efficacy and retention, including the lack of human contact with study participants. It is a common observation that standalone treatments have tremendous challenges with nonuse and trial attrition [25,61].

### Conclusions

Although many MOST screening experiments utilize factorial experimental designs, full factorial trials are particularly efficient in terms of cost and logistics when leveraged for standalone digital treatments. The marginal costs of adding users accrue primarily due to research costs and quite minimally due to intervention expenses. Accordingly, MOST has the potential to promote the rapid advancement of digital health treatments. This is particularly important for standalone treatments; despite mounting feasibility evidence, such interventions frequently report suboptimal weight loss outcomes. For these interventions to have population-level impact, we must make their outcomes more robust. Charge is designed to address this goal. Subject to positive findings here and in a future efficacy trial, the intervention will be low cost, immediately scalable, and ready for dissemination. This will be of great potential use to the millions of Americans with obesity and the providers who treat them.

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### Acknowledgments

Financial support for this project is provided by a National Institutes of Health grant (5R01DK109696).

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### Conflicts of Interest

GGB holds equity in Coeus Health and serves on the scientific advisory board of WW (formerly Weight Watchers). DS serves on the clinical advisory board of Omada Health. These organizations had no role in the study design, data collection, data analysis, interpretation of data, writing of the report, or the decision to submit the article for publication.

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Multimedia Appendix 1

Randomization conditions by group.

[[DOCX File, 17 KB - resprot\\_v10i1e19506\\_app1.docx](#)]

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## Abbreviations

- GPAQ 2:** Global Physical Activity Questionnaire version 2  
**iOTA:** interactive obesity treatment approach  
**mHealth:** mobile health  
**MOST:** multiphase optimization strategy  
**SF-12:** 12-item Short Form Health Survey  
**SF-36:** 36-item Short Form Health Survey  
**TAM:** Technology Acceptance Model

*Edited by G Eysenbach; submitted 22.04.20; peer-reviewed by R Shaw, S Schembre; comments to author 11.05.20; revised version received 06.10.20; accepted 01.12.20; published 18.01.21.*

*Please cite as:*

Bennett GG, Steinberg D, Bolton J, Gallis JA, Treadway C, Askew S, Kay MC, Pollak KI, Turner EL  
*Optimizing an Obesity Treatment Using the Multiphase Optimization Strategy Framework: Protocol for a Randomized Factorial Trial*  
*JMIR Res Protoc* 2021;10(1):e19506  
URL: <http://www.researchprotocols.org/2021/1/e19506/>  
doi: [10.2196/19506](https://doi.org/10.2196/19506)  
PMID: [33459600](https://pubmed.ncbi.nlm.nih.gov/33459600/)

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Protocol

# Self-Administered Behavioral Skills–Based At-Home Virtual Reality Therapy for Chronic Low Back Pain: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** Chronic pain is one of the most common and debilitating health conditions. Treatments for chronic low back pain typically focus on biomedical treatment approaches. While psychosocial treatments exist, multiple barriers prevent broad access. There is a significant unmet need for integrative, easily accessible, non-opioid solutions for chronic pain. Virtual reality (VR) is an immersive technology allowing innovation in the delivery of behavioral pain treatments. Behavioral skills-based VR is effective at facilitating pain management and reducing pain-related concerns. Continued research on these emerging approaches is needed.

**Objective:** In this randomized controlled trial, we seek to test the efficacy of a self-administered behavioral skills-based VR program as a nonpharmacological home-based pain management treatment for people with chronic low back pain (cLBP).

**Methods:** We will randomize 180 individuals with cLBP to 1 of 2 VR programs: (1) EaseVRx (8-week skills-based VR program); or (2) Sham VR (control condition). All participants will receive a VR headset to minimize any biases related to the technology's novelty. The Sham VR group had 2D neutral content in a 3D theater-like environment. Our primary outcome is average pain intensity and pain-related interference with activity, stress, mood, and sleep. Our secondary outcomes include patient-reported physical function, sleep disturbance, pain self-efficacy, pain catastrophizing, pain acceptance, health utilization, medication use, and user satisfaction. We hypothesize superiority for the skills-based VR program in all of these measures compared to the control condition. Team statisticians blinded to treatment assignment will assess outcomes up to 6 months posttreatment using an approach suitable for the longitudinal nature of the data.

**Results:** The study was approved by the Western Institutional Review Board on July 2, 2020. The protocol (NCT04415177) was registered on May 27, 2020. Recruitment for this study was completed in July 2020, and data collection will remain active until March 2021. In total, 186 participants were recruited. Multiple manuscripts will be generated from this study. The primary manuscript will be submitted for publication in the winter of 2020.

**Conclusions:** Effectively delivering behavioral treatments in VR could overcome barriers to care and provide scalable solutions to chronic pain's societal burden. Our study could help shape future research and development of these innovative approaches.

**Trial Registration:** ClinicalTrials.gov NCT04415177; <https://clinicaltrials.gov/ct2/show/NCT04415177>

**International Registered Report Identifier (IRRID):** RR1-10.2196/25291

(*JMIR Res Protoc* 2021;10(1):e25291) doi:[10.2196/25291](https://doi.org/10.2196/25291)

## KEYWORDS

chronic pain; virtual reality; behavioral medicine; behavioral health; pain treatment; randomized controlled trial

## Introduction

Chronic pain is one of the most common reasons adults seek medical care [1]. Chronic pain affects between 50 and 116 million Americans, more than cancer, diabetes, and cardiovascular disease combined [1-4]. Other estimates suggest that 25 million American adults live with moderate to severe chronic pain (ie, pain scoring 4-7 on a visual analog scale and lasting over 3 months) that limits their activities and diminishes their quality of life [5,6]. Because of this great need, it is imperative to develop and test effective treatments for chronic pain.

Pain treatment and management often emphasize biomedical approaches, such as pharmacology or surgical procedures. Historically, opioids were commonly prescribed for pain treatment and management. These agents can yield both inconsistent and suboptimal results [7] and carry numerous personal and public health risks. The Centers for Disease Control and Prevention (CDC), the Centers for Medicare & Medicaid Services (CMS), and the Department of Health and Human Services recommended nonpharmacological modalities as first-line treatments for pain, including behavioral treatments [8,9]. Low-risk behavioral treatments may facilitate improved outcomes and analgesia while minimizing health risks.

Indeed, evidence-based behavioral treatments are effective for treating chronic pain. Therapies such as cognitive behavioral therapy for chronic pain, mindfulness-based stress reduction [10,11], and acceptance and commitment therapy [12] have been shown to modify cognitions and behaviors that influence the perception of pain. Although behavioral therapies show some promise, multiple barriers prevent chronic pain patients from accessing these behavioral treatment alternatives [13]. Strict reliance on skilled therapists that are in short supply, travel burdens, long durations of treatments, inadequate insurance coverage, and high costs can all contribute to a lack of treatment accessibility and patient engagement [14-16]. Furthermore, almost 85% of patients do not report meaningful analgesia from their pain medications (ie, they do not experience a long-term  $\geq 50\%$  reduction in their pain levels) [17]. Therefore, there is an urgent need for effective and comprehensive solutions for chronic pain and behavioral treatment delivery methods that are accessible to the entire spectrum of individuals affected by this concern.

Digital therapeutics for chronic pain are cost-effective, available on-demand, can be delivered in the home, and improve the risk-benefit profile well above the current standard of care. In particular, virtual reality (VR) therapeutics show promise as

effective treatments for acute and chronic pain [18-24]. With the first pain reduction VR program, SnowWorld, patients with pediatric burn undergoing physical therapy noted a 27%-44% reduction in pain ( $P < .05$ ) in comparison to within-subject control [25]. To date, VR has been used in numerous clinical settings to reduce pain and improve outcomes in complex regional pain syndrome [26], chronic headache/migraine pain [27], fibromyalgia [28,29], and chronic musculoskeletal pain [30]. Technology allows for an immersive, multisensory, and interactive virtual treatment experience. By stimulating the visual, auditory, and proprioception senses, VR facilitates distraction to limit the user's processing of nociceptive stimuli, which has been shown in functional magnetic resonance imaging studies [31]. Most importantly, VR therapeutics have the potential to enhance pain education and effectively deliver evidence-based behavioral interventions.

A randomized clinical trial recently examined the effectiveness of a 21-day skills-based VR program for chronic pain compared to the same content delivered in audio form [32]. The VR skills-based program was superior in improving pain intensity and pain-related interference with activity, sleep, mood, and stress compared to the audio-based treatment, with results strengthening after 2 weeks. Results suggested that VR's immersive components enhanced VR participants' outcomes relative to those who completed an audio treatment [31]. Nevertheless, it is unclear to what extent these positive outcomes were due to the VR technology's novelty and whether VR effects are durable. Therefore, this study seeks to conduct a randomized controlled trial to test the effectiveness of a comprehensive 56-day behavioral skills-based VR therapeutic program (skill-based VR) in chronic low back pain (cLBP). This study will elucidate the immediate and long-term effects of this proposed treatment while comparing it to a nontherapeutic control condition designed to account for this technology's novelty.

We hypothesize that therapeutic VR will significantly benefit self-reported pain intensity and pain-related outcomes compared to our control condition throughout this 8-week treatment and follow-up period. This study will address the following 4 objectives:

- The primary objective is to assess the impact of skills-based VR on changes in patient-reported pain and pain interference throughout an 8-week intervention and in comparison to a placebo VR condition.
- The secondary objective is to assess the impact of skills-based VR on changes in patient-reported satisfaction (Patient's Global Impression of Change [PGIC]) throughout

- an 8-week intervention and in comparison to a placebo VR condition.
- The tertiary objective is to assess the impact of skills-based VR on changes in patient-reported opioid use, physical function, pain coping, and health outcomes immediately following the intervention relative to a preintervention baseline and in comparison to a placebo VR condition.
- The exploratory objective is to assess the impact of skills-based VR on changes in patient-reported pain levels, opioid use, physical function, pain coping, health outcomes, and satisfaction for 6 months following intervention and in comparison to a placebo VR condition.

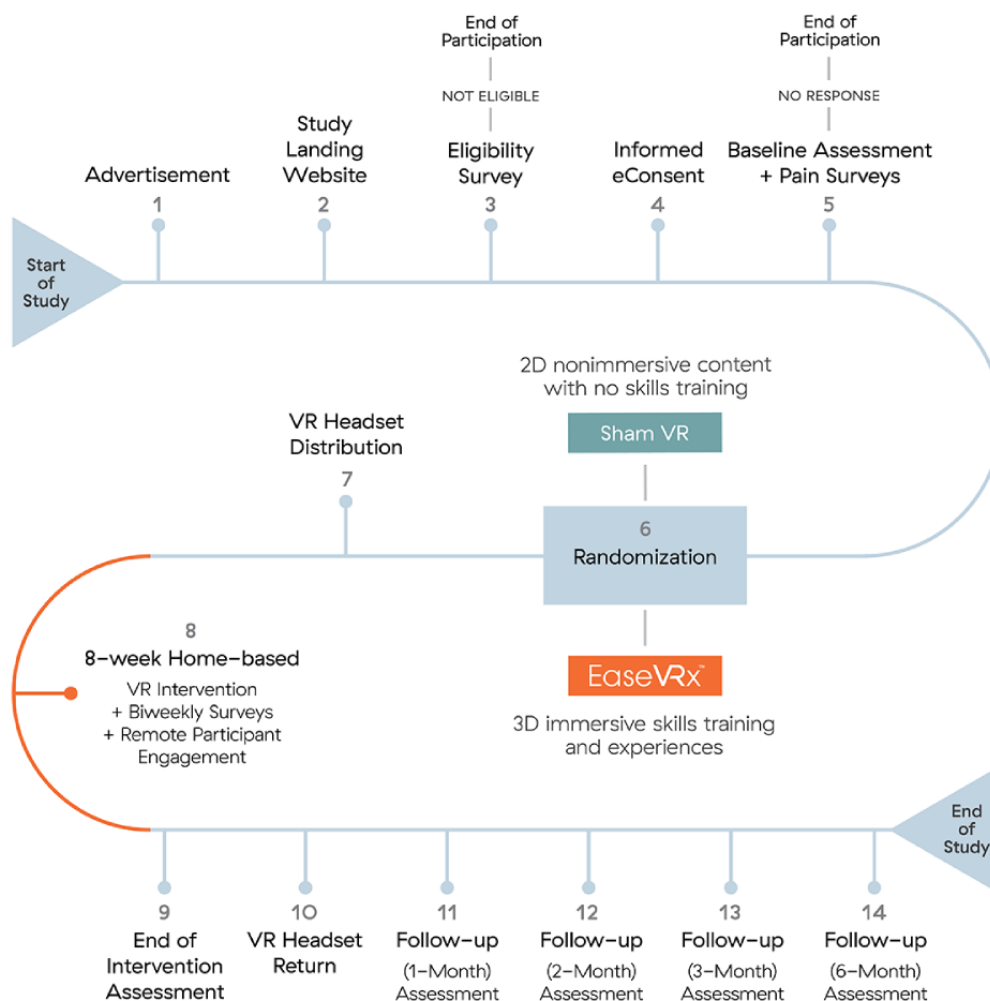
clinical trial in which 180 community-based individuals with cLBP will be randomly assigned to a 56-day skills-based VR therapeutic program (EaseVRx) and a 56-day control VR condition (Sham VR). Participants will be followed for 8.5 months after randomization. Participant eligibility will be assessed with an electronic screener survey. Once enrolled in the study, participants will complete a 2-week baseline assessment period, an 8-week VR program, a posttreatment assessment, and up to 4 posttreatment follow-ups over 6 months. During their 2-week baseline period, participants will be required to complete their baseline assessment and at least one of three pain surveys in order to progress to the treatment phase of the study in which they will receive a VR headset with their assigned treatment to be completed at home (Figure 1).

## Methods

### Overview

We will conduct a single-cohort, double-blinded (participant and analysts), cross-sectional, placebo-controlled randomized

**Figure 1.** Timeline of protocol activities: This figure depicts each of the steps that participants in this study will go through, starting from the moment they receive an advertisement for the study until the end of our follow-up assessments.



Team statisticians blinded to participant treatment assignment will examine outcomes immediately following treatment and after 1, 2, 3, and 6 months following treatment. The 6-month postintervention assessment is exploratory. Our primary outcome

will be average pain intensity and pain interference on activity, sleep, mood, and stress. Our secondary outcomes include self-reported change in average pain intensity, physical function, sleep disturbance, pain catastrophizing, pain self-efficacy, pain

acceptance, skills use, health utilization, medication use, and treatment usage and satisfaction.

The protocol for this trial has been approved by the Western Institutional Review Board. All participants will be required to give their informed consent during their online screening before enrollment in the study.

### Study Sample, Setting, and Recruitment

Community-based individuals with cLBP will be recruited nationally through chronic pain organizations (eg, American Chronic Pain Association) and advertising on social media platforms such as Facebook and Twitter. Additionally, study advertisements will be emailed to professional contacts at several medical clinics with requests to forward among medical colleagues nationally. All advertisements will direct interested individuals to a landing page where detailed study information exists. Interested individuals will be directed to complete an online REDCap Cloud (nPhase, Inc.) screening form to assess their eligibility.

The online screening will automatically classify individuals as eligible or ineligible using survey logic based on our inclusion/exclusion criteria. Ineligible individuals will receive a message thanking them for their interest and participation in

the screening process, inform them of their ineligibility, and be given a list of chronic pain resources. Eligible individuals will be redirected to an electronic consent form to provide their signature and complete enrollment.

Enrolled participants will progress to the study's treatment phase if they complete a baseline survey and at least one of three pain surveys during the 2-week baseline period. Following the 2-week baseline period, participants will be randomized to a treatment group. The study will enroll 180 adults (age 18-85 years) with cLBP who meet study criteria (Textbox 1). This sample size accounts for expected attrition.

### Inclusion and Exclusion Criteria

Textbox 1 lists the inclusion and exclusion criteria. The reason that radicular symptoms were excluded was to create a degree of homogeneity within the population recruited. Chronic lower back pain with radicular symptoms is often treated differently from those that do have those symptoms. Additionally, we require that participants be willing and available to participate during the study (8.5 months). Participants were asked to complete biweekly surveys during the 56-day treatment to which they are assigned and complete the posttreatment follow-up assessments (1, 2, 3, and 6 months).

**Textbox 1.** Inclusion and exclusion criteria. DVPRS: Defense and Veterans Pain Rating Scale; VR: virtual reality.

#### Inclusion criteria

1. Men and women aged 18-85.
2. Diagnosis of low back pain without radicular symptoms.
3. Pain duration of at least six months.
4. Average pain intensity of  $\geq 4$  on the 0-10 DVPRS Pain Scale for the past month at screening.
5. English fluency.
6. Willing to comply with study procedures/restrictions.
7. Access to Wi-Fi.

#### Exclusion criteria

1. Unable to understand the goals of the study due to cognitive difficulty.
2. Current or prior diagnosis of epilepsy, seizure disorder, dementia, migraines, or other neurological diseases that may prevent the use of VR.
3. Medical condition predisposing to nausea or dizziness.
4. Hypersensitivity to flashing light or motion.
5. No stereoscopic vision or severe hearing impairment.
6. Injury to eyes, face, or neck that prevents comfortable use of VR.
7. Cancer-related pain.
8. Moderate level of depressive symptoms (subclinical) as indicated by the Patient Health Questionnaire-2 (PHQ) [33,34] depression screen score of  $>2$ .
9. Previous use of EaseVRx for pain.
10. Current participation in any interventional research study or completed participation in the past 2 months.
11. Currently pregnant or planning to become pregnant during the study period.
12. Does not have access to Wi-Fi during participation in the study.
13. Currently works at or has an immediate family member who works for a digital health company or pharmaceutical company that provides treatments for acute or chronic pain.



## Randomization and Blinding

Enrolled participants will be randomized 1:1 and assigned to 1 of 2 treatment arms: a 56-day skills-based VR program (EaseVRx) and a 56-day control VR condition (Sham VR). Random assignment will rely on REDCap Cloud's automatic program to ensure blinded randomization and equal numbers in both treatment arms. This will be a double-blinded study wherein participants and statisticians will be blinded to treatment. An independent research coordinator will label each group as Group A and Group B randomly before sending any data sets to the statistician. Three staff members (LG, IM, and BB) will be unblinded to the treatment groups and will not be involved in any data analyses.

## Study Interventions

Participants in both the EaseVRx and Sham VR conditions will receive a Pico G2 4K headset with either EaseVRx or Sham VR condition. These devices will be mailed to the participant's self-reported address. Study staff will monitor participant progress through twice-weekly surveys of device use and provide guided technical support. The following sections describe the components of the study interventions.

### VR Headset and Software

This study will use a Pico G2 4K all in one head-mounted display that delivers VR images and sounds. We selected the Pico G2 4K because it is commercially available, widely used, inexpensive, has minimal visual latency, and is much easier for participants to use than many other devices. The user's exhale, a major mechanic of the EaseVRx program, is measured by the microphone embedded in the Pico G2 hardware, offering biodata-enabled immersive therapeutics. This hardware allows for displaying 3D images (EaseVRx) and 2D images (Sham VR).

### Skills-Based VR (EaseVRx)

Participants randomized and allocated to this treatment arm will receive a multimodal, skills-based, self-management VR program, called EaseVRx (AppliedVR), that incorporates evidence-based principles of cognitive behavioral therapy and mindfulness. Developed by AppliedVR in partnership with a pain psychology expert, the program provides pain neuroscience education and trains users on evidence-based pain and stress management strategies via immersive and enhanced biofeedback experiences. EaseVRx combines biopsychosocial pain education, diaphragmatic breathing training, relaxation exercises, and executive functioning games to provide a mind-body approach toward living better with chronic pain. The standardized 56-day program delivers a multifaceted combination of skills training through a prescribed sequence of daily virtual experiences. Each VR experience lasts between 2 and 16 minutes, with an average

duration of 6 minutes of treatment time. The VR treatment modules were designed to minimize triggers of emotional distress or cybersickness. These modules include:

- Interoceptive modules: biofeedback-like environments that shift in nature to reflect a progressively enhanced state of relaxation.
- Education modules: visually guided lessons explain why the VR exercises are relevant to their pain and specific topics relevant to behavioral medicine for pain.
- 360 video modules: high-quality 360 videos with voiceovers, music, breathing effects, and sound effects that are designed to maximize relaxation and participant engagement.
- Game modules: games are designed to maximize immersive distraction to decrease their perception of pain.
- Dynamic breathing modules: interactive virtual worlds where the user experiences a gamified biofeedback session and is introduced to awareness of their breath via visualization. These modules become increasingly challenging to better train participants in the practice of diaphragmatic breathing.

### Sham VR

VR-CORE guidelines suggest using an active control in VR clinical trials and promoting nonimmersive, 2D content within a VR headset as an optimal placebo [23]. Thus, participants in the Sham VR group will receive the same Pico G2 4K headset as participants in the immersive VR groups, but instead of 360-degree, 3D, interactive content specially selected for efficacy, they will only view 2D nature footage with neutral music layered on top that is selected to be neither overly relaxing nor distracting. The experience of Sham VR is similar to watching a large-screen TV. The content that is displayed in the VR sham will be viewed in a void theater. The void theater will consist of a solid black environment with the 2D content displayed on a "screen" in front of the user. The screen will take up a significant portion of the field of view of the participant, but appear to be distant enough to minimize any sense of immersion caused by viewing 3D content. The void theater screen will be fixed in place such that the user is capable of looking away from the screen if they so choose. The content for the VR sham will be 2D stock nature videos, all displayed in the void theater. The videos have been chosen to be more distracting than relaxing, and the majority of them contain animals engaging in play, grazing, grooming, or other inoffensive behaviors. There will be 20 videos that will be rotated over the 56 sessions, with a duration between 2.5 and 5 minutes, which corresponds directly with durations in the EaseVRx program. Figure 2 provides a visualization of the kinds of content each VR program would provide.

**Figure 2.** Interventions: This figure depicts the Skills-Based VR condition and control VR condition.



### Technical Support

Participants will be provided with onboarding material as well as emails describing the study procedures and details. Instructional videos will be made available to participants, and access to remote technical support will be provided. VR usage data for both treatment groups will be surveyed twice a week for the intervention's 8-week duration.

Survey data will be monitored for completion and technical support staff will be available. Participants will receive a telephone number and email address to contact support staff as needed. The technical support staff will also reach out if there is low adherence to the devices, lack of survey data, or low battery power detected on the headset's remote monitoring dashboard. Twice weekly, the research staff will review the REDCap Cloud survey dashboard to assess if participants are completing the study. If a survey is missed, the REDCap Cloud system will send up to 2 reminders 24 hours apart. If the participant does not respond to the reminders, a research staff member will send an email or SMS text message to understand why there has been no response and encourage them to re-engage with the study. If the survey remains incomplete after 2 weeks of no data, the participant will be deemed lost to follow up. The participant could come back to the study at any time.

### Study Measures

This section details the measurement and methods used to assess each variable. [Table 1](#) outlines the categories, name, rank, and number of items for all measures. The time interval for collecting these measures is provided in [Table 2](#).

#### Demographics

Demographic variables will include age, gender, level of education, race, ethnicity, employment status, annual household income, relationship status, duration of back pain (years since onset), state of residence, and zip code. In order to perform geospatial coding, rural–urban commuting area codes will be downloaded from a public data set provided by the United States Department of Agriculture Economic Research Service. Using MS Excel, participant zip codes will be matched to the rural–urban commuting area data set to classify participants living in rural or urban areas.

#### Average Pain Intensity

The Defense and Veterans Pain Rating Scale (DVPRS) [35] will be used to measure average pain intensity over the previous

24 hours using an 11-point numeric rating scale (0=no pain; 10=as bad as it could be; nothing else matters).

#### Pain Interference With Activity, Mood, Sleep, and Stress

The DVPRS interference scale (DVPRS-II) will be used to measure pain interference with activity, sleep, mood, and stress over the past 24 hours [36] (0=does not interfere; 10=completely interferes).

#### Patient Global Impression of Change

Aligning with IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) recommendations for pain research [37,38], Patient Global Impression of Change will be assessed using the question, “Since the beginning of VR treatment, how would you describe the changes (if any) in activity limitations, symptoms, emotions and overall quality of life-related to your low back pain?” on a 7-point scale ranging from 1 (No change or condition is worse) to 7 (A great deal better, and a considerable improvement that has made all the difference).

#### Physical Function and Sleep Disturbance (PROMIS)

The NIH Physical Function and Sleep Disturbance (PROMIS) [39] short-form measures will be used to assess physical function (version 6b [40]) and sleep disturbance (version 6a [41]) over the past 7 days. Higher scores on physical function signify greater function, whereas higher scores for sleep disturbance reflect greater symptom severity. The conversion table within the scoring manuals, made available from the Person-Centered Assessment Resource [39,42], will be used to calculate the individual short-form T scores using the Item Response Theory scoring algorithms. Specifically, based on published item parameters, T scores (latent trait estimates) will be computed for each individual's response pattern using the Bayesian expected a posteriori method [43-45]. This has been widely applied within pain research [35-37,39-41,43-48].

#### Pain Catastrophizing

The 13-item Pain Catastrophizing Scale (PCS) [49] is a validated instrument widely used clinically and in pain research to assess patterns of negative cognition and emotion in the context of actual or anticipated pain. Despite having discrete subscales for rumination, magnification, and feelings of helplessness related to pain, prior work has shown that the PCS operates unidimensionally [50] and Cook et al (unpublished). Aligning with prior work [32] and the goal of brevity, the following 4 PCS items will be used: “It's terrible and I think it's never going

to get any better,” “I become afraid that the pain will get worse,” “I can’t seem to keep it out of my mind,” and “I keep thinking about how badly I want the pain to stop.” Respondents rate the frequency with which they experience such thoughts on a scale from 0 (Not at all) to 4 (All the time). The 4 numerical ratings will be summed to create a total score and index for pain catastrophizing.

### ***Pain Self-Efficacy***

Pain Self-Efficacy was assessed in 2 ways. First, the 2-item Pain Self-Efficacy Questionnaire (PSEQ-2) will be administered as a validated instrument used to assess respondents’ confidence in their ability to engage in various daily activities despite their chronic pain [51]. The PSEQ-2 consists of the following 2 items: “I can still accomplish most of my goals in life, despite the pain”, and “I can live a normal lifestyle, despite the pain.” Respondents will use a 7-point scale to rate their response from 0 (Not at all confident) to 4 (Completely confident). Scores for the 2 items are summed to create a total score. Second, participants will be asked to rate their overall confidence in their ability to manage their pain on a 10-point scale with 1 (Not at all Confident) to 10 (Very Confident). Following the intervention, this section will be divided into 2 items measuring their overall confidence levels while inside of VR and outside of VR.

### ***Chronic Pain Acceptance***

The Chronic Pain Acceptance Questionnaire (CPAQ-8) short form is an 8-item validated instrument that assesses one’s engagement in personally meaningful activities despite pain, as well as efforts directed at controlling pain (example item: “I am getting on with the business of living no matter what my level of pain is”) [52]. Respondents rate each item using a 6-point scale ranging from 0 (never true) to 5 (always true).

### ***Device Utilization***

The custom device utilization survey is a single-item instrument that assesses the number of VR sessions completed since the last time it was asked. Respondents select either (1) 0, (2) 1, (3) 2, (4) 3, or (5) 4 or more. This survey is administered on a biweekly basis.

### ***System Usability Scale***

The System Usability Scale is a validated, 10-item attitude Likert scale giving a global view of subjective assessments of usability (example item: “I thought the system was easy to use.”) [53]. Participants rate each item using a 5-point response scale ranging from “Strongly Disagree” to “Strongly Agree.” Some

items are reverse scored, a multiplier is applied to the sum total, and total SUS scores range from 0-100.

### ***Immersive Tendencies Questionnaire***

The Immersive Tendencies Questionnaire (ITQ) is a 29-item survey that measures difference in tendencies of individuals to experience presence [54]. The involvement subscale was chosen by the coauthors to reduce participant burden with just 7 items that focus on propensity to be engaged with content such as reading a book or watching a movie.

### ***Assessment of Affect***

The Positive and Negative Affect Schedule (PANAS) is a validated 20-item survey to assess the affect of each participant [55]. They will be asked to the extent they have felt specific emotions on a Likert scale from 1 “Very Slightly or Not at All” to 5 “Extremely.”

### ***Prescription Opioid and Analgesic Medication Use***

A custom survey was also created to assess analgesic medication use. The medication survey consists of 3 main questions to assess for the use of the following: prescription medication, over-the-counter medication, or other medications. Prescription opioid data will be converted to a standardized morphine milligram equivalent daily dose using the Centers for Medicare & Medicaid Services “Opioid Oral Morphine Milligram Equivalent (MME) Conversion Table” [56]. Endorsement of prescription medications will prompt additional items to collect the type of medication, frequency of use, dose, happiness with one’s current prescribed medication regimen, and interest in changing one’s current prescribed medication regimen.

### ***Health Care Utilization***

We will also assess cLBP health care utilization in terms of frequency of steroid injections, lower back surgery, emergency department visits, hospital admissions, and unplanned physician visits over various periods.

### ***Additional Custom Surveys***

Several custom surveys were developed for the study, including one designed to assess satisfaction with each condition. Another assesses device usability, enjoyment or difficulties, and the likelihood to continue treatment. Additional items will assess pain knowledge and pain management skills use (eg, use of relaxation and controlled breathing during the previous 7 days). We will also assess patient perception of the study arm using a single item administered to both groups in the 6-month follow-up survey.

**Table 1.** Variable/category, measure name, rank, and number of items for all measures.

Variable or Category	Measure	Number of items or units
<b>Primary Outcome</b>		
Pain intensity/Pain interference (activity, mood, sleep, stress)	DVPRS-I <sup>a</sup> Pain Scale and DVPRS-II Pain Scale Measures [36]	5
<b>Secondary Outcomes</b>		
Global impression of change	Patient's Global Impression of Change (PGIC) [38]	1
Physical function	PROMIS <sup>b</sup> Physical Function [40]	6
Sleep disturbance	PROMIS Sleep Disturbance [41]	6
Acceptability	Custom Patient Satisfaction	8 + 15 open-ended questions
Adherence	Custom Device Utilization survey	1
Adherence	VR <sup>c</sup> usage data	Seconds/week
Pain self-efficacy	Pain Self-Efficacy Questionnaire (PSEQ) [51] (general) and Custom Pain Self-Efficacy Questionnaire with VR as a referent (inside the VR headset and outside the VR headset)	2 in each
Pain acceptance	Chronic Pain Acceptance Questionnaire (CPAQ) [52]	8
Pain catastrophizing	Pain Catastrophizing Scale (PCS <sup>d</sup> ) [49]	4
Pain medication	Custom Analgesic Medication Use Survey	3 with branching logic to additional 7
Health care utilization	Custom health care utilization survey for cLBP <sup>e</sup>	5 at baseline and 6 at all other time-points
<b>Other measures</b>		
Assessment of affect	Positive and Negative Affect Schedule (PANAS) [55]	20
Susceptibility to virtual reality treatment	Involvement subscale from the Immersive Tendency Questionnaire (ITQ – Involvement subscale) [54]	7
Acceptability	System Usability Scale (SUS) [53]	10
Perceived treatment assignment	Perceived Treatment Assignment survey	1

<sup>a</sup>DVPRS: Defense and Veterans Pain Rating Scale.

<sup>b</sup>PROMIS: Physical Function and Sleep Disturbance.

<sup>c</sup>VR: virtual reality.

<sup>d</sup>The 4 questions were selected from the PCS to decrease participant burden.

<sup>e</sup>cLBP: chronic lower back pain.

**Table 2.** Timeline of measures.

Measure	Pre-treatment (days -14 to 0)		Active treatment (days 1-56)		Postintervention (months 1-6 after the end of the study)			
	Baseline assessment (Day -14)	Pain surveys (Days -10, -7, -4, and 0)	Biweekly surveys	End of treatment (day 56)	Follow up 1 month	Follow up 2 months	Follow up 3 months	Follow up 6 months
DVPRS-I <sup>a</sup> and DVPRS-II	X	X	X	X	X	X	X	X
PGIC <sup>b</sup>				X	X	X	X	X
PROMIS <sup>c</sup> physical function	X			X	X	X	X	X
PROMIS sleep disturbance	X			X	X	X	X	X
Pain self-efficacy measures	X			X	X	X	X	X
PCS <sup>d</sup>	X			X	X	X	X	X
CPAQ-8 <sup>e</sup>	X			X	X	X	X	X
Opioid use	X			X	X	X	X	X
Health care utilization	X			X				
Patient satisfaction					X	X	X	X
Device utilization			X	X				
VR <sup>f</sup> usage data			X	X				
PANAS <sup>g</sup>	X			X				
SUS <sup>h</sup>				X				
ITQ <sup>i</sup> —involvement subscale	X							
Perceived treatment assignment								X

<sup>a</sup>DVPRS: Defense and Veterans Pain Rating Scale.

<sup>b</sup>PGIC: Patient's Global Impression of Change.

<sup>c</sup>PROMIS: Physical Function and Sleep Disturbance.

<sup>d</sup>PCS: Pain Catastrophizing Scale.

<sup>e</sup>CPAQ-8: Chronic Pain Acceptance Questionnaire.

<sup>f</sup>VR: virtual reality.

<sup>g</sup>PANAS: Positive and Negative Affect Schedule.

<sup>h</sup>SUS: System Usability Scale.

<sup>i</sup>ITQ: Immersive Tendencies Questionnaire.

### Data Collection, Quality Control, and Confidentiality

All questionnaires will be completed by participants electronically via the REDCap Cloud platform. We will collect information at every stage of recruitment, randomization, and treatment in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines [57]. The Western Institutional Review Board approved this study. Given the safety of the device seen in past studies [7,31], Western Institutional Review Board did not deem that this study would require Data Safety and Monitoring Board oversight.

### Compensation

Participants will receive a total of US \$150 (US \$6 per completed survey) for their participation in the entire study. Two payments will be processed. The first payment will be distributed at the end of the 8-week program (US \$126 possible; prorated) and upon return of their VR headset (prepaid shipping

will be provided). The second payment will be distributed after the last follow-up survey (US \$24 possible; prorated). All payments will be in the form of an Amazon eGift Card.

In addition to their monetary compensation, all participants will be eligible to receive a gift VR headset 6 months after their completion of treatment if they complete 16 or more of the 21 surveys administered during the active treatment phase, confirm their interest in receiving a VR headset, and return their VR treatment study headset.

### Safety Monitoring

Participants were provided with contact information and encouraged to contact as needed. Safety will be monitored by following up with participants for any adverse events they communicate to the support staff. Additionally, adverse experiences with using VR will be assessed using the question, "Did you experience any motion sickness or nausea while using VR?" on 4-point with 0 (Never), 1 (Sometimes), 2 (Often), and



3 (Always). Similar to prior work, VR side effects will be assessed at the end of treatment [32].

### Sample Size Determination

In terms of sample size considerations, a power analysis was performed using data from a recent at-home cLBP study that we conducted. DVPRS pain intensity scores were collected from 39 individuals at baseline, during, and immediately following a 21-day, skills-based VR intervention, and from 35 individuals at baseline, during, and immediately following an audio-only version of the 21-day program. The average difference score was 1.48 for the VR group and was 0.756 for the audio-only group (on an 11-point scale). Assuming an  $\alpha$  level of .05 and 90% power, we would need 45 participants per group to observe a treatment  $\times$  time interaction. In case of high attrition (40%), we will randomize at least 75 participants per group and if possible up to 90 participants per group.

### Statistical Analyses

#### General Approach

Checks of assumptions underlying statistical procedures will be performed and all corrective procedures will be applied as necessary. All analyses will involve 2-sided hypothesis tests, with  $\alpha=.05$  and adjusted for any multiple comparisons within the family of tests as appropriate.

Group equivalence will be assessed through univariate tests of association between treatment groups (EaseVRx/Sham VR) for all baseline demographic and clinical variables with chi-square and Kruskal–Wallis tests applied as appropriate. If statistically significant differences between groups are found for any variables ( $P<.05$ ), those will be controlled for in the mixed models.

The data will be analyzed in a mixed-model framework (PROC GLIMMIX in SAS) with 3 explanatory factors: treatment group, time, and time  $\times$  treatment group. Treatment group, EaseVRx versus Sham VR, will be specified as a between-subjects factor. Time will be specified as a within-subjects factor. The effect of interest will be the time  $\times$  treatment group effect which tests whether the treatment group influenced the trajectory of the key variables over time.

The analytic method used will not involve imputing missing data for estimating the significance of the effects specified in the model. However, the predicted values from the estimated model will be used for reporting the findings. Given the safety of this treatment, there is no plan to conduct interim analyses.

#### Primary Analyses

The primary endpoint will be the time course of DVPRS-I Pain scale rating at baseline (defined as the average of 3 DVPRS-I Pain Scale ratings obtained during the 2 weeks before enrollment/randomization), at 8 weekly time points (twice per week) across the 8-week intervention, and immediately following the intervention. We will use a linear mixed model as described above.

#### Secondary Analyses

Several analyses will be proposed.

First, we will compare the PGIC scale at end of treatment and follow-ups.

Second, we will repeat similar analyses as above for 2 time points, baseline and immediately following the 8-week intervention for opioid drug use, PROMIS physical function, PROMIS sleep disturbance, PSEQ-2, PCS, and CPAQ-8.

Finally, we will repeat similar analyses as above for 2 time points, the day immediately following the 8-week intervention and 1 month after the intervention for DVPRS Pain Rating, opioid drug use, PROMIS physical function, PROMIS sleep disturbance, PSEQ-2, PCS, and CPAQ-8.

#### Exploratory Analyses

A number of exploratory analyses will be conducted, all of which envisage the above linear mixed modeling strategy with time points and variables as specified below.

First, we will assess Intervention  $\times$  Time effects for a number of health-related outcome metrics (eg, number of steroid injections, emergency department visits, hospital admissions) at 2 time points, Day 9 and immediately following the 8-week intervention.

Second, we will repeat the above analyses for the period comprising the end of the 8-week intervention and at 3 and 6 months after the intervention.

Third, we will assess Intervention  $\times$  Time effects for DVPRS Pain Rating, opioid drug use, PROMIS physical function, PROMIS sleep disturbance, PSEQ-2, PCS, CPAQ-8, Patient satisfaction, and PANAS for the periods comprising the 8-week intervention and at 1, 2, 3, and 6 months after the intervention. We will use a 2-factor ANOVA with intervention (EaseVRx vs Sham VR) as an independent groups factor and time as a dependent groups factor. Two-sided post hoc  $t$ -tests (adjusted for multiple comparisons) will be utilized to isolate the locus of any effects.

Fourth, we will examine the time course of changes in pain skills (eg, controlled breathing, meditation) from baseline, at the end of the 8-week intervention, and at 1, 2, 3, and 6 months after the intervention only in the EaseVRx group. We will use a one-factor repeated-measures ANOVA. Two-sided post hoc  $t$ -tests (adjusted for multiple comparisons) will be utilized to isolate the locus of any effects. When appropriate, we will also utilize more robust statistical approaches that better address missing data and do not assume distributional normality, such as bootstrapping.

In subsequent manuscripts, we will explore potential covariants of treatment response and possible mechanisms of actions.

## Results

The study was approved by the Western Institutional Review Board on July 2, 2020. The protocol (NCT04415177) was registered on May 27, 2020. Recruitment for this study was completed in July 2020 and data collection will remain active until March 2021. In total, 186 participants were recruited. Multiple manuscripts will be generated from this study. The

primary manuscript will be submitted for publication in the winter of 2020.

## Discussion

### Protocol Overview

VR for chronic pain is an emerging area of behavioral medicine and science with heightened relevancy during the COVID-19 pandemic. Many people are environmentally isolated and in need of effective home-based pain care. This study protocol builds upon research that previously demonstrated that a 21-day behavioral medicine skills VR program effectively reduced chronic pain intensity and pain-related interference in activity, mood, sleep, and stress at the end of treatment. This study protocol addresses several unknowns that remain in the scientific literature for VR for chronic pain. First, the study will test a VR program of longer duration (56 days) and better aligns with the duration of current “gold-standard” behavioral medicine for chronic pain, typically over 8 weeks of treatment time. Second, the study will test treatment effects captured at the end of treatment and the *durability* of treatment effects measured at several distal posttreatment time points (months 1, 2, 3, 6). Third, the study will include a Sham VR, which will provide a visual treatment (2D nature scenes) that will control for the novelty of a headset device and visual stimuli while omitting active behavioral medicine skills training. The inclusion of the Sham VR group will also allow for exploration of the mechanisms of therapeutic VR. Fourth, a broad range of relevant metrics have been included to characterize the psychological response to VR and aid in the conduct of responder analyses and identification of subgroups; results could inform the development of future tailored immersive therapeutics or study designs. Fifth, all study headsets will capture participant use data, thereby allowing for the quantification of participant engagement and calculation of treatment dose thresholds associated with treatment effects. Sixth, the study will capture analgesic medication use and data on health care utilization specific to back pain; these data will allow for the conduct of exploratory analyses examining the impact of VR on these factors for the subset of participants using these treatments. Seventh, the study will occur within the context of the COVID-19 pandemic and will inform self-administration of home-based VR and engagement during COVID-19 specifically.

The study design’s strength is that it will be conducted remotely and untethered from the medical system. This design will increase the ecological validity of data derived from a home-based, national, pragmatic sample of people with cLBP who will self-treat in their home environment. Additional aspects of methodological rigor include participant blinding and randomization to the treatment group.

### Limitations

The key limitations of this study protocol include the following. First, all data will be either self-reported by the study participant

or collected by the device (eg, use data for frequency and duration). Because the study is pragmatic and will include a national sample, we will not verify medical diagnoses or prescribed pain medication types and doses. Second, the study is specific to cLBP and findings may not generalize to other pain conditions. However, we note that people with cLBP often report having 2 or more comorbid pain conditions (Darnall et al, unpublished). As such, chronic back pain is not often experienced in isolation.

Digital behavioral health treatment studies typically report relatively low treatment engagement rates among participants with rates ranging between 20% and 60% [32,58-60]. While prior research evidenced good engagement for therapeutic VR for chronic pain, engagement rates for a 2D Sham VR are unknown and we may risk disparate engagement rates between the 2 treatment groups. While the study team has endeavored to minimize such discrepancy by enhancing the Sham VR’s face validity, we anticipate some treatment group discrepancy would naturally occur if one treatment is experienced broadly as less rewarding or effective.

Our plan to enroll a national sample over the internet lends a mix of strengths and limitations. Participants recruited via the internet are likely to be more technologically savvy than the general population seeking medical care from a health care system. It could be argued that our study results may not generalize to people who are less likely to engage with the internet and technology. However, we also note that treatment studies that are conducted within traditional medical settings typically involve more in-person contacts and enhanced placebo effects (ie, halo effect) that would be likely to yield more positive treatment expectations and outcomes. We underscore that our study design will not benefit from medical setting placebo effects.

Finally, aligning with prior work, data on adverse effects will be collected at the end of the study. We acknowledge that these methods introduce the potential for recall bias. However, previous study participants reported easily recalling adverse experiences at the end of the study due to their specificity and salience (eg, cybersickness) [32].

### Conclusions

This study will be one of the most rigorous in assessing the impact of self-administered VR therapy in community-based individuals with chronic lower back pain and the first to use a placebo VR therapy program. Its remote design will allow it to be completed during a global pandemic in a pragmatic and nationally representative sample. This will also be the first study to assess VR therapy’s durability for chronic pain over a 6-month posttreatment follow-up period. Results from this study will provide critical data on how individuals with chronic lower back pain may use self-administered VR therapy at home for symptom management and functional improvement.

### Acknowledgments

This study was supported financially by AppliedVR, Inc.

## Conflicts of Interest

LG, TM, and IM are employees of AppliedVR, Inc. JS is the President of AppliedVR, Inc. BD is chief science advisor for AppliedVR. BB and PK are consultants to AppliedVR, Inc. RL has an advisory role with Applied VR, Inc.

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## Abbreviations

- CDC:** Centers for Disease Control and Prevention
- cLBP:** chronic lower back pain
- CMS:** Centers for Medicare & Medicaid Services
- CPAQ:** Chronic Pain Acceptance Questionnaire
- DVPRS:** Defense and Veterans Pain Rating Scale
- ITQ:** Immersive Tendencies Questionnaire



**MME:** morphine milligram equivalent  
**PANAS:** Positive and Negative Affect Schedule  
**PCS:** Pain Catastrophizing Scale  
**PGIC:** Patient's Global Impression of Change  
**PHQ:** Patient Health Questionnaire  
**PROMIS:** Physical Function and Sleep Disturbance  
**PSEQ:** Pain Self-Efficacy Questionnaire  
**SUS:** System Usability Scale

*Edited by G Eysenbach; submitted 27.10.20; peer-reviewed by LA Lee, T Jones; comments to author 17.11.20; revised version received 28.11.20; accepted 08.12.20; published 19.01.21.*

*Please cite as:*

*Garcia LM, Darnall BD, Krishnamurthy P, Mackey IG, Sackman J, Louis RG, Maddox T, Birckhead BJ  
Self-Administered Behavioral Skills-Based At-Home Virtual Reality Therapy for Chronic Low Back Pain: Protocol for a Randomized  
Controlled Trial  
JMIR Res Protoc 2021;10(1):e25291  
URL: <https://www.researchprotocols.org/2021/1/e25291>  
doi: [10.2196/25291](https://doi.org/10.2196/25291)  
PMID: [33464215](https://pubmed.ncbi.nlm.nih.gov/33464215/)*

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Protocol

# Impact of Teleconsultation on Patients With Type 2 Diabetes in the Brazilian Public Health System: Protocol for a Randomized Controlled Trial (TELEconsulta Diabetes Trial)

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## Abstract

**Background:** Although the Brazilian Unified Health System (SUS) offers universal health coverage, access to quality care is often limited by social inequality and location. Although telemedicine has been shown to be an important tool in the efforts to overcome this problem, because it can provide access to specialist care and break the geographical barriers to health care, there are no national studies demonstrating its use in public health.

**Objective:** This study aims to test the hypothesis that remote consultation can be as effective as standard face-to-face consultation for type 2 diabetes mellitus in the Brazilian public health system and to assess the associated costs related to teleconsultation in public health scenarios, for patients referred from Primary Health Care units of the SUS for specialist care.

**Methods:** This is a pragmatic, phase 2, unicentric, open-label, noninferiority, blinded allocation, data-blinded, centrally randomized clinical trial. The inclusion criteria will be adults, both sexes,  $\geq 18$  years old, glycated hemoglobin ( $HbA_{1c}$ )  $\geq 8\%$ . Outcomes will be evaluated by assessing symptoms, laboratory exams, anthropometric measurements, blood pressure, adverse events, and satisfaction level for 6 months. The costs of the teleconsultation will be assessed using the time-driven activity-based costing (TDABC) method to compare the costs with the face-to-face consultations. The noninferiority margin was set at 0.5%. Assuming an SD of 1.3% for both groups, true difference between the means of zero, and a type I error level of 5% (one-sided), it was estimated that 117 individuals per group would be necessary to achieve 90% power. Statistical analysis of the efficacy will be done using intention-to-treat and per-protocol approaches.

**Results:** The results from this trial will be reported according to the CONSORT guidelines. The trial was approved by the institutional review board on October 5, 2019. Data collection started in January 2019 and is expected to finish in 2022. At the time of manuscript submission, 18 participants were recruited.

**Conclusions:** Our expectations are that providing remote access to health care will result in improvements in the health and quality of life of patients with type 2 diabetes and reduce costs and that both patients and clinicians will benefit from and be satisfied with this technology.

**Trial Registration:** Registro Brasileiro de Ensaios Clínicos RBR-8gpgyd; <https://ensaiosclinicos.gov.br/rg/RBR-8gpgyd>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/23679

(*JMIR Res Protoc* 2021;10(1):e23679) doi:[10.2196/23679](https://doi.org/10.2196/23679)

**KEYWORDS**

remote consultation; diabetes mellitus; telemedicine; telehealth; costs; public health

**Introduction**

According to the 2016 Global Burden of Disease [1], despite the increase in both quality of life and access to health care observed since 1990, there are still many countries in which health inequalities remain, particularly in relation to cancer and noncommunicable diseases, such as asthma, chronic obstructive pulmonary disease, and diabetes. These diseases have a significant impact on quality of life [2], and this is particularly true in the case of diabetes, because it has a range of serious complications in situations where it is poorly controlled by the individual, such as cardiovascular disease, chronic kidney disease, blindness, and lower limb amputation [3], many of which could be avoided by providing better access to health care.

**Figure 1.** Regions of Brazil related to this project.



Although there is increasing evidence for the use of remote consultation worldwide [9-11], in Brazil, under Resolution number 1643/2002 [12] of the Federal Council of Medicine, medical consultations by telephone or internet cannot be conducted directly between health professionals and patients. Thus, currently, teleconsulting is only allowed when there is a health professional at both ends of the communication channel, except in the COVID-19 pandemic situation. Also, there are no national studies in Brazil that address the effectiveness and costs involved in teleconsultation service in the public health system. If teleconsulting directly between the physician and the patient can be shown to be safe and effective, this would provide strong evidence to change the current regulations, freeing up one professional from the consultation and driving down costs. The main objective of this study is to test the hypothesis that remote consultation can be as effective as standard face-to-face consultation for type 2 diabetes in the Brazilian public health system and to assess the associated costs related to teleconsultation in public health scenarios.

**Methods**

TELEConsult Diabetes is a pragmatic, phase 2, single-center, open-label, noninferiority trial with central randomization that

In 2016, Brazil was ranked 96th among 195 countries regarding access to health care and quality of life, according to the Global Burden of Disease [1]. Despite a slight improvement in the health index (from 46.5 in 1990 to 63.8 in 2016), access to health care is still one of the largest indicators of social inequality [4]. While the inhabitants of São Paulo, Brazil's largest city (Figure 1), have access to 2.81 doctors per 1000 inhabitants, in the northeast region, this proportion is about 1.41 doctors, and in some states, this proportion can even reach <1 doctor per 1000 inhabitants [4]. When considering physicians of all medical specialties, almost 70% of these professionals are concentrated in the south and southeast regions of the country [5]. To improve medical access, there is a need to develop strategies that can not only enhance local primary care but also improve the regulatory processes and the organization of specialized health care in Brazil [6-8].

will evaluate the efficacy and safety of specialized remote consultation compared to face-to-face consultation in patients with type 2 diabetes mellitus referred by primary health care units to specialist care in the Unified Health System (SUS) [13].

The inclusion criteria are adults of both sexes,  $\geq 18$  years old, established diagnosis of type 2 diabetes, and either not insulin dependent (with any level of glycemic control measured by glycated hemoglobin [HbA<sub>1c</sub>] accordingly to local protocol [14-17]) or insulin dependent (HbA<sub>1c</sub> >8%). Exclusion criteria are patients <18 years old or with type 1 diabetes, women with gestational diabetes or diagnosed during pregnancy, and patients with chronic renal failure with estimated or measured creatinine clearance <30 mL/min/m<sup>2</sup> [18].

Brazil has a universal public health care system called SUS, which is structured around the principle of primary care and operates by integrating other services and levels of care, such as specialized care, into the system for the whole population. The main goal of primary care in Brazil is to provide basic care and to coordinate other levels of care throughout the health system network, regulating referrals to specialist care [8].

The Telehealth Center of Santa Catarina state uses a system that does not represent the reality in most Brazilian states. First,

the primary care physicians request a teleconsultation with a specialist. This consultation involves both the primary care physicians and the specialist. Following this first contact, the primary care physician decides whether the patient needs to be referred to a face-to-face consultation with the specialist [19,20]. This system of compulsory flow established and operating in Santa Catarina state is the ideal setting to investigate the potential of remote consultation in primary health care, compared to face-to-face consultations.

The participant will be identified by the primary care physician and the Telehealth Center of the state of Santa Catarina, and the regulatory department of the Municipal Health Office of Joinville will determine if she or he meets the eligibility criteria. Patients with type 2 diabetes mellitus may be recruited from any of the city's 70 primary care centers. A researcher will contact the patient by telephone to tell them about the trial and invite them to participate in the study. If the patient agrees, they will be told that they need to provide their written consent, and an informed consent form will be posted to them prior to reading and assessment for their participation in the study. Then, 2-5 days after sending the informed consent form, the researcher will again telephone the patient to confirm their interest in participating in the trial. If the response is still positive, they will schedule a home visit at a convenient time with the patient, in the presence of a legal representative or relative if they so wish. During the visit, any questions related to the study will be answered. After signing and agreeing to participate in this study, the researcher will tell the participant about the next steps: Their data will be randomized in a system created especially for this trial, and they will be scheduled for a face-to-face consultation or for a remote consultation with the specialist. By the end of this home visit, the participant will have been advised about the study, their participation, the date and place of the research consultation, and that there are no costs involved.

To calculate the real cost of a teleconsultation service to compare with the cost of the face-to-face service and to generate a cost parameter for the primary health care units for this type of service, the time-driven activity-based costing (TDABC) method will be used [21,22]. In addition to the costs of the resources used, this method also considers the amount of time spent on each stage of the process, enabling the identification of stages where the teleconsultation speeds up or slows down the process, reducing or increasing costs in relation to face-to-face consultation.

This study will also include other indicators, such as the transportation costs for the patients and physicians in a "real-word" scenario, to carry out cost-effectiveness estimates. Finally, we intend to discuss issues related to the reduced costs that increased access to medical care, via teleconsultation, can generate for the system.

The randomization list will be generated electronically using appropriate software. Randomization will be performed in blocks of 4 at a 1:1 ratio. Confidentiality of the randomization list will be ensured by setting up a central database and the use of an electronic case report form. Access to the system will be granted through specific usernames and passwords given to each investigator or study team. The patient will be allocated

to one of the treatments (remote consultation or face-to-face consultation) only after being registered in the system. Given the nature of the intervention, blinding is not feasible. However, data analysis will be performed by a statistician blind to patient allocations.

Participants in both groups will be assisted by 1 of a team of 4 endocrinologists from the public outpatient clinic. They will take turns to provide assistance in the 2 modalities. The remote consultation with the intervention group will involve only the specialist and the participant. These consultations will take place in 1 of the 6 primary care units chosen to cover the main regions of the city. In each of these units, the research team set up a room with a computer, microphone, and camera to deliver the remote consultation, assisted by the same team of endocrinologists.

The same physicians will undertake both the remote consultation and the face-to-face consultation, with the same duration (30-60 minutes). All the physicians are specialists medically trained in endocrinology and experienced in caring for patients with diabetes in different settings and as part of the city's specialist care network. A protocol based on national and international guidelines specifically designed for the study [17,23-25] will be used to ensure that all the consultations are as similar as possible. The physicians were instructed to follow the protocol to avoid any bias related to the consultation. The protocol includes instruction on the questions to be asked about the participant's health and the medicines they are using, the scale to be used for hypoglycemia evaluation [26], and the medications to be prescribed (following current guidelines). At the end of the consultation, participants from both groups receive, in addition to medical advice and drug prescriptions, guidance on any laboratory tests that need to be carried out before the next consultation.

The primary outcome will be a change in HbA<sub>1c</sub> levels at 6 months after randomization. However, we will perform a prespecified analysis 3 months after randomization.

Secondary outcomes will be fasting blood glucose, complete blood count, urea, creatinine, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, systolic and diastolic blood pressure, body weight, BMI, frequency of hypoglycemia, and incidence of adverse events. In addition, in the intervention group, we intend to evaluate the satisfaction of the endocrinologists and the patients with the video conference system using a structured questionnaire [23].

A specific quality of life in diabetes questionnaire will be used with patients with diabetes mellitus in the first and last research consultations in both groups [27-29]. In addition, we will estimate the actual cost of the remote consultation service, using the TDABC method [21,22] to obtain the unit cost of remote consultation in the primary health care units.

This trial is registered with the Ethics and Research Commission (03434218.1.2001.5362).

## Results

This study was approved and funded by the Brazilian Ministry of Health in October 2018 and was approved by the institutional review board in October 2019. Data collection started in January 2019 and is expected to finish in 2022. At the time of manuscript submission, 18 participants were recruited.

The primary objective of this study is to confirm the noninferiority of remote consultation in comparison with face-to-face consultation assessed by the change from baseline in HbA<sub>1c</sub> (%) at 6 months. The noninferiority margin was set at 0.5%. Assuming an SD of 1.3% for both groups, true difference between the means of zero, and a type I error level of 5% (one-sided), it was estimated that 117 individuals per group would be necessary to achieve 90% power [30]. In order to accommodate for a maximum dropout rate of 5%, the sample size was increased to 124 individuals per group. Sample size calculation was performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

The primary endpoint in this study is the change from baseline in HbA<sub>1c</sub> (%) at 6 months. The assessment of noninferiority of remote consultation in relation to face-to-face will be conducted according to the CONSORT guidelines [31], using the confidence interval approach to the difference in the mean of the primary variable between the 2 groups. If the upper limit of the 90% bilateral CI is lower than the established noninferiority margin (0.5%), the noninferiority of the remote consultation group relative to the face-to-face group is declared at the 5% significance level. In addition, an analysis of covariance (ANCOVA) model will be constructed using the main effects of treatment and baseline HbA<sub>1c</sub> as the covariate.

Adjusted means by treatment will be presented as well as an estimate of the difference between adjusted means. A 90% 2-sided CI, based on the ANCOVA model, will be computed for the difference between adjusted means. If the upper limit of the 90% bilateral CI is lower than the established noninferiority margin (0.5%), the noninferiority of the remote consultation group relative to the face-to-face group is declared at the 5% significance level [32-34]. The primary endpoint will be analyzed for the intention-to-treat (ITT) and per-protocol populations. If the proportion of missing data is greater than 5%, sensitivity analyses for missing data imputation will be performed [35,36].

The secondary endpoint is the change from baseline in HbA<sub>1c</sub> at 3 months, which will be evaluated with ANCOVA. Adjusted means (with 95% CI) by treatment will be presented. Mixed effects, repeated measures models will be considered for secondary endpoints defined by continuous variables over time

(baseline, 3 months, 6 months). Comparison of secondary endpoints defined by categorical data will be evaluated using chi-square or Fisher exact tests. Secondary endpoints will be performed as 2-sided tests with an alpha of 5%, and 95% CIs will be reported. The proportion of adverse events will be compared between the 2 groups via a Fisher exact test. The secondary endpoints will be analyzed on the ITT population.

Baseline characteristics will be compared and summarized by treatment groups for the ITT population. Categorical data will be summarized by numbers and percentages. Continuous data will be summarized by mean, SD, and range if data are normal and median and IQR if data are skewed. Normality will be assessed by visual inspection of histograms and with the Shapiro-Wilk normality test [36]. Baseline variables will be compared with the chi-square test or Fisher exact test for categorical variables and the *t* test or Mann-Whitney test for continuous variables. Statistical analyses will be performed using SAS version 9.4.

## Discussion

Brazil is a country of continental proportions, with great heterogeneities and gaps in access to health care, types of health services, and specialized medical professionals. Lack of access to health services is one of the main indicators of social inequality in Brazil. Thus, to improve access, there is a need to build strategies that impact primary health care, the processes that regulate access, and the organization of specialist care. In this context, studies have shown telemedicine to be equivalent to face-to-face care, and it can be an effective solution to increasing patient access to services, especially to specialist doctors.

Providing evidence of the efficacy and safety of remote treatment for different conditions in Brazil will contribute to improving patients' access to the public health system, including specialist doctors. This evidence can also help to remove restrictions placed on remote consultation by the Brazilian Federal Medicine Council, which currently restricts direct specialist-to-patient consultation. This model of improved access can help to meet the health needs of the population, breaking the geographical barriers that a country like Brazil imposes on the provision of health services. In addition to greater access to health care, the use of telemedicine has potential economic benefits for health systems and can be used safely to deliver a quality service.

Our expectations are that providing remote access to health care will result in improvements in the health and quality of life of patients with type 2 diabetes and reduce costs and that both patients and clinicians will benefit from and be satisfied with this technology.

## Acknowledgments

The authors would like to thank Anna Maria Buehler and Jefferson Gomes Fernandes, MD for their invaluable contribution to the initial elaboration of this research protocol and Tiago da Veiga Pereira, who participated in the writing and technical editing of this manuscript. The study received funding from the SUS Institutional Development Support Program (PROADI-SUS) of the Ministry of Health of Brazil.



## Conflicts of Interest

None declared.

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## Abbreviations

**ANCOVA:** analysis of covariance

**HbA<sub>1c</sub>:** glycated hemoglobin

**ITT:** intention-to-treat

**SUS:** Unified Health System (in Portuguese)

**TDABC:** time-driven activity-based costing

*Edited by G Eysenbach; submitted 19.08.20; peer-reviewed by E Franco, A Benis; comments to author 23.09.20; revised version received 15.10.20; accepted 20.10.20; published 21.01.21.*

*Please cite as:*

Rodrigues DLG, Belber GS, Padilha FVDQ, Spinel LF, Moreira FR, Maeyama MA, Pinho APNM, Júnior AA

*Impact of Teleconsultation on Patients With Type 2 Diabetes in the Brazilian Public Health System: Protocol for a Randomized Controlled Trial (TELEconsulta Diabetes Trial)*

*JMIR Res Protoc* 2021;10(1):e23679

URL: <https://www.researchprotocols.org/2021/1/e23679>

doi: [10.2196/23679](https://doi.org/10.2196/23679)

PMID: [33475516](https://pubmed.ncbi.nlm.nih.gov/33475516/)

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Protocol

# Evaluating the Effectiveness of an E-Mental Health Intervention for People Living in Lebanon: Protocol for Two Randomized Controlled Trials

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## Abstract

**Background:** The lack of availability of evidence-based services for people exposed to adversity globally has led to the development of psychological interventions with features that will likely make them more scalable. The evidence for the efficacy of e-mental health from high-income countries is compelling, and the use of these interventions could be a way to increase the coverage of evidence-based psychological interventions in low- and middle-income countries. Step-by-Step is a brief (5-session) intervention proposed by the World Health Organization as an innovative approach to reducing the suffering and disability associated with depression.

**Objective:** This study aims to evaluate the effectiveness and cost-effectiveness of a locally adapted version of Step-by-Step with Syrian nationals (trial 1) and Lebanese nationals and other populations residing in Lebanon (trial 2).

**Methods:** This Step-by-Step trial involves 2 parallel, two-armed, randomized controlled trials comparing the e-intervention Step-by-Step to enhanced care as usual in participants with depressive symptoms and impaired functioning. The randomized controlled trials are designed and powered to detect effectiveness in 2 populations: Syrians in Lebanon (n=568) and other people residing in Lebanon (n=568; Lebanese nationals and other populations resident in Lebanon). The primary outcomes are depressive symptomatology (measured with the Patient Health Questionnaire-9) and functioning (measured with the World Health Organization Disability Assessment Scale 2.0). Secondary outcomes include anxiety symptoms, posttraumatic stress disorder symptoms, personalized measures of psychosocial problems, subjective well-being, and economic effectiveness. Participants are mainly recruited through online advertising. Additional outreach methods will be used if required, for example through dissemination of information through partner agencies and organizations. They can access the intervention on a computer, tablet, and mobile phone through a hybrid app. Step-by-Step has 5 sessions, and users are guided by trained nonspecialist “e-helpers” providing phone-based or message-based support for around 15 minutes a week.

**Results:** The trials were funded in 2018. The study protocol was last verified June 20, 2019 (WHO ERC.0002797) and registered with ClinicalTrials.gov (NCT03720769). The trials started recruitment as of December 9, 2019, and all data collection was completed in December 2020.

**Conclusions:** The Step-by-Step trials will provide evidence about the effectiveness of an e-mental health intervention in Lebanon. If the intervention proves to be effective, this will inform future scale-up of this and similar interventions in Lebanon and in other settings across the world.

**Trial Registration:** ClinicalTrials.gov NCT03720769; <https://clinicaltrials.gov/ct2/show/NCT03720769>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/21585

(*JMIR Res Protoc* 2021;10(1):e21585) doi:[10.2196/21585](https://doi.org/10.2196/21585)

## KEYWORDS

e-mental health; psychological interventions; guided-self-help; global mental health; adversity; Lebanon; Syrians

## Introduction

Most people suffering from mental health problems do not access mental health care. It is estimated that in low- and middle-income countries, the majority (76%-85%) of people suffering from mental disorders receive no treatment at all [1]. This disparity is even bigger in communities exposed to adversities where the prevalence of mental health problems is higher and resources are often scarce [2]. The lack of availability of evidence-based services for people exposed to adversity globally has led to an interest in developing psychological interventions that are more likely to be scalable in low-resource settings [3].

Lebanon has a history of political instability that has negatively impacted the development of the country. There are approximately 1.5 million Syrian refugees in Lebanon, of which 74% are lacking legal status [4]. The country's resources are extremely stretched, and the growing number of refugees puts extra pressure on the labor market and infrastructure. The treatment gap for mental health problems is estimated at over 90% by the National Mental Health Programme at the Ministry of Public Health (MoPH) [5]. A national epidemiological survey (involving 2857 people in Lebanon) published before the Syrian civil war showed that 1 in 6 people met the criteria for a mental disorder, with 27.0% of these "serious" [6]. Only 1 in 9 respondents with a mental disorder had ever obtained any treatment. More recent data show that the situation has improved, but treatment seeking still remains low, with a treatment gap of approximately 80% [7]. Affordable and accessible mental health care is very limited in Lebanon. MoPH data from 2015 show that there are 1.26 psychiatrists and 3.42 psychologists per 100,000 population and 97% of the mental health care staff works in private practice in Lebanon, which limits access to affordable care [5]. Since 2015, the MoPH in Lebanon has trained staff in more than 70 primary health care centers nationwide on the assessment and management of people with mental health conditions following World Health Organization (WHO) Mental Health Gap Action Programme (mhGAP) guidelines [8]. With a high prevalence of mental health problems in both refugees and the Lebanese host community and limited resources, there is a considerable need to scale up mental health and psychosocial support services in Lebanon.

E-mental health, which is the use of electronic devices to provide mental health interventions, could be a way to increase the coverage of evidence-based psychological interventions in a sustainable manner. In high-income countries, guided, online, self-help programs have been found to be as effective as the same interventions provided face-to-face [9-11]. In addition, such programs have been shown to reduce symptoms of mental disorders in routine care [12]. With ample evidence supporting the use of e-mental health, a number of countries now include e-mental health in their national mental health strategies and treatment guidelines (eg, the Netherlands, the United Kingdom, Australia, New Zealand, Scandinavian countries [13], and Lebanon [5,14]). In Lebanon, a substantial proportion of the population has access to mobile phones (92%) and the internet (78%) [15]. This suggests that many Lebanese have the means to access an e-health intervention, with this percentage likely to rise in the coming years [16]. The adult literacy rate is 88%, with youth literacy at 96% [17]. Syrians in Lebanon also have access to smartphones and the internet, with 80% reporting access at the household level (eg, 1 phone per household) [18]. The potential of digital interventions is that they can reach more people than more in-person interventions, which commonly have high dropout rates.

Step-by-Step is a brief (5-session) e-mental health intervention for depression proposed by the WHO as an innovative approach to reducing the suffering and disability associated with mental health issues [19]. It has been carefully designed and comprehensively adapted for use in Lebanon (including for refugees residing in Lebanon [20]). Step-by-Step is guided by trained nonspecialist "e-helpers" providing phone-based or message-based support to Step-by-Step users for around 15 minutes a week. It can also be used with different guidance models including no contact or contact on demand.

This paper describes the protocol for 2 randomized controlled trials (RCTs) of Step-by-Step in Lebanon. The study protocol has been informed by previous formative work [20,21], and an uncontrolled pilot [14] and a feasibility RCT, which has been submitted for publication, showed the acceptability and feasibility of Step-by-Step. The feasibility RCT was not powered to evaluate treatment effects, although estimates for complete cases at postassessment showed a significant reduction of depressive symptoms, anxiety, and posttraumatic stress and an improvement of functioning and well-being. The



intention-to-treat (ITT) analysis showed a marginally nonsignificant effect on functioning and a trend in the expected direction for the other measures. These results indicate the importance of evaluating the effectiveness of Step-by-Step in fully powered RCTs. Because of the specific needs of different populations, the research effort is evaluating Step-by-Step with Syrians in Lebanon and other populations residing in Lebanon (eg, Lebanese and other refugee groups). Given the potentially substantial differences in experiences of migration and recent trauma between these 2 groups and that separate funding was received for the evaluations of Step-by-Step in these 2 groups, 2 RCTs were planned. The RCTs are powered to evaluate effectiveness and cost-effectiveness of Step-by-Step in the 2 populations. As the 2 RCTs use the same infrastructure and protocol, this paper describes both of them at the same time.

## Methods

### Objectives

This study aims to evaluate the effectiveness and cost-effectiveness of a locally adapted version of Step-by-Step in people residing in Lebanon, including Lebanese nationals, displaced Syrian people, and other populations resident in Lebanon. The RCTs will compare the e-intervention Step-by-Step to enhanced care as usual (ECAU) in participants with depressive symptoms and impaired functioning. One RCT will involve Syrian populations in Lebanon, and the other will involve other people residing in Lebanon.

### Design and Setting

The study is designed as 2 pragmatic, parallel, 2-arm RCTs. Participant-level outcomes will be measured at 3 time points: baseline (t0), posttreatment (t1), and follow-up (t2). Posttreatment (t1) has been set at 8 weeks after baseline (t0), and follow-up (t2) has been set at 3 months after posttreatment (t1), so 5 months after baseline (t0). Posttreatment is the primary outcome for the study. In both RCTs, Step-by-Step will be compared to ECAU in 1 RCT with Syrians in Lebanon (hereafter called “Syrian” group) and in the other RCT with other populations residing in Lebanon (eg, Lebanese and other refugee groups, hereafter called “Lebanese and others” group). Both RCTs use the exact same infrastructure, and the study is powered to detect effectiveness for both groups.

The primary hypothesis is that at posttreatment (8 weeks after baseline), in both the “Syrian” and “Lebanese and other” groups, people receiving Step-by-Step will have less severe depressive symptoms (measured with the Patient Health Questionnaire [PHQ-9]) and higher levels of functioning (measured with the World Health Organization Disability Assessment Scale [WHODAS] 2.0) compared to people receiving ECAU. The secondary hypothesis is that people receiving Step-by-Step will report fewer anxiety symptoms, posttraumatic stress disorder (PTSD) symptoms, and personally identified psychosocial problems as well as higher levels of subjective well-being. In addition, we hypothesize that offering Step-by-Step is more cost effective than ECAU.

## Study Arms

### Step-by-Step intervention

Step-by-Step is brief (5 sessions) and has been designed to primarily address depressive symptoms [19]. Behavioral activation is the main active therapeutic agent in the intervention, as it is easy for users to engage with, has a very strong evidence base for depression [22,23], and can easily be adapted to a minimally guided, internet delivery model [24]. The intervention follows a narrative story-based approach to convey information together with illustrations and weekly exercises. The narrative and exercises aim to increase behavioral activation, including pleasurable activities and social support. Additional strategies to support this include 2 stress management techniques, a gratitude and positive self-talk exercise, and mood tracking where a user is regularly prompted to enter their mood on a graphical 5-point Likert scale. The story and its illustrations have been adapted to the local context, considering linguistic and cultural nuances within the different populations residing in Lebanon (broadly speaking, Lebanese, Syrian, and Palestinian people). Separate papers have been published with more information about the concept behind Step-by-Step [19] and about the adaptation process for Lebanon [20].

In brief, the Step-by-Step narrative has male and female versions with 2 versions per gender: 1 broadly for married people with children and 1 for younger single people without children. The text content is slightly adapted across these versions, but the therapeutic content stays the same. There are also different versions of the illustrations allowing people the choice between a bearded or unbearded character or a character with or without a headscarf. This accounts for gender differences and provides broad tailoring for the main cultural groups of target users. The language used in the intervention is simple so it can easily be understood, and the intervention has audio recordings of all the written text that can be played by people with lower levels of literacy. More information on the intervention can be found in Carswell et al [19] and Abi Ramia et al [20].

The intervention was first developed as an internet intervention and then developed into an iOS and Android app [21] that can be used mostly offline on mobile devices and into a web app that can be accessed via a web browser. These RCTs are testing Step-by-Step as a guided self-help intervention in which Step-by-Step is supported by trained nonspecialist research assistants (called “e-helpers”), who have weekly phone-based or message-based contact lasting approximately 15 minutes with users to provide support and guidance. E-helpers have an undergraduate degree in psychology or social work and work under the regular supervision of trained mental health practitioners. They will receive a 4.5-day training in the research protocols and the intervention itself, including how to guide users in implementing the techniques learned in the intervention and how to use the online system. They are supported in this by a manual and clear session-by-session outlines for the support contacts. Knowledge and therapeutic skills covered in the e-helper training include working with people with depression and other mental health problems, identifying and dealing with crisis situations, and responding to adverse events (AEs). E-helpers need to pass a competency test to be involved in the

RCTs. During the trials, fidelity checks will be conducted to ensure adherence to the guidance protocol using a treatment fidelity checklist. The supervisor and the study coordinator will supervise up to 5% of the responsive support contacts through listening in to calls and reviewing messages.

Weekly clinical supervision will be provided to e-helpers by a clinical supervisor from MoPH with a good understanding of the Step-by-Step intervention and research project. Clinical supervision will ensure fidelity of the guidance provided and involves discussion of difficulties encountered in supporting the users of the intervention, as well as self-care for e-helpers. In addition, weekly supervision on research processes will be provided by the local study coordinator.

### **Enhanced Care as Usual (ECAU)**

ECAU will consist of basic psychoeducation and referral to evidence-based care. If randomized into the ECAU condition, users will first receive basic psychoeducation on depression via the hybrid app. The text for the psychoeducational messages is taken from the first session of Step-by-Step to make sure the information provided is identical. After receiving the psychoeducation, ECAU users will receive a list of selected primary health care facilities with staff trained in the mhGAP where they can seek evidence-based care as usual consisting of assessment and pharmacological or psychosocial management of mental health conditions according to mhGAP [8].

### **Randomization**

Upon completion of the baseline assessment, participants will be randomized to either the intervention or ECAU, using a 1:1 allocation ratio. The randomization is handled by an algorithm for permuted block randomization that is built into the app and not accessible to the research team. The algorithm generates a random sequence of blocks with varying length. In each block, the number of seats for both groups is even, and the order is fully random.

### **Sample Size Calculation**

A recent meta-analysis of depression treatments in low- and middle-income countries has been conducted with 32 RCTs, looking at different intervention types, formats (eg, guided self-help, group therapy), and comparators (eg, waitlist, treatment as usual) [25]. An effect size of 0.73 (Hedges  $g$ ) was found for symptoms of depression. Moreover, a recent meta-analysis of internet-based and mobile-based interventions for the treatment of depression in high-income countries, including 19 RCTs, showed an effect size of 0.90 (Hedges  $g$ ) when comparing these treatments with the waitlist condition [26,27]. Despite these relatively high effect sizes reported in literature, the power calculation for these RCTs was completed for a more conservative (but still clinically significant) effect size of Cohen  $d = 0.5$ .

Assuming one primary outcome, power of 90%, and  $\alpha$  of .05, the 2 RCTs need 85 participants in each of the 2 arms, in order

to be able to detect a moderate effect size of 0.5. For the 2 primary outcomes considered, this yields a complete power (ie, the probability to detect statistically significant effects of at least 0.5 on both outcomes, given that both effects truly exist) ranging from 81% (independence between outcomes) to 90% (perfect correlation between outcomes). For individual power (ie, the probability of detecting an effect of 0.5 or larger for a particular outcome, given that the specific effect truly exists), applying a Bonferroni multiple testing procedure to control the family-wise error rate at or below an  $\alpha$  of .05 yields an individual power of 84% [28]. We note that Bonferroni is overly conservative in the case of dependency between outcomes, such that the true family-wise error rate is likely to be somewhat below 5% [28].

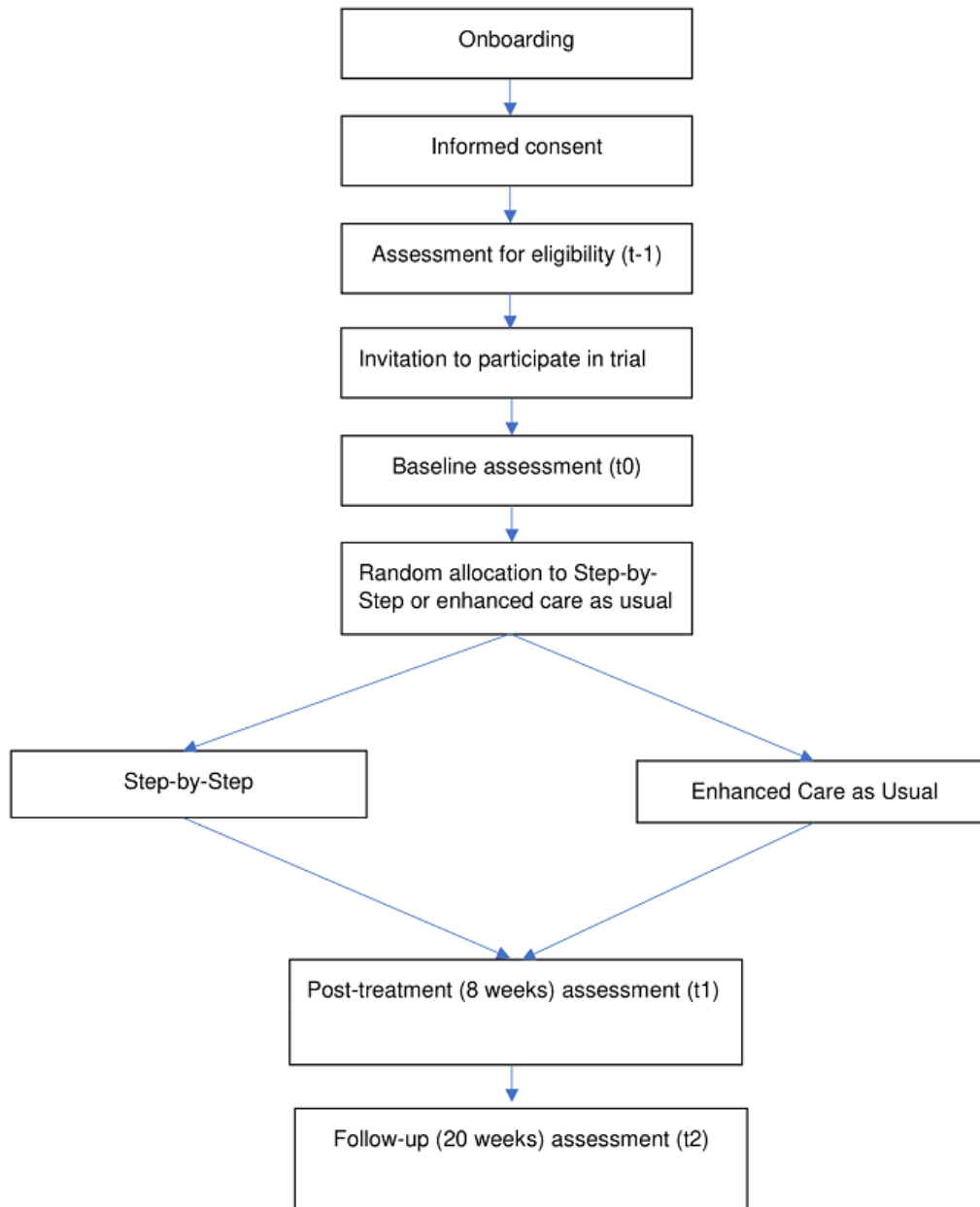
In our feasibility RCT, we found a dropout rate of 70%, which is consistent with other e-mental health studies [29,30]. Accounting for a dropout rate of 70% [ $(2*85)/(1-0.70)=568$ ], 568 displaced Syrian people and 568 other people residing in Lebanon will thus be recruited for the trials such that 85 are estimated to complete the intervention (complete 4 of 5 sessions) in the intervention arms of each trial.

### **Participants**

Any person aged over 18 years, residing in Lebanon, who can understand and speak Arabic or English, and has access to an internet-connected device is eligible to participate. Additional inclusion criteria are scoring 10 or above on the PHQ-9 [31] and scoring above 16 on the WHODAS for functional impairment [32]. Minors (under the age of 18 years) and people who have plans to end their life (as indicated by an answer of “yes” on an additional screening question - “In the past month, have you had serious thoughts or a plan to end your life?”) will be excluded from the study. Participants who answer “yes” to this additional screening question will be considered at imminent risk of suicide and will receive an on-screen message explaining that they may need additional mental health support with advice to go to an emergency room or call the national suicide hotline (Embrace Lifeline) established by the MoPH for suicide prevention. They will also be presented a list of facilities providing mhGAP care, encouraged to seek help, and provided with additional self-care tips.

### **Procedures**

The research procedures can be found in Figure 1. Recruitment of participants will be conducted through online advertising, primarily a social media campaign comprising of posts including videos, animations, gifs, and images. The posts will be disseminated through multiple channels, including the social media platforms of the National Mental Health Programme (NMHP) at the MoPH in Lebanon. The campaign will be conducted by a professional communication company in close collaboration with the NMHP team. Additional outreach methods will be used where required, for example, dissemination of posts through partner agencies and organizations.

**Figure 1.** Flow chart of the study procedures.

People interested can access the website or download the native iOS or Android app version of Step-by-Step. They will enter the onboarding section of the app with information about Step-by-Step and the research project. The onboarding section of the app also contains an animation that explains the most important points in a short video.

People will apply to join the study by following on-screen instructions in the app or on the website. After giving consent, they will be asked to create an account. They will be asked to indicate their age and complete an initial self-screening measure (PHQ-9, WHODAS 2.0, and additional suicide screening question). If an individual meets the inclusion criteria, he or she is asked to complete the study baseline questionnaires. Upon completion of the baseline assessment, the individual will be randomized to either the intervention or ECAU, using a 1:1 allocation ratio in the program. If the individual does not score over the clinical cut-off on the PHQ-9, a box will appear saying

that the intervention may not be a good fit for them and suggesting they seek support from a health care worker.

At sign-up, users will be asked to choose at least one method of follow-up contact from phone call, email, or SMS for reminders of the assessments. People allocated to Step-by-Step are also asked to confirm their contact preferences for regular support from e-helpers. Applicants will be able to contact a member of the study team throughout the self-screening and recruitment process for free, using telephone or messaging services. On completion of enrollment upon sign-up, research staff will either call or send a message to users in the control group (depending on their preferred contact option) to thank them for their participation in the study and to remind them of the format of the study (eg, posttreatment and follow-up questionnaires). Users who access the study through the app (ie, not via web browser) will be asked if they would like to receive notifications on their smartphone. These notifications

will cover (1) assessments due (both conditions), (2) new sessions available (only intervention condition), (3) monthly automated messages to remind users of the upcoming assessments and to thank them for their ongoing participation in the study assessments (both conditions), and (4) mood tracking (only intervention condition). Users will receive an explanation at the beginning of the study about the purpose and reasons for these notifications and can opt out of some or all of the notifications at any time. If assessments are due, e-helpers will contact users (both intervention and control participants) via their preferred method of contact (eg, phone, email). As remuneration, users will receive US \$20 phone credit for completion of all questionnaires at all time points.

### **Informed Consent**

All research participants will be asked for individual, electronic, informed consent. A known challenge in informed consent procedures in resource-limited settings is applicants feeling pressure to answer assessment questions because they see the research process as a route to access services and other resources. This problem is expected to be diminished by the fact that the recruitment will mainly be done through social media instead of face to face. All participants will go to the site on their own accord and be provided with detailed information at the start of the intervention. Before requesting consent, full information on the study will be provided in a video animation in the local language, which will also be available as both written and audio files, as part of the consent form. Applicants will receive information about what they can expect (ie, group allocation, assessments, reminders). In addition, they will be reminded that they are free to withdraw at any time and that nonparticipation will not affect, in any way, their access to usual health care.

E-helpers will receive in-depth training on the informed consent process and will be working in accordance with this protocol. All data and informed consent will be collected online, with telephone or messaging support from e-helpers if necessary. Respondents who decide to participate will be asked to electronically sign the consent form.

### **Outcome Measures**

#### ***Primary Outcomes***

The primary outcomes are levels of depressive symptoms measured with the PHQ-9 [31] and levels of functioning

measured with the WHODAS 2.0 [32] at posttreatment (8 weeks after baseline).

The PHQ-9 is a well-known 9-item instrument measuring presence and severity of depression [31]. As a severity measure, the PHQ-9 score may range from 0 to 27, since each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day). The PHQ-9 has been validated in the Lebanese population with a cut-off score of 10 or above indicating moderate depression [33]. The PHQ-9 is now one of the main outcome measures worldwide that is used in research on psychological interventions and has been chosen as one of the core metrics for research on psychological interventions that should be included in all studies on psychological interventions for depression and distress funded by the Wellcome Trust, the National Institute of Mental Health, and other major funders [34].

The WHODAS 2.0 is a generic assessment instrument assessing health and disability [32]. It is used across all diseases, including mental, neurological, and substance use disorders, and in many global regions. It is simple to administer, is applicable across cultures, and can be used in all adult populations. WHODAS 2.0 covers 6 domains (cognition, mobility, self-care, getting along, life activities, participation). It assesses difficulties people have across these domains during the last 30 days. Difficulties are scored as none, mild, moderate, severe, or extreme.

#### ***Secondary Outcomes***

Secondary outcomes include levels of subjective well-being (WHO-5) [35], levels of anxiety symptoms (Generalized Anxiety Disorder-7 [GAD-7]) [36], and levels of PTSD symptoms (PTSD Checklist for DSM-5 [PCL-5]) [37]. In addition, subjective problems are assessed using the Psychological Outcomes Profile Instrument (PSYCHLOPS) [38]. Satisfaction will be assessed using the 3-item version of the Client Satisfaction Questionnaire (CSQ) [39], and service utilization will be measured with an adapted version of the Client Service Receipt Inventory (CSRI) [40]. Please see [Figure 2](#) for an overview of the different measures at different time points.



**Figure 2.** Schedule of enrollment, interventions, and assessments for Step-by-Step (SPIRIT figure). CSQ: Client Satisfaction Questionnaire 3; GAD: Generalized Anxiety Disorder; PCL-5: PTSD Checklist for DSM-5; PHQ: Patient Health Questionnaire; PSYCHLOPS: Psychological Outcomes Profile Instrument; SRI: Service Receipt Inventory; WHO: World Health Organization; WHODAS: World Health Organization Disability Assessment Scale.

	STUDY PERIOD				
	PARTICIPANTS ( <i>direct beneficiaries</i> ) – participants of Step-by-Step or Enhanced Care as Usual arm				
	Enrollment	Allocation	Baseline assessment	Mid-line assessment 8 weeks	End-line assessment 20 weeks
TIMEPOINT	$t_{-1}$		$t_0$	$t_1$	$t_2$
<b>ENROLLMENT:</b>					
Allocation		X			
Eligibility screen	X				
Informed consent	X				
<b>INTERVENTIONS:</b>					
Step-by-Step			←————→		
Enhanced Care as Usual			←————→		
<b>ASSESSMENTS:</b>					
Functioning (WHODAS)	X			X	X
Depressive symptoms (PHQ-9)	X			X	X
Well-being (WHO-5)			X	X	X
Anxiety symptoms (GAD7)			X	X	X
PTSD symptoms (PCL-5)			X	X	X
Self-report wellbeing (PSYCHLOPS)			X	X	X
Service Utilization (SRI)			X	X	X
Client Satisfaction (CSQ-3)				X	
Depression symptoms (PHQ-4)			During intervention		

The WHO-5 Well-Being Index is a 5-item questionnaire measuring current psychological well-being and quality of life, rather than psychopathology [35]. Scores range from 0 to 25. The scale has demonstrated sensitivity to change in well-being and is available in multiple languages.

The GAD-7 is a 7-item self-report questionnaire for generalized anxiety disorder widely used in primary and specialist care as an indicator of anxiety symptoms [36]. It consists of Likert scale questions including items on nervousness, anxiety, restlessness, and fear. It is being included in this study as a means to investigate whether the intervention, which includes a stress reduction exercise and cognitive coping strategies, may reduce comorbid symptoms of anxiety. The GAD-7 has been validated in the Lebanese population [33].

PTSD symptoms during the past week will be measured using the abbreviated 8-item version of the PCL-5 [37]. Items are rated on a 5-point scale from 1 to 5 and add up to a total severity score of 30. The previous short version of the PCL (PCL-6) [41] that was based on the diagnostic criteria of DSM-IV has shown good psychometric properties and has been tested in diverse cultural settings, including Lebanon [42].

PSYCHLOPS [17] is a person-centered outcome measure consisting of 4 questions across 3 domains: problems (2 questions), functioning (1 question), and well-being (1 question). Participants are asked to indicate self-identified problems. Responses are scored on an ordinal 6-point scale producing a maximum score of 20 (5 points per question). The pre- and

postintervention versions of PSYCHLOPS consist of the same 4 questions but the posttherapy version adds an overall evaluation question (determining self-rated outcome ranging from “much better” to “much worse”). PSYCHLOPS has been validated in primary care populations across several countries [20,21]. It is currently used in WHO studies in Pakistan, Kenya, and Uganda.

The CSQ [39] is an easily scored and administered 8-item measure that is designed to measure client satisfaction with mental health services. It includes an additional free response field as well as the 8 questions that are scored on a Likert scale. To decrease questionnaire burden, this study used the 3-item version of the CSQ [43].

The CSRI was developed for the collection of data on service utilization and related characteristics of people with mental disorders, as the basis for calculating the costs of care for mental health cost-effectiveness research [40]. The CSRI was adapted for online use within a large European Union-funded program, the STRENGTHS program [21], further adapted by the team for use in Lebanon and pilot-tested in the feasibility RCT.

During the course of the intervention, the PHQ-4 [44] will be used to monitor depressive symptoms on a weekly basis regardless of progress in the sessions. The 4-item version has shown good psychometric properties, and the Arabic version was validated among displaced Syrian people in Germany [44,45].



Data on sociodemographic information (sex, age, education, marital status, and work status) will be collected through questions A1-A5 of the 12-item self-report version of the WHODAS 2.0. In addition, users will be asked where they heard about the study.

### Data Management

Most data will be collected electronically in the app, and all electronic data will be stored on password-protected computers. The data collected through computers or devices will be downloaded from the platform and migrated into a data analysis software program. Hardcopies of data from the study (for example, from qualitative interviews and supervision notes) will be safely stored in locked cabinets. No personal data will be used in publications or presentations. The accuracy of data storage and output will be monitored bi-weekly by an external person.

Because of the nature of this innovative intervention and the data being collected online, considerable emphasis has been given to privacy and security of client data. Programming of the iOS and Android apps and web versions is being managed by Freie Universität Berlin. The intervention software and all procedures involving the software will be developed in compliance with the European Union General Data Protection Regulation.

### Data Analyses Plan

#### Statistical Analyses

For the 2 RCTs, both ITT analysis (including all randomized participants) and completers' analyses (per protocol) will be carried out. First, the mean differences between the 2 treatment arms at baseline, postintervention, and 3-month follow-up will be determined. Then, the treatment effect will be estimated based on ITT analysis using regression estimation models with the principal predictor being treatment assignment status. Missing outcome observations for participants will be imputed using multiple imputation exploiting prescores and a set of prespecified background characteristics (gender, age, education, and severity of symptoms). Given that there are 2 primary outcomes of interest, we will impute using multivariate normal regression using an iterative Markov Chain Monte Carlo method based on initial treatment assignment. The aforementioned prespecified covariates and baseline measurement of primary endpoint will be added to the baseline model for improved precision. Potential bias concerns as a result of nonrandom missing outcome observations will be addressed by estimating Lee bounds. Then, 95% confidence intervals will be constructed, both for the regression-generated point estimates and Lee bounds [46] interval estimates. To further tighten confidence interval bounds in the context of differential and potentially nonrandom attrition between treatment arms, Random Forest Lee Bounds will be estimated (using the approach in Cornelisz et al [47]).

These treatment effect analyses will be performed for both primary outcome measures, PHQ-9 and WHODAS 2.0. Concerns of multiple testing error will be addressed by maintaining an experiment-wise type I error of 5%. In order to address potential heterogeneity, treatment effects will be estimated for subgroups (eg, based on prescores). Finally,

average treatment effects on the treated will be estimated treatment and corresponding measures of clinically meaningful change, and numbers needed to treat (using the approach in Furukuwa et al [48]) will be explored.

In addition, the same analyses will be carried out for analyzing clinical outcomes measured at each assessment time: anxiety (GAD-7), wellbeing (WHO5), posttraumatic stress reactions (PCL-5, 8-item version), and self-identified symptoms (PSYCHLOPS).

#### Health Economic Analysis

The health economic evaluation will be conducted from the perspective of the health care system to determine the difference in costs over the difference in outcomes in the intervention arm as compared to the ECAU condition.

Costs include intervention cost (eg, costs for hosting and maintaining the intervention, costs for e-helpers) plus health care costs (eg, participants' service use as assessed with the adapted CSRI). In addition, we will attempt to compute costs stemming from productivity losses owing to absenteeism and presenteeism (work cut back). Costs will be expressed in international dollars for the reference year 2019.

In the health economic evaluation, the central outcome will be treatment response defined as a pre-post symptom reduction of at least 50% on the PHQ with PHQ posttest scores below the cut-off of 10, thus indicating a clinically significant reduction in depressive symptoms. Treatment response will be defined in a similar way for WHODAS 2.0.

Costs, C, and effects, E, will be combined in the incremental cost-effectiveness ratio (ICER) defined as  $(C_1 - C_0)/(E_1 - E_0)$ , where subscripts 1 and 0 refer to the intervention and ECAU conditions, respectively. The ICER can be interpreted as the additional cost per treatment responder.

Stochastic uncertainty in the ICER will be captured as a scatter of simulated ICERs over the ICER plane using 2500 bootstraps. For decision-making purposes, an ICER acceptability curve will be plotted indicating the likelihood that the intervention can be regarded as more cost-effective than the ECAU condition given a range of willingness-to-pay ceilings. Finally, sensitivity analyses will be directed at uncertainty in the main cost-drivers. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline [49] will be followed when reporting the cost-effectiveness analysis.

#### Qualitative Evaluation

To evaluate satisfaction with Step-by-Step, barriers and facilitators to adherence, and relevant information for scale-up, semistructured interviews will be conducted with a subsample of Step-by-Step participants (including both completers as well as noncompleters), control arm participants, e-helpers, supervisors, and other key informants. Up to 10 people per group will be interviewed. This number is based on previous experience of the number of participants needed to reach saturation. Data will be analyzed thematically. In addition, as part of process monitoring, a sample of session notes from e-helper records of their contacts with clients, as well as supervision records, will be reviewed and analyzed.

Informed consent will be reconfirmed from all participants immediately prior to interviews, and the interviews will take place face to face or over phone by trained interviewers. Interviewers will be using a draft semistructured interview guide with key questions that are identified for exploration, with additional prompt questions to fully explore each question in depth. Key areas that are explored include the general experience of using Step-by-Step, acceptability, feasibility, user satisfaction, and perceived effectiveness. Interviews will be conducted no longer than 4 weeks after the final outcome assessments and are expected to last no longer than 1 hour.

### Qualitative Data Analyses

The qualitative data collected from key informant interviews and notes during the process evaluation will be analyzed thematically. The transcribed and translated data will be coded in NVivo [50] by multiple raters, and interrater reliability will be calculated using Kappa scores. Qualitative data will be analyzed using thematic analysis and triangulation.

### Ethical Considerations

The intervention is based on evidence-based therapeutic techniques, and it is unlikely that distress will increase because of participation in the program. E-helpers will have access to the weekly depression scores (measured with the PHQ-4) of the participants and can therefore monitor distress levels over the course of the intervention. Participants who show symptom worsening (ie, a change in category from mild to moderate or moderate to severe) will be automatically flagged by the system. All involved research staff will be trained in communication skills, providing support, responding to distress, and procedures for AEs, including referral procedures.

All AEs and serious adverse events (SAEs) reported spontaneously by the participant or identified through study measures at any time will be recorded by the e-helpers. They will then notify the research coordinator and clinical supervisor for immediate follow-up action. All AEs will be followed up by the e-helper and the clinical supervisor on a regular basis. If, during self-screening or treatment, an AE should occur (eg, the participant discloses plans to end their life or there is a serious protection concern requiring assistance), e-helpers will assist the users by following protocols that are based on local pathways and laws in Lebanon. Any AEs and SAEs along with actions taken will be documented and reported to the local ethical review committee (ERC). SAEs will be reported within

24 hours (on working days) and AEs within 2 business days. The local ERC will review any SAEs as soon as possible and any AEs each month. They will determine any appropriate action with respect to ongoing study conduct. All SAEs will be reported to the WHO ERC.

Ethical approval has been received locally from Saint-Joseph's University in Beirut (Protocol: CEHDF862) and by the WHO Ethical Review Committee (Version 7; Protocol ID: ERC.0002797).

## Results

The trials were funded in 2018. The study protocol (version 7) was last verified on June 20, 2019 (WHO ERC.0002797) and registered with ClinicalTrials.gov (NCT03720769). The trials started recruitment as of December 9, 2019, and all data collection was completed in December 2020. Subsequent protocol modifications will be reported to funders, institutional review boards, and registered with ClinicalTrials.gov.

## Discussion

Formative work [19-21], an open pilot [14], and a feasibility RCT preceded and informed this study protocol for RCTs to evaluate the effectiveness and cost-effectiveness of Step-by-Step in Lebanon. The RCTs will contribute to the evidence base for the potential of guided psychological self-help using task-shifting in low- and middle-income countries [3]. It will also contribute to the growing evidence base for the potential of digital interventions to reach broader populations with evidence-based care [51-53] and will address a gap in the evidence base in low- and middle-income countries [54].

Step-by-Step is an innovative approach to reducing the suffering and disability associated with psychological distress in a middle-income country, and after testing, WHO aims to release the intervention with adaptation and implementation guidance for use in other settings. However, merely testing the effectiveness of the intervention and releasing it as a public good will not be enough to ensure the intervention will reach people that need help and can benefit from it. After successfully testing the effectiveness of Step-by-Step in RCTs, a next step would be to study ways to implement the intervention outside of a research context and identify sustainable implementation models that will support scale-up of this intervention or similar interventions in Lebanon and other countries.

### Acknowledgments

We thank all the e-helpers (Ahmad Akar, Gaelle Fahed, Layal Hamze, Yara Hasbany, Maria Hayek, Sally Khoury, the NMHP management team, AFMM, WHO Lebanon, UNHCR, Abaad, and IMC Lebanon) for their support in working out the procedures for these RCTs.

This evaluation of Step-by-Step is supported by Elhra/R2HC (for the RCT with Syrians in Lebanon) and Fondation d'Harcourt (for the RCT with other people residing in Lebanon). These sponsors had no role in the collection, management, analysis, and interpretation of data, nor did they have a role in the decision to submit the report for publication. The authors alone are responsible for the views expressed in this article, and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

## Authors' Contributions

All authors contributed to the development of the protocol. EvH led the drafting of the manuscript. All authors were involved in the development of the study protocol submitted for ethical approval. IC and CvK developed the statistical analysis, and FS developed the cost-effectiveness analysis. The manuscript has been reviewed and commented on by EvH, JAR, KC, MvO, RC, MHS, SB, PC, EZ, FS, IC, CvK, and PN. All authors have reviewed and approved the final version of the manuscript.

## Conflicts of Interest

None declared.

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## Abbreviations

- AE:** adverse event
- CHEERS:** Consolidated Health Economic Evaluation Reporting Standards
- CSQ:** Client Satisfaction Questionnaire
- CSRI:** Client Service Receipt Inventory
- ECAU:** enhanced care as usual
- ERC:** ethical review committee
- GAD-7:** Generalized Anxiety Disorder-7
- ICER:** incremental cost-effectiveness ratio
- ITT:** intention-to-treat
- mhGAP:** Mental Health Gap Action Programme
- MoPH:** Ministry of Public Health
- NMHP:** National Mental Health Programme
- PCL-5:** PTSD Checklist for DSM-5
- PHQ:** Patient Health Questionnaire
- PSYCHLOPS:** Psychological Outcomes Profile Instrument
- PTSD:** posttraumatic stress disorder
- RCT:** randomized controlled trial
- SAE:** serious adverse event
- WHO:** World Health Organization



**WHODAS: World Health Organization Disability Assessment Scale**

*Edited by G Eysenbach; submitted 18.06.20; peer-reviewed by H van Marwijk, P Kumar; comments to author 18.07.20; revised version received 31.08.20; accepted 10.11.20; published 28.01.21.*

*Please cite as:*

*van 't Hof E, Heim E, Abi Ramia J, Burchert S, Cornelisz I, Cuijpers P, El Chammay R, Harper Shehadeh M, Noun P, Smit F, van Klaveren C, van Ommeren M, Zoghbi E, Carswell K*

*Evaluating the Effectiveness of an E-Mental Health Intervention for People Living in Lebanon: Protocol for Two Randomized Controlled Trials*

*JMIR Res Protoc 2021;10(1):e21585*

URL: <http://www.researchprotocols.org/2021/1/e21585/>

doi: [10.2196/21585](https://doi.org/10.2196/21585)

PMID: [33507158](https://pubmed.ncbi.nlm.nih.gov/33507158/)

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Protocol

# Effect of Switching to the Tobacco Heating System Versus Continued Cigarette Smoking on Chronic Generalized Periodontitis Treatment Outcome: Protocol for a Randomized Controlled Multicenter Study

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## Abstract

**Background:** Smoking is a significant risk factor for periodontal disease and tooth loss, as shown in several clinical studies comparing smokers and nonsmokers. Although only a few longitudinal studies have assessed the outcome of periodontal disease after smoking cessation, they indicated that recovery after nonsurgical treatment was more successful in those who had quit smoking. As part of tobacco harm reduction strategies, substituting cigarettes with alternative, less harmful tobacco products is an approach complementary to cessation for smokers who would otherwise continue to smoke. The Tobacco Heating System (THS), developed by Philip Morris International (commercialized as IQOS), is part of the heat-not-burn product category. The IQOS device electrically heats tobacco instead of burning it, at much lower temperatures than cigarettes, thereby producing substantially lower levels of harmful and potentially harmful constituents, while providing the nicotine, taste, ritual, and a sensory experience that closely parallel those of cigarettes. Phillip Morris International has published the results from a broad clinical assessment program, which was established to scientifically substantiate the harm reduction potential of the THS among adult healthy smokers switching to the THS. The program is now progressing toward including adult smokers with smoking-related diseases.

**Objective:** The goal of this study is to demonstrate favorable changes of periodontal endpoints in response to mechanical periodontal therapy in patients with generalized chronic periodontitis who completely switched to THS use compared with continued cigarette smoking.

**Methods:** This is a randomized controlled two-arm parallel-group multicenter Japanese study conducted in patients with chronic generalized periodontitis who switch from cigarettes to THS compared with smokers continuing to smoke cigarettes for 6 months. The patients were treated with mechanical periodontal therapy as per standard of care in Japan. The primary objective of the study is to demonstrate the beneficial effect of switching to THS use compared with continued cigarette smoking on pocket depth (PD) reduction in all sites with an initial PD $\geq$ 4 mm. The secondary objectives include evaluation of other periodontal parameters (eg, clinical attachment level or gingival inflammation) and overall oral health status upon switching to THS. Safety was monitored throughout the study.

**Results:** In total, 172 subjects were randomized to the cigarette (n=86) or THS (n=86) groups, and all 172 completed the study. The conduct phase of the study is completed, while data cleaning and analyses are ongoing.

**Conclusions:** This study is the first to test a heat-not-burn tobacco product in smokers with an already established disease. The results should further strengthen the evidence that switching to THS can significantly reduce the risk of smoking-related diseases if favorable changes in the evolution of chronic generalized periodontitis after mechanical therapy are found when compared with continued cigarette smoking.

**Trial Registration:** ClinicalTrials.gov NCT03364751; <https://clinicaltrials.gov/ct2/show/NCT03364751>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/15350

(*JMIR Res Protoc* 2021;10(1):e15350) doi:[10.2196/15350](https://doi.org/10.2196/15350)

## KEYWORDS

smoking; tobacco; periodontitis; oral health; Tobacco Heating System; modified risk tobacco product; clinical attachment level; probing depth; periodontal pocket

## Introduction

Smokers are at higher risk of developing periodontal diseases [1-4]. This association has been shown in numerous studies, including evidence of a dose-response relationship between smoking intensity and the risk for periodontitis, as both the number of cigarettes smoked and the duration of smoking are positively associated with disease risk [4-6]. The magnitude of the relative risk estimated for periodontal disease associated with smoking varies from 1.4 to 5.0 in different studies [4]. In a Japanese study, the odds ratio of having periodontitis among current smokers compared with those who had never smoked was 1.74 [7].

The pathophysiological mechanisms involved in the increase of periodontal disease prevalence in active smokers mainly involve alteration of the inflammatory host response. Specifically, an increased release of inflammatory mediators occurs due to chronic exposure to the harmful and potentially harmful constituents (HPHCs) of cigarette smoke produced by the combustion of tobacco [8,9]. The inflammation not only contributes to tissue damage but also negatively impacts the reparative and regenerative potential of the periodontium and the cell lining of the oral cavity in general [1,10]. The presence of proinflammatory cytokines can be assessed from the gingival crevicular fluid collected from the pockets of diseased teeth, as described by Tymkiw et al [10], and serves as a quantifiable marker of inflammation. Additionally, smoking has been shown to cause dose-dependent quantitative and qualitative changes in the subgingival microflora (ie, increased abundance of *Porphyromonas gingivalis* and *Tannerella forsythia*), which also contribute to creating an unfavorable environment for the periodontium [11]. However, the exact understanding of periodontal microbiology is still evolving [12].

In chronic periodontitis, clinical parameters, including periodontal pocket depth (PD) and clinical attachment level (CAL), were found to be increased in smokers compared with those of nonsmokers (reviewed in [13]). Conversely, bleeding on probing (BOP), erythema, edema, and the inflammatory response associated with plaque accumulation have been shown to be less pronounced or delayed in smokers compared with those of never smokers [14-18]. Several studies have assessed the differences of periodontal parameters between smokers and former smokers, which clearly suggest that smoking cessation is beneficial for subjects undergoing therapy for chronic periodontitis [13,15,19-22]. Only two prospective studies could be identified that followed smokers after smoking cessation [23,24]. Although the results showed some benefits of quitting, the study particularly highlighted the difficulty of conducting studies of this nature owing to high dropout rates and low compliance in completing cessation. Alternatively, asking

subjects in a dental setting to switch to nicotine-containing products that are likely to be safer alternatives than smoking cigarettes seems to be an avenue that may be more successful, as suggested by the pilot study of Holliday et al [25]. In all studies, the most consistent findings were favorable changes in PD in nonsmokers or former smokers, whereas changes in CAL were hardly ever found to be statistically significant.

The role of nicotine in the development and maintenance of periodontitis is not clear [26,27]. Available literature suggests that nicotine affects gingival blood flow, cytokine production, and neutrophil and other immune cell function [28]. Although nicotine replacement therapy (NRT) is part of smoking cessation programs, it has not been reported as a major issue for periodontitis to date. Similarly, the first studies on e-cigarettes and oral health could not conclusively demonstrate a negative role of nicotine on the improvement of periodontitis [29,30], although both smoking cessation [17] and switching to e-cigarettes [31] have been associated with increased BOP. Thus, an increase in BOP might simply reflect the effect of decreasing smoke toxicants rather than an effect of vaping itself.

The first line of treatment in periodontal diseases is to restore a healthy periodontium by mechanically removing supra- and subgingival plaque and calculus deposits (an intervention called scaling and root planing [SRP]), with or without antibiotic treatment [32]. In more severe cases, or cases that do not resolve after nonsurgical intervention, surgery is usually performed. Patients are also instructed on how to improve their oral hygiene. Per the recommendations of dental and health care associations such as the World Health Organization [33,34] and Japanese Society of Periodontology [35], patients should be informed of the importance of primary prevention of tobacco use and on smoking cessation programs, which would also contribute as an intervention for oral health diseases [36,37].

Philip Morris International (PMI) develops, assesses, and commercializes a portfolio of innovative products intended to (1) significantly reduce the risk of smoking-related disease compared with continued cigarette smoking and (2) be accepted by smokers as substitutes for cigarettes. The Tobacco Heating System (THS), developed by PMI and commercialized in more than 40 countries under the brand name IQOS, consists of tobacco sticks (eg, Marlboro *HeatSticks* in Japan), a holder, and a charger. The THS holder heats the tobacco stick for up to 6 minutes to a temperature not exceeding 350°C, which is too low to initiate combustion. The elimination of combustion allows the nicotine to be delivered to the THS user in a way that is similar to cigarettes while significantly reducing the production of and exposure to HPHCs [9].

Smoking cessation remains the best way to decrease the risk of developing smoking-related diseases; however, THS is meant

as an alternative for those who would otherwise continue to smoke. The evidence available to date for THS has demonstrated that its aerosol contains significantly reduced levels of HPHCs, resulting in reduced exposure to HPHCs in volunteer healthy smokers who switched from cigarettes to THS, as assessed by measuring urinary biomarkers of exposure to selected HPHCs [38-41]. The magnitude of reduction was comparable to that observed in smokers who abstained from smoking, which has been referred to as the “gold standard” for the assessment of candidate reduced risk products [42,43]. Longer exposure studies of at least 6 months have shown favorable biological changes in smokers switching to THS, thereby reflecting improvement of several pathophysiological pathways that may eventually lead to the development of tobacco-related diseases, such as inflammation, oxidative stress, or endothelial dysfunction [44,45]. Preclinical data on gingival [46] and oral epithelial [47] human organotypic cultures showed minor histopathological alterations and minimal cytotoxicity upon THS aerosol exposure compared with exposure to cigarette smoke as well as a very significantly reduced overall impact, as illustrated by the measurement of inflammatory mediators and by transcriptomic and metabolomic analyses. Considering the available preclinical and clinical data on exposure reduction, it is conceivable to assume that the reduction in exposure to toxicants may lead to favorable changes in the outcome of a standard of care treatment of chronic generalized periodontitis for patients who switch to THS compared with those who continue smoking cigarettes.

## Methods

### Study

This is a randomized controlled two-arm parallel-group multicenter study comparing the treatment outcome of patients with chronic generalized periodontitis who switch from cigarettes to THS versus those who continue to smoke cigarettes for 6 months. This open-label study was conducted in 26 dental clinics in Japan and followed the principles defined in the International Conference on Harmonisation Guideline for Good Clinical Practice [48,49], Ministerial Ordinance on Good

Clinical Practice for Drugs (Ministry of Health and Welfare, 1997 as last amended by the Ordinance of Ministry of Health, Labor and Welfare No. 9 of January 22, 2016) [50], Declaration of Helsinki [51], and other applicable regulations. Prior to the initiation of any study procedures, the protocol was approved at each site by the associated institutional review board. The study is registered in the US ClinicalTrials.gov registry with the identifier NCT03364751. The study was completed on December 15, 2018, and the data are currently being processed to obtain the results.

### Recruitment

This study enrolled current adult smokers of any brand of commercially available cigarettes who did not intend to quit smoking during the study and who had been diagnosed with chronic generalized periodontitis, as defined by the Japanese guidelines on periodontology [35]. Patients who were identified by dental practices participating in this study as potentially eligible were provided with information about the study, and if interested, they were invited to the screening visit (visit 1). At least 172 participants were planned to be randomized. Enrollment was stopped when this number was reached.

All patients included in the study were first advised that the best way of preventing further periodontal disease progression is to stop smoking as defined in the Japanese guidelines for periodontitis. From visit 1 onward, information on the risks of smoking and advice to quit smoking were given to all patients at every visit, including a debriefing of patients to address any intended or unintended beliefs they might have about IQOS to ensure that the patients had an accurate understanding of product risks, including an understanding that IQOS has not been demonstrated to be less harmful than cigarettes.

The main inclusion and exclusion criteria are listed in [Textbox 1](#). In brief, participants needed to have at least a 5-year smoking history with an average of 10 cigarettes per day based on self-reporting and had to be Japanese. Study participants received information on the study prior to signing the informed consent form.



**Textbox 1.** Main inclusion and exclusion criteria.

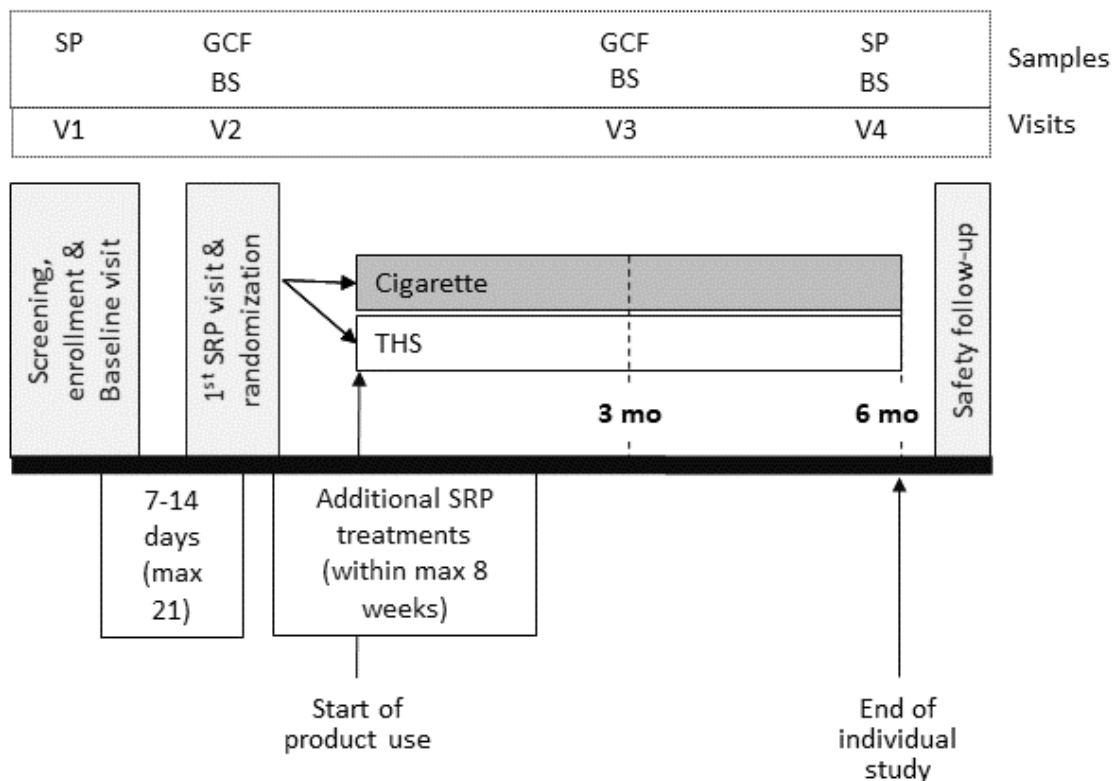
<p><b>Inclusion Criteria</b></p> <ul style="list-style-type: none"><li>• Signed informed consent form</li><li>• Japanese ethnicity</li><li>• Aged <math>\geq 30</math> years</li><li>• Smoked on average at least 10 commercially available cigarettes per day (no brand restriction) for at least 5 years prior to visit 1 based on self-reporting. Smoking status will be verified based on a urinary cotinine test (ie, cotinine <math>\geq 200</math> ng/mL)</li><li>• Has at least 15 natural teeth, excluding the teeth that need to be extracted or whose mobility grade is <math>\geq 3</math></li><li>• Diagnosed with generalized chronic periodontitis (ie, more than 30% of diseased teeth with a pocket depth <math>\geq 4</math> mm), considering only teeth that do not need to be extracted or whose mobility grade is <math>\geq 3</math></li><li>• Does not intend to quit smoking during the study</li></ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"><li>• Self-reported history of diagnosed systemic diseases (eg, stroke or acute cardiovascular event within the last 5 years, diabetes, active cancer) or any other conditions that in the opinion of the investigator would jeopardize the safety of the participant or affect the validity of the study results</li><li>• Has orthodontic appliances</li><li>• Received root planing therapy within the 6 months prior to visit 1</li><li>• Received surgical periodontal therapy within 3 years prior to visit 1</li><li>• Identifiable premalignant changes of the oral mucosa at visit 1</li><li>• Treated within the 3 months prior to visit 1 with systemic antibiotics or treated with topical antibiotics applied in the mouth</li><li>• Continuous systemic use of steroidal or nonsteroidal anti-inflammatory drugs for more than 20 days during the past 30-day period (except for low-dose aspirin, <math>\leq 300</math> mg, for prevention of thrombus/embolus in angina pectoris, myocardial infarction, transient ischemic cerebrovascular accidents, bypass operations, and similar)</li><li>• Women who are pregnant, breastfeeding, or planning a pregnancy within the course of the study</li></ul>
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All subjects received financial compensation according to a payment scale agreed by the Institutional Review Board, which covered their time and transportation costs to and from the dental clinic. Additionally, patients who quit smoking or were using IQOS, or those who quit smoking and started using IQOS, would not forfeit their financial compensation.

**Study Design****Overview**

The study design is illustrated in [Figure 1](#), including four scheduled visits. From visit 2 to visit 4, the patients were asked not to drink, eat, chew gum, use mouthwash, or brush their teeth for at least 30 minutes before collection of oral samples (ie, subgingival plaque, gingival crevicular fluid, or buccal swabs).

**Figure 1.** Design of the study. Eligibility criteria were checked at V1. Enrolled subjects were randomized at V2. Periodontal assessments were performed at V1, V3, and V4. Times of collection of buccal samples are indicated on the chart. BS: buccal swabs; GCF: gingival crevicular fluid; mo: month; SP: subgingival plaque; SRP: scaling and root planing; V: visit; THS: Tobacco Heating System.



### Screening, Enrollment, and Baseline Visit (Visit 1)

Patients were invited to visit 1 by the investigator, following a standard visit to the investigator's dentistry practice or by referral. During this visit, after signing the informed consent form, all eligibility criteria were checked, including periodontal assessments, which was also used as the baseline assessment for enrolled patients.

Concerning intention to quit, patients were questioned about their smoking history, and self-reported current tobacco and nicotine-containing tobacco product use over the past month at visit 1. Patients were also asked if they were planning to quit smoking during the study, after having been provided with smoking cessation advice. There was no specific questionnaire on motivation to quit, as no cessation arm was included in this study.

### First SRP Treatment and Randomization Visit (Visit 2)

The first SRP treatment was performed on visit 2. Patients were treated using SRP as per the standard of care recommended by the Japanese Society of Periodontology [35]. The number of visits for these treatments was left up to the investigator to decide, as it can be quite variable between patients and between dentists (see section "Unscheduled Visits for Following Treatments").

Patients were informed of their randomized study arm during visit 2 and could start using their allocated product immediately after the randomization.

This study was designed as an ad libitum study, without product use restriction, to mimic "real life" conditions as closely as possible. THS devices were distributed to the patients by the sites after randomization, and any variant of *HeatSticks* available on the Japanese market could be used. All patients were asked to buy their own cigarettes or *HeatSticks* according to their needs for the study. They were instructed to use their allocated product.

### Unscheduled Visits for Following Treatments

The following SRP treatments were performed in subsequent visits after visit 2 as agreed between the site and the patient ("unscheduled visits" as per the protocol definition). The number and timing of these SRP visits were flexible, but all treatments had to be completed within 8 weeks after visit 2.

### Investigational Period (Visit 3 and Visit 4)

The investigational period consisted of a visit at 3 and 6 months after the randomization visit (visit 3 and visit 4, respectively), during which all periodontal assessments were made.

### Safety Follow-up Period

After the procedures of discharge, patients entered a 7-day safety follow-up period. Any nonserious adverse event that was

ongoing during the safety follow-up period was to be followed up by the investigator during that period until it had been resolved, stabilized (ie, no worsening of the condition), or an acceptable explanation had been found (eg, a chronic condition). All serious adverse events were to be actively followed up by the investigator, despite their continuation after the end of the safety follow-up period, until their resolution, stabilization (ie, no worsening of the condition), or an acceptable explanation had been found (eg, a chronic condition).

### Randomization

The study followed a two-arm parallel randomization design with the following strata: (1) daily cigarette consumption over the month prior to visit 1 and visit 2; and (2) severity of disease (based on the size of PD) in smokers with generalized chronic periodontitis [35]. This selection was based on the fact that the degree of smoking exposure is related to the severity of periodontal destruction [5,52], and that the pretreatment PD and CAL have been shown to affect the response to therapy [53,54].

Randomization was performed through the Interactive Web/Voice Response System (IxRS) at visit 2. Patients were randomized into one of the two study arms (THS arm and cigarette arm) at a 1:1 ratio, using a stratified randomization based on daily cigarette consumption over the month (30 days) prior to visit 1 (10-19 cigarettes/day vs >19 cigarettes/day) and disease severity (<5 mm PD vs ≥5mm PD) in smokers with generalized chronic periodontitis. As per Japanese guidelines [35], disease severity is based on the tooth site having the most severe condition of PD [35].

### Blinding

Due to the nature of the exposure, blinding of the participants to the product was not possible. However, blinding of the examiners to the randomization arm of their patients was attempted, as described previously [16,24,55,56], to reduce the potential bias of the periodontal assessments that could be introduced by the smell of tobacco on patients using cigarettes, which is not present in patients using THS. If the examiner was

unblinded, this had to be reported, but the patient was not discontinued from the study. Blinding was instead ensured by asking the patients to wash their hands before the examination, and the examiners all wore the same type of mask that neutralizes odors. Because mouthwash could influence the collection of samples, the patients were instructed not to use mouthwash during the study.

Additionally, even though limited, a certain degree of blinding has been applied during the study, including for data review. The clinical scientist and biostatistician will remain blinded to the subject randomization arm and actual CAL and PD values after randomization until database lock.

### Outcome Measures

All study objectives and endpoints are listed in Table 1. The choice of the primary and secondary objectives was based as a selection of (1) the most published periodontal endpoint (ie, reduction of PD, which has been shown to occur rather rapidly after mechanical therapy [within 3 to 6 months] and is more representative of the overall state of inflammation), (2) the most clinically relevant endpoint (ie, CAL change, which is more representative of tissue destruction and is thus a determinant of the increased risk of tooth loss), and (3) the most susceptible to change upon smoking cessation.

The assessment of both parameters, the primary objective for PD at 6 months and the secondary objective for CAL, will provide evidence on both the effect of using THS on inflammation status and on tissue repair, and will provide information about the modification of the healing profile related to switching to THS. All dental variables measured in this study were further selected based on the following criteria: (1) commonly assessed by dentists, (2) acceptability by patients, (3) robustness of the method (ie, index or evaluation criteria are available to assess improvement of periodontal disease), and (4) clinical relevance to support the objectives of the study. These variables include change in the gingival index score, change in tooth mobility (grade), change in plaque control record, and change in BOP scores.

**Table 1.** Objectives and endpoints of the study.

Objectives	Endpoints
<b>Primary objective</b>	
To demonstrate the effect of switching to THS <sup>a</sup> use compared to continued cigarette smoking on the response of PD <sup>b</sup> to mechanical periodontal therapy	Mean PD reduction in all sites with initial PD $\geq$ 4 mm after mechanical periodontal therapy (6 months)
<b>Secondary objectives</b>	
To evaluate the effect of switching to THS use compared to continued cigarette smoking on the response of PD and CAL <sup>c</sup> to mechanical periodontal therapy over time	Mean PD change in sites with initial PD $\geq$ 4 mm after mechanical periodontal therapy (3 months only); mean CAL change in sites with initial PD $\geq$ 4 mm after mechanical periodontal therapy (3 and 6 months)
To evaluate the differences of periodontal parameters in the response to periodontal therapy in patients who switch to THS use compared with those who continue to smoke cigarettes	Change in mean full-mouth CAL (3 and 6 months); change in mean full-mouth PD (3 and 6 months); mean PD change in sites with initial PD $<$ 4 mm, 4-5 mm, 5-6 mm, 6-7 mm, and $\geq$ 7 mm (3 and 6 months); mean CAL change in sites with initial PD $<$ 4 mm, 4-5 mm, 5-6 mm, 6-7 mm, and $\geq$ 7 mm (3 and 6 months); change in the number of sites with PD $<$ 4 mm, 4-5 mm, 5-6 mm, 6-7 mm, and $\geq$ 7 mm (3 and 6 months); change in GI <sup>d</sup> score (3 and 6 months); change in tooth mobility (grade) (3 and 6 months); change in PCR <sup>e</sup> (3 and 6 months); change in BOP <sup>f</sup> scores (3 and 6 months)
To evaluate the levels of biomarkers of exposure over the exposure period in patients who switch to THS use and patients who continue to smoke cigarettes	Urinary nicotine equivalents, total 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol and 2-cyanoethylmercapturic acid (3 and 6 months)
To describe self-reported tobacco or nicotine-containing product use over the duration of the study in patients switching to THS use and patients who continue to smoke cigarettes	Number of self-reported tobacco- or nicotine-containing product use
To monitor safety	Incidence of adverse events/serious adverse events, including those related to device events (eg, device malfunction/misuse) over the duration of the study
<b>Exploratory objectives</b>	
To determine quantitative changes in the inflammatory response by measuring inflammatory and immunoregulatory mediators in the GCF <sup>g</sup> in patients switching to THS use compared with those continuing to smoke cigarettes	Measurement of proinflammatory and immunoregulatory mediators in the GCF (3 months)
To evaluate the microbiological status in patients switching to THS use compared with those continuing to smoke cigarettes	Microbiological status from subgingival plaque samples (6 months)
To evaluate the transcriptomics profile of buccal swabs in patients switching to THS use compared with those continuing to smoke cigarettes	Full transcriptomics profile assessment of buccal swabs derived from the right and left buccal mucosa (3 and 6 months)

<sup>a</sup>THS: Tobacco Heating System.

<sup>b</sup>PD: periodontal pocket.

<sup>c</sup>CAL: clinical attachment level.

<sup>d</sup>GI: gingival inflammation score.

<sup>e</sup>PCR: plaque control record.

<sup>f</sup>BOP: bleeding on probing.

<sup>g</sup>GCF: gingival crevicular fluid.

### Classification of Product Use Exposure

Although the patients were requested to use solely the product allocated to their respective study arm, it was likely that not all patients randomized to the THS or cigarette arms were going to be exclusive users of their randomized product at all times during the study. Patients were not excluded from the study if they concomitantly used THS and cigarettes or other tobacco- or nicotine-containing product (TNPs) available on the Japanese market (eg, heat-not-burn products other than THS, e-cigarettes, smokeless tobacco pipe, smokeless tobacco,

cigars/pipes/kiseru/shisha, and NRT). However, as the participants in this study were cigarette smokers at enrollment, it was assumed that use of TNPs other than cigarettes or THS was going to be minimal over the investigation period. Thus, classification of patients according to a specific pattern of use will focus on cigarette and/or THS use only over the study duration.

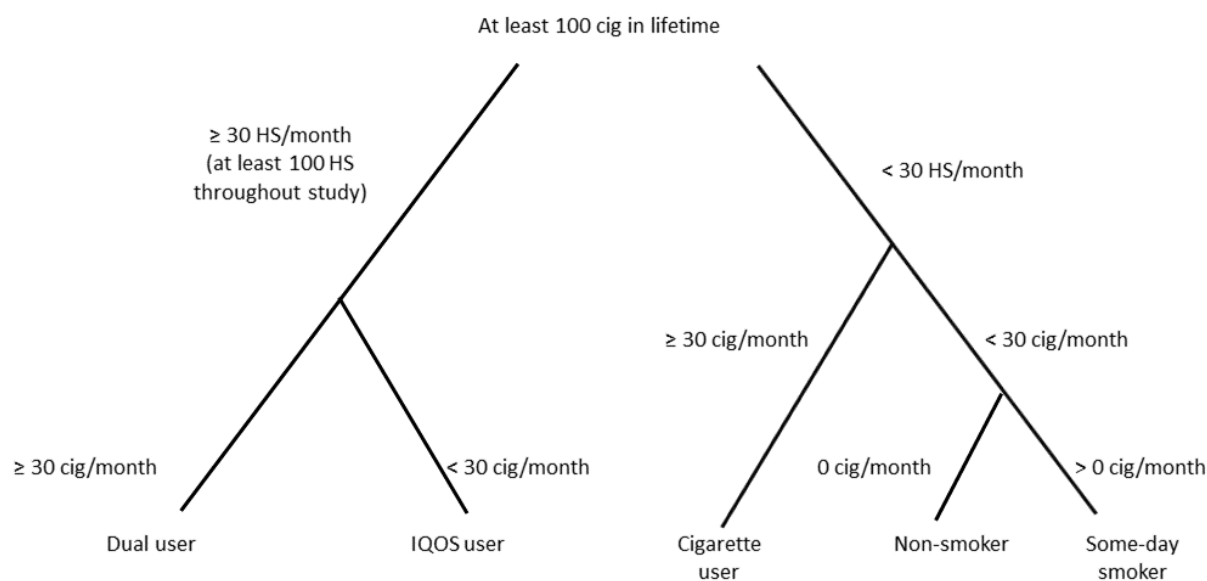
Product use pattern categories will be specified based on the average number of products used per month of each category (ie, *HeatSticks* or smoked cigarettes) as self-reported in the



product use questionnaire over the study duration. Actual product use pattern categorization is described in Figure 2. As per the US Centers for Disease Control, an “every day” smoker is defined as an adult who has smoked at least 100 cigarettes in his or her lifetime and who now smokes every day. A “some-day” smoker is defined as an adult who has smoked at least 100 cigarettes in his or her lifetime, who now smokes but does not smoke every day. Based on the definition of a daily smoker, and when considering that one cigarette per day is still

associated with an increased risk of developing a disease [57,58], a cigarette smoker in this study was defined as a patient using 30 cigarettes or more per month. Based on a comparable definition, a patient who is defined as a THS user would be an adult who has used at least 100 *HeatSticks* and who uses THS every day. Patients not included in the cigarette, THS, or dual user categories will be considered as a category “other,” and their data will not be analyzed.

**Figure 2.** Product use classification tree. Cig: cigarette; HS: HeatSticks.



## Study Hypothesis

The primary study hypothesis is that there will be a favorable difference in the mean of all sites with an initial PD $\geq$ 4 mm at 6 months in exclusive THS users compared with smokers who continue to smoke cigarettes among patients with generalized chronic periodontitis.

## Statistical Analyses

### Power

In the literature reviewed, the papers of Rosa et al [24] and Preshaw et al [23] describe the results of assessments comparable to the study described in this protocol, in that they include some requirements on the minimum PD for inclusion, comparison of smokers with former smokers, and means with SD or SEM and sample size.

For this study, because there are no available data on the effects of a heat-not-burn product on the improvement of periodontitis, it was therefore assumed that the cigarette arm will have similar results to those obtained in previous studies for current smokers, and that the results in the THS arm will be somewhat comparable to previous findings in former smokers.

Based on the published data and recommendations from clinical practice guidelines of the American Dental Association [59],

the estimates with PD differences and SD between smokers and nonsmokers will be based on data assessed at 3, 9, and 12 months. With an  $\alpha$  of 2.5%, power of 80%, SD of 0.5, and effect difference of 0.25 mm, the sample size needed in each arm was determined to be 64 patients. By considering a 25% dropout rate and product switching, 86 patients per arm (ie, 172 patients in total) were considered needed to adequately power the study.

### Planned Analyses

The primary analysis will evaluate the change in PD from baseline, which will be calculated for each patient across all periodontal sites with a baseline PD $>$ 4 mm, resulting in one value per patient per endpoint for each visit (baseline, month 3, and month 6). The primary analysis will be performed on patients as per product use exposure (refer to the section on product categories) using a mixed model for repeated measurements. The model will include the PD change from baseline as the dependent variable, adjusting for daily cigarette consumption and disease severity at visit 1; full-mouth PD at visit 1; exposure group; and its interaction with visit. Clinical site will be included as a random effect. The interaction between cigarette consumption at visit 1 and product use, interaction between disease severity at visit 1 and product use, time since last SRP, number of target tooth/teeth extracted, number of nonmeasured target tooth/teeth extracted, and baseline tooth

mobility will be assessed by a model selection algorithm using likelihood ratio tests.

The analysis of PD at 3 months and of CAL at 3 and 6 months will also be performed as secondary endpoints using a similar model with an adjustment for multiplicity for the secondary testing of CAL and PD.

Biomarkers of exposure will be analyzed as concentration data adjusted for creatinine on a logarithmic scale using mixed model repeated measures with the biomarkers of exposure geometric mean value as the dependent variable, adjusting for daily cigarette consumption at baseline, sex, visit, baseline biomarkers of exposure level, exposure group, and its interaction with visit. Clinical site will be included as a random effect. The modeling assumptions will be evaluated similarly to that in the primary analysis, except that time since last SRP, number of target tooth/teeth extracted, number of nonmeasured target tooth/teeth extracted, and baseline tooth mobility will not be included as covariates.

## Data and Sample Collection

### Baseline Data Collection

Patient demographics (sex, date of birth, ethnicity) were collected at baseline. Periodontal assessments that were part of the eligibility criteria will be used as baseline measures for enrolled patients.

### PD and CAL Measurements

The probe used in this study was a PCPUNC15 (#30) manufactured by Hu-Friedy. Measurements were recorded in 1-mm increments and were rounded to the nearest millimeter based on visual judgment. PD was measured as the distance from the gingival margin to which a probe penetrates the pocket.

Full-mouth PD was measured based on 6 sites per tooth (6-site measurement method: mesial, mid, and distal aspects of the buccal and palatal/lingual surfaces) at a pressure of approximately 20 g using the intended probe at visit 1, visit 3, and visit 4. At least 4 of the 6 sites per tooth had to be evaluated and have measurements recorded for the tooth to be included in the assessment.

When PD was not measurable on more than 2 sites, the assessment of the tooth was considered as missing, and all periodontal assessments for that tooth were excluded from the calculation of the means over all teeth. CAL was measured as the distance from an invariable reference point such as the cemento-enamel junction to the bottom of the pocket, also using the 6-site measurement method in the full mouth at visit 1, visit 3, and visit 4. As for PD, when CAL was not measurable on 1 or 2 of 6 sites on visit 1, the site(s) were skipped, but the tooth could still be included in the assessment. When CAL was not measurable on more than 2 sites, the whole tooth was skipped. The number of teeth lost during the study will be included as a covariate in the models of PD and CAL.

### Other Dental Assessments

BOP in the full mouth was determined to assess inflammatory status in the pocket and was evaluated as a binary variable (YES or NO) at 6 sites per tooth at visit 1, visit 3, and visit 4. By

gentle probing (approximately 20 g pressure), the site was assessed as YES if bleeding occurred within 30 seconds.

Tooth mobility was assessed according to the Miller classification [60], with grades from 0 to 3 (from less to more severe) corresponding to how much a tooth moves horizontally, in the full mouth at visit 1, visit 3, and visit 4.

The presence of plaque (based on the plaque control record) on individual tooth surfaces in the full mouth was assessed following the method of O'Leary et al [21], in which plaque retention in the dentogingival areas of the mesial, distal, facial, and lingual tooth surfaces is determined as a binary variable (YES or NO) recorded at visit 1, visit 3, and visit 4. A routine plaque disclosing agent was used at each clinical site.

For assessing the degree of gingival inflammation, 6 surfaces of each of the target teeth were rated according to the score developed by Löe and Silness [61], with grades from 0 to 3 (from less to more severe), based on visual evaluation of redness, edema, ulceration, and tendency for spontaneous bleeding.

### Sample Collection

Subgingival plaque, buccal swab, and gingival crevicular fluid samples were collected from the participants. Collection of gingival crevicular fluid samples will allow for assessment of inflammatory markers in the oral environment, whereas the plaque samples were collected to evaluate changes in the periodontal microbiome over time after switching to THS compared with continuing to smoke cigarettes. Transcriptomics profiling of buccal swab samples will provide a complete picture of genes that are differentially regulated when switching to THS compared with cigarette smoking.

Collection of spot urine from participants should allow for evaluation of adherence to the allocated products by measuring biomarkers of exposure that can distinguish users of conventional cigarettes from users of smokeless tobacco products (such as THS). The biomarkers of exposure to be evaluated are 2-cyanoethylmercapturic acid (CEMA), total 4-(methylnitrosamino)-1-(3 pyridyl)-1-butanol (NNAL) or nicotine-derived nitrosamine ketone, and nicotine equivalents (NEQ). All values will be reported over the levels of urinary creatinine.

### Questionnaires

At visit 1, patients were asked to report how many cigarettes per day on average they had smoked over the last 5 years (smoking history) as well as for how many years they had smoked, including how many cigarettes per day they had smoked on average since they started smoking. Throughout the study, they were then asked to report monthly what TNPs they had used over the last month, and on average, how many per day.

## Results

The first subject was screened on November 8, 2017, and the last subject was out on December 14, 2018 (on December 21, 2018, when considering the safety follow-up period). Final results will be published in 2021.

## Discussion

### Expected Outcomes

Only a few longitudinal studies have assessed the outcome of periodontal disease after smoking cessation, but they indicate that the recovery in PD, and to a lesser extent in CAL, after nonsurgical treatment is more successful in those who quit smoking [23,24,56,62,63]. Studies in smokers, nonsmokers, and former smokers indicate that smoking cessation has a beneficial effect on the outcome of periodontal treatment, and thus that the negative impact of tobacco use on periodontal disease is reversible within a timeframe of a few weeks to a few years, depending on the clinical endpoint assessed [15,16,20,62,64-66]. In this study, the effect of switching from cigarette smoking to the use of THS will be evaluated, which will demonstrate whether or not it is beneficial on the improvement of periodontitis following a nonsurgical, mechanical treatment. The change of PD was chosen as the primary endpoint rather than the change of CAL, because data on CAL showing changes in smokers vs nonsmokers or quitters are sparser than data on PD and are not very consistent [13].

All other endpoints should provide data on the effect of switching to THS on oral health in general, including buccal inflammation and microbiome composition.

Biomarkers of exposure to CEMA, total NNAL, and NEQ will serve as indicators of overall exposure of the patients to cigarettes throughout the study, as they can provide a good estimate of the exposure to tobacco smoke, which should be significantly reduced in users of THS. Because nicotine is expected to be delivered with THS at levels comparable to that delivered via cigarettes, the levels of NEQ are not expected to be lower in THS users than cigarette users, but they will serve as an overall estimate of exposure to tobacco.

### Limitations

To demonstrate a favorable effect of switching to THS compared with continuing smoking cigarettes, patients should ideally be exclusive users. There are no data suggesting a minimum amount of cigarettes per day that would not trigger any detriment to the periodontal status. Product consumption is based on self-reporting; thus, there cannot be any strict verification that what the participants report is true. A chemical verification could in principle be performed by measuring urinary levels of biomarkers of exposure, but this would require collection of 24-hour urine to obtain a reliable result. Instead, spot urine was collected in this study and the biomarkers of exposure levels will be adjusted to creatinine to adjust urinary excretion rates. The reliability of spot urine, taken at different times during the day depending on when the patient went to the visit, will need to be evaluated, but may prove to be of reduced relevance compared to 24-hour urine collection.

The effect of nicotine on periodontitis has not been largely investigated; however, NRT is proposed to patients who are willing to quit smoking to reduce withdrawal effects [67-70]. There is no clear evidence that nicotine alone has a detrimental effect on the recovery of diseased gums [30]. Because THS delivers nicotine but greatly reduces the levels of other HPHCs,

this study may help to differentiate the effects of nicotine from those of HPHCs on the improvement of periodontitis.

The measurement of PD or CAL can be quite variable, as described by Leroy et al [71]. This variability depends on (1) how the examiner makes the measurement, with the depth of penetration, angulation, and force applied being major factors of variability; and (2) the accuracy of the probe itself, which can vary even in the same batch from a production line. Intraexaminer reproducibility has nevertheless been shown to be high, with calibration and operator training, rather than operator experience, being fundamental for reproducibility [72].

Prior to the start of the study, the investigators attended a formal calibration training session to ensure and confirm that standardized measurements would be performed. The calibration session was designed to ensure a certain alignment of the different examiners in their periodontal assessment, as recommended for periodontal clinical research, as bias is easily introduced when several examiners take part in a study [73]. The weight applied by the probe was tested (20-25 g), as well as the measurement of PD, on 4 sites, and the ability to detect calculus. The number of different examiners in this study is unusually high when compared to other clinical studies on periodontitis; thus, whether intraexaminer variability will be an issue or not remains to be determined when analyzing the data. Only SRP was part of the care provided, unless otherwise decided by the investigator (eg, in the case of worsening of the condition). The same type of probe was used in each center. All dentists had to pass a Good Clinical Practice certification, and they were supported by Clinical Research Organization staff at every step of the protocol. The sample size was calculated based on former publications and was actually one of the largest samples ever tested in a longitudinal study on periodontitis and SRP.

### Comparison With Prior Work

Most studies performed to date on smoking and periodontitis have included cigarette smokers. Products such as heat-not-burn or e-cigarettes as alternatives to smoking have appeared relatively recently, and health-related outcome studies on these products are still extremely scarce. In 2016, a pilot study followed smokers with mild periodontitis who switched to e-cigarette use for up to 2 weeks, which found a statistically significant increase in gingival inflammation when tobacco smokers switched from smoking to vaping [31]. The authors did not report that smoking cessation leads to comparable effects [16,17,74], which is in alignment with the description that BOP and the inflammatory response associated with plaque accumulation are reduced or delayed in smokers compared to never smokers [14-16]. New studies on the effects of e-cigarettes and oral health are now being published; however, these are mainly cross-sectional studies and have not shown any effect of switching or of the effects on periodontal treatment [75-77]. A prospective study comparing the effect of full-mouth ultrasonic scaling on cigarette smokers, e-cigarette users, and nonsmokers with periodontitis found no significant difference in plaque control record, BOP, and PD at 3 and 6 months after treatment between the e-cigarette users and the nonsmokers, while the smokers had significantly higher scores of plaque

control record and PD at the 6-month follow up [78]. Overall, these studies seem to indicate that e-cigarette users have a better periodontal status than cigarette users, but likely not as good as that of never smokers. This study is thus the first of its kind by enrolling an estimated number of smokers with chronic generalized periodontitis that should be sufficient to demonstrate whether THS can indeed favorably influence the improvement of diseased teeth after standard of care treatment compared with patients who continue to smoke cigarettes.

## Conclusions

This study is part of a multilayered assessment program designed to evaluate whether THS can potentially reduce the risk of smoking-related diseases relative to continued smoking. The results of this study will confirm whether the reduction in exposure to HPHCs, excluding nicotine, when switching from cigarettes to THS leads to statistically significant favorable changes in the improvement of periodontal pockets following mechanical therapy, and follows the direction expected upon smoking cessation. This study will provide further evidence to substantiate the reduced risk potential of THS.

## Acknowledgments

The authors deeply appreciate the contributions of all the investigators and other clinical/research staff involved in this study.

## Conflicts of Interest

The work reported in this publication involved a candidate reduced risk product developed by PMI Research & Development. All authors are employees of PMI. PMI is the sole source of funding and sponsor of this project.

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## Abbreviations

- BOP:** bleeding on probing
- CAL:** clinical attachment level
- CEMA:** 2-cyanoethylmercapturic acid
- HPHC:** harmful and potentially harmful constituents

**NEQ:** nicotine equivalents  
**NNAL:** 4-(methylnitrosamino)-1-(3 pyridyl)-1-butanol  
**NRT:** nicotine replacement therapy  
**PD:** pocket depth  
**PMI:** Philip Morris International  
**SRP:** scaling and root planing  
**THS:** Tobacco Heating System  
**TNP:** tobacco- or nicotine-containing product

*Edited by G Eysenbach; submitted 04.07.19; peer-reviewed by Y Ren, R Holliday, T Muto; comments to author 10.03.20; revised version received 30.04.20; accepted 11.12.20; published 18.01.21.*

*Please cite as:*

*Pouly S, Ng WT, Benzimra M, Soulan A, Blanc N, Zanetti F, Picavet P, Baker G, Haziza C  
Effect of Switching to the Tobacco Heating System Versus Continued Cigarette Smoking on Chronic Generalized Periodontitis  
Treatment Outcome: Protocol for a Randomized Controlled Multicenter Study  
JMIR Res Protoc 2021;10(1):e15350  
URL: <http://www.researchprotocols.org/2021/1/e15350/>  
doi: [10.2196/15350](https://doi.org/10.2196/15350)  
PMID: [33459599](https://pubmed.ncbi.nlm.nih.gov/33459599/)*

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Protocol

# He Korowai Manaaki (Pregnancy Wraparound Care): Protocol for a Cluster Randomized Clinical Trial

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## Abstract

**Background:** Maternal and infant health inequities between Māori (the Indigenous peoples of Aotearoa New Zealand) and New Zealand European women are well documented and cannot be explained solely by socioeconomic status. A research center-iwi (tribal group) partnership aims to address these disparities and improve maternal and infant health outcomes by implementing an augmented maternity care pathway (He Korowai Manaaki) to improve access to services and evidence-informed care.

**Objective:** The objective of this study is to test whether an augmented maternity care pathway improves Māori infant health outcomes.

**Methods:** This is a Kaupapa Māori (by, with, and for Māori) cluster randomized clinical trial involving 8 primary care practices allocated to either an intervention arm or control arm. The intervention arm comprises an augmented maternity care pathway (He Korowai Manaaki) offering clinical care through additional paid health care appointments and improved access to social support (eg, housing, transport). The control arm is usual care. The primary outcome is increased timely vaccination for Māori infants, defined as all age-appropriate vaccinations completed by 6 months of age.

**Results:** Recruitment commenced in November 2018 and was completed in June 2020, with 251 enrolled women recruited in intervention primary care practices before 20 weeks of pregnancy. Publication of results is anticipated in late 2023.

**Conclusions:** The results will inform primary health care policy including whether the provision of augmented maternal care pathways reduces disparities in the structural determinants of health. If effective, He Korowai Manaaki will strengthen the health and well-being of pregnant Māori women and their babies and improve their health outcomes, laying a strong foundation for lifelong health and well-being.

**Trial Registration:** Australian New Zealand Clinical Trials Registry ACTRN12619001155189; <https://tinyurl.com/yypbef8q>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/18154

(*JMIR Res Protoc* 2021;10(1):e18154) doi:[10.2196/18154](https://doi.org/10.2196/18154)

**KEYWORDS**

maternity; inequity; Indigenous health; Māori; pregnancy; Kaupapa Māori; socioeconomic; primary health care; methodology



## Introduction

### Background

Protecting the health and well-being of expectant mothers and their families helps ensure that they and their baby/ies are well cared for and supported to have good maternal outcomes. In Aotearoa New Zealand, Indigenous Māori women have higher rates of adverse pregnancy outcomes compared to non-Māori women. Māori infants have an infant death rate of 5.9 per 1000 births compared to 3.2 per 1000 births among non-Māori [1]. Māori pregnant women and children also experience substantial socioeconomic disadvantages. Even so, the health inequities between Māori and New Zealand European women and infants are well documented and cannot be explained solely by socioeconomic status [2]. Reducing these health and socioeconomic disparities is an urgent priority.

At the invitation of the iwi (tribal group), He Korowai Manaaki (a protective cloak) was designed to surround pregnant woman and their children with the best evidence-informed, timely care and the best environment. As an augmented maternal care pathway, He Korowai Manaaki was designed to improve health and well-being through pregnancy and baby's first 2 years of life and beyond.

Aotearoa New Zealand's unique midwifery-led model of maternity care, established nearly 30 years ago, was purported to hold the potential to improve health outcomes for Māori [3]; however, Māori women and whānau (family) continue to experience persistent health inequities that impact well-being throughout the maternity continuum [4]. Underrepresentation of Māori midwives at all levels of the profession is indicative of a colonized infrastructure with Māori childbirth knowledge treated with skepticism [4].

Most women begin their pregnancy journey with their primary health care provider; however, the current model does not easily support continued primary health care practice involvement during pregnancy nor postpartum. Transitioning to a lead maternity carer (LMC; typically a midwife) can lead to fragmented, siloed care, inhibiting a seamless pregnancy pathway [2] and potentially contributing to health disparities for Māori women and babies [5].

Therefore, changes in the structure of the maternity health system are required, as improved coordination between midwives and general practitioners could be of great benefit for both equity of outcomes and efficiency of health service delivery [6].

### Iwi Partnership

The research center Te Tātai Hauora O Hine (The Centre for Women's Health Research, Victoria University of Wellington) was invited to partner with iwi/tribal group Ngāti Pāhauwera and develop a wraparound approach to maternity care. The aim of this approach was the provision of a seamless maternal and infant care pathway with improved access to both clinical and social support [7].

The guiding principles of the Ngāti Pāhauwera strategic plan are *Pakatō i te ata*, *Pakatō i te ahiahi*, *Māuri mahi Māuri ora*

(planning for the future health and well-being of the people), and *Mahia nga māhi o Kahukura* (imagining and creating a better future). These guiding principles provide foundations for the research partnership [7] and the resulting He Korowai Manaaki pathway (ACTRN12619001155189).

Grounded in a Kaupapa Māori (by, with, and for Māori) inquiry paradigm, this research prioritizes Māori ways of knowing and being, promotes a structural analysis of inequality [8], and aims to benefit Māori through the reduction of disparities [8-10]. The research practices reflect tikanga Māori (Māori customs), including the importance of place, relationships, and Māori self-determination [8,9].

### Aims

This study aims to implement an augmented maternity care pathway (He Korowai Manaaki) to improve Māori maternal and child health outcomes and to improve access to services (health, education, Well Child Tamariki Ora [WCTO], oral health, contraception, general practice) for pregnant Māori women and their infants.

We hypothesize that the He Korowai Manaaki pathway, with early, evidence-informed care and ongoing wraparound support opportunities, will improve the health outcomes of Māori infants. If successful, this pathway will serve as a prototype for an augmented national maternity care pathway.

## Methods

### Design

This study is a cluster randomized clinical trial with 2 study arms for pregnant women enrolled with primary care practices (PCPs). Practices are the unit of randomization. Intervention PCPs utilize the He Korowai Manaaki pathway for the pregnant women in their practice. Control PCPs continue usual care. For collection of data, all women in the intervention are individually consented, in contrast to the control arm where deidentified data is collected without individual consent.

### Research Approval

Research ethics approval was granted by the Health and Disability Ethics Committee of New Zealand (17/STH/136) in August 2017.

### Study Sites

All 15 PCPs in the urban Hawkes Bay region of Aotearoa New Zealand were approached; 8 provided informed written consent to participate in the cluster randomized clinical trial and were randomized: 4 to intervention and 4 to control. All pregnant women enrolled as a patient of an intervention PCP are eligible for the intervention.

### Sample Size

A total of 8 practices and 216 Maori participants (4 practices and 108 Maori participants in each group) will provide 80% power at a two-sided  $\alpha$  of .05 to detect an 18.5% difference in the proportion of infants who receive all age-appropriate vaccinations by 6 months of age between the groups. For these figures, we have assumed an average cluster size of 27,

intracluster correlation coefficient of 0.01, and that 83.5% of the infants will receive all age-appropriate vaccinations by 6 months of age in the intervention group and 65% in the control group. Our total sample size requires 432 pregnancies (216 control, 216 intervention).

Based on the expected recruitment rate and pregnant women meeting the entry criteria for the core intervention (ie, seen in a PCP before 20 weeks of pregnancy), He Korowai Manaaki is offered through intervention practices to all pregnant women for approximately 18 months from the commencement of the study to obtain the required sample size.

### Randomization

Practices are the unit of randomization. Each of the 8 PCPs was randomly allocated to either the intervention arm (He Korowai Manaaki) or the control arm (usual care) of the trial. Covariate constrained randomization [11,12] was used to minimize potential imbalance between intervention and control arms in the size of the Māori population aged less than 1 year. Information on enrollment size and numbers of Māori patients aged less than 1 year was collected for each of the 8 participating PCPs. All possible allocations of these PCPs to the 2 trial arms were then enumerated using an algorithm blinded to the practice names. The list of allocations was then narrowed down to the ones that gave approximate balance in the numbers of Māori aged less than 1 year across the 2 arms, with each arm having 4 clusters (PCPs). Finally, the actual allocation was chosen randomly from this constrained list, thereby achieving an acceptable allocation while retaining randomness in the selection process. No practices dropped out of the study.

### Control Arm (Usual Care)

Women enrolled in control practices who are pregnant during the study period receive usual care and will be included as controls in the trial. In Aotearoa New Zealand, usual care means that a woman chooses their LMC, and for most women, their LMC is an independent or self-employed midwife [13]. A high proportion of the control cohort is likely to have engaged with primary care early in pregnancy but continued primary health care involvement during pregnancy and postpartum is unlikely. Usual care for the control cohort is expected to be predominantly midwifery-led pregnancy care.

### Intervention Arm (He Korowai Manaaki)

The He Korowai Manaaki intervention addresses both clinical care (pregnancy, postpartum, neonatal, and reproductive health) and the structural determinants of health (eg, housing, transport) with a best-practice pathway. He Korowai Manaaki includes responses to recommendations from the New Zealand Perinatal and Maternal Mortality Committee [14] and is in line with recommendations to address structural determinants of health by the Select Health Committee Inquiry into Improving Child

Health Outcomes [15]. As a practice service change, He Korowai Manaaki is facilitated through primary care-held appointments including an extended first visit (First Touch), a follow-up visit, a third trimester visit, and a 6-week postnatal whānau (family) visit. Usual lead maternity care continues throughout.

General practitioners, nurse practitioners, and practice nurses at intervention PCPs were asked to attend an introductory training session on He Korowai Manaaki to enable the practice service change. The in-practice session provided by the researchers included education refreshers of evidence-based antenatal care, postnatal care, and contraception as well as information on the 4 study-funded appointments and utilization of the pregnancy wraparound care computerized advanced form installed into their practice management system. Education refresher sessions are provided by the researchers and associated experts over the course of the trial.

Clinicians in intervention PCPs work from the computerized advanced form to support care, screening, and navigation to allied services. This includes referrals to specialist care and services meeting the needs of wraparound care (eg, housing program, social work services, driving licensing programs, and dental practices).

Intervention practices are also supported to provide contraception of the woman's choice, free of charge (see third trimester appointment and 6-week postnatal appointment in [Textbox 1](#)) and support with transport to pregnancy-related appointments (see First Touch appointment in [Textbox 1](#)).

Posters and published material on display at each intervention practice inform the enrolled population of the He Korowai Manaaki practice change taking place for the duration of the research project. All women identifying as pregnant in a primary care appointment are informed that their practice is offering an augmented pathway of care for pregnant women as part of the research project.

Information about the project is also shared with individual women by the general practitioner, nurse practitioner, or practice nurse. Each woman is asked to provide informed written consent for their deidentified outcome data (pregnancy and infant health information) to be shared with the research group in the future. The augmented pathway visits ([Textbox 1](#)) are explained, with the First Touch appointment then being offered to all women (with no data being shared for nonconsenting women). All women are then invited to attend the other study appointments (free of charge), and a recall for the next appointment is set.

There are no exclusions. The augmented pathway of care is available at any stage of pregnancy, for all pregnancies (low-risk and high-risk).

**Textbox 1.** He Korowai Manaaki appointment descriptions.

First Touch appointment - an extended first antenatal appointment that includes:

- Time taken to respond fully to concern and queries
- Offer of screening for congenital abnormalities, sexually transmitted infections, family violence, and maternal mental health, with referrals as warranted
- Diagnosis of any underlying medical conditions, with referral to secondary care as appropriate
- Identification of risks (maternal age, obesity, maternal mental health problems, multiple pregnancy, socioeconomic deprivation, maternal medical conditions, previous preterm deliveries) with referral to secondary care as appropriate
- Navigation to lead maternity carer (LMC)
- Offer of prescribed pregnancy medications (folic acid, iodine)
- Whānau (family) checklist to assess whether support is required for transport to appointments, safe housing, finance, and oral health with connection offered to existing services and support

Follow-up appointment, including:

- Follow-up of tests that have been ordered, making sure all appropriate referrals have been made
- Ensure enrollment with LMC
- Administration of maternal vaccinations, when appropriate

Third trimester appointment (open to woman's midwife or whānau [family] to attend), including:

- Maternal vaccinations and planning for infant(s), including the provision of best-practice information about maternity health, child health
- Conversation about and planning for postnatal contraception

6-week postnatal appointment (open to woman's midwife or whānau [family] to attend), including:

- Addressing any concerns and answer queries
- Provision of free contraceptive
- Screening for infections, family violence, and maternal mental health, with referrals as appropriate
- Education around nutrition, smoking, alcohol use, and drug use
- Education around pelvic health, navigation to women's physio service as appropriate
- Navigation to oral health care services
- Navigation to support services such as Family Start, Well Child/Tamariki Ora, and Early Childhood Education services

**Primary Outcome Measures**

The primary outcome is the increase in timely vaccinations for Māori infants. Timely vaccination is defined as all age-appropriate vaccinations completed by 6 months of age.

**Secondary Outcome Measures**

Secondary outcomes include infant hospitalizations and length of stay until 1 year of age as well as obstetric, delivery, and infant outcomes plus service engagement outcomes (contraception, oral health, WCTO, Early Childhood Education [ECE]; see [Table 1](#)).

**Table 1.** Outcome variables and data sources.

Data source	Data source description	Examples of outcome variables
ELI <sup>a</sup>	The Ministry of Education information system for Early Childhood Education (ECE) collects information on participating children's enrollment and attendance.	Infant registration with ECE/Te Kōhanga Reo at 2 years of age <sup>b</sup>
MAT <sup>c</sup>	The MAT provides statistical, demographic, and clinical information about selected publicly funded maternity services up to 9 months before and 3 months after a birth. It also contains inpatient and day-patient health event data on pregnancy, birth, and the postnatal period for mother and baby, sourced from the National Minimum Dataset (administered by the MOH <sup>d</sup> ).	Maternal ethnicity; smoking status at time of booking with a maternity care provider and at 2 weeks postdelivery <sup>b</sup> ; hospitalization episodes <sup>b</sup> ; antenatal screening <sup>b</sup> ; plurality; parity; mode of delivery <sup>b</sup> ; Apgar scores <sup>b</sup> ; birthweight; gestational age at delivery <sup>b</sup> ; infant hospitalization in first year of life <sup>b</sup> ; breastfeeding status at infant discharge <sup>b</sup> , 2 weeks <sup>b</sup> , and 6 weeks
MOH	The MOH receives data from different parts of the health sector through the utilization of health services or mandatory reporting national collections and also from national population health surveys.	Infant registration to oral health services at 2 years of age <sup>b</sup>
MORT <sup>e</sup>	The MORT classifies the underlying cause of death for all deaths registered in New Zealand and all registerable stillbirths using the World Health Organization Rules and Guidelines for Mortality Coding.	Infant mortality <sup>b</sup> , ethnicity, date of death, gestational age at death, birthweight, diagnostic codes on cause of death, sudden and unexpected death indicator
NIR <sup>f</sup>	The NIR is a computerized information system that has been developed to hold immunization details of New Zealand children (administered by the MOH).	Infant vaccination at 6 weeks <sup>g</sup> , 3 months <sup>g</sup> , 5 months <sup>g</sup> , and 15 months <sup>b</sup>
NHI <sup>h</sup>	The NHI is a system used by public hospitals and other health and disability support services to assign an alphanumeric identifier (the NHI number) to people who use their services.	NHI number, area deprivation, ethnicity (maternal and infant)
NMDS <sup>i</sup>	The NMDS is a national collection of public and private hospital discharge information, including coded clinical data for inpatients and day patients (hospital events).	Ethnicity; diagnostic codes (ICD-10 <sup>j</sup> ) <sup>b</sup> ; maternal, antenatal, or postnatal hospital admissions (public) <sup>b</sup> ; discharge dates and length of stay; infant hospital admissions (public) <sup>b</sup> ; discharge dates and length of stay
PHO <sup>k</sup>	The PHO provides a national enrollment collection that holds patient enrollment data.	Infant engagement with general practitioner <8 weeks postdelivery or after infant discharge from hospital <sup>b</sup>
WCTO <sup>l</sup>	The WCTO program is a series of health assessments and support services for children and their families from birth to 5 years and is a gateway for parents to access primary and specialist health care, education, and social services. WCTO providers submit service coverage and data to the MOH.	Attendance at scheduled WCTO infant appointments at 8-10 weeks <sup>b</sup> , 3-4 months <sup>b</sup> , 5-7 months <sup>b</sup> , 9-12 months <sup>b</sup> , and 15-18 months <sup>b</sup> ; breastfeeding status at 3 months and 6 months <sup>b</sup>

<sup>a</sup>ELI: Early Learning Information System – Ministry of Education.

<sup>b</sup>Secondary outcome.

<sup>c</sup>MAT: National Maternity Collection.

<sup>d</sup>MOH: Ministry of Health.

<sup>e</sup>MORT: Mortality Collection.

<sup>f</sup>NIR: National Immunisation Register.

<sup>g</sup>Primary outcome.

<sup>h</sup>NHI: National Health Index.

<sup>i</sup>NMDS: National Minimum Dataset.

<sup>j</sup>ICD-10: International Classification of Diseases, Tenth Revision.

<sup>k</sup>PHO: Primary Health Organisation.

<sup>l</sup>WCTO: Well Child/Tamariki Ora.

## Data Collection

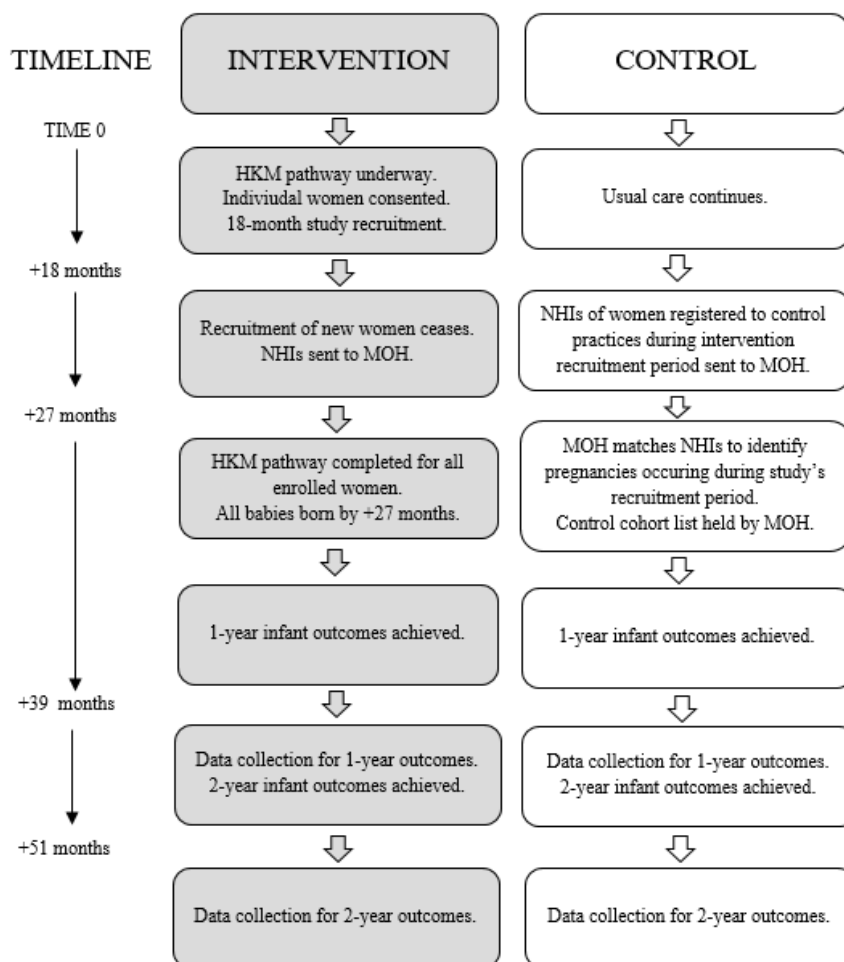
The data for our study are generated from national and local information collections, as described by Filoche et al [16]. In Aotearoa New Zealand, the Ministry of Health (MOH) is responsible for the oversight and funding of the country's 20 district health boards. Select clinical information is routinely

reported by each health board to the MOH and is collated into national datasets with operational responsibility by the Client Insights and Analytics group. Outcome data will be collected using Aotearoa New Zealand's unique patient National Health Index (NHI) number to source clinical and demographic data from multiple national datasets (Table 1).

At study end, intervention practices will send the NHIs of women who have provided consent for their deidentified outcome data to be collected and analyzed (linked to the NHI of an infant) to the MOH. The MOH will also receive from each control practice the NHIs of women registered with them during the study's recruitment period. To identify the control group (women enrolled with PCPs, pregnant during the study period)

and the associated linked infant(s) following the relevant designated time period (Figure 1), the MOH will match the NHIs provided by the control practices to national datasets containing maternity, pregnancy, and delivery information (eg, the National Maternity Collection and the National Minimum Dataset).

**Figure 1.** He Korowai Manaaki (HKM) timeline. MOH: Ministry of Health; NHI: National Health Index.



## Study Variables

Primary and secondary outcomes will be tracked by patient NHI without names. The NHIs will be matched to multiple national databases (Table 1) up until the infant is 2 years of age to source clinical and demographic data to provide a combined data source for (1) sociodemographic information (ethnicity, New Zealand Index of Deprivation [socioeconomic status], maternal age), (2) clinical information (parity, plurality, LMC, gestational age at booking), (3) obstetric outcomes (gestation at delivery, cesarean section, Apgars, mortality, and morbidity), (4) antenatal screening (LMC registrations), (5) smoking status (maternal smoking status at booking and after delivery), (6) vaccination status (timely access to age-appropriate immunizations), (7) infant hospitalizations (cause of mortality, intraventricular hemorrhage [bleed in brain], oxygen required on discharge, and length of stay in neonatal intensive care unit), (8) access to child health services (number of oral health or WCTO visits, general

practice registrations), and (9) access to ECE (ECE registrations).

## Analysis

Data analysis will occur as soon as outcome data are available for the intervention and control arms. Within a Kaupapa Māori inquiry paradigm [8-10], the primary analysis is for Māori, with secondary analysis for non-Māori [17]. An intention-to-treat analysis will be undertaken [18] using individual participant data. All pregnancies will be analyzed (regardless of the number of He Korowai Manaaki appointments attended), with the primary cohort being women seen in a PCP before 20 weeks of pregnancy.

The rate of infant hospitalizations will be analyzed using Poisson regression, and if there is evidence of overdispersion or underdispersion, then negative binomial model will be used. A generalized linear mixed model with a logit link will be used to analyze binary outcomes, and a linear mixed model will be



used to analyze continuous outcomes. All regression models will adjust for potential personal and care-related confounders and for the effect of clustering within practices. Sensitivity analyses will be undertaken for the primary outcome to determine the impact of missing data, and per protocol analyses will be conducted. The consistency of effects for prespecified subgroups will be assessed using tests for heterogeneity.

Descriptions of rates, rate ratios, odds ratios, and respective 95% confidence intervals will be reported. Results will be aggregated, and no individual practice will be identifiable.

## Results

This cluster randomized clinical trial is underway with 8 PCPs. Practices have been randomized to either the intervention arm or control arm. Recruitment of women ended in June 2020, with 293 women enrolled in the intervention arm, of which 251 women (the primary cohort) were seen in a PCP before 20 weeks of pregnancy. Data collection will commence in early 2022 and be complete by mid-2023, and the analysis results are anticipated to be published in late 2023. The explicit and conscious decision to use an indigenous lens when analyzing the data allows outcomes to be viewed with a focus on advantage and privilege rather than one of disparity.

## Discussion

Quality, culturally responsive maternal care is expected and essential to the achievement of Māori pregnancy, birthing, and motherhood aspirations of “hapū ora” [19], that is, the health and well-being of Māori mothers-to-be and their babies. Pregnancy is an important period during which health and support services can provide information, care, and resources to enable the optimal environment for fetal and neonatal stages

of life [19]. Quality antenatal care is especially important as part of a continuum of health care for mothers and as the starting point for the child’s developmental trajectory [20]. Māori women have a higher prevalence of maternal risk factors compared to other women and have greater maternity needs [21]; yet, their access to maternal health care and social support does not reflect this. As primary maternity care is considered to be a key enabler of health and well-being, it is pivotal that we find structural solutions that support hapū ora [19].

This augmented pathway enabled through primary care aims to achieve equitable outcomes by meeting the structural determinants and health needs of pregnant Māori women. If successful, the findings of this trial will inform Māori policy makers and service providers to bring about system changes.

## Limitations

The study limitations include whether PCPs find He Korowai Manaaki useful in their practice. Given the heterogeneous make-up of PCPs, the benefits for each practice may vary depending on their population, resources, and needs. The study does not measure which component(s) of the pathway are taken up; however, an intention-to-treat analysis is widely accepted as the gold standard for assessing the superiority of the intervention in randomized trials [18].

Further, this study will be carried out in an urban area with a high Māori population, and the results may not be generalizable to other areas and other communities.

## Conclusions

The results of this study will inform policy and clinical pathways for Māori and be valuable in informing agencies about the potential health and well-being gains from an iwi-initiated augmented national maternity care pathway accessible through primary care.

## Acknowledgments

This study is funded by Te Kanuihera Rangahau Hauora O Aotearoa (The Health Research Council of New Zealand). BL, senior author and principal investigator, conceived the study and has overall responsibility for the study. MB, CL, BL, and FC guide the project. FS drafted the manuscript. NS provided statistical input and guided the methodology. All authors contributed to the study design and manuscript writing and approved the final manuscript.

## Conflicts of Interest

None declared.

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## Abbreviations

- ECE:** Early Childhood Education
- LMC:** lead maternity carer
- MOH:** Ministry of Health
- NHI:** National Health Index
- PCP:** primary care practice
- WCTO:** Well Child Tamariki Ora

*Edited by G Eysenbach; submitted 09.02.20; peer-reviewed by S Kildea, F Goodyear-Smith; comments to author 12.06.20; revised version received 01.10.20; accepted 15.12.20; published 29.01.21.*

*Please cite as:*

*Lawton B, Storey F, Sibanda N, Bennett M, Lambert C, Geller S, Edmonds L, Cram F  
He Korowai Manaaki (Pregnancy Wraparound Care): Protocol for a Cluster Randomized Clinical Trial  
JMIR Res Protoc 2021;10(1):e18154*

*URL: <http://www.researchprotocols.org/2021/1/e18154/>*

*doi: [10.2196/18154](https://doi.org/10.2196/18154)*

*PMID: [33512321](https://pubmed.ncbi.nlm.nih.gov/33512321/)*

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Protocol

# Live Video Adaptations to a Mind-Body Activity Program for Chronic Pain and Cognitive Decline: Protocol for the Virtual Active Brains Study

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## Abstract

**Background:** Chronic pain (CP) and cognitive decline (CD) are costly, challenging to treat, prevalent among older adults, and worsen each other over time. We are iteratively developing Active Brains-Fitbit (AB-F), a live video program for older adults with CP and CD that teaches mind-body skills and gradual increases in step count. AB-F has demonstrated feasibility; acceptability; and signs of improvement in emotional, physical, and cognitive functions when delivered in person to older adults.

**Objective:** We are conducting a feasibility randomized controlled trial (RCT) of AB-F versus a time- and dose-matched educational control (health enhancement program [HEP]) in older adults with CP and CD. Here, we describe virtual adaptations to our study protocol, manualized treatments, evaluation plan, and study design in response to feedback from former participants and COVID-19. We will evaluate the feasibility benchmarks and the potential of AB-F to improve physical, emotional, and cognitive functions.

**Methods:** This is a single-blind pilot RCT. Participants are randomized to AB-F or HEP. Patients are recruited through pain clinic referrals, institutional registries, and flyers. Interested participants are screened for eligibility via telephone and provide electronic informed consent. After randomization, participants are mailed all study documents, including their treatment manual, an ActiGraph accelerometer, and a Fitbit (separate envelope for AB-F only). Both conditions are manualized and delivered over 8 weekly sessions via Zoom. Participants complete self-report and performance-based (6-min walk test and Montreal Cognitive Assessment) outcome measures via Zoom at baseline and post intervention. Primary outcomes are a priori set feasibility (recruitment, quantitative measures, and adherence), acceptability, credibility, expectancy, and satisfaction benchmarks. Secondary outcomes are physical, cognitive, and emotional functions as well as intervention targets (social function, pain intensity, pain-specific coping, and mindfulness).

**Results:** The trial is ongoing. We have recruited 21 participants (10 AB-F and 11 HEP) across 2 rounds. Only 2 participants have withdrawn (1 before baseline and 1 before the first session). All 19 remaining participants have completed the baseline assessment. In the first round, attendance is high (11 out of 12 participants completed all 4 sessions so far), and AB-F participants are adherent to their Fitbit and step goals (5 out of 6 participants).

**Conclusions:** Preliminary findings are promising for the feasibility of our completely virtual AB-F intervention. However, these findings need to be confirmed at the trial conclusion. This study will answer important questions about the feasibility of delivering a completely virtual mind-body activity program to older adults with comorbid CP and CD, which, to our knowledge, is unprecedented. Details on integrating multiple digital platforms for virtual assessments and intervention delivery will inform treatment development for older adults and those with comorbid CP and CD, which is crucial during the COVID-19 pandemic.

**Trial Registration:** ClinicalTrials.gov NCT04044183; <https://clinicaltrials.gov/ct2/show/NCT04044183>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/25351

**KEYWORDS**

chronic pain; cognitive decline; physical activity; mind-body therapies; aged; telemedicine; mobile phone

**Introduction****Background**

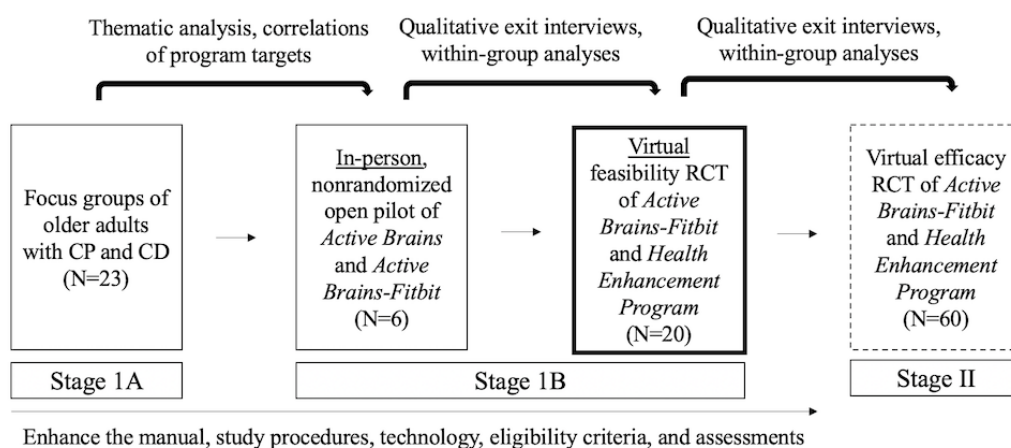
Chronic pain (CP), or pain that persists for more than 3 months, is common in the United States, costly to the health care system, and difficult to treat [1]. CP becomes more prevalent with increasing age, affecting 25-50% of community-dwelling older adults [2] and over 80% of nursing home residents [3]. Cognitive decline (CD) [4], defined as subjective (ie, self-report only) or objective (ie, confirmed by formal testing) decreases in cognitive performance that surpass normal aging [2], is a growing public health priority as life expectancy increases. There is a bidirectional relationship between CP and CD [5]. Older adults with CP are twice as likely to endorse CD [4] and are at greater risk for neurodegeneration [6], which in turn exacerbates perceptions of CP [7]. CP [8,9] and CD [10] exacerbate each other, placing individuals on a *disability spiral* of worsened physical, emotional, and cognitive functioning [11,12].

Unfortunately, current treatments are inadequate for addressing the CP-CD comorbidity among older adults [4,13]. CP and CD are often initially treated with medications, which are limited in efficacy [14] (eg, lack cognitive benefits) [15]; increase the risk of adverse events, such as falls [16]; and are associated with harmful side effects that can worsen CD [17]. Nonpharmacological interventions for CP that teach adaptive

coping skills can improve physical, emotional, and social functioning [18] but overlook the needs of older adults with CD. Walking-based mind-body activity programs may be feasible and effective in addressing the CP-CD comorbidity among older adults [19-22].

We are iteratively developing the first mind-body activity program to address the CP-CD comorbidity among older adults using the National Institute on Aging (NIA) Stage Model [23], which emphasizes early refinement before efficacy testing (Figure 1). First, we developed Active Brains (AB) and Active Brains-Fitbit (AB-F) using qualitative data from patient focus groups (stage 1A) [13]. Both programs teach identical mind-body skills to address the CP-CD comorbidity and increase participants' step count, but AB-F participants set individualized quota-based step goals [21] reinforced by a Fitbit [24]. In a nonrandomized open pilot trial (stage 1B), both programs similarly displayed (1) preliminary feasibility and acceptability when delivered in person; (2) within-group improvements for pain intensity, pain-specific coping, physical function, and cognitive function; and (3) high participant satisfaction [13]. Qualitative individual exit interviews assisted in further optimizing the program components and study methodology [13]. Participants in the Fitbit group found the device useful for monitoring their progress in real time, enhancing motivation, and reinforcing individualized goals, which align with positive perspectives of technology to modify health behaviors [25,26].

**Figure 1.** Iterative stages of Active Brains-Fitbit development. The study described in this protocol is outlined in bold. The subsequent efficacy randomized controlled trial is outlined by a dashed line. CD: cognitive decline; CP: chronic pain; RCT: randomized controlled trial.



These findings informed 2 main decisions in the preparation for a future stage II efficacy trial. First, because AB and AB-F performed similarly with regard to both feasibility benchmarks and preliminary effects and participants in the AB-F group found using a Fitbit to monitor and safely increase step count beneficial, our next stage 1B trial will be a single-blind pilot randomized controlled trial (RCT) of AB-F versus an attention placebo control (health enhancement program [HEP]) [27]. Second, due to COVID-19, many of the exit interviews after our in-person trial were conducted virtually [28], and

participants generally preferred this remote modality. Qualitative results from our previous work [29] highlighted participants' interest in live video delivery to overcome barriers to in-person attendance commonly experienced by older patients, such as lack of flexible scheduling, difficulty coordinating transportation, and travel costs [30]. Further, a growing body of research shows that older adults can effectively use technology [31], including live video [32] and wearable devices. Our virtual adaptations to mind-body interventions for patients with neurofibromatosis [33,34], stroke, and CP [35] suggest



that older adults with CP and CD [13] may also be amenable to AB-F delivered via live video. The findings will inform a subsequent pilot RCT to test feasibility benchmarks of the ability to randomize individuals to the intervention (AB-F) or control (HEP) as well as deliver the programs and conduct all study procedures virtually.

### Objectives

Here, we describe live video adaptations to study procedures and delivery of AB-F versus HEP in older adults with CP and CD within a single-blind RCT. We hypothesize that AB-F delivered via live video would meet a priori feasibility (recruitment, quantitative measures, and adherence), acceptability, credibility, expectancy, and satisfaction benchmarks similar to our in-person trial. Patients' in-depth perceptions of technology will be assessed, including virtual assessment and intervention delivery via exit interview focus groups with participants after the programs as well as through a post intervention self-report survey. The results will inform a subsequent efficacy RCT (stage II) of AB-F versus HEP, both

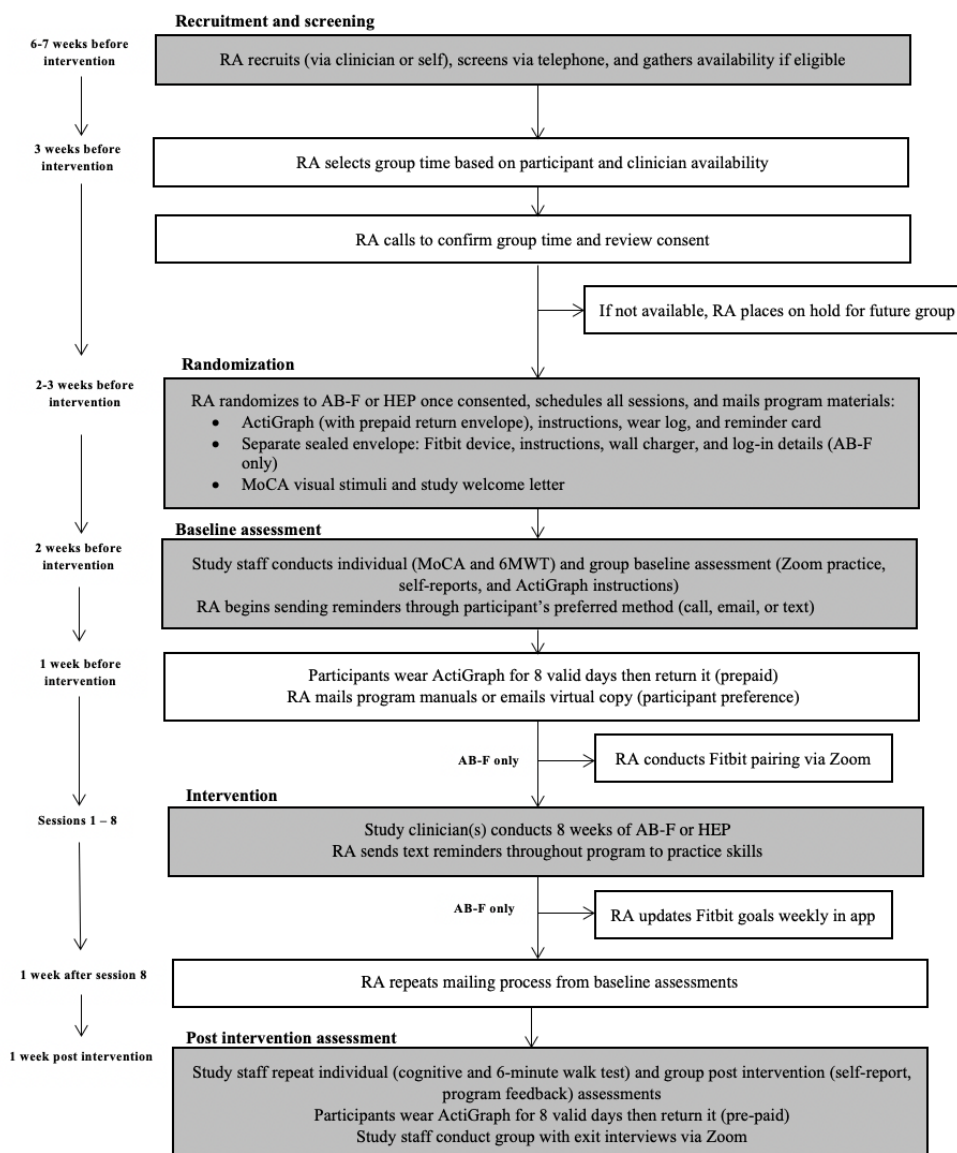
delivered in group via live video. The following hypotheses will be tested: (1) AB-F is superior to HEP in improving objective, performance-based, and self-reported measures of physical, cognitive, and emotional function outcomes; (2) AB-F-related improvements will sustain over time; and (3) program targets (eg, mindfulness and coping) and relevant clinical and demographic variables will serve as mediators and moderators of improvement in outcomes.

### Methods

#### Study Design and Setting

This single-blind feasibility RCT of AB-F versus a time- and dose-matched educational control (HEP) in older adults with heterogeneous CP and CD is being conducted at a large academic medical center in the Northeastern United States. Our institutional review board (IRB) approved this study (#2018P002152). Figure 2 presents a diagram of the study design and timeline of the procedures outlined below.

**Figure 2.** Study design and timeline. AB-F: Active Brains-Fitbit; HEP: health enhancement program; MoCA: Montreal Cognitive Assessment; RA: research assistant; and 6MWT: 6-min walk test.



## Inclusion and Exclusion Criteria

Textboxes 1 and 2 present the criteria and rationale for study inclusion and exclusion, respectively. These eligibility criteria are consistent with similar mind-body trials with patients with CP [18,35] and our earlier program development work with this

population [13,29]. The criteria are meant to be as inclusive as possible by allowing individuals with any type of musculoskeletal CP and any type of subjective or objective CD to participate to maximize generalizability consistent with NIA guidelines [23].

### Textbox 1. Study inclusion criteria and rationale.

#### Inclusion criteria and rationale

- Male and female outpatients, aged 60 years or older. Population under study
- Have nonmalignant chronic pain for more than 3 months. International Association for Study of Pain [36] criteria
- Self-report cognitive decline, such as forgetting names or obligations, getting lost, and having to repeat information. Population of study
- Able to perform a 6-min walk test at an accelerated pace. Program will involve increasing the number of steps for the primary physical function outcome measure
- Free of concurrent psychotropic or pain medication for at least 2 weeks before initiation of treatment or stable on current psychotropic or pain medication for a minimum of 6 weeks and willing to maintain a stable dose. Treatment confound
- Cleared by a medical doctor for study participation and no self-reported concerns about physical functioning on the Physical Activity Readiness Questionnaire [37]. Human subject concern, risk
- Has access to a smartphone with Bluetooth 4.0 capability to enable the Fitbit device and 6-min walk test (*Timed Walk*) [38] app and a computer for video software (Zoom for remote assessments and treatment sessions). Necessary for pairing with Fitbit and storing/downloading data, conducting physical function assessments remotely, and virtual group sessions

### Textbox 2. Study exclusion criteria and rationale.

#### Exclusion criteria and rationale

- Diagnosed with a medical illness expected to worsen in the next 6 months (eg, malignancy). Treatment confound
- Serious mental illness or instability for which hospitalization may be likely in the next 6 months. Feasibility, participant safety
- Self-reported current suicidal ideation. Participant safety
- Lifetime history of schizophrenia, bipolar disorder, or other psychotic disorder. Treatment confound
- Current substance abuse or dependence and current substance use disorder, within the past 6 months. Treatment confound
- Practice of yoga/meditation, or other mind-body techniques, once per week for 45 min or more within the last 3 months or less. Treatment confound
- Regular use of Fitbit in the last 3 months. Treatment confound
- Engage in regular intensive physical exercise for more than 30 min a day. Treatment confound
- Unable to walk without the use of assistance (eg, walker, cane, and wheelchair). Treatment confound

## Recruitment and Screening

Participant recruitment and screening was initiated in August 2020. To facilitate local recruitment of older adults with comorbid CP and CD, we established interdisciplinary partnerships with the Memory Disorders Division, Center for Pain Medicine, the Psychological Assessment Center, and the Osher Center for Integrative Medicine Clinical Program within our institution. Participants may also present to hospital-affiliated or regional medical practices that treat CP or CD and meet the study criteria. Our IRB-approved recruitment flyer is distributed to physicians at these recruitment sites and public online groups for CD and/or CP (eg, open forums for CD and Facebook groups for individuals with CD and their loved ones). Use of virtual recruitment and enrollment as well as live video intervention delivery allows geographically diverse older adults to participate in the study.

A trained research assistant with experience in coordinating mind-body intervention trials for CP recruits and screens participants by phone from a private location. The research assistant provides study details to interested participants and screens for eligibility via phone. Those who express interest and wish to participate in the study may opt to review the consent form briefly with a member of the study staff via phone during the initial screening conversation. The research assistant makes 3 contact attempts before discontinuing and maintains an updated log of all screening attempts for study data reports. The principal investigator, a licensed clinical health psychologist with expertise in older adults, mind-body interventions, CP, and CD, reviews all cases before enrollment to confirm eligibility. We have successfully used this strategy in prior intervention development trials conducted remotely [39,40].

## Enrollment

Our goal was to enroll and randomize up to 10 participants for each of the 2 rounds in this pilot RCT (N=20) and to deliver the programs in small groups of 5-6 participants, consistent with guidelines for conducting virtual group interventions [41,42]. The research assistant coordinates with eligible and interested participants via phone to select an appropriate time for group meetings based on the availability of the majority of participants. The research assistant emails participants the consent form and asks them to return an electronically signed copy within 48 hours. If needed, the research assistant contacts participants to answer remaining questions about the consent form (ie, how to electronically sign). Participants are considered enrolled when they have returned the signed informed consent form via email, are randomized, and attend at least one session. Participants earn US \$30 for each assessment (baseline and post intervention, US \$60 in total), US \$10 for each intervention session (8 sessions, US \$80 in total) and homework (AB-F only), and US \$30 for the exit focus group (US \$170 in total).

## Randomization to Treatment Arm

Randomization occurs after consent but before the baseline assessment to allow time for mailing the Fitbit to those in AB-F. Randomization follows a block design (blocks of 12) to ensure that equal numbers of patients are split into the AB-F or HEP groups. To maintain single-arm blinding, the study staff refer to the AB-F and HEP as AB1 and AB2, respectively. After randomization, the research assistant sends the Zoom appointment information for group sessions for the 10 weeks of the study, including the following: (1) the baseline assessment to practice Zoom, receive accelerometer instructions, and complete self-reports via Research Electronic Data Capture (REDCap); (2) 8 intervention sessions; and (3) post intervention to readminister self-reports and review accelerometer instructions. The research assistant also mails each participant a package that contains a folder with: (1) a welcome letter from the principal investigator (AV), (2) testing materials for the Montreal Cognitive Assessment (MoCA) [43] and accelerometer (wear-time log, instructional document, and reminder card), and (3) a prepaid envelope to mail the accelerometer back to the study staff. The AB-F group receives an additional sealed envelope with a Fitbit, charger, wall-plug, instructions on the device, and log-in information. AB-F participants are asked to not open that envelope until their Fitbit pairing session, and all participants are notified of their group assignment after all baseline assessments are complete.

## Live Video and Technology Considerations for Older Adults With CP and CD

Prior research shows that older adults face several barriers to adopting new technology, including decreased learning and memory capacity, lower self-efficacy, and decline in vision and motor skills [44-47]. To optimize feasibility, acceptability, and adherence, we follow guidelines for facilitating older adults' use of technology, such as leveraging social support [48], providing reassurance, and linking to personal relevance [49,50], and allowing time for self-directed learning and experimentation to develop confidence [51]. We use additional strategies to further promote familiarity with the specific technologies used

in this virtual RCT. First, the research assistant gauges individualized levels of technical support needed by asking participants: (1) whether they have used Zoom before, (2) which laptop and smartphone devices they own, (3) if they have an in-person support who can help them troubleshoot, and (4) whether they prefer an online or physical copy of the program manual. Second, we instruct participants to contact study staff for technological assistance at any time. Third, the study clinician and research assistant collaborate via text messaging to provide real-time technical support during session appointments (eg, connection or audio/video issues). Fourth, the research assistant immediately contacts participants who missed a group session to schedule a make-up with the study clinician to prevent missed material. Fifth, participants in both groups may consent to electronic reminders (phone calls, text messages, or email based on preference) to increase session attendance and adherence to technology. Text messages are sent once a day during the study, and participants may opt out at any point. Sixth, the study clinician allots up to 10 min at the start of each session to overcome technological barriers that emerge. We describe specific live video adaptations to our procedures using the technologies below.

### *Live Video Delivery*

We use live video (Zoom) for all study procedures, including assessments and intervention delivery. We developed the live video procedures using our experience in delivering virtual mind-body programs in prior studies [39,52,53] and consultations with the Society of Behavioral Medicine Behavioral Informatics Special Interest Group. The research assistant sends download instructions to participants who are unfamiliar with Zoom and offers individualized technical support as needed. Two weeks before the first treatment session, the research assistant schedules a 90-min group baseline assessment via Zoom with all participants and study staff to provide a tutorial and explain the accelerometer and self-report baseline assessments (refer to the Assessment Procedures below). During this baseline assessment, the study staff guide participants in enabling their audio/video and positioning their camera appropriately. In case multiple participants encounter technical challenges at once, additional research assistants are on standby for the duration of the call. Participants learn the procedures and rationale for using the following Zoom functions during group sessions: gallery view to see all participants, camera mode to enable video, mute to limit noises in their environments when not speaking, and host mute capabilities in the event that participants cannot mute themselves or forget to do so when appropriate. Participants are also informed of the privacy features of Zoom (eg, encryption and password protection) and that sessions will be audio recorded.

### *Fitbit Step Count*

Participants in the AB-F group receive their Fitbit, charger, wall-plug, Fitbit account information, and user manual via mail in a separate sealed envelope. Following the 1-week baseline accelerometer assessments, all participants in the AB-F group meet the research assistant via Zoom to pair their Fitbit to a Bluetooth-enabled smartphone. Participants are instructed to keep their device in a safe location or charging until the first

group session. Participants wear the Fitbit from the first session to post intervention (except while bathing). Fitabase, a secure web-based data collection platform, allows the research assistant to remotely monitor participants' daily Fitbit data for adherence and to ensure that the Fitbit is not being worn before the first session (to prevent biasing the baseline assessment). The research assistant sets AB-F participants' weekly walking goals, which appear on their watch and smartphone app, by logging into their Fitbit account on a computer. Participants are sent weekly emails with their updated walking goal, based on the goal set the previous week and whether or not the goal was met. The research assistant also sends weekly text message reminders to charge and synchronize the device.

### **Accelerometer Step Count**

After consenting and randomization, participants receive a wGT3X-BT ActiGraph accelerometer [54] in the mail and a folder that contains a wear log, a reminder card, and simple instructions with photos to properly wear the device. During the group baseline, the study staff asks participants to open the mailed envelope to review the accelerometer procedures and discuss solutions to common issues (eg, forgetting to wear the device and interference with clothing) detailed in our prior qualitative work [13]. All participants wear the accelerometer over their right hip, log each time they put the device on and take it off, and record their daily walking or any other exercise (to corroborate the objective step count data) for 8 days. Participants then return the accelerometer using a prepaid envelope. The research assistant provides daily reminders to wear the accelerometer and complete the log using the participants' preferred method of contact (phone, email, or text). The research assistant uses these check-ins, along with data monitoring in the ActiLife software [55], to confirm that all participants record 8 days (ie, 1 week plus the day of the assessment) of valid accelerometer wear ( $\geq 7$  hours/day) at baseline and post intervention. Participants with 5 or fewer valid days are either given an extension before returning the accelerometer back or are mailed the device again. Our mailing procedure is similar to the recent accelerometer protocols [56].

### **6-Min Walk Test**

Participants complete the 6-Min Walk Test (6MWT) [57] using an app (*Timed Walk*) on their smartphone [38] at baseline and post intervention. *Timed Walk*, which measures walking distance within a fixed timeframe using smartphone-based GPS, is a valid performance-based measure of physical function and is a reliable alternative to traditional laboratory assessments [38]. Study staff assist participants with downloading *Timed Walk* via the app store during an individual Zoom session (15 min). Participants are instructed to self-administer the 6MWT using *Timed Walk* by walking outside on flat terrain and emailing or calling the research assistant to submit their results. To ensure safety and increase adherence, participants create a plan to complete the 6MWT on a familiar route at a specific time and date with support from a friend or family member for safety (eg, driving the participant to a familiar area) or technology (eg,

navigating the app and submitting the results), if needed. We protect participants' privacy by providing information about the GPS location and steps data collected during consent and recommend deleting the app until the post intervention assessment.

### **MoCA**

Study staff also administer the MoCA [43] following audio-visual guidelines [58] at baseline and post intervention during the individual Zoom session (before completing the 6MWT). We instruct participants via email to have the visual stimuli (mailed in the packet of study materials) and a pen ready for the virtual MoCA administration. Participants hold their answers to the first 3 MoCA items (trials, cube, and clock) to the video camera for study staff to screenshot and score.

### **Self-Report Measures**

Participants complete questionnaires online via REDCap [59] during the group assessments (baseline and post intervention) via Zoom. The research assistant emails participants a secure link to complete the questionnaires. The research assistant aids participants in accessing their email and clicking on the REDCap link while remaining connected to Zoom. The study clinician mutes all participants to aid focus during the completion of the questionnaires. Participants are encouraged to use the *hand raise* function on Zoom or temporarily unmute themselves for technical support or to ask clarifying questions about the self-reports as needed. The research assistant remains on the Zoom call and monitors participants' questionnaire completion status using the REDCap dashboard but does not influence their responses. If participants encounter significant difficulties that prevent them from completing the questionnaires during the baseline session (eg, due to technology or CD symptoms), the research assistant schedules a call with the participant the following day to troubleshoot and ensure that all questionnaires are completed. Study staff review all questionnaires for missing data and errors that were not prevented by the REDCap response validation features.

### **Treatment Arms**

The 8 treatment and 2 assessment sessions (all 90 min) are delivered to both treatment arms concurrently via Zoom over a total of 10 weeks. Participants can attend the online group sessions from their home or another private place with a personal computer. Both treatment arms are delivered by trained clinicians under the direct supervision of health psychologists with expertise in mind-body and walking interventions, geropsychology, and CP. We follow the National Institutes of Health recommendations [60] and our previously developed clinical adherence protocol to assess treatment fidelity of both programs [39]. The clinicians complete fidelity checklists after each session and undergo weekly supervision to reinforce protocol adherence. We will confirm fidelity to both programs by independently coding adherence in a random sample (10%) of the audio recorded sessions. Table 1 outlines the 8 AB-F and HEP sessions.



**Table 1.** Session outline for the Active Brains-Fitbit and health enhancement program for older adults with chronic pain and cognitive decline.

Session	AB-F <sup>a</sup> topic	AB-F skills and session content	HEP <sup>b</sup> topic	HEP skills and session content
1	CP <sup>c</sup> and CD <sup>d</sup> : the disability spiral	Myths about pain, unhelpful pain alarm, disability spiral, mind-body connection, deep breathing, and gratitude practice	Program overview and CP and CD	Understanding CP and CD, connection between CP and CD, and impact of stress
2	“Walk All Over” the disability spiral	Quota-based walking, choosing meaningful activities, setting a walking plan, education on increasing daily walking, self-compassion, and barriers to using the Fitbit	The connection between CP, CD, and physical wellness	Connection between CP and CD
3	Mindfulness and pain	Mindfulness, breathing meditation, body scan, mindful moments, and pain awareness	Sleep and wellness	Sleep hygiene, cognitive and physical health
4	Mindfulness of pain sensations	Noticing unhelpful alarms, mindfulness of pain meditation, mindful walking, and overcoming barriers to walking	Exercise and wellness	Physical exercise, maintaining healthy weight, and tips for getting active
5	Building cognitive reserve	Education on cognitive abilities, CP-CD connection, coping with cognitive difficulties, engaging your intellect, and cognitive mindful moments	Nutrition I: the basics	Basic nutrition, portion size and calories, and understanding food labels
6	Strengthening social support for CP and CD	Social support and the pain cycle, types of social support, reducing loneliness: get active together, social support in CP and CD, and effective communication	Nutrition 2: healthy weight and weight loss	Eating healthier meals and snacks, eating out healthy, and weight loss and BMI
7	Coping skills to get back on track	CP, CD, and values; why we walk; getting back on track with walking; and stop and breathe, reflect, and choose	Managing your health care for CP and memory-related problems	Communicating with doctors, health diary, medical emergencies, and medication adherence
8	Staying on track and maintaining your progress	The powerful self, staying on track, reflecting on Active Brains skills, and resiliency plan	Review of Active Brains 2	Overview of program skills

<sup>a</sup>AB-F: Active Brains-Fitbit.

<sup>b</sup>HEP: health enhancement program.

<sup>c</sup>CP: chronic pain.

<sup>d</sup>CD: cognitive decline.

## AB-F

Full details on the AB-F program can be found in our prior work [13]. Briefly, AB-F encourages gradual increases in daily step count through individualized goal setting using quota-based (eg, meeting a step goal of 5000 steps) rather than pain-contingent walking, reinforced by Fitbit [24]. AB-F also targets the CP and CD comorbidity by teaching mind-body; pain-cognition awareness; as well as cognitive, emotional, and social functioning skills. On the basis of the qualitative results from our stage 1B exit interviews, we enhanced the AB-F manual to (1) increase education and time spent on mindfulness, gratitude, and self-compassion skills; (2) strengthen goal setting through simplified walking plans that prioritize repetition and problem solving; (3) improve brain health education and practical strategies for compensating with CD; (4) enhance sensitivity to visual impairments by streamlining the text, adding visuals, and using an age-friendly font (type and size); and (5) refine the final session on maintaining progress beyond the program. We further modified specific program components directly impacted by COVID-19, including walking (eg, emphasizing outdoors and physically distant locations and wearing a mask), cognitive (eg, maintaining mental stimulation during quarantine), and social skills (eg, using technology to remain connected and reducing loneliness). Participants email

their homework log that documents their walking progress, mind-body and gratitude practice, and pain ratings by the morning of each session for the study clinician’s review (AB-F only).

## HEP

Our previous work provides full details on HEP [27]. Briefly, this active control accounts for the effect of time spent as well as feedback and support from group members and the study clinician. Participants receive lifestyle education consistent with public health recommendations and standards for health promotion (eg, physical activity, sleep, nutrition, healthy weight, and medical appointments). The program has been successfully used as an active control in multiple prior studies [33,39,40]. We adapted the HEP to include population-specific information on CP and CD symptoms. Reminders to practice the mind-body and activity skills in AB-F are matched with reminders of the health education learned for the HEP.

## Feasibility Markers

Table 2 contains the a priori set benchmarks and criteria that align with our prior in-person trial [29] and similar feasibility pilot studies [35,39,61]. We will assess the feasibility (recruitment, quantitative measures, and adherence),



acceptability, credibility, expectancy, and satisfaction of both programs delivered virtually.

**Table 2.** Feasibility and acceptability of the programs.<sup>a</sup>

Marker	Description	Criteria
Feasibility of recruitment	Proportion of patients who agreed to participate from the total contacted	<ul style="list-style-type: none"> <li>Excellent: <math>\geq 80\%</math> of contacted patients agree to participate</li> <li>Good: <math>\geq 70\%</math> of contacted patients agree to participate</li> </ul>
Program acceptability	Proportion of participants who attended 6 out of 8 sessions (including makeups)	<ul style="list-style-type: none"> <li>Excellent: <math>\geq 80\%</math> of participants attend 6 out of 8 sessions</li> <li>Good: <math>\geq 70\%</math> of participants attend 6 out of 8 sessions</li> </ul>
Credibility and expectancy	Proportion of participants above the Credibility and Expectancy Questionnaire [62] midpoint	<ul style="list-style-type: none"> <li>Excellent: <math>\geq 80\%</math> of participants rate credibility and expectancy above the scale midpoint</li> <li>Good: <math>\geq 70\%</math> of participants rate credibility and expectancy above the scale midpoint</li> </ul>
Therapist adherence to manual	Clinician adherence to audio recording, progress note, and checklist with content delivered	<ul style="list-style-type: none"> <li>Excellent: 100% of audio recordings, progress notes, and checklists were completed with 100% of content delivered</li> <li>Good: <math>\geq 75\%</math> of audio recordings, progress notes, and checklists were completed with 100% of content delivered</li> </ul>
Feasibility of quantitative measures	Number of questionnaires entirely missing in more than 25% of participants	<ul style="list-style-type: none"> <li>Acceptable: No questionnaires were entirely missing in <math>&gt;25\%</math> of participants and or had an internal reliability below 0.70</li> </ul>
Adherence to homework	Proportion of participants who completed at least 5 out of the 7 homework logs	<ul style="list-style-type: none"> <li>Excellent: <math>\geq 80\%</math> of participants complete at least 5 out of the 7 homework logs</li> <li>Good: <math>\geq 70\%</math> of participants complete at least 5 out of the 7 homework logs</li> </ul>
Adherence to ActiGraphs and Fitbit	Number of participants with valid ActiGraph data ( $\geq 7$ hours) for 6 out of 8 days; number of participants who wore the Fitbit for 5 out of 7 days. We also report the number of days participants step count goal was met	<ul style="list-style-type: none"> <li>Excellent: <math>\geq 80\%</math> of participants with valid ActiGraph data on <math>\geq 6</math> out of 8 days per week</li> <li>Good: <math>\geq 70\%</math> of participants with valid ActiGraph data on <math>\geq 6</math> out of 8 days per week</li> <li>Excellent: <math>\geq 80\%</math> of participants wear the Fitbit at least 5 of the 7 days per week</li> <li>Good: <math>\geq 70\%</math> of participants wear the Fitbit at least 5 of the 7 days per week</li> </ul>
Modified patient global impression of change	Participant ratings of overall improvement in program outcomes	<ul style="list-style-type: none"> <li>Lower scores reflect higher amounts of perceived improvements</li> </ul>
Client satisfaction	Proportion of participants above the Client Satisfaction Questionnaire midpoint [63]	<ul style="list-style-type: none"> <li>Excellent: <math>\geq 80\%</math> of participants rate satisfaction above the scale midpoint</li> <li>Good: <math>\geq 70\%</math> of participants rate satisfaction above the scale midpoint</li> </ul>
Program safety and adverse events	Number of adverse events reported by participants throughout the program	<ul style="list-style-type: none"> <li>Excellent: no adverse events linked to program participation are reported and considered</li> <li>Good: mild adverse events are reported in <math>\leq 10\%</math> of participants linked to program participation</li> </ul>

<sup>a</sup>We set benchmarks based on development guidelines [64,65] and our feasibility pilots [29,35,39,61].

## Quantitative Assessments

We selected quantitative measures informed by the CP and CD literature and by our prior mixed methods study [13,29], which provided preliminary evidence for signals of improvement in this population. Following the Initiative on Methods,

Measurement, and Pain Assessment in Clinical Trials criteria [66], we measured physical function comprehensively with an objective measure (accelerometer step count), a performance-based measure (6MWT using *Timed Walk*), and several self-report measures (questionnaires). **Textbox 3** provides brief descriptions of all quantitative assessments.

**Textbox 3.** Study measures and constructs.

## Demographics

- Date of birth, gender, weight, height, handedness, race/ethnicity, marital status, educational level, employment status, occupation, income, pain diagnoses, length of chronic pain, comorbid medical conditions, current/history of mental health condition, current pain medication, and brain health lifestyle behaviors. *Pre*

## Pain

- Numerical Rating Scale; measures pain intensity at rest and during activity. *Pre and Post* [67]
- Use of rescue analgesics. *Weekly homework log and self-report*

## Physical function: self-reported

- World Health Organization Disability Assessment Schedule 2.0: measures for disability in 6 domains: cognition, communication, transportation, self-care, daily responsibilities, and engaging in community activities. *Pre and Post* [68]
- Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function v.1.2.8b; assesses level of difficulty with daily function. *Pre and Post* [69]
- The Godin Leisure-Time Exercise Questionnaire: measures the number of times per week physical activity with different intensities (light, moderate, and strenuous) is performed. *Pre and Post* [70]

## Physical function: ambulatory (objective)

- Accelerometer (ActiGraph) [54]: measures activity during 8 days in terms of number of steps. *Pre and Post*

## Physical function: performance-based

- 6-min walk test via the *Timed Walk* app: assesses distance walked at a fast pace in 6 min in meters using smartphone GPS. *Pre and Post* [38]

## Cognition: objective

- Montreal Cognitive Assessment: measures cognitive domains (ie, attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation) used to detect level of cognitive decline. *Pre and Post* [43]

## Cognition: self-reported

- Everyday Cognition Scale: assesses cognitive functioning by comparing with current performance on cognitive tasks to a decade ago. *Pre and Post* [71]

## Emotional function

- PROMIS depression, v1.0.8b: assesses negative mood, views of self, engagement in daily living, and social components. *Pre and Post* [72]
- PROMIS anxiety, v1.0.8a: assesses fear, worry, hyperarousal, and somatic symptoms. *Pre and Post* [72]

## Social functioning

- PROMIS emotional support v4a: assesses level of perception of having close relationships. *Pre and Post* [73]
- UCLA Loneliness Scale: assesses level of perception of isolation. *Pre and Post* [74]

## Pain-specific coping

- Pain Catastrophizing Scale: assesses hopelessness, helplessness, and rumination about pain. *Pre and Post* [75]
- Pain Self-Efficacy Questionnaire: measures level of self-efficacy for performing activities of daily living despite pain. *Pre and Post* [76]

## General coping

- Measures of Current Status: assesses ability to engage in a series of general healthy coping skills (eg, relaxation, being aware of tension, expressing needs, confidence in coping, and assertiveness). *Pre and Post* [77]
- Cognitive and Affective Mindfulness Scale-Revised: assesses usage of mindfulness skills. *Pre and Post* [78]
- Gratitude Questionnaire: measures ability to experience daily gratitude. *Pre and Post* [79]
- Self-Compassion Scale: measures level of how understanding individuals are able to be to themselves in a stressful situation. *Pre and Post* [80]
- Tampa Kinesiophobia Scale: measures extent of impact on physical activity due to fear of pain or injury. *Pre and Post* [81]
- Chronic Pain Acceptance Questionnaire: measures the level in which one is able to engage in activity, despite their pain. *Pre and Post* [82]

## Exit Focus Group Procedures

All participants will have the opportunity during the post intervention REDCap survey to provide feedback on the program via Likert questionnaires and open responses on the study technology (Zoom, virtual MoCA, and *Timed Walk*), Fitbit (AB-F group only), procedures, treatment manuals, support from study staff, and expectations of the program. In addition, we will conduct a brief virtual exit interview focus group (30 min) via Zoom during the post intervention assessments with both AB-F and HEP participants to further explore the impressions of the program and inform the next trial. Given prior optimization of the program via qualitative methods, the exit focus groups will gather impressions about the virtual delivery of skills and the technological aspects of the program. We will follow our procedures for conducting virtual focus groups [83] and guidelines for collecting qualitative data [84,85].

## Data Analysis

Consistent with guidelines for early feasibility studies [86,87] and the NIA Stage Model, our mixed method analysis will not assess efficacy [23]. However, we will evaluate whether this virtual pilot RCT achieved similar feasibility and acceptability to our prior in-person trial [29]. Our target sample size is appropriate for exploring feasibility and outcomes for future trials [86] and is consistent with our previously published pilot studies [29,35,39,61]. The frequency and proportions of the feasibility benchmarks will be calculated separately for AB-F and HEP. Additional quantitative analysis will focus on descriptive statistics for each measure, within-group pre-post comparisons using paired *t* tests, Cohen *d* effect sizes to explore signals of improvement in AB-F, and exploratory correlations between outcomes (physical, cognitive, and emotional function) and program targets (eg, mindfulness and coping). Qualitative analysis will be primarily deductive [88] using the framework method based on our prior work [13], allowing for some inductive flexibility to explore the unexpected needs and preferences of participants [89].

## Results

The trial is ongoing. As of October 2020, we have recruited 21 participants (10 AB-F and 11 HEP) across 2 rounds of groups. One participant dropped before the baseline assessment (scheduling conflict) and 1 dropped before the first AB-F session (technology barriers and receiving surgery). All 19 remaining participants have completed the baseline assessment. In the first round of groups, attendance is high (11 out of 12 participants completed all 4 sessions so far). AB-F participants are adherent to their Fitbit (5 out of 6 participants wore the device at least 6 out of 7 days all 4 weeks), and 5 out of 6 participants have met their weekly step goals for at least half (2) of the sessions conducted so far (4). We have retained 2 participants who underwent a medical procedure (1 shoulder surgery and 1 skin cancer surgery) unrelated to the program.

## Discussion

### Scientific Contribution

CP and CD are frequently comorbid among older adults [4]. CP symptoms exacerbate CD and vice versa [5], leading to a *disability spiral* of worsened physical, cognitive, and emotional functioning [11,12]. The AB-F program addresses an important clinical gap, as no effective treatments are currently available for this population. The 2 AB-F development studies conducted thus far provide preliminary evidence that combining mind-body and activity skills with Fitbit is feasible; acceptable [13,29]; and shows promise for improving physical, cognitive, and emotional outcomes among older adults with CP and CD. This protocol provides a blueprint for an entirely virtual, single-blind feasibility RCT of AB-F versus a time- and dose-matched educational control (HEP) in older adults with CP and CD. Importantly, our technological adaptations are consistent with older patients' evolving preferences for live video delivery and bypass barriers to nonpharmacological treatments identified in the literature [30] and older adults in our prior studies (eg, transportation) [13,29] as well as the recent threat of COVID-19. To our knowledge, this is the first trial to integrate a live video, a smartphone, and wearable technologies to enhance treatment development for older adults with CP and CD.

This mixed methods study will help us maximize the feasibility, credibility, acceptability, and adherence of the AB-F and HEP programs. Quantitative and qualitative data will be integrated to corroborate the feasibility of AB-F, contextualize the findings at multiple levels (group and individual participant), explore whether technological adaptations helped or hindered participation, and understand changes in the outcomes [90]. The results will inform a subsequent virtual efficacy RCT (NIA stage II; Figure 1). In the future efficacy RCT, we will test our hypothesis that AB-F is superior to HEP in improving physical, cognitive, and emotional functioning in older adults with CP and CD. In the fully powered trial, we will test the mechanistic hypotheses that AB-F indirectly improves these outcomes through additional targets, such as increasing mindfulness, self-compassion, and pain resilience, while decreasing pain catastrophizing and kinesiophobia.

### Preliminary Findings

Although this trial is ongoing, preliminary findings are promising for the feasibility of both programs and our study methodology conducted virtually. Older adults with CP and CD appear to be able to engage in remote data collection and live video group participation, including the use of multiple technology platforms (ActiGraph, Fitbit, and Zoom). This suggests that our protocols for recruitment and teaching technology as well as our overall methodology show promise. Direct participant feedback will help us further address the technological challenges that our target population might experience. However, qualitative studies [91], including our prior work in this population [13,29], suggest that older adults are motivated to learn the live video [32] and wearable [92,93] technology used in this study. Our exit focus groups and *lessons learned* from study staff will help us develop further strategies

to make the multiple technologies used during the program more accessible to older adults with CP and CD.

### Limitations

Despite the novelty of our entirely virtual mind-body and activity program, there are several limitations. First, our recruitment was restricted by the racial and ethnic distribution of patients at our pain clinic and memory clinic. Our future efficacy RCT will need to focus specifically on recruiting a sample that is representative of the US racial and ethnic composition by ensuring that we approach all racial and ethnic minorities or engage in targeted recruitment at the national level. Second, we did not formally assess the level of cognitive impairment at screening. Although no participants had a baseline MoCA score indicative of dementia (<18) [94], we plan to administer the Portable Mental Health Questionnaire [95] in

future trials to screen for severe CD that would interfere with the programs or study procedures.

### Conclusions

Consistent with the early stages of the NIA model [23], optimizing our remote delivery procedures before conducting the virtual efficacy RCT is critical for ensuring feasibility, aligning the AB-F with our target population, and detecting meaningful changes [87]. If successful, the AB-F will be the first completely virtual intervention for older adults with CP and CD and can be routinely incorporated into telehealth practices. The need for nonpharmacological interventions that are amenable to remote delivery, such as mind-body and activity programs, has grown in response to COVID-19. We hope that in-depth descriptions of live video adaptations of study procedures will assist researchers conducting virtual clinical trials of similar programs for in-need populations.

### Acknowledgments

This work was supported by a supplement from the NIA (3R34AT009356-02S1) to an R34 grant funded by the National Institute of Complementary and Integrative Health (1R34AT009356-01A1).

### Conflicts of Interest

None declared.

### Multimedia Appendix 1

Peer review report by the National Center for Complementary and Integrative Health.

[PDF File (Adobe PDF File), 148 KB - [resprot\\_v10i1e25351\\_app1.pdf](#)]

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## Abbreviations

- AB:** Active Brains
- AB-F:** Active Brains-Fitbit
- CD:** cognitive decline
- CP:** chronic pain
- HEP:** health enhancement program
- IRB:** institutional review board
- MoCA:** Montreal Cognitive Assessment
- NIA:** National Institute of Aging
- PROMIS:** Patient-Reported Outcomes Measurement Information System
- RCT:** randomized controlled trial
- REDCap:** Research Electronic Data Capture
- 6MWT:** 6-min walk test

*Edited by T Derrick; submitted 02.11.20; this is a non-peer-reviewed article; accepted 13.11.20; published 04.01.21.*

*Please cite as:*

*Mace RA, Doorley JD, Popok PJ, Vranceanu AM*

*Live Video Adaptations to a Mind-Body Activity Program for Chronic Pain and Cognitive Decline: Protocol for the Virtual Active Brains Study*

*JMIR Res Protoc 2021;10(1):e25351*

*URL: <https://www.researchprotocols.org/2021/1/e25351>*

*doi: [10.2196/25351](https://doi.org/10.2196/25351)*

*PMID: [33208301](https://pubmed.ncbi.nlm.nih.gov/33208301/)*

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Protocol

# Using a Mobile Health Intervention (DOT Selfie) With Transfer of Social Bundle Incentives to Increase Treatment Adherence in Tuberculosis Patients in Uganda: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** The World Health Organization's End TB Strategy envisions a world free of tuberculosis (TB)—free of deaths, disease, and suffering due to TB—by 2035. Nonadherence reduces cure rates, prolongs infectiousness, and contributes to the emergence of multidrug-resistant TB (MDR-TB). Moreover, MDR-TB is a growing, complex, and costly problem that presents a major obstacle to TB control. Directly observed therapy (DOT) for treatment adherence monitoring is the recommended standard; however, it is challenging to implement at scale because it is labor-intensive. Mobile health interventions can facilitate remote adherence monitoring and minimize the costs and inconveniences associated with standard DOT.

**Objective:** The study aims to evaluate the effectiveness of using video directly observed therapy (VDOT) plus incentives to improve medication adherence in TB treatment versus usual-care DOT in an African context.

**Methods:** The DOT Selfie study is an open-label, randomized controlled trial (RCT) with 2 parallel groups, in which 144 adult patients with TB aged 18-65 years will be randomly assigned to receive the usual-care DOT monitoring or VDOT as the intervention. The intervention will consist of a smartphone app, a weekly internet subscription, translated text message reminders, and incentives for those who adhere. The participant will use a smartphone to record and send time-stamped encrypted videos showing their daily medication ingestion. This video component will directly substitute the need for daily face-to-face meetings between the health provider and patients. We hypothesize that the VDOT intervention will be more effective because it allows patients to swallow their pills anywhere, anytime. Moreover, patients will receive mobile-phone-based “social bundle” incentives to motivate adherence to continued daily submission of videos to the health system. The health providers will log into a secured computer system to verify treatment adherence, document missed doses, investigate the reasons for missed doses, and follow prespecified protocol measures to re-establish medication adherence. The primary endpoint is the adherence level as measured by the fraction of expected doses observed over the treatment period. The main secondary outcome will be time-to-treatment completion in both groups.

**Results:** This study was funded in 2019. Enrollment began in July and is expected to be completed by November 2020. Data collection and follow-up are expected to be completed by June 2021. Results from the analyses based on the primary endpoint are expected to be submitted for publication by December 2021.



**Conclusions:** This random control trial will be among the first to evaluate the effectiveness of VDOT within an African setting. The results will provide robust scientific evidence on the implementation and adoption of mobile health (mHealth) tools, coupled with incentives to motivate TB medication adherence. If successful, VDOT will apply to other low-income settings and a range of chronic diseases with lifelong treatment, such as HIV/AIDs.

**Trial Registration:** ClinicalTrials.gov NCT04134689; <http://clinicaltrials.gov/ct2/show/NCT04134689>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/18029

(*JMIR Res Protoc* 2021;10(1):e18029) doi:[10.2196/18029](https://doi.org/10.2196/18029)

## KEYWORDS

tuberculosis; mHealth; digital health; eHealth; directly observed therapy; video observed therapy; DOT Selfie; treatment adherence; Africa

## Introduction

The World Health Organization's End TB Strategy envisions a world free of tuberculosis (TB)—free of deaths, disease, and suffering due to TB—by 2035 [1]. In 2018, TB killed an estimated 1.5 million people, with 10 million new cases of the disease worldwide [2]. Nonadherence to medication is a common, complex, and costly problem, which hampers TB control [3]. It reduces cure rates, prolongs infectiousness, and contributes to the emergence of multidrug-resistant TB (MDR-TB) strains [4-7].

MDR-TB is on the rise, with an estimated 580,000 cases reported worldwide in 2018 [2] compared to 480,000 in 2014 [8]. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommend directly observed therapy (DOT) for TB treatment to monitor and provide treatment support for affected people whenever feasible [9,10]. When implemented properly, DOT fosters high levels of treatment adherence and early detection of adherence problems, adverse drug reactions, and worsening TB symptoms [9].

The WHO estimates that approximately 50% of patients who start treatment often fail to adhere to their prescribed medication regimens, particularly in low- and middle-income countries [11]. However, DOT is difficult to implement in low-resource settings such as Africa. Major barriers that hinder the effectiveness of DOT are TB stigma, patients forgetting to meet with TB providers or treatment supporters, the inconvenience of daily face-to-face meetings, high costs of travel, insufficient capacity of the public health workforce, and long patient waiting times at health facilities [12,13]. Therefore, innovative ways to overcome these barriers are urgently needed.

Mobile health (mHealth) tools have shown promise as alternative interventions to in-person DOT [14-16]. For example, SMS text messages and real-time electronic monitors have been used to improve adherence to antiretroviral treatment in Uganda [17]. Video directly observed therapy (VDOT) that uses a smartphone app to record videos of medication intake presents a novel way to monitor adherence remotely and overcome health system barriers of treatment delivery [18,19]. VDOT enables patients to submit videos showing daily medication intake for observation by TB care providers without the need to meet in-person. Only a few published observational studies have evaluated VDOT, including 2 from Africa [19-24]. One pilot

study from Kenya showed video observed therapy to be both technically feasible and acceptable to patients and health professionals [23]. Similarly, a recent pilot done in Uganda showed VDOT to be feasible and acceptable to patients for the monitoring and support of TB treatment [24]. The efficacy of VDOT has been evaluated in 3 randomized controlled trials (RCTs) in the United States, United Kingdom, and Moldova, which have shown it to be feasible, acceptable, cost-saving, and convenient to patients [25-27]. However, to our knowledge, no published RCTs comparing VDOT to usual care have been reported in Africa.

The current study will adapt an existing VDOT platform and a smartphone app that was developed by researchers at the University of California in San Diego, California, United States [18], to suit the African context. Specifically, we will translate SMS text reminders and social bundle incentives to motivate adherence. Using mHealth tools in a context-specific way is expected to promote effective patient self-management and improve patient-provider interactions. Mobile technology has the potential to facilitate greater patient reach, anonymity, information dissemination, as well as the implementation of interventions and services in diverse contexts and settings [28,29]. Upon successful completion of this trial, we expect our findings to contribute to evidence that informs the adoption and scale-up of VDOT for use in low-income countries.

## Methods

### Trial Design

The DOT Selfie study is an open-label RCT. A total of 144 adult patients with a confirmed diagnosis of drug-susceptible TB who are initiating treatment or are within 1 month of treatment initiation at designated TB clinics will be randomized into 2 parallel groups. Of the 144 participants, 72 will be randomized into a control group to receive the usual-care DOT (UC-DOT), and 72 will be randomized into the intervention group to receive a smartphone with the VDOT app to video-record daily medication intake for review via a secure cloud system. All study participants will attend 2 monthly clinic visits at 2, 4, and 6 months (or at the end of treatment), during which clinical and sputum assessments will be performed.

### Eligibility Criteria

Participants will be included if they are (1) new or retreatment patients with clinically or microbiologically confirmed TB who

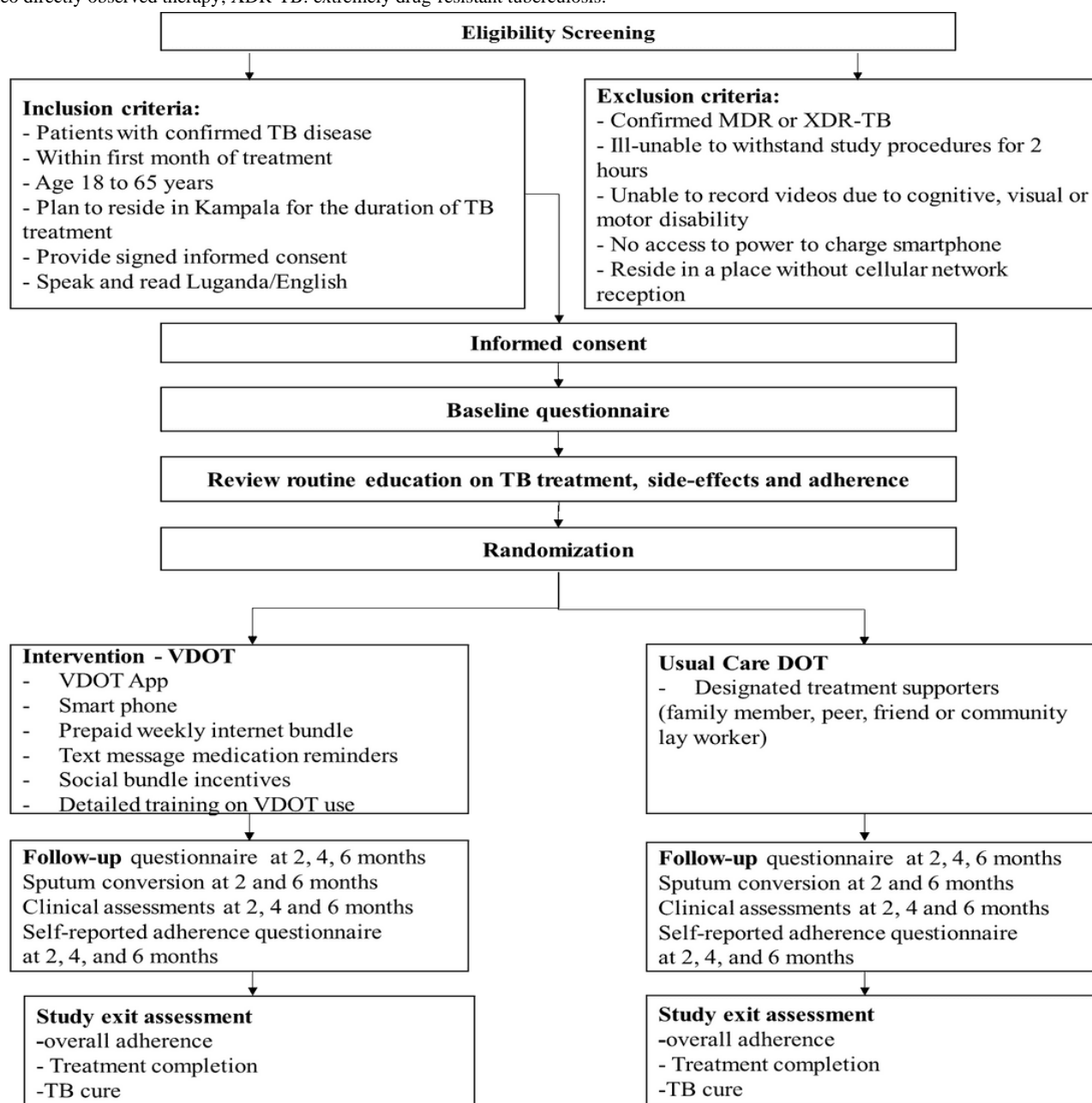
initiated treatment within 1 month (we chose to enroll both new and retreatment cases since adherence barriers exist in both groups), (2) aged 18 to 65 years, (3) planning to reside in Kampala, Uganda, for the entire period of 6 months while on treatment to facilitate close follow-up, (4) able to provide signed informed consent, and (5) able to speak and read English or Luganda (the local dialect). Participants will be excluded if they (1) are confirmed to have drug-resistant TB (MDR- or XDR-TB); (2) are very ill patients (ie, those who feel that they would not be able to withstand 2 hours of study procedures at enrollment); (3) have a cognitive, motor, visual, or hearing disability that prevents full participation in VDOT (eg, disabilities that prevent holding a phone or an inability to swallow medication as whole pills); and (4) do not have access to a power source to charge the smartphone or reside in areas without cellular network coverage.

### Study Setting and Recruitment

The primary study site will be the Lubaga TB clinic in Kampala, Uganda. Other public clinics, such as Kawala, Kitebi, or Kisenyi, which provide free TB services, will be used as secondary sites to supplement study recruitment. The study clinic sites are all located about 10-15 km from Kampala city center and, together, treat approximately 1000 TB patients annually. We estimate that a total of 8-10 patients per week, or

32-40 patients per month, will be enrolled by the research team. Since the selected sites treat roughly 90-100 TB patients a month, we will use consecutive sample selection to enroll every eligible subject in each arm until the required sample size is achieved. With this recruitment rate, we expect to complete participant enrollment within 4-5 months. The primary recruitment strategy is to screen patients who are newly diagnosed or those that will visit the clinic within the first month of their treatment. Eligibility will be assessed by a trained research assistant who will describe the study to the eligible patient and answer any study-related questions. Patients who are interested in participating will be required to provide written consent, after which they will be invited to complete a baseline questionnaire ([Multimedia Appendix 1](#)). The baseline questionnaire will ask questions about (1) patients' TB diagnosis and initial treatment; (2) socio-demographics and income; (3) experience with cellphones, smartphones, and technology; (4) transportation and other costs; (5) social and personal life; (6) knowledge of TB disease and treatment; (7) privacy and confidentiality concerns; (8) current family and friend support; and (9) perceived stigma from the community. All participants will be educated on TB, including treatment, side effects, and the need for adherence. Thereafter, they will be randomized to one of 2 groups. The participant flow is described in [Figure 1](#).

**Figure 1.** DOT Selfie participant flow diagram. DOT: directly observed therapy; MDR-TB: multidrug-resistant tuberculosis; TB: tuberculosis; VDOT: video directly observed therapy; XDR-TB: extremely drug-resistant tuberculosis.



## Study Procedures

### Randomization

We will randomize 144 participants with an equal allocation ratio of 1:1 to receive either VDOT or UC-DOT. An equal allocation was chosen to optimize the power of the study [30]. Permuted block randomization with block sizes of 4 and 6 will be used to allocate participants to intervention or control groups while maintaining balance across groups. Each block will have a specified number of randomly ordered treatment assignments [30]. Additionally, stratified randomization will be done according to sex to ensure equal representation of men and women in each study group [30]. The stratification is justified because sex is an important variable that influences adherence to TB treatment [31]. A computer program will randomly generate study arm assignments within block sizes of 4 and 6.

This randomization will minimize the likelihood that the study team will be able to predict the next study arm assignment. Each block will contain equal proportions of control and intervention. Within each block will be 4 or 6 sealed, opaque allocation envelopes, depending on the block size. Blocks and allocation envelopes will be sequentially numbered according to the computer-generated randomization schedule. Each allocation envelope will contain an assignment card on which the study group assignment (UC-DOT or VDOT) will be printed. To assign a patient to a study group, blocks will be selected in their sequential order. Allocation envelopes within them will be selected sequentially as well. Each envelope will be opened only after the participant details have been written on it. Carbon paper inside the envelope will transfer participants' details to the assignment card. Allocation envelopes will be sealed using tamper-proof security tape.

### **Blinding**

Due to the nature of the interventions, it is not possible to blind study participants or research nurses and interviewers after assignment to a study arm. This is because, as part of the study procedures research, nurses must observe participants swallow their pills via VDOT, and at follow-up visits, interviewers must collect participant data regarding medication adherence. The research staff allocating participants to study groups during randomization will be blinded to the sequence. This is to minimize the likelihood that the research staff will be able to predict the next study arm assignment. Study investigators will be blinded to the allocation and any preliminary analyses before the end of the study. Only the trial statistician will be unblinded to the analyses. The data collection tools used for this purpose include information about how pill-swallowing is conducted (UC-DOT or VDOT), thus making the study group assignment obvious.

### **Description of Standard Procedures**

The trial and intervention are described according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [32]. Regardless of the assigned study group, all participants will attend an initial face-to-face educational session, which will provide information on (1) the importance of medication adherence according to the daily TB drug regimen; (2) the correct way to take TB pills, including dose, timing, and the importance of taking pills whole; (3) storage of pills and what to do in the event of a missed dose; and (4) the importance of reporting (in-person or through the VDOT app) any problems related to TB medications, such as side effects, adverse events, symptoms, lost pills, lost or malfunctioning smartphone or app, etc, as well as any study-related issues.

### **Control: Usual-Care Directly Observed Therapy (UC-DOT)**

Participants will receive UC-DOT as administered in routine clinical practice under the Uganda National TB program. Routine DOT typically involves treatment observation 3-5 times per week by a designated treatment supporter who could be a trained community worker, a volunteer lay-worker, a family member, a friend, or community linkage facilitator, with the weekend doses self-administered. The name and phone contact details of each designated treatment supporter for each patient are documented. The treatment observation and support occur at any location mutually agreed upon between the patient and their treatment supporter. To document adherence, the patient records daily doses taken on a predesigned treatment card issued at the clinic and returns it at every routine visit. Adherence is further assessed using patient self-reports, pill counts, and clinic attendance for prescription refills. Study research assistants will work in partnership with designated treatment supporters to collect study information on adherence from clinic records coupled with a structured adherence questionnaire at follow-up visits. Patients in the UC-DOT control group will be followed up for missed doses and routine visits according to the National TB program guidelines. Research staff will only follow up with participants for scheduled study visits and procedures.

### **Intervention: Asynchronous Video Directly Observed Therapy (VDOT)**

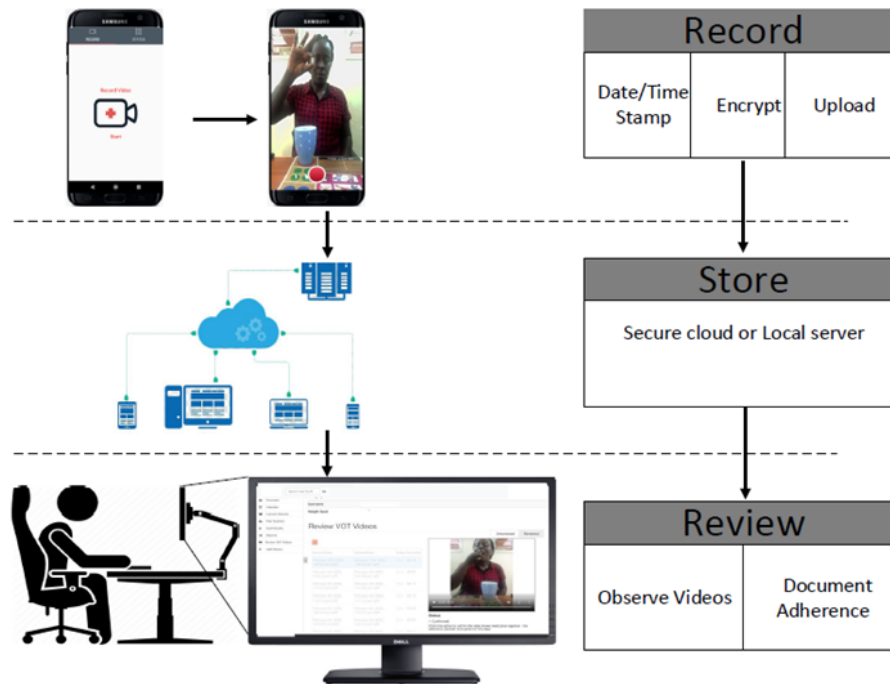
Upon assignment to the intervention study group, participants will receive detailed training (in English or Luganda) on the VDOT app using a training manual provided by the VDOT software developer. The asynchronous VDOT intervention comprises a smartphone with a SIM card, the preloaded VDOT app, a free weekly internet data subscription of 350 MBs paid for by the study at commercial rates, and daily SMS text message medication reminders. The VDOT app is a free downloadable app through the App Store, and the system is Health Insurance Portability and Accountability Act (HIPAA)-compliant and has been validated [33]. Additionally, patients will receive a weekly incentive in the form of social bundles or airtime minutes each time they successfully submit videos for 7 consecutive days. The smartphone will have a unique phone number to ensure that SMS reminders and other phone communications are sent specifically to study participants. The VDOT app is free and downloadable from the Play Store. A unique personal identification number (PIN) will be assigned to each person at registration in the VDOT system to facilitate login into the VDOT app. The PIN will be a security feature that will prevent nonstudy participants, such as other family members or friends, from accessing the app. The app is equipped with video recording features that allow patients to record videos of themselves swallowing pills 7 days each week (Figure 2). To ensure safety and to address concerns that side effects may be missed with limited face-to-face contact, patients are also encouraged to report any adverse events on the daily videos. After the recording ends, an automatic, encrypted, time-stamped video is transferred through a cellular connection and uploaded to a secure cloud server for storage and playback. This enables patients to securely and confidentially record and submit daily medication doses. Once a submission is completed, the patient cannot retrieve or access the video. The smartphone will automatically receive the internet bundles to facilitate video submission.

The VDOT system has a feature to adapt the text messages either in English or Luganda (Figure 3). These text messages will include reminders to motivate patients to continue taking their medications. An example of these messages is "It's time to take your pills and send a video. Taking your pills will help you get better." A single SMS text will be sent to each participant in the morning as a reminder; a second text will be sent within 8 hours of the first if a video is not received by the system.

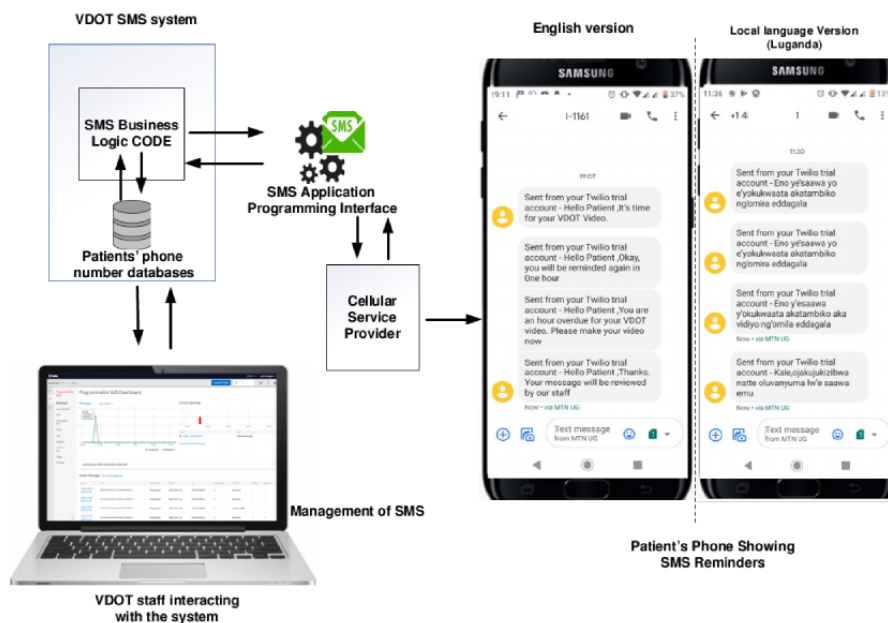
At the clinic, a trained study nurse will log into a secured, HIPAA-compliant VDOT system via a tablet or laptop to download and review patients' daily videos and document medication adherence. On days when video recording or uploads are not possible, medication adherence will be assessed using patient self-reports, pill counts, and prescription refills at the clinic. The nurse will thus be able to track missed doses and reported side effects, and follow up with appropriate support or advice. Participants will sign an agreement to return the smartphone to the clinic upon completing their full course of treatment.



**Figure 2.** Schematic of asynchronous video directly observed therapy (VDOT) system.



**Figure 3.** Video directly observed therapy (VDOT) SMS text messaging system.



**Follow-up of Participants With Missed Videos or Study Visits**

A predefined follow-up protocol will be used to contact study participants in cases of missed doses or videos. The research staff will make 2 phone call attempts within the first 24 hours of a missed, expected video to establish dosing history and the reason for missing videos. If there is no response from the participants within 72 hours, the research team will escalate the follow-up to a field visit to trace the participant at home or work. After a period of 2 weeks from when the intensive, active

follow-up protocol has been completed, there will be a waiting interval of 2 weeks, hoping that the participant will call back or return to the clinic for a routine visit. If the participant does not show up for the scheduled clinic visit, the national TB program staff will get involved in support of the patient. A declaration of “lost to follow” will be made if the participant does not return for 2 consecutive months, in line with the standard World Health Organization’s guidelines [34].



### ***Criteria for Discontinuing or Modifying Allocated Interventions for Trial Participants***

Patients may voluntarily withdraw from the study for any reason, at any time. After consultation with the protocol chair, the investigator may also withdraw participants from the study to protect their safety or if patients are unwilling or unable to comply with the required study procedures. Reasons for all cases of nonadherence and nonretention will be retrieved and documented in case report forms. Randomized patients who are prematurely discontinued from the study at any time will have their clinical and laboratory evaluations performed, if possible, and will also continue receiving treatment for TB and routine health services. According to standard definitions provided by Friedman et al [35], a participant who is assigned to the VDOT but who fails to adhere to the intervention will be considered a dropout, whereas a participant who discontinues the intervention but continues to take treatment under the usual-care procedures will be considered a cross-over [35]. Participants who withdraw, dropout, or cross-over will be included in the primary intention-to-treat analysis.

### **Study Outcomes**

The primary outcome measure is the level of adherence calculated as the fraction (proportion) of expected doses observed (FEDO) over the 6 months of treatment or by the end of the study following randomization. Since direct observation as a way of measuring medication adherence may be challenging to employ consistently in the UC-DOT group, we will also use self-reports and pill counts as indirect measures of adherence and then triangulate the results. Time-to-treatment completion will be assessed as the main secondary outcome. Other outcomes will be sputum smear conversion at 2 and 6 months or the end of treatment, clinical response as a measure of self-reported improvement in TB symptoms, and weight gain at 2, 4, and 6 months or the end of treatment. Other outcomes will be self-reported side effects, the occurrence of adverse events, and patient satisfaction at the exit of the study. Patient satisfaction will be evaluated in 2 ways: (1) overall satisfaction with VDOT or UC-DOT, and (2) satisfaction with specific areas, such as the VDOT technology and app use; information and training received; interaction with treatment supporters, health providers, or research staff; and privacy and confidentiality during medication intake. Additionally, at study exit, we will conduct individual qualitative interviews for both UC-DOT and VDOT participants to capture detailed information about participant experiences during the study.

Study measurements will be done at baseline and follow-up at months 2, 4, and 6 to ensure close monitoring of all patients in treatment. All participants, regardless of the study group, will complete a questionnaire at these follow-up visits (Multimedia Appendix 2 and 3). The follow-up questionnaire will address issues such as (1) patients' current use and any changes in experience with a cell phone, such as acquiring a personal cell phone or smartphone; (2) transportation and other costs to and from the TB clinic; (3) TB treatment experiences using VDOT or UC-DOT; (4) experiences when using a phone to record videos or when receiving support under the usual DOT; (5) satisfaction with TB and VDOT or UC-DOT; (6) ongoing

support received during treatment; (7) side effects experienced; (8) difficulties with medication supply or transportation to the clinic; and (9) privacy, confidentiality, and stigma concerns. For internal validity, adherence will also be measured at follow-up visits by pill counts (when possible) and using a 10-item self-reported adherence questionnaire [36] (Multimedia Appendix 4).

### **Qualitative Exit Interview**

In-depth interviews will be conducted at the exit of the study to gather detailed information to enrich the understanding of the quantitative data. This will involve intensive individual interviews with a small number of study participants to explore their general experiences, operations, processes, and outcomes that they perceive as resulting from their involvement in VDOT or usual-care DOT. We will also specifically probe the participants' experiences of stigma, privacy, gender, and socio-cultural issues. To ensure representation of a wide variety of views, participants will be purposively selected based on sex, age, and observed experiences during the time in the study. For example, we will ensure both younger and older and male and female participants are included. In terms of treatment experiences, patients with low, moderate, and high adherence will also be selected accordingly. We will aim to interview a total of 20-30 patients with equal numbers from each study arm. The final number of participants to be interviewed will be determined based on the attainment of thematic saturation (ie, the point at which interviewing more respondents will yield no new information on the topics of interest) [37]. Interviews will be audio-recorded and transcribed. We will use thematic analysis to code, identify key patterns or themes, and then summarize the findings. ATLAS.ti software (version 9; ATLAS.ti Scientific Software Development GmbH) will be used in the coding and detailed processing of the data.

### **Data Management**

All study questionnaires will be administered using electronic forms on ODK (Open Data Kit) using laptops or tablet devices. Data in the form of videos collected from the VDOT system will be held on a secure HIPAA-compliant cloud server and will be backed up nightly locally in Uganda. Weekly data integrity reports will be run on the system using an automated routine. Monthly data exports will be made, and data will be merged into the master data file. The master data file will be stored at the University of Georgia on a password-protected network with access restricted to study personnel. This will be automatically backed up daily. The master data file will use the unique study number allocated at the time of randomization but will not include personal identifier information. This identifiable information will be held in a separate password-protected file on the same network drive in the form of a lookup table.

### **Sample Size**

This trial is powered on the primary outcome measure and based on a comparison of the medication adherence level between the UC-DOT group and the VDOT group. The calculated sample size is 124 in order to achieve a chi-square test difference of 0.85 versus 0.63 (difference 0.22 and odds ratio 0.30) between the groups. We assumed an attrition rate of 14%, guided by

published literature; this was based on a randomized controlled trial comparing a digital adherence intervention and usual care in Kenya in which the overall loss to follow-up rate was 11.7% (9.9% in the usual-care DOT arm and 1.76% in the digital intervention arm) [38]. By inflating the attrition rate to 14%, we erred on the higher side of attrition. In contrast, another RCT of asynchronous VDOT done in the United Kingdom had a higher attrition rate of 23%; however, the study population was very different from our current study in that it included 58% of homeless subjects [15]. At a 14% attrition rate, the estimated final sample size was 144 participants with 72 subjects per group. This would provide a power of 80% to detect a 22% difference in the primary outcome between the 2 comparison groups (85% VDOT vs 63% DOT) based on a 2-sided significance level of 5%. Sample size tables were used to estimate precision. All calculations were performed using the SAS statistical software package (version 9.3; SAS Institute).

### Statistical Analyses

Intention-to-treat analysis will be conducted where all patients will be analyzed according to the arm to which they were originally randomized. VDOT treatment observations will be classified as completed if ingestion of all medicines is observed, or if videos are received but not viewable because of a technical complication (given that patients would have no control over whether videos were corrupted). The sensitivity analysis will consider only videos for which all medications are observed as completed. An adherence proportion will be observed for each individual in this study. Let  $p_{ij}$  be the adherence proportion for individual  $j$  ( $j=1, \dots, n$ ) in treatment group  $i$  ( $i=0$  for VDOT and  $i=1$  for UC-DOT). Then, let  $p_0$  and  $p_1$  equal to the average FEDO in the VDOT and UC-DOT arms, respectively. Similarly, let  $s_0 = \text{s.e.}(p_0)$  be the standard error of  $p_0$ , and similarly, let  $s_1$  be the standard error of  $p_1$ . The standard  $t$  test statistic will be used to calculate a  $P$  value based on the following statistic:



The Welch  $t$  test will be used to calculate significance. However, since we do not have estimates of  $s_0$  and  $s_1$ , this formula is not useful for power calculation. Therefore, to calculate power and sample size, we treat the response for each individual as binary (0 or 1), indicating adherence or nonadherence. This corresponds to using an adherence cutoff value of FEDO with equal-to or greater than 80% as a threshold for adherence. This binary response variable for adherence will be used in the final analysis to facilitate comparison with previous clinical trials [15].

Univariate statistics will be used to describe the baseline characteristics of the study population, the prevalence of individual clinical responses, and the level of adherence. Similar analyses will be repeated for secondary outcomes. Multivariable logistic regression analyses will be done to test for significant associations between study groups (VDOT/ UC-DOT) as the main exposure and the primary binary outcome of adherence ( $\geq 80\%$ ; yes/no). Age and HIV status are set a priori as potential confounders that will be adjusted for in all the models. Sex will not be adjusted since the randomization is stratified by sex. Other covariates that will be adjusted for in the models include education level, income, and smartphone ownership, previous

TB treatment, HIV status, and other clinical variables at baseline. Crude and adjusted odds ratios with 95% confidence intervals will be presented, and statistically significant  $P$  values will be less than .05.

Secondary analyses of time-to-treatment completion will provide another outcome that can be used to compare the 2 groups according to TB program performance indicators. Survival analysis to compare the median time-to-treatment completion between study groups with associated log-rank tests will be performed. Crude and adjusted Cox proportional hazards regression analyses will be performed to determine factors associated with time-to-treatment completion. Cox proportional hazards ratios with corresponding 95% confidence intervals will be presented. Other analyses comparing trends at months 2, 4, and 6 in adherence, sputum conversion, and clinical response will be performed. These repeated measures data will be modeled as a discrete-time Markov chain or Poisson process [30]. Analyses will be done using Stata (version 14; StataCorp) and R (version 3.3.2; R Core Team) software.

### Plan for Handling Missing Data

We expect that study participants may drop out or miss visits, thus producing missing data and compromising the ability to conduct an intent-to-treat analysis and draw conclusions about the causal link between the method of monitoring and medication adherence. Since there is no universal method of analyzing missing data [39,40], we will follow the guidelines of the National Research Council (NRC) on the handling of missing data in clinical trials [41]. We will focus on 2 critical elements: (1) careful conduct of the study to limit the amount of missing data, and (2) analysis that makes full use of information on all randomized participants. Careful attention will be paid to assumptions about the nature of the missing data underlying estimates of treatment effects. We will use approaches identified by Little and Rubin [42,43] based on 3 categories for classifying how missing data are generated: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).

### Data and Safety Monitoring

Since this pilot RCT study employs a low-risk intervention, is not blinded, and does not involve vulnerable populations, we plan to perform a limited scope of data and safety monitoring. The main focus will be on the safe execution of the study protocol as planned [44]. The principal investigators and co-investigators of the study have constituted an independent data monitoring committee to ensure that the trial is conducted according to the approved protocol, including participant recruitment, accrual and retention, participant risk versus benefit, adverse events, periodic assessments of data quality, timeliness, and other factors that may affect study outcomes. All adverse events will be reported to the University of Georgia Institutional Review Board and the Makerere School of Public Health Research Ethics Committee. Summary reports of adverse events will be made to the National Institutes of Health (NIH) in the progress report at the end of month 4, 6, and the final report, unless the nature of a particular event warrants reporting to NIH immediately.

Interim monitoring will be performed after enrolling 50% (36/72) of patients in the VDOT intervention and control groups. This will be done to ensure that the study is conducted according to the protocol and also to check on the level of adherence in both study groups. All analyses will be led by the study biostatistician. Stopping rules will not be applied to this pilot RCT because there is no evidence to inform the threshold for the clinically important difference (ie, the minimum magnitude of the treatment benefit large enough to offset the treatment harms) [44,45]. Stopping the trial would be justified only on the basis of strong evidence of net benefit or harm [45], conditions which are rarely met in small pilot trials like our study.

### **Plans for Collecting, Assessing, Reporting, and Managing Solicited and Spontaneously Reported Adverse Events and Other Unintended Effects of Trial Interventions or Trial Conduct**

An adverse event in this study is any untoward medical occurrence in a patient that is temporally related to the research, whether or not it is related to the intervention or the patient's participation in the research. Data on all adverse events will be collected after informed consent has been provided and patients have been enrolled in the study. This will continue throughout the study. If a patient experiences an adverse event after providing informed consent but has not started to receive the study intervention, the event will be reported as not related to the study intervention. An adverse event that meets the criteria for a serious adverse event between study enrolment and the end of the study will be reported to the local institutional review board as a serious adverse event.

A serious adverse event for this study is any untoward medical occurrence that is believed by the investigators to be causally related to the study drug and either results in death, is life-threatening, results in severe or permanent disability, requires inpatient hospitalization, or is a significant hazard as determined by the data monitoring committee. Serious adverse events that occur after a patient is discontinued from the study will not be reported unless the investigators believe the event may have been caused by a study intervention or protocol procedure. This will be determined based on a temporal relationship to the study intervention and whether the event is unexpected or unexplained given the patient's clinical course, previous medical conditions, and concomitant medications.

Potential serious adverse events will include lost to follow-up, death from tuberculosis, data security breaches, violence toward study personnel during patient interaction, complaints about the study from patients, or study clinics. These will be reported to the study coordinator and the study chief investigator, who will look into the matter and discuss it with the affected patient's case managers, and findings will be reported to the trial steering committee and data monitoring committee.

## **Results**

The study was funded in July 2019 and has been approved by the institutional review boards of the University of Georgia (November 12, 2019) and Makerere University (February 26,

2020). Due to the COVID-19 pandemic, study enrollment was delayed for 4 months. Participant enrollment into the RCT began in July and will continue through November 2020. Follow-up will continue through June 2021, when data collection is expected to be completed. Analysis, interpretation, and preliminary dissemination of results are planned for June 2021 to August 2021, through local workshops and scientific conferences. The main results are expected to be published by December 2021. Since the study is being conducted during the ongoing COVID-19 pandemic, there might be unintended negative impacts on the delivery of usual care with DOT. Access to treatment for people with TB is likely to be interrupted as community health workers, doctors, and laboratories devote their energies and resources to the COVID-19 response. There is a potential risk that prevention and treatment programs for the existing conditions will be disrupted. Although such disruptions could inflate the effectiveness of VDOT given that the technology use limits in-person contact, we can only speculate on the magnitude of this effect. The degree to which study findings will be generalizable to nonpandemic times may also be altered. To address some of these concerns, questions related to the impact of COVID-19 on access to routine TB services have been included in the baseline and follow-up questionnaires. This will facilitate further interpretation of the results in the context of prevailing circumstances. Separate studies are needed to evaluate the impact of COVID-19 on the health system and patient care.

## **Discussion**

### **Rationale**

Nonadherence to treatment in patients with TB is a serious obstacle to the realization of the World Health Organization's End TB Strategy goals [46] because it is responsible for the emergence of multidrug resistance and prolonged periods of infectiousness [4,47]. Currently, there is a lack of universally feasible, acceptable, and effective strategies to monitor and support adherence to TB treatment. This creates a critical need to evaluate VDOT applications under more diverse conditions and settings to define their function and compare them with traditional approaches to treatment monitoring [48,49]. Mounting evidence suggests increased utility and effectiveness of accessible mobile technologies in enhancing the monitoring of patients with chronic diseases [48-50]. The increased utility can be attributed to the increasing affordability and reliability of smartphones in both high- and low-income settings, while the expansion of cellular and internet networks in developing countries is responsible for the effectiveness of mHealth technologies. Therefore, VDOT is a promising alternative way to mitigate the adverse impact of nonadherence on individuals, families, and communities, especially in underserved populations in Africa.

### **Ethical Implications**

As it is currently practiced in Uganda, in-person DOT has the potential to be stigmatizing for patients, as it may result in unwanted public disclosure of patient disease status. This fear of—or reality of—stigmatization can negatively impact patient autonomy in regard to treatment-seeking behavior and treatment



adherence [51]. However, mHealth technologies such as VDOT are likely to be less stigmatizing as they do not require health workers to visit patients at home or work. The remote nature of interaction minimizes the chances of unintended exposure of private information. The flexibility of making video recordings at the patient's desired time and place greatly enhances privacy [46]. Patients agreed that VDOT promotes autonomy and a sense of control over their health [18]. Nonetheless, even with the use of VDOT, the potential for stigma, unintended disclosure, and a loss of autonomy could still be present given that videos contain identifiable information like the patients' faces. At the study exit, we will conduct qualitative interviews with study participants selected to discuss their varying experiences with both VDOT and UC-DOT successes, concerns, and failures that may have affected their adherence to treatment during the study.

This protocol describes the design and methods of a randomized control trial assessing the effectiveness of using VDOT plus incentives to improve medication adherence in TB treatment in Uganda. This RCT leverages the accessible features of mobile phone technology to deliver VDOT remotely, in a less intrusive and less cumbersome way, than in-person DOT. It explores a patient-led management approach that is more convenient, enabling patients to take medications on their schedule.

### Strengths in the Context of Prior Work

The proposed study is innovative because it is the first time that an RCT will be conducted to evaluate VDOT in an African setting. The control participants receiving usual-care DOT will provide an important comparison that will enrich our understanding and inform future interventions using VDOT and other mHealth programs. Fundamentally, Kampala, Uganda (the proposed site of the pilot study), has a significantly higher incidence of TB disease (201 cases per 100,000 in 2017) than any of the other locations where VDOT has been evaluated to date [2].

### Potential Limitations

We anticipate that a few smartphones may be lost or stolen throughout the study duration. This study will document any phone losses and replace phones to allow participants to continue in the study. Phones may run out of battery power and turn off during video recording. To minimize this issue, patients will be

trained and encouraged to ensure that phones are always charged nightly or before recording videos. Interruptions in the electrical power supply may prevent patients from charging their phones to take videos when taking their medications. As such, some adherence records may be incomplete; information gaps will be filled by using alternate data sources such as self-reports [36]. Cellular network connectivity problems may limit VDOT recordings by patients; unless patients travel to remote, rural areas of Uganda, we expect this situation to be rare. Although pill counts and self-reports are indirect measures of adherence, they are acceptable proxies in the absence of more direct demonstrations of adherence [36]. As described above, VDOT has less potential to infringe upon patient autonomy and cause stigmatization compared to the in-person DOT. Lastly, the results of the study will be generalizable to TB patient populations in urban settings in the context of the ongoing COVID-19 pandemic. However, infrastructural and technical limitations may prevail against the implementation of VDOT or similar technology interventions in rural settings.

### Conclusion

The significance of this study is at least 3-fold. First, the expected positive impact is the potential to adapt and scale a technology-based alternative to the DOT strategy, one that is contextualized to the local setting, convenient, and cost-saving for patients and the health care system. This RCT is highly relevant because the setting (Kampala, Uganda) has a much higher incidence of TB than any of the other locations in which VDOT has been evaluated to date. Second, it will provide the first RCT data on the use of VDOT in an African country. According to the NIH, "there is a need to stimulate research utilizing mHealth tools aimed at the improvement of adherence to treatment, effective patient-provider communication, and self-management of chronic diseases in underserved populations" [52]. Third, this pilot RCT will be a first step to meeting the urgent need to develop new mHealth tools and test existing ones for contextual acceptability, feasibility, and efficacy to mitigate the serious public health consequences of medication nonadherence. Our long-term goal is to revolutionize patient monitoring, improve patient-provider communication, and promote self-management by utilizing mobile health tools that are contextualized to the African setting.

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### Acknowledgments

This study is funded by the United States National Institutes of Health, Grant #1 R21 TW011365.

The funders do not have any role in study design; in the collection, management, analysis, and interpretation of data; in the writing of the report; or the decision to submit the report for publication. The funders will not have any authority over the study activities.

We acknowledge the support of Dr. Noah Kiwanuka; the Epidemiology in Action research group members at the University of Georgia; Maria E Castellanos, Samuel Kirimunda, Trang Quach, and the research study team members; and Gloria Nassanga, Daphine Kyaine, and Mitchell C Geno at Lubaga study site in Uganda, who have contributed greatly to the revision of the research protocol.

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### Conflicts of Interest

None declared.

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## Multimedia Appendix 1

Baseline questionnaire, version 2.1.

[\[PDF File \(Adobe PDF File\), 758 KB - resprot\\_v10i1e18029\\_app1.pdf \]](#)

## Multimedia Appendix 2

Usual-care directly observed therapy (UC-DOT) follow-up questionnaire.

[\[DOCX File , 26 KB - resprot\\_v10i1e18029\\_app2.docx \]](#)

## Multimedia Appendix 3

Video directly observed therapy (VDOT) follow-up questionnaire.

[\[DOCX File , 29 KB - resprot\\_v10i1e18029\\_app3.docx \]](#)

## Multimedia Appendix 4

Self-reported adherence questionnaire.

[\[DOCX File , 37 KB - resprot\\_v10i1e18029\\_app4.docx \]](#)

## Multimedia Appendix 5

NIH peer-review report.

[\[PDF File \(Adobe PDF File\), 125 KB - resprot\\_v10i1e18029\\_app5.pdf \]](#)**References**

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## Abbreviations

- DOT:** directly observed therapy
- FEDO:** fraction of expected doses observed
- HIPAA:** Health Insurance Portability and Accountability Act
- MDR-TB:** multidrug-resistant tuberculosis
- mHealth:** mobile health
- NIH:** National Institutes of Health
- PIN:** personal identification number
- RCT:** randomized controlled trial
- TB:** tuberculosis
- UC-DOT:** usual-care directly observed therapy
- VDOT:** video directly observed therapy
- XDR-TB:** extremely drug-resistant tuberculosis

*Edited by G Eysenbach; submitted 29.04.20; peer-reviewed by M DiStefano, J Haberer, I Contreras; comments to author 12.06.20; revised version received 10.08.20; accepted 16.09.20; published 05.01.21.*

*Please cite as:*

*Sekandi JN, Onuoha NA, Buregyeya E, Zalwango S, Kaggwa PE, Nakkonde D, Kakaire R, Atuyambe L, Whalen CC, Dobbin KK  
Using a Mobile Health Intervention (DOT Selfie) With Transfer of Social Bundle Incentives to Increase Treatment Adherence in  
Tuberculosis Patients in Uganda: Protocol for a Randomized Controlled Trial*

*JMIR Res Protoc 2021;10(1):e18029*

*URL: <https://www.researchprotocols.org/2021/1/e18029>*

*doi: [10.2196/18029](https://doi.org/10.2196/18029)*

*PMID: [32990629](https://pubmed.ncbi.nlm.nih.gov/32990629/)*

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Protocol

# A Community-Developed, Web-Based Mobile App Intervention Addressing Social Work and Legal Needs of Black Sexual Minority Men Living With HIV: Protocol for a Randomized Comparison Trial

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## Abstract

**Background:** Black sexual minority men (BSMM) are disproportionately affected by HIV. Los Angeles County (LAC) carries a substantial burden of the HIV epidemic in California. Negative effects of both psychosocial and structural barriers highlight the timely need to increase HIV treatment among BSMM. Successful HIV interventions based on social media and mobile phone technology have been demonstrated. This protocol describes LINX LA, a study that tests LINX, a web-based mobile app that provides tailored social services, legal resources, and peer support for BSMM living with HIV (BSMM+) in LAC using a randomized comparison trial.

**Objective:** During phase 1, the LINX LA study aims to engage in an iterative design process to develop the LINX App using qualitative data to inform and tailor the mobile app technology and its functionality. In phase 2 of LINX LA, we will test the efficacy of the LINX App compared with the LINX App Plus to improve HIV treatment outcomes (ie, antiretroviral therapy adherence, viral suppression) among BSMM+ in LAC by addressing social work and legal needs and developing a forum for peer support.

**Methods:** In this study funded by the California HIV/AIDS Research Program, we will recruit and enroll BSMM+ participants (aged ≥18 years) in LAC (N=400) to participate in a 12-month study that includes access to the LINX App, which provides a forum for peer support and tailored content aimed at improving the use of social and legal resources. All participants will also receive survey-based interviews at 3 time points (at baseline and 6- and 12-month intervals) and weekly text message surveys that assess medication and treatment adherence. Treatment adherence and viral suppression will be extracted from medical record data. Half of the participants will also be randomly assigned to receive 3 individualized coaching sessions (at 1-, 3-, and 6-month intervals) and the ability to directly message their coach via the LINX App. Over the course of the study, LINX App participants will receive a minimum of US \$130 in cash and LINX App Plus participants will receive a minimum of US \$190. We hypothesize that participants enrolled in LINX App Plus will demonstrate greater improvement in HIV outcomes compared with LINX App participants.

**Results:** The LINX study will test the efficacy of a web-based mobile app intervention for BSMM+ in LAC (N=400). The LINX App seeks to increase participants' knowledge of HIV; to facilitate access to necessary social and legal services, including information and referrals; and to increase social support across participants by providing a mediated forum for engagement.

**Conclusions:** The implementation of LINX LA aims to develop and test a culturally tailored approach to improve the HIV treatment outcomes of BSMM+.



International Registered Report Identifier (IRRID): PRR1-10.2196/19770

(JMIR Res Protoc 2021;10(1):e19770) doi:[10.2196/19770](https://doi.org/10.2196/19770)

## KEYWORDS

HIV; AIDS; mobile apps; African Americans; men's health; sexual minority; treatment adherence; mobile phones

## Introduction

### Background

African American people accounted for 42% of new HIV diagnoses in the United States in 2018 [1]. Black sexual minority men (BSMM) are further disproportionately affected by HIV. BSMM accounted for 26% of new HIV diagnoses and 37% of new diagnoses solely among all sexual minority men (SMM) in the United States in 2017 [2].

In California, the annual number of HIV diagnoses increased by 0.8% from 2013 to 2017; the rate of HIV infection, however, decreased in California during the same period by 2.4% [3]. In 2017, the number of people living in California diagnosed with HIV was 135,082 individuals [3]. Within this group, 73.6% of these individuals were in HIV care and 63.3% of these individuals achieved viral suppression [3]. African American people living with HIV experienced lower rates of HIV treatment engagement in California compared with White, Latino, Asian, and Pacific Islander people [3].

Los Angeles County (LAC) carries a substantial burden on the HIV epidemic in California. In 2017, 31.6% of all newly diagnosed HIV infections in California came from LAC. Of all people living with HIV in California, 38.1% are from LAC [3]. Within LAC, African American people represented 25% of new HIV diagnoses in 2016 [4]. Between 2015 and 2016, the rate of HIV diagnoses decreased for White people in LAC; however, for African American people, the rate of HIV diagnoses increased during the same period [5]. Approximately 84% of all LAC HIV diagnoses in 2016 were among the SMM. Among those newly diagnosed SMM, linkage to and retention in HIV care was less common among African American people than among White, Latino, or Asian and Pacific Islander people [5].

Data on the continuum of care for people living with HIV in LAC in 2016 revealed that 52% of African American people were linked to care, 65% were engaged in care, 49% were retained in care, and 52% achieved viral suppression [5]. These figures, when compared with people living with HIV across California, indicate that LAC's African American people living with HIV fare worse in terms of HIV outcomes as they have been proportionately less likely to be engaged in care and to achieve viral suppression [3].

Socioeconomic predictors, such as income status, may provide perspective on linkage to HIV care, as African American people experience poverty at a disproportionately higher rate than other racial/ethnic groups in the United States [6]. Poverty is associated with an increased risk of HIV diagnosis among some BSMM, which may also affect the health of BSMM living with HIV (BSMM+) [1] as racism continues to serve as a structural barrier to HIV services for BSMM+ [7]. Black people living with HIV who experience greater racial discrimination were

less likely, as documented in prior research, to have an undetectable viral load and a high CD4 cell count [7]. African American people also expressed higher levels of medical mistrust, especially those living with HIV [8]. Higher general medical mistrust is a significant predictor of lower continuous HIV medication adherence over time [9].

Structural racism is related to the decreased likelihood of reporting antiretroviral therapy (ART) use among young BSMM+ [10]. The impact of racism on BSMM+ must be understood in the context of homophobia and HIV-related stigma. BSMM are less likely to disclose their sexual identity or sexual activity to their health care providers compared with SMM from other racial/ethnic groups [11]. These multiple layers of systemic, intersecting oppression and the resulting stigma that BSMM+ face can negatively affect health-seeking behaviors and HIV treatment engagement and highlight the need for tailored interventions for BSMM+.

### Culturally Tailored Mobile App Interventions

HIV interventions that address self-efficacy and resilience are effective in promoting health behaviors [12]. Previous studies highlight strengths-based approaches as appropriate for increasing the use of HIV services by recognizing how BSMM+ overcome challenges to care [12]. Interventions that focus exclusively on risk highlight what is lacking and reinforce harmful stereotypes about individuals facing overlapping stigma [12]. In addition, social support networks are vital to sustain healthy behaviors among BSMM+. HIV interventions that facilitate peer social support build resilience through avenues of emotional and informational support. These social exchanges are opportunities for BSMM+ to empower each other, encourage healthy behaviors, and provide information on HIV-related resources. Such interventions promote resilience processes to combat the negative effects of multiple stigmas, including those related to racial minority identity, sexual minority identity, and HIV status [12,13].

The use of social media and mobile phone technology have been proven to be effective avenues for HIV intervention [12,14,15] because they are widely available and acceptable methods for HIV intervention [16]. Mobile apps and social media platforms allow interventions and information regarding HIV to be more accessible to communities that have been deemed *difficult to reach* due to multiple stigmas [14]. Although these platforms are virtual, community partnership remains essential to maintain sustained engagement and effectiveness as collaboration ensures tailored messaging for key populations such as BSMM+ [12]. In addition, online spaces facilitate social connectivity while giving BSMM+ the ability to remain anonymous, should they choose [12].

Existing technologies, including HIV-focused mobile apps, are available to the public; however, usage remains to be low

[17,18]. Technology created to address the needs of people living with HIV focuses specifically on HIV education, access to services (eg, HIV testing, linkage to care), maintaining communication between the patient and provider to support adherence and retention in care, and to support the work of providers [19]. Through its formative work, the LINX web-based mobile app (LINX LA) study identified a gap in existing mobile apps. No health mobile apps at this point focus on the complex structural and psychosocial barriers that BSMM+ face to improve HIV outcomes, including upstream factors such as housing and homelessness, lack of access to public benefits, and other social and legal needs. This study aims to test the efficacy of a web-based platform designed by and tailored for BSMM+ that provides social and legal resources as well as a forum for peer support. First, we hypothesize that participants in the LINX App Plus condition will demonstrate improvement in HIV outcomes as compared with those in the LINX App arm of the study. Second, we hypothesize that by offering social and legal services case management, the study could address 2 primary issues faced by many BSMM+—housing and financial instability.

## Methods

### Overview

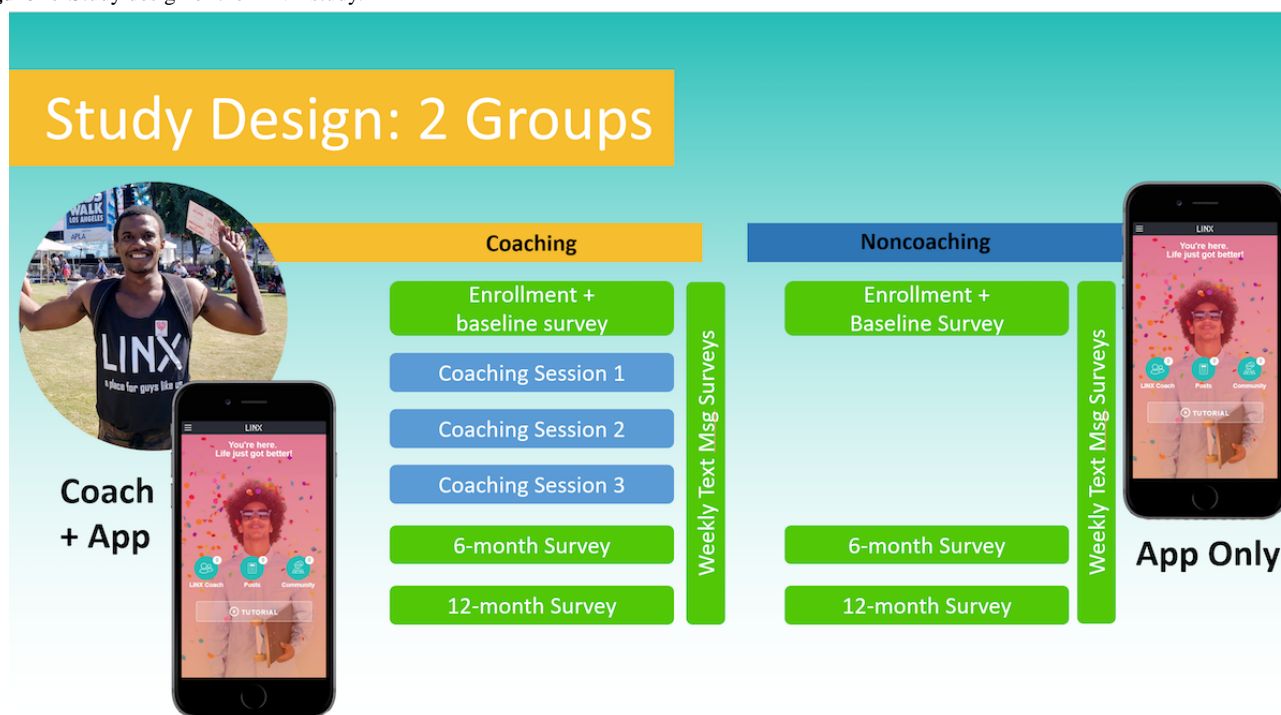
The proposed study is a randomized comparison trial of a web-based mobile app titled *LINX*. Participants will be randomly

assigned to either the intervention (ie, treatment group) or the comparison group. Those in the intervention group will receive the app and access to a LINX Coach (*LINX App Plus* condition) and those in the comparison group will receive the LINX Mobile app only (*LINX App* condition). Participants in both arms of the study will remain on the mobile app for 12 months. The overarching goal of the study is to evaluate the efficacy of LINX App Plus compared with LINX App to improve HIV treatment outcomes (ie, ART adherence, viral suppression). The research team did not register this study at ClinicalTrials.gov because it did not involve randomization to a true control group. Owing to ethical concerns about withholding the mHealth intervention, all participants received the app; half were randomized to receive coaching.

### Target Population

The goal of the study is to recruit a minimum of 400 participants for the study. Half of the sampling group (200 individuals) will be randomly assigned to the LINX App condition and the other half will be assigned to the LINX App Plus condition (Figure 1). To be eligible for the study, participants must be aged at least 18 years old or older and must be male, Black or African American, and gay, bisexual, or other sexual minority. Participants must also own a smartphone, be living with HIV, reside in LAC, and be able to provide informed consent.

Figure 1. Study design of the LINX study.



### Mobile App Development

In phase 1, we conducted qualitative interviews with BSMM+ in LAC focused on technology use patterns, HIV diagnosis and engagement in care, and social and legal service needs. Using these data, we worked with a private sector technology partner, Philosophie Group Inc [20], to engage in an iterative,

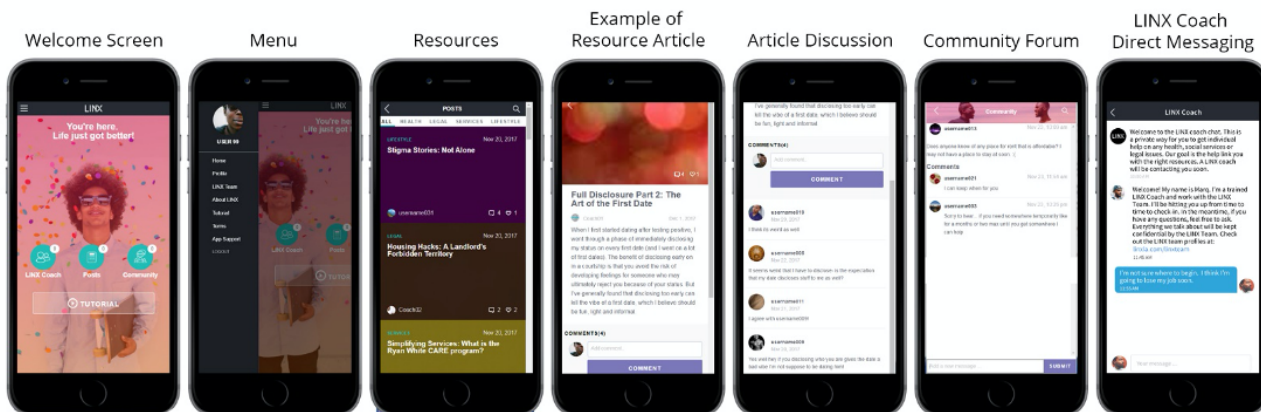
user-centered design process to develop the LINX App. Throughout the intensive 6-week design process, we developed an interactive prototype and conducted moderated interviews with BSMM+ (n=20) and HIV service providers (n=11). Participants tested the functionality of a paper prototype of the LINX App through moderated interviews and to evaluate the prototype according to user experience principles (eg, content

and delivery of content is useful, findable, accessible, desirable, usable, and credible). The phase 1 design process ended with a 1-week pilot test of the LINX App with BSMM (n=14), including members of the LINX LA Study Community Advisory Board (CAB).

Study staff developed a library of content including over 1000 informational posts in areas of need identified during phase 1 and issues raised during moderated interviews. The 6 main categories include health, fun, legal, relationships, services, and

housing with a focus on sharing information related to HIV knowledge, HIV-related services in the community, legal rights and resources available to people living with HIV, and social services and programs. Users can also create their own content on the app, including both creative and informational posts. With the ability to post photos and videos using YouTube and Vimeo platforms, posts have the potential to be dynamic and engaging. Examples of the app interface with mockup text are shown in [Figure 2](#).

**Figure 2.** LINX App user interface.



**Recruitment**

Recruitment strategies will include the following efforts ([Textbox 1](#)).

**Textbox 1.** Recruitment strategies.

<p>Meetings with key stakeholders</p> <ul style="list-style-type: none"> <li>Attend in-person meetings with key collaborators in the community including Public Health Departments, community clinics, Los Angeles County (LAC) HIV Commission, and other health care and social service providers serving Black sexual minority men (BSMM) in LAC</li> <li>Community partners, stakeholders, researchers, and staff will test and review the mobile app live and distribute study materials to their networks</li> <li>Due to the COVID-19 pandemic, our meetings will be held on the internet using the Zoom Video Communications platform</li> </ul> <p>In-app referral program</p> <ul style="list-style-type: none"> <li>LINX LA has a built-in referral function to allow participants to refer people directly from the app</li> <li>Once a referral is made, LINX staff will be notified to follow up</li> <li>Participants will receive a US \$20 Amazon e-gift card for every person successfully referred into the study</li> </ul> <p>Referral program</p> <ul style="list-style-type: none"> <li>Noninvestigator health care, social and other service providers, and community members will be able to refer others into the study</li> <li>Referrers are sent a referral code, information about the study, a suggested pitch they can use to talk about the study, and a digital referral card to post on the internet</li> <li>Referrers will receive a US \$20 Amazon e-gift card for every person successfully referred into the study</li> </ul> <p>In-person outreach events</p> <ul style="list-style-type: none"> <li>Staff will distribute flyers and business cards for the study at locations including community events tailored to attracting BSMM, clinics and health centers, bars and clubs, retail businesses, community forums, social service organizations, and other community-based service providers</li> <li>Owing to the COVID-19 pandemic, all in-person outreach events will be put on hold; instead, all outreach will be conducted via phone, social media, and email</li> </ul> <p>Web-based promotion</p> <ul style="list-style-type: none"> <li>Participants will be recruited through web-based methods using targeted advertising on social networking sites (eg, Facebook.com, Twitter.com, SCRUFF.com, Grindr.com, Craigslist.org, Jack'd [Jackd.com], Bareback Real Time Sex [BarebackRT.com], Black Gay Chat Live [BGCLive.com]) in addition to direct email campaigns</li> <li>Staff will engage social media influencers, people with a large number of social media followers, to help widen the reach of our web-based promotion</li> </ul>
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**Community Engagement**

During phase 2 of the LINX study, researchers and study staff will engage in a range of collaborative activities to ensure that research activities are responsive to and understand community needs, views, and expectations.

***APLA Health: Community-Based Program Implementation***

The LINX study will strategically subcontract with APLA Health, a social service organization with over 35 years of work serving LA communities affected by HIV/AIDS, to implement the LINX LA study's coaching activities. The LINX Coach will be hired from within the community and trained by and embedded within APLA Health's well-established outreach, prevention, and social services department to ensure cross-training and resource sharing between researchers and community partners. This collaboration will enable underresourced participants to access APLA Health's full range of in-house wraparound services—social support groups, housing navigation, mental health, benefits counseling, and health care services. APLA Health provides essential services, so their full range of services is still available (albeit some

services are limited to specific locations) during the COVID-19 pandemic.

***Arming Minorities Against Addiction and Disease Institute: Community-Driven Capacity Building and Social Events***

The research team will partner with the Arming Minorities Against Addiction and Disease (AMAAD) Institute, a social services organization serving lesbian, gay, bisexual, transgender, and queer (LGBTQ) people of color in South Los Angeles. Since 2014, AMAAD developed a community-driven project to empower young LGBTQ African American people to share personal experiences and life skills through art. This partnership will accomplish several goals: (1) generate culturally appropriate content for the LINX App; (2) create and sustain social support to address isolation and disconnectedness among BSMM+; (3) identify and train BSMM+ *study ambassadors* to talk about the study and recruit peers into the study; and (4) build individuals' capacity in editorial writing and content creation. During the ongoing COVID-19 pandemic, many AMAAD Institute programs and services, such as support groups, capacity building workshops, and training, have moved to a web-based conferencing platform (ie, Zoom Video Communications Inc).



### ***CAB: Input and Feedback***

The LINX CAB, made up of community members, community organization partners, and social service providers, will be established at study inception and meet on a quarterly basis to provide feedback and input on study materials, procedures, recruitment strategies, receive updates about the study, and solve implementation challenges. CAB members primarily include BSMM, including individuals living with HIV. During the COVID-19 pandemic, CAB meetings will be held on the internet via the Zoom Video Communications conferencing platform.

### ***Community Outreach and Engagement: Resource Gathering and Recruitment***

LINX researchers and study staff, which include community members with substantial community organizing and networking experience engaged in the LINX phase 1 formative work, will make efforts to engage with community-based organizations, clinics and health centers, HIV service providers, stakeholders, and community venues that serve or represent LGBTQ African American people across LAC. Activities will include resource sharing and cross-promoting programs and services via LINX LA-branded social media. By regularly attending resource fairs, provider network meetings, and other community meetings, LINX LA study staff will access up-to-date information on social service programs, which will facilitate effective linkages for LINX LA study participants. During the ongoing COVID-19 pandemic, in-person attendance of resource fairs and meetings have transitioned to web-based conferencing platforms.

### ***Online Community Engagement: A Social Networking Extension of LINX***

The LINX LA study team developed and maintained several LINX LA-branded social media accounts on platforms (eg, Twitter, Facebook, Tumblr, and Instagram) that are popular with users that match the study's target demographic. The LINX LA study's presence on social media serves to add to and amplify Black queer voices in the media and in the community and, in doing so, will assist the research project by providing another accessible online space for LINX App and non-LINX App users to engage followers interested in LINX LA's curated feed who may also be interested in the LINX LA study. Growing a social media following that allows LINX LA to reach more users via followers' networks goes beyond what is possible with traditional recruitment methods.

Words used to describe the LINX LA social media brand, developed in consultation with the LINX LA CAB, include *young, hip, Black, queer, empowering, and positive*, and LINX LA features original and shared content that reflects those themes and messages. Content will include posts about Black queer voices in popular culture, inspirational quotes, monthly themes, community resources, upcoming events, music playlists and videos, and articles about Black queer experiences and experiences of people living with HIV. To enhance reach and effectiveness, the LINX staff will use social media best practices, and analytics will be used to assess the effectiveness of various strategies.

### **Enrollment Process**

To see if an individual is eligible to enroll, potential participants must first complete a screening that can occur via email, in-person, by phone, or on the web. During the screening, LINX LA study staff will collect information regarding name or alias, age, gender identity, sexual orientation, HIV status, and race and ethnicity. The study staff then schedules in-person enrollment appointments via the participant's preferred mode of contact. During enrollment, participants are screened for consent and asked to provide additional consent for study staff to access medical records, to provide HIV verification, and to complete a baseline assessment. During the ongoing COVID-19 pandemic, the research staff are not engaging in any in-person activities until the university and the institutional review board (IRB) that oversees the study lift restrictions related to in-person human subjects research. All enrollment activities will be conducted over Zoom Video Communications or by phone.

### **Onboarding**

After enrollment, participants were assisted by study staff to download the LINX App. Study staff will inform participants of the duration and compensation schedule for the study. Once the app is downloaded, the participant will be instructed how to log into the app and navigate the user interface based on the arm of the study to which the participant is assigned. Participants will be instructed on how to create a post, and the terms and conditions of use will be reviewed in detail.

### **Coaching Sessions**

Participants are randomly assigned to one of 2 conditions. Those assigned to LINX App Plus have access to a LINX Coach. The LINX Coach delivers 3 manualized intervention sessions via phone calls during the first 6 months of the study (ie, 1 session every other month). These sessions are adapted from a manualized intervention to promote HIV medication adherence developed by Wagner et al [21]—the adherence readiness program.

On the basis of the information, motivation, and behavioral skills model of behavior change, the 3 coaching sessions are conducted over the phone. Using additional counseling techniques based on motivational interviewing, the LINX Coach conducts 3 sessions approximately 2 months apart. Each session includes learning objectives, described in detail below. During these sessions, the LINX Coach helps to identify any social and legal needs the participant may have, provides the participant with social support and needed referrals to legal and social service providers throughout the LAC, and helps motivate participants to identify and pursue their own HIV treatment and adherence goals. The LINX Coach follows-up with participants to ensure that linkages to services have occurred. The LINX Coach also maintains regular contact with participants via 2-way messaging in the LINX App.

In session 1, learning objectives include being able to identify, with LINX Coach support, outstanding social work and legal needs and to discuss HIV treatment engagement issues that the participant may be experiencing. These objectives are achieved by discussing the intervention and expectations of the participants, the participants' attitudes, beliefs, and goals toward

treatment engagement and addressing issues discussed with the LINX Coach that are within the scope of the LINX intervention through linkage to social and legal resources.

In session 2, learning objectives include developing problem-solving skills, where the LINX Coach helps participants apply those skills to the social work and legal needs the participant may be experiencing. The LINX Coach also offers support for the participant to improve and/or maintain continued treatment engagement by addressing issues identified by the participant in session 1. This work is achieved by directly identifying barriers to engagement in care, outlining a strategy for success, and developing strategies to improve social support.

In session 3, the LINX Coach delivers the third and final coaching session. The learning objectives for this session include the participant identifying their own successful strategies for treatment engagement and troubleshooting, with help from the LINX Coach for any remaining social work and legal needs. The participant will design a plan for ongoing treatment engagement. Success in the third session is defined by the participants' ability to both think and act independently as it relates to the identified social work, legal needs, and treatment engagement issues.

### **Weekly Medication Adherence Assessments**

Brief text message surveys will be distributed to all study participants to capture weekly medication adherence. The survey comprised 1 to 3 questions asking about adherence in the prior week and, if a participant reports missing their medication, a query about why they may have missed it. Participants who complete the 2-minute survey will earn 1 entry into the monthly raffle for a US \$100 e-gift card. Individuals can choose not to participate or to opt out of the survey.

### **Incentives**

Participants in the LINX App condition will receive up to US \$130 in cash, e-gift cards, or web-based cash payment (ie, PayPal Holdings Inc, Venmo LLC, and Cash App by Square Inc). Participants will receive US \$30 for the baseline assessment, US \$40 for the 6-month posttest interview, and US \$60 for attending the 12-month follow-up interview. LINX App Plus participants will receive the same incentives as those in the LINX App condition including additional incentives for each completed coaching session. Participants in the LINX App Plus condition can receive up to US \$190 in cash, e-gift cards, or web-based cash payment, as they receive a US \$20 incentive per coaching session completed.

### **Discharge From the Study**

Participants will be discharged from the study after completing their 12-month follow-up interview. After discharge, all individually identifiable data related to the participants will be destroyed.

### **Regulations and Ethics**

The research and ethics presented in this study were reviewed and approved by the North Campus IRB of the University of California, Los Angeles (UCLA; IRB#17-001615) with UCLA

acting as the IRB on record for all LINX community partners. Additional terms to ensure confidentiality were provided to the participants. These terms include protection for all study-related data obtained by all LINX LA study staff, which includes employees, contractors, volunteers (paid or unpaid), and other professionals staffing the project.

Technical concerns related to data privacy were considered throughout phase I during the app development process. The mobile app is housed by a Health Insurance Portability and Accountability Act-compliant hosting platform often used by health care entities. In collaboration with the UCLA Information Technology and UCLA Compliance departments, considerations related to data storage and data in transit were considered, including the institution's legal and ethical duties related to the handling of personally identifiable information. User terms for the mobile app were drafted to include specific guidelines on sharing data and personal information and the particular limitations to privacy for individuals who disclose information on the LINX LA app. Users are instructed to select a display name, different from their legal name, and advised not to include full facial photos, phone numbers, and email addresses to protect their identity. Procedures and protocols are established to address participants that may require intervention under the law (eg, participants expressing suicidal ideation) and participants who may be engaging inappropriately on the LINX App.

### **Primary Outcomes**

The primary outcomes that the study will measure include the degree to which using the LINX App may impact medication adherence and viral suppression. These primary outcomes were assessed through self-reported data verified through an independent medical chart review. The study will measure how outcomes differ between the LINX App and LINX App Plus conditions and whether the intensity of use of the platform (ie, intervention dosage) is associated with these outcomes.

### **Secondary Outcomes**

The overarching framework that informs the study is a social determinant of health model, where we recognize that structural factors (eg, housing instability and poverty) are upstream factors influencing individual-level health behaviors. The information, motivation, and behavioral skills model is the mechanistic model of behavior change. We posit that in the short term, the LINX App will serve to increase participants' HIV knowledge and help create connections among the participants and connections to existing community-based resources. This may impact both treatment adherence and address issues related to social isolation and stigma. For participants in the LINX App Plus arm of the study, we hypothesize that by offering social and legal services case management, the study could address 2 primary issues facing many in the target population—housing and financial instability.

### **Assessment Measures**

The baseline, 6-month, and 12-month surveys comprised 12 topic areas (Table 1).

**Table 1.** Primary and secondary outcomes of the study.

Outcomes	Measures	Variables
<b>Primary</b>		
Technology use	Multiple items	Likert scale, range 1-5
Medication adherence	Self-reported medication adherence; HIV medical record data	Dichotomous; Yes or No HIV medication adherence or HIV-associated medical appointment
Viral suppression	Viral load and CD4 counts	Continuous
<b>Secondary</b>		
Unemployment	Unemployed, part-time, or full-time	Nominal
Unstable housing	Homeless, marginally housed, or housed	Nominal
Access to health care provider	Multiple items	Nominal and multiple dichotomous items
Social support	Multidimensional scale of perceived social support	Continuous
Connectedness to gay community	Items adapted from Healthy Young Men study	Ordinal
Peer norms for HIV treatment	Perceived peer norms scale	Continuous
Sociodemographic	Multiple items	Nominal and integer
Victimization and discrimination	Victimization and discrimination questionnaire	Nominal
Ethnic identity	Multigroup ethnic identity measure revised	Likert scale, range 1-5

## Measuring and Maximizing Engagement

User data will be measured using metrics such as the number of logins and the amount of time spent on the app, posts created by participants, comments posted, and the messages transmitted between the LINX Coach and participants. Change indicators will also be measured through text message surveys administered weekly, in-person assessment surveys, or via Zoom Video Communications or phone calls at 3 points over the year (baseline assessment, posttest survey at 6 months, and follow-up survey at 12 months after enrollment) and assessments of HIV-related clinical outcomes.

## Statistical Analyses

Statistical methods, models, and procedures will be selected according to the research hypotheses being tested and the types of measures involved. We will set  $\alpha < .05$  as the level for statistical significance but will use appropriate corrections for multiple comparisons (eg, Bonferroni and Hochberg correction) to ensure that the actual overall effective type 1 error remains at a .05 level for the tests to be conducted. The frequency and patterns of missing data were carefully evaluated. To avoid potential bias resulting from missing data, imputation (eg, hot deck or multiple imputation) will be conducted, and statistical significance tests and modeling will be conducted with and without the imputed values. The findings from these analyses will be compared, and any difference will be evaluated. Potential nonlinear relationships between continuous predictors (eg, participants' age) and outcomes (eg, CD4 count, viral load) will be evaluated through spline functions (eg, cubic spline) [22].

## Planned Analytic Approach

Descriptive statistics of all measures involved (background characteristics, potential moderators and mediators, and outcomes) will be calculated to inform the bivariate analyses and subsequent statistical modeling. On the basis of the nature

of the key outcome measures (continuous, categorical, or binary), we will use a full spectrum of analytical approaches to evaluate the data including analysis of variance, analysis of covariance, linear regression, and logistic (binary or ordinal) regression. With 3 time points, repeated-measures mixed effect models will also be applied to model the global fixed effect as well as individual participants' random variation. Our approach to modeling will be to first examine the raw associations with bivariate analyses and then the adjusted and controlled association. Confounding relationships are evaluated through changes in the regression coefficient. The final models will be selected based on goodness-of-fit measures, such as r-square, likelihood ratio, c-statistics, and analysis of covariance, a penalized likelihood. Estimates of effect will be presented with associated 95% confidence limits and associated *P* values.

Preliminary analyses will describe associations between potential predictor variables between both arms of the randomized controlled trial. The initial focus will be to understand the associations between predictors and specified outcomes and to identify confounding or co-linearity that may impact later analyses. We will also describe correlations across various domains to inform the development of our final comprehensive model. We will develop base models predicting engagement in HIV care from demographic predictors (ie, age, education, income, housing status) to identify demographic variables that will be controlled for (as confounding variables or effect modifiers) when examining associations between intervention effects and outcomes. Analyses will be performed to determine robustness and to understand potential confounding or collinearity between predictors. Testing of significance for independent variables will include Wald chi-square tests for continuous or dichotomous variables and/or global goodness-of-fit tests if polytomous categorical variables are regressed. Estimates of effect will be presented with associated 95% confidence limits and associated *P* values.



## Sample Size Calculation and Power Analysis

Our proposed sample size is based on a comparison of the main outcome of linkage to HIV care between the study arms of the LINX App and LINX App Plus conditions based on a priori logistic regression sample size calculations in PASS 2008 software. Calculations assume linkage-to-care base rates across conditions of 70% based on 2013 estimates of linkage to care within 3 months of an HIV diagnosis for African American people. We also assume a type 1 error of .05 and type 2 error of .2 (or power 80%). Our targeted enrollment of 200 participants in each condition will give us enough power to detect a difference in HIV linkage between LINX App and LINX App Plus arms as low as 12.5%. In addition to comparisons between the 2 study arms as a dichotomous measure, we will also compare linkage to care and other outcomes by intervention dosage as a continuous measure. Comparisons of continuous measures often increase power analyses relative to comparison of dichotomous measures; this comparison is similarly anticipated to do so in our study.

## Results

### Expected Outcomes

The strengths of this trial are rooted in its work to address the effect of HIV among a group of individuals hit hard by the epidemic. In LAC, BSMM are facing an increase in the numbers of new HIV diagnoses, and linkage to care has historically been a specific challenge for these men. The high level of need provides an opportunity to make a measurable impact through this trial. The intervention's focus on social services and legal needs is distinct. Although structural barriers are resistant to change and require sustained efforts, including advocacy at a policy level, specific assistance provided to ameliorate the effects of these barriers is achievable. This work will be a defining hallmark of the intervention. Finally, the use of mobile technology to foster a voice and a collective identity across BSMM+ and as an avenue for accessing resources and promoting social support, although not new, is still a strategy worth exploring.

The LINX LA study's contribution will be to increase the understanding of how to develop technology for and by the communities targeted by an intervention and how to establish programmatic structures to ensure that the platform maintains a strengths-based lens in lifting voices from the same community. Investment in such strategies has the potential to improve ART adherence and increase viral suppression among BSMM+.

### Expected Timeline

The LINX App was completed and recruitment and enrollment for the trial started in May 2018 on a rolling basis. Owing to the outbreak of COVID-19, the collection of survey data at 3 time points over 12 months will pose a challenge. Nonetheless, the length of the study per patient will be 12 months. We expect to complete data collection 12 months after the last participant has been enrolled in the study, that is, by January 2021, and plan the dissemination of results subsequently.

## Discussion

### Limitations: Recruitment Challenges

There are potential challenges to this trial. It employs convenience sampling techniques to recruit the target population, which limits generalizability. In addition, if recruitment fails to yield the required number of participants, we may not have adequate statistical power to detect effects of intervention conditions on outcomes. To address these uncertainties, we plan to compare our sample to data from other projects focused on BSMM+ in LAC. The LAC Division of HIV and STD Programs has implemented a clinic-based medical care coordination (MCC) program to increase viral suppression (VS; <200 c/mL) among people living with HIV at high risk for poor health outcomes (eg, diagnosed with HIV in the past 6 months, on ART without VS, out of care for more than 6 months). The MCC program collects clinical data across 35 Ryan White Program-funded clinics across the county serving these populations, including those that identify with our target population. Comparing results from the study with data from participants in the county's MCC program will help to address this gap.

Recruitment of BSMM+ may be challenging in LAC due to the sheer size of the county and the study's eligibility criteria, requiring participants to be both living with HIV and identifying as a sexual minority. For this reason, study staff will implement a diverse set of strategies to engage varied audiences during the recruitment period, including web-based efforts and in-person efforts detailed in [Textbox 1](#). The study will also offer participants with transportation assistance. By providing access to ride-sharing resources through Lyft Concierge services, participants will be able to meet study staff at the location of their choice. This additional support has proven effective in reducing the number of cancelled meetings between study staff and participants [18].

### Limitations: Engagement and Retention Challenges

This service should also help with a potential foreseeable challenge—the retention of participants. Study staff will develop a targeted retention plan that looks at maximizing every opportunity that the study staff may have when meeting participants. This includes walking participants through a process of updating multiple points of contact information and ensuring that participants have access to LINX LA so that efforts to promote engagement continue to reach participants. Another planned strategy includes tracking all contact with participants and identifying problems with communication at the earliest possible time point. For example, by reviewing weekly text message data, the staff can identify which participants have mobile phone numbers that may be out of service or otherwise may not be receiving study text messages.

Finally, although creative content developed by members of the community is a key strategy to driving traffic to LINX LA, the study will be challenged to command the attention of participants who currently spend time on other social media and web-based platforms. Given the significant investment in developing a mobile app for and by BSMM+, the study will need to remain nimble in its efforts to engage participants on



the platform. Thus, an ongoing review of back-end user data, including analytics on usage patterns, combined with feedback provided by participants during assessments and coaching sessions must drive future strategies to retain an engaged pool of participants.

## Acknowledgments

The authors would like to acknowledge the contributions of their expert CAB members, many of whom are Black LGBTQ individuals. They also thank their community partners, including APLA Health and the AMAAD Institute for their assistance in coordinating the study. They would also like to thank UCLA staff and affiliates for their assistance in coordinating the study and assisting with manuscript preparation, including Robert Gamboa, Kelly Gluckman, Maynard Hearn, Shellye Jones, Gregory Victorienne, Giselle Ruballos, Nina Young, Rosalia Alvarado, Sharon Lau, Tiffany Luu, Heliud Garcia, Arthur Sun, Paulette Orhii, and Jack Hjerpe. The authors are supported by the California HIV/AIDS Research Program (HD15-LA-061).

## Conflicts of Interest

None declared.

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## Abbreviations

**AMAAD:** Arming Minorities Against Addition and Disease Institute

**ART:** antiretroviral therapy

**BSMM:** black sexual minority men

**CAB:** Community Advisory Board

**CD4:** cluster of differentiation 4

**IRB:** institutional review board

**LAC:** Los Angeles County

**LGBTQ:** lesbian, gay, bisexual, transgender, and queer

**LINX App:** LINX web-based mobile app arm

**LINX App Plus:** LINX web-based mobile app with LINX Coach arm

**LINX LA:** LINX web-based mobile app

**MCC:** medical care coordination

**UCLA:** University of California, Los Angeles

**VS:** viral suppression

*Edited by G Eysenbach; submitted 05.05.20; peer-reviewed by D Tan, D Moskowitz; comments to author 29.08.20; revised version received 12.11.20; accepted 17.11.20; published 06.01.21.*

*Please cite as:*

*Miyashita Ochoa A, Paneda CC, Wu ESC, Maxwell KE, Garth G, Smith T, Holloway IW*

*A Community-Developed, Web-Based Mobile App Intervention Addressing Social Work and Legal Needs of Black Sexual Minority Men Living With HIV: Protocol for a Randomized Comparison Trial*

*JMIR Res Protoc* 2021;10(1):e19770

URL: <https://www.researchprotocols.org/2021/1/e19770>

doi: [10.2196/19770](https://doi.org/10.2196/19770)

PMID: [33404514](https://pubmed.ncbi.nlm.nih.gov/33404514/)

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Protocol

# Use and Effect of Web-Based Embodied Conversational Agents for Improving Eating Behavior and Decreasing Loneliness Among Community-Dwelling Older Adults: Protocol for a Randomized Controlled Trial

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## Abstract

**Background:** An unhealthy eating pattern and loneliness negatively influence quality of life in older age. Embodied conversational agents (ECAs) are a promising way to address these health behaviors in an engaging manner.

**Objective:** We aim to (1) identify whether ECAs can persuade community-dwelling older adults to change their dietary behavior and whether ECA use can decrease loneliness, (2) test these pathways to effects, and (3) understand the use of an ECA.

**Methods:** The web-based eHealth app PACO is a fully automated 8-week intervention in which 2 ECAs engage older adults in dialogue to motivate them to change their dietary behavior and decrease their loneliness. PACO was developed via a human-centered and stakeholder-inclusive design approach and incorporates Self-determination Theory and various behavior change techniques. For this study, an unblinded randomized controlled trial will be performed. There will be 2 cohorts, with 30 participants per cohort. Participants in the first cohort will immediately receive the PACO app for 8 weeks, while participants in the second cohort receive the PACO app after a waiting-list condition of 4 weeks. Participants will be recruited via social media, an online panel, flyers, and advertorials. To be eligible, participants must be at least 65 years of age, must not be in paid employment, and must live alone independently at home. Primary outcomes will be self-assessed via online questionnaires at intake, control, after 4 weeks, and after 8 weeks, and will include eating behavior and loneliness. In addition, the primary outcome—use—will be measured via data logs. Secondary outcomes will be measured at the same junctures, via either validated, self-assessed, online questionnaires or an optional interview.

**Results:** As of July 2020, we have begun recruiting participants.

**Conclusions:** By unraveling the mechanisms behind the use of a web-based intervention with ECAs, we hope to gain a fine-grained understanding of both the effectiveness and the use of ECAs in the health context.

**Trial Registration:** ClinicalTrials.gov NCT04510883; <https://clinicaltrials.gov/ct2/show/NCT04510883>

**International Registered Report Identifier (IRRID):** PRR1-10.2196/22186

(*JMIR Res Protoc* 2021;10(1):e22186) doi:[10.2196/22186](https://doi.org/10.2196/22186)

**KEYWORDS**

embodied conversational agent; health behavior change; loneliness; eating behavior; older adults

## Introduction

### Background

Unhealthy eating and loneliness negatively influence quality of life (QoL) in older age [1,2]. Statistics show that in the Netherlands, almost 60% of people over 65 are obese [3], and 57% of community-dwelling older adults are at risk for undernutrition [4]. Both are important risk factors for chronic diseases and are clearly associated with unhealthy eating behaviors. As eating is regarded as a social activity, loneliness is associated with a loss of pleasure in eating and cooking [5] and is a significant predictor of malnutrition [6]. Loneliness can be defined as the discrepancy between a person's desired and achieved levels of social relationships [7]. In the Netherlands, over 50% of older adults indicate that they experience loneliness, a percentage that is even higher among people without a partner [8]. The expected increase in the coming years [9] in this group of single, community-dwelling older adults will exacerbate this problem. However, it is challenging to realize an actual change in eating behavior and deal with loneliness.

Embodied conversational agents (ECAs) have been proposed as a promising technological tool to persuasively address these health behaviors, with the aim of changing users' attitudes or behaviors through persuasion and social influence rather than through coercion [10]. ECAs can be defined as "more or less autonomous and intelligent software entities with an embodiment used to communicate with the user" [11]. A typical user interface consists of a human-like ECA with prewritten dialogues, including multiple choice answer options [12]. ECAs can make an intervention for coaching people in a healthy lifestyle more engaging than traditional electronic health interventions [12]. This ability is often ascribed to ECAs' capacity to establish and maintain an emphatic relationship [12,13]. Early studies show that older adults who interact with an ECA form a relationship with the ECA and consider it a companion [14], including those from populations in which

eHealth literacy is generally lower [15]. ECAs are perceived as enjoyable, usable, and acceptable for addressing health behavior change [16-18].

Nonetheless, interventions with an ECA are not immune to declining use over time, meaning that this issue must be addressed in ECA design to prevent limited long-term health effects [12]. Furthermore, and even more importantly, evidence of ECA effectiveness and underlying working mechanisms is scarce and remains inconclusive [12]. This limits the possibility to learn from others' efforts and prevents knowledge accumulation.

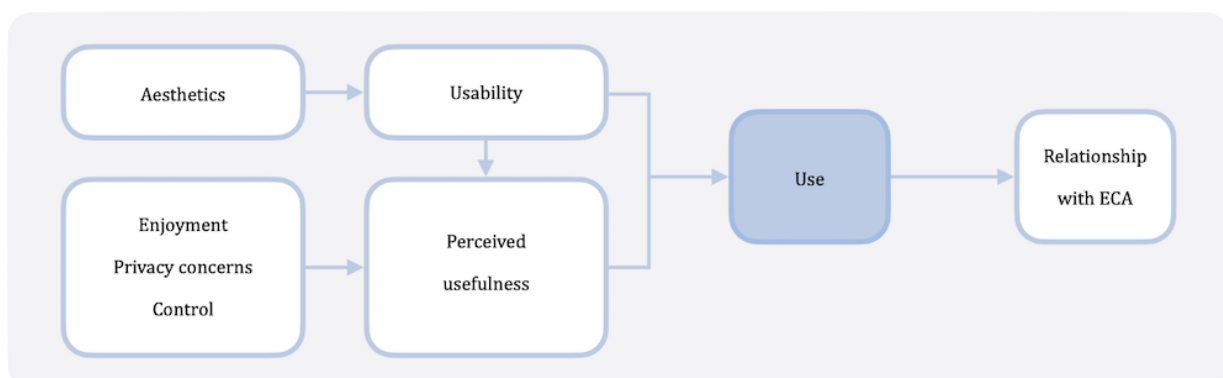
### Objectives

We present the protocol for an 8-week evaluation of the PACO service. Consisting of 2 ECAs, PACO is a web-based app that aims to achieve dietary behavior change and decrease loneliness among single, community-dwelling older adults. The goal of the evaluation is to (1) identify whether ECAs can persuade community-dwelling older adults to change their dietary behavior and decrease their loneliness, (2) assess the pathways to effects, and (3) understand ECA use. The latter 2 goals will allow us to explain the occurrence (or the lack) of an effect from using the intervention and can therefore serve to support the design of future ECAs.

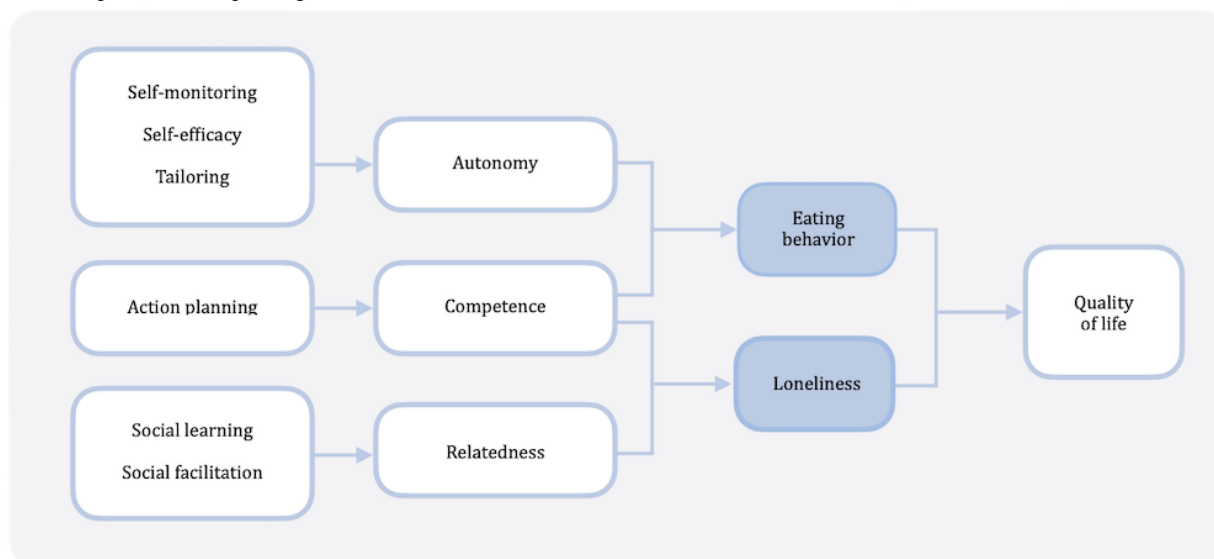
### Conceptual Models

In order to conceptualize and measure engagement, Cole-Lewis et al [19] state that it is necessary for users to have appropriate levels of interaction with the technology and that the behavioral change components are relevant. Hence, we present 2 conceptual models. The first is a conceptual model explaining ECA use (CEU; Figure 1). With this model, we aim to explain the factors that determine the use of an ECA intervention in this context. The second is a conceptual model explaining health effects (CHE; Figure 2). With this model, we aim to explain the mechanisms behind the observed change in eating behavior and loneliness.

**Figure 1.** Conceptual model explaining embodied conversational agents (ECA) use, known as CEU.





**Figure 2.** Conceptual model explaining health effects, known as CHE.

Use is at the center of the conceptual model explaining ECA use. It is assumed that an eHealth intervention will not be used if it does not create any benefit (perceived usefulness) or if it has a substantial number of usability problems [20]. Visual aesthetics, defined as an orderly and clear design, are closely related to many of the design rules advocated by usability experts [21]. In the case of patient portals, aesthetics have thus been found to influence usability in the context of explaining technology acceptance [22]. We expect perceived usefulness to be influenced by 3 user experience factors. Perceiving something as enjoyable is linked to a positive effect on use when the system is perceived to be useful [23]. Willingness to share personal information and preferences (ie, the absence of privacy concerns) is argued to be a prerequisite for convenience and a useful system [24]. The last factor is control, which refers to “the extent to which the user can bring about or prevent particular actions or states of the system if she has the goal of doing so” [25]. Especially in human-computer interaction literature, control has been identified as a crucial factor in the occurrence of perceived usefulness and use [26,27]. Furthermore, there is robust evidence that usability has a direct effect on perceived usefulness [28]. In turn, use is hypothesized to act as an antecedent of the intensity of an end user’s relationship with an ECA [14].

Self-determination Theory (SDT) comprises the basis of the conceptual model explaining health effects [29]. Briefly, SDT postulates that human beings have 3 essential psychological needs: autonomy (the feeling of being the origin of one’s own behaviors), competence (feeling effective), and relatedness (the need to feel belongingness and connectedness with others). Self-monitoring and self-efficacy are associated with increased autonomy [30]. Tailoring is a more generic behavior change technique (BCT), which, in our case, refers to a tailored recipe book. We hypothesize that the possibility of generating a tailored recipe book leads to an increased feeling of being in control. Action planning is found to be supportive of increasing competence [31]. Both social learning and social facilitation are expected to lead to an increase in relatedness, as they both connect people. In turn, a decrease in loneliness and an

improvement in eating behavior is expected to lead to more positive health-related QoL outcomes [1,2].

## Research Questions

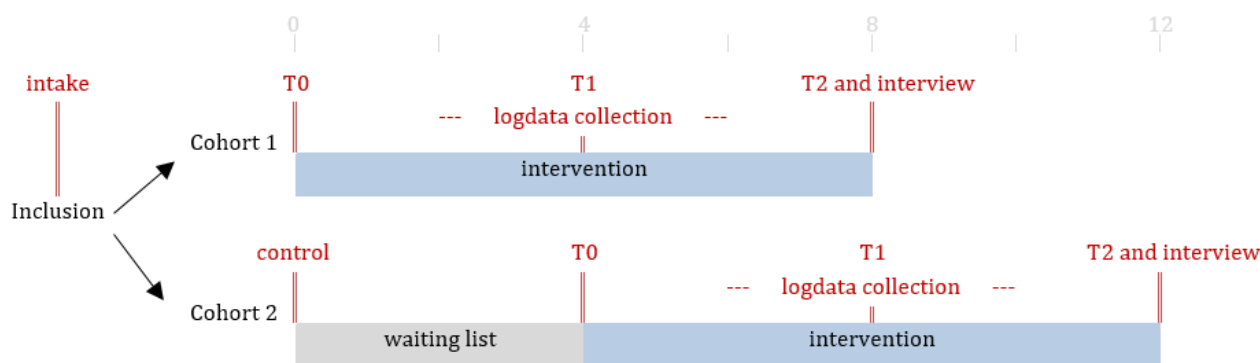
Our research questions focus on both use and health outcomes. The research questions related to use are as follows: (1) What factors affect the use of the ECA? (2) Does use affect the users’ relationship with the ECA? (3) What is the use of PACO over time? (4) How do users experience PACO use? We will test the CEU to answer research question (RQ) 1 and 2. Via data log analyses (RQ3) and interviews (RQ4) we aim to explain the findings related to the CEU. This way, we will triangulate results.

The research questions related to health effects are as follows: (1) To what extent does PACO reduce loneliness and improves eating behavior and, ultimately, QoL? (2) To what extent does PACO increase autonomy, competence, and relatedness? (3) How does PACO use affect the loneliness and eating behavior of older adults? We will test the CHE to answer RQ1. For RQ2 and RQ3, we will compare the effect of using PACO at different time points, including control.

## Methods

### Study Design

An unblinded randomized controlled trial will be carried out. At the time of study protocol submission, all preparations have been made to start recruitment. There will be 2 cohorts (Figure 3). Participants in the first cohort will receive the 8-week PACO app immediately. Participants in the second cohort will receive the PACO app after a 4-week waiting-list condition and serve as a control group. A combination of various data collection methods will be used for this study, including questionnaires (control, at intake, T0, T1, and T2), data log collection during the intervention period, and an optional interview afterward. The T0 questionnaire will mark the start of the intervention, T1 will be completed after 4 weeks of use, and T2 after 8 weeks of use (Figure 3).

**Figure 3.** Study design.

## Participants

We aim to include a total of 60 participants: 30 in cohort 1 and 30 in cohort 2. The number of participants is based on the 10-times rule, a widely used minimum-sample-size estimation method for partial least squares structural equation modeling (PLS-SEM) [32]. This method was discussed with a statistician. In addition, we considered the current practices in the field [12], the explorative nature of this study, and the staff available to provide support.

Participants will be considered eligible if they are aged 65 years or older, are not in paid employment, and live alone independently at home. These inclusion criteria fit a potential target audience of almost 1 million people [33]. In addition to these criteria, participants need to speak Dutch to use the app, should be able to use a tablet or computer by themselves, and should have a wireless internet connection at home, which is required for the app. The latter 2 criteria seem feasible, as 94.5% of all older Dutch adults aged 65-75 years have internet access at home, with 77% using the internet daily [34]. Apart from willingness to provide informed consent, there are no exclusion criteria.

## Recruitment

The project members will recruit participants via different routes. An email will be sent out to an existing online panel of older adults (*Ouderenpanel*). Flyers will be distributed in neighborhoods, community centers, sports canteens, and other settings frequently attended by older adults. Advertorials will be placed in local and community newspapers and on social media. Both the flyers and the advertorials will contain a short link to the PACO website with more information and the form to sign up. Lastly, participants will be encouraged to invite relatives.

## Procedure

Interested people can visit a website to view more information, or they can contact the researchers. People can choose to receive

the information letter and consent form by post ([Multimedia Appendix 1](#)) or view and complete the form online. After providing informed consent, participants will be invited to complete the intake questionnaire. In this questionnaire, they will be asked to report their demographics (gender, age, educational level, health conditions, risk of malnutrition [35], and eHealth literacy [36]), whether they own a device to use for the study, and their motivation to participate. A copy of the signed informed consent will be sent to all participants by mail. The researchers will mail people who do not return the informed consent by post to check whether something has gone wrong or they do not wish to participate (no explanation will be required).

After completing both the informed consent and the intake questionnaire, participants will be assigned a random 4-digit research number. To allocate participants to a cohort, they will be randomly assigned a digit, either 1 or 2, in a list generated by Excel (version 16.0.13426.20274; Microsoft). Participants will receive an email from author LK containing their research number, information on their allocated cohort, and a copy of the information letter and the signed informed consent.

Participants in cohort 2 will first be asked to complete the additional control questionnaire ([Table 1](#)) and will start the intervention period after 4 weeks. At the start of the intervention period, participants will receive an email with instructions for the onboarding process. The email will contain a video message from the researchers introducing themselves and the project, as well as a link to the freely available PACO website. Once participants have created an account, they will be asked to complete the T0 questionnaire, assessing the health parameters and relationship with the ECA. Participants will be phoned within 2 working days and asked whether they have any questions. If a participant does not wish to be called, this can be indicated by email. If a participant needs help, the researchers will offer to visit the participant. A logbook will be kept of all such contacts. If participants do not have a tablet or a computer, they will be given a tablet for the duration of the study.

**Table 1.** Metadata and factors measured via questionnaires, per study phase.

Metadata and factors	Questionnaires			
	Control	T0	T1	T2
<b>Metadata questionnaire</b>				
Total number of questions, n	46	56	65	88
Minutes to complete	10 -20	15-20	15-20	25-30
<b>Conceptual model explaining health effects</b>				
Eating behavior	✓	✓	✓	✓
Loneliness	✓	✓	✓	✓
Autonomy, competence, and relatedness	✓	✓	✓	✓
Quality of life	✓	✓	✓	✓
<b>Conceptual model explaining ECA<sup>a</sup> use</b>				
Relationship with ECA <sup>a</sup>		✓	✓	✓
Usability				✓
Enjoyment				✓
Aesthetics				✓
Privacy concerns				✓
Control				✓
Perceived usefulness				✓
<b>Other constructs</b>				
User experience			✓	
Willingness to pay				✓

<sup>a</sup>ECA: embodied conversational agent.

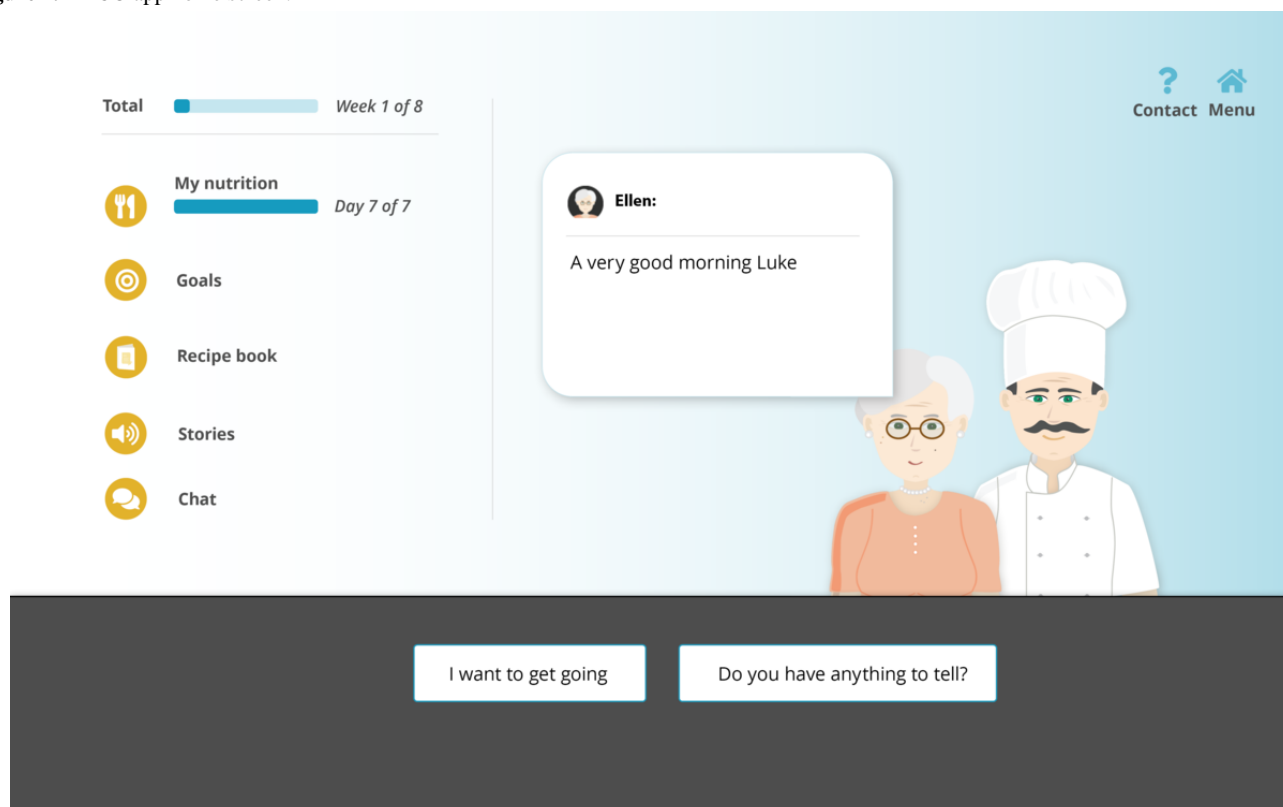
After 4 weeks of use, participants will receive an email with an invitation to complete the online T1 questionnaire, assessing all their health factors, their relationship with the ECA, and their user experience. After 8 weeks of use, participants will receive an email with an invitation to complete the T2 questionnaire, assessing all their health and use factors and willingness to pay. In addition, participants will be asked whether they are open to an interview lasting half an hour, in which the researcher will ask about their user experience.

At all stages of the study, participants will be able to contact the researchers by email or phone for any questions or problems. In the PACO app, there is a contact form. Depending on the participant's problem and preference, one of the researchers will email, phone, or visit the participant. If a participant has not interacted with PACO for 7 days, the participant will also be contacted and asked whether there are any problems.

## Intervention

### *PACO App*

PACO is a fully automated web-based eHealth app in which 2 ECAs engage in dialogue with older adults in order to motivate them to change their dietary behavior and decrease their loneliness (Figure 4 and Multimedia Appendix 2). The app consists of 5 modules, each one applying different BCTs (Table 2). During the onboarding process, the ECAs introduce themselves and explain the PACO program. There is a daily dialogue between either Herman (the cook, who provides nutritional advice) or Ellen (the peer, who provides social advice) and the user. Users are asked to use the food diary module for the first 7 days in order to increase their awareness of their eating behavior. All other modules become available when the food diary has been completed for 7 days or automatically after 14 days. During and after the 8-week program, the ECAs encourage users to continue the health behavior changes that they have implemented during the intervention in their daily lives.

**Figure 4.** PACO app home screen.**Table 2.** The modules of the PACO app.

Week	Module	Behavior change technique	SDT <sup>a</sup> component, target behavior	Rationale
1	Food diary	Self-monitoring	Autonomy, eating behavior	Users record what they have eaten, with whom, and how they appreciated the meal. There is an option to set reminders. When users know what they eat and drink, we aim to give them the feeling that they are able to change their behavior [37], leading to an actual change in eating behavior.
2-8	Goals	Action planning	Competence, eating behavior and loneliness	Users can choose from a list of social and eating goals. Via dialogue, Ellen explains the goal and provides tips. Users create a personal action plan and track their progress, with the option to set reminders. When users carry out their plans, we aim to improve their feelings of competence [31], leading to changes in eating behavior and feelings of loneliness.
1-8	Recipes	Tailoring and self-efficacy	Autonomy, eating behavior	Via dialogue, Herman helps users select a healthy and easy-to-prepare recipe (>280), based on users' dietary wishes and preferences. By assisting users in cooking their own meals in line with their preferences, we hope to increase feelings of autonomy via self-efficacy [38], leading to a change in eating behavior.
1-8	Stories	Social learning	Relatedness, loneliness	Users can listen to stories from other older adults about physical or virtual social activities they perform. Ellen can provide more information on the activity. When users learn from each other, we hope that they will feel more related to others and have fewer feelings of loneliness [39,40].
1-8	Chat	Social facilitation (peer support)	Relatedness, loneliness	Via WhatsApp groups, users can interact with one another. Ellen is also included and asks questions. When users interact with one another, we hope that they will experience increased feelings of relatedness and decreased feelings of loneliness [41,42].

<sup>a</sup>SDT: Self-determination Theory.

### Development of the Intervention

The PACO development process was based on the first 3 steps of the Center for eHealth Research and Disease Management (CeHRs) Roadmap [43]: the contextual inquiry, the value

specification, and the design phase. The contextual inquiry phase consisted of 3 parts. First, the current practices in designing and evaluating ECAs for coaching people in the health context were identified via a scoping review [12]. Second, factors contributing to healthy living and healthy and unhealthy



eating among Dutch community-dwelling older adults were identified via a 7-day diary and via multiple focus groups [44]. Third, an initial stakeholder analysis was carried out, and key stakeholders were identified [45].

During the value specification phase, healthy eating tips were explored via 2 additional focus group sessions [44]. The preferred approach, source, and tone of voice for healthy eating tips were discussed. In addition to the focus group, interviews were held with key stakeholders in order to identify their requirements [45].

The design phase of the PACO app was based on the previous 2 phases. In addition, the SDT [29] was used as a foundation. Self-monitoring, action planning, tailoring, self-efficacy, social learning, and social facilitation were selected as BCTs. In the design phase, first, 3 ECAs were created, each with a different role. In order to ascertain their persuasiveness, an online experiment using various mockups was carried out. Via a focus group, the findings were discussed, and the layout of the 2

preferred ECAs was improved. All input was used to create a first version of the app, which was tested via a usability study [46]. All usability issues were resolved, leading to the final app.

### Data Collection

The main study parameters include use, eating behavior, and loneliness. Use will be assessed via data logs, which will be collected by the PACO app. More specifically, data logs contain the user ID, timestamp, dialogue, and ECA (either Ellen or Herman). In addition, data logs contain the number of goals achieved, the diary input, and the chat history. Eating behavior will be self-assessed by 3 open questions, based on a 24-hour recall format. The questions include the following: (1) Did you eat fruit yesterday? If so, what kinds of fruit, what time, and how many grams per piece? (2) Did you eat vegetables yesterday? If so, what kinds of vegetables, what time, and how many grams per piece? (3) Did you drink yesterday? If so, what kinds of drink, what time, and how many glasses, cups, or milliliters? Loneliness will be self-assessed via a questionnaire (Table 3).

**Table 3.** Details of the questionnaires.

Factor	Questionnaire	Items, n	Scale	Modifications
Loneliness	De Jong Gierveld Loneliness Scale [47]	6	1-5	None
Autonomy, competence, and relatedness	Basic Psychological Need Satisfaction and Frustration Scales [48-50]	24	1-5	None
QoL <sup>a</sup>	Brief Older People's Quality of Life [51]	13	1-5	Translated to Dutch
Relationship with ECA <sup>b</sup>	Rapport Scale [52-54]	10	1-5	Translated to Dutch; 'virtual coach' instead of 'coordinator'
Usability	System Usability Scale [55]	10	1-5	Translated to Dutch
Enjoyment	Affect Scale [56]	4	1-5	Translated to Dutch
Aesthetics	Classic Aesthetics [21]	5	1-7	Translated to Dutch
Privacy concerns	Concern for Privacy Scale [24]	4	1-7	Translated to Dutch
Control	Active Control [57]	4	1-7	Translated to Dutch; 'PACO' instead of 'website'
Perceived usefulness	Perceived Usefulness Scale [28,58]	3	1-5	Translated to Dutch; 'PACO' instead of 'the robot'

<sup>a</sup>QoL: quality of life.

<sup>b</sup>ECA: embodied conversational agent.

The secondary study parameters include self-determination (autonomy, competence, relatedness), QoL, relationship with ECA, usability, enjoyment, aesthetics, privacy concerns, control, and perceived usefulness. All these parameters will be measured via validated, self-assessed, online questionnaires.

In addition, 2 other parameters include willingness to pay and user experience. Both parameters will be assessed via self-compiled questionnaires. Participants will be asked whether they are willing to pay for PACO (*yes/no*) and the amount they are willing to pay for PACO for 3 months [€0, €5 (USD \$6.09), €10 (USD \$12.18), or €20 (USD \$24.35) per month]. Via a questionnaire, participants will be asked 9 open-ended questions about their user experience in general (eg, How did you experience using PACO the last 4 weeks?) and per module (eg, Which modules did you perceive as useful, and why?). In addition, participants will be asked why they kept using PACO, why they stopped using PACO, and whether they wish to share

something else. Via an interview of approximately 30 minutes, participants will be asked about their general experience, the modules, how and where they used PACO, experienced behavior change, and the two coaches. Via these questions, we aim to gain a more fine-grained understanding of users' experiences and triangulate our quantitative results.

### Data Analysis

Descriptive statistics will be used for participant demographics, data logs, and willingness-to-pay data. Data logs will be used to determine the frequency of login, time spent on each module, time spent in total, time of use, and time of dropout. If a participant has not interacted with PACO for 14 consecutive days, they will be treated as a dropout and omitted from further analysis. The within-subject *t* test will be used to compare effects between control, T0, T1, and T2. PLS-SEM will be used in 2 phases per model to test the conceptual models. In phase 1, the measurement model will be validated by testing the constructs

separately to determine internal validity [using structural equation modeling (SEM)-oriented criteria and a traditional Cronbach alpha]. In addition, it will be determined whether there is multicollinearity. If there is an acceptable measurement model, phase 2 will be carried out. The causal model will be tested and, if necessary, optimized. A conservative approach will be adopted whereby the theoretical model will be adjusted only if this results in a large improvement in the model. The quality of the causal model will be determined on the basis of PLS-SEM specific goodness-of-fit indices. All analyses will be performed in SPSS (version 24; IBM Corp) and SmartPLS (version 3; SmartPLS GmbH).

Audio recordings of the interviews will be transcribed until data saturation is reached. The transcripts of, and answers to, the open user-experience questions will be uploaded in ATLAS.ti qualitative data analysis software (version 8.4; ATLAS.ti Scientific Software Development GmbH). Analysis will be guided by a thematic analysis approach [59], combining a deductive and an inductive approach. The protocol for the focus group will be used to generate deductive codes. An initial list of inductive codes will be generated by LK and supplemented independently by another researcher. Differences will be discussed, leading to a final and agreed upon codebook. Each transcript will be coded by LK and another project member. Differences will be discussed again, leading to a final coded transcript.

### Ethical Considerations

The study has been approved by the medical ethical committee of Wageningen University (number NL73121.081.20) and has been registered at ClinicalTrials.gov before the enrolment of participants (identifier NCT04510883). As participants are not exposed to any risks, a data safety monitoring board will not be used during the study. Participants will invest time in this study; they have to complete multiple surveys and use the PACO app for 8 weeks. We believe that this duration and data collection are needed to gain a fine-grained understanding of the app's use, relationship development, and the process of health behavior change. The main benefit to participants is that they gain insight into their health behavior via the PACO app. In addition, in prior studies, we found that participants highly appreciate the attention given to them via such studies.

Prior to the study, people will receive an information letter. They will have 2 weeks of consideration time and can contact the researcher (LK) or an independent expert with any questions. Participants can leave the study at any time for any reason if they wish to, without any consequences; participants will not be replaced.

All collected data will be kept in secure online databases that are password-protected, with access limited to the study team.

### Results

As of July 2020, we have begun recruiting participants.

## Discussion

### Overview

ECAs seem to be a promising means of addressing health behavior change in general, including among community-dwelling older adults. In this paper, we have described the protocol for an unblinded randomized controlled trial among older adults, with the goal of understanding the use and health effects of ECAs that provide nutritional advice. The intervention at the center of this evaluation is called PACO and provides 2 ECAs, one that offers nutritional advice (a cook) and one that offers social advice (a peer). The intervention was developed via a human-centered and stakeholder-inclusive design approach, incorporating theory and various BCTs. At the time of writing, evidence on the effectiveness and underlying working mechanisms of ECA use for health purposes remains inconclusive [12]. In order to explain the effects (or the absence thereof), we developed 2 conceptual models. The first model explains the use of an ECA intervention, and the other explains the mechanisms behind the observed change in eating behavior and loneliness after using an ECA intervention. Via the randomized controlled trial, both models will be tested, and use, user experience, and potential health effects will be assessed. In this way, we aim to generate insight into the effect and design of ECAs that go beyond the PACO service and that serve the eHealth community in general [60].

### Limitations

Like any evaluation plan, ours has some limitations. The first limitation relates to our recruitment strategy. We expect to include more women than men. In previous studies [44], we found women to be more interested in lifestyle-related studies, resulting in focus group sessions with an overrepresentation of women. However, given that there are more single women than men in older age groups in the Netherlands [61], a majority of women is a realistic reflection of society. Another aspect of our recruitment strategy is that participants are encouraged to invite relatives, and this might induce a risk of contamination. If a closely related person joins the study, we will monitor this meticulously to see whether contamination takes place, and whether and how it influences our results.

Second, use of the ECA intervention might be influenced by the study itself. Participants know that they are expected to complete multiple questionnaires and will be called by phone if they do not use the app for 7 days. Thus, participants might be inclined to use the app more often than if the intervention were applied outside a randomized controlled trial setting. However, in order to understand the determinants affecting use and health effects, the questionnaires are essential, and a phone call is needed to ensure that there are no technical issues influencing use.

### Conclusion

By unraveling the mechanisms behind the use of a web-based service that offers 2 ECAs, we hope to gain a fine-grained understanding of both the effectiveness and the use of ECAs. These insights will boost the design, the use, and the usefulness of ECAs in health behavior change.

## Acknowledgments

This protocol is part of the PACO project, funded by The Netherlands Association for Health Research and Development (ZonMw): ZonMw Create Health program grant number 40-44300-98-110. The PACO project is a collaboration between Wageningen University & Research, Roessingh Research and Development, the National Foundation for the Elderly, and Waag.

## Conflicts of Interest

None declared.

### Multimedia Appendix 1

Information letter and informed consent.

[\[PDF File \(Adobe PDF File\), 760 KB - resprot\\_v10i1e22186\\_app1.pdf\]](#)

### Multimedia Appendix 2

Peer-review report.

[\[PDF File \(Adobe PDF File\), 380 KB - resprot\\_v10i1e22186\\_app2.pdf\]](#)

### Multimedia Appendix 3

CONSORT-eHEALTH checklist (V1.6.1).

[\[PDF File \(Adobe PDF File\), 1480 KB - resprot\\_v10i1e22186\\_app3.pdf\]](#)

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## Abbreviations

- BCT:** behavior change technique
- ECA:** embodied conversational agent
- CEU:** conceptual model explaining ECA use
- CHE:** conceptual model explaining health effects
- PLS-SEM:** partial least squares structural equation modeling
- QoL:** quality of life
- RQ:** research question

**SDT:** Self-determination Theory  
**SEM:** structural equation modeling

*Edited by G Eysenbach; submitted 06.07.20; peer-reviewed by A Lazard, A Coe; comments to author 26.08.20; revised version received 20.10.20; accepted 17.11.20; published 06.01.21.*

*Please cite as:*

*Kramer LL, Mulder BC, van Velsen L, de Vet E*

*Use and Effect of Web-Based Embodied Conversational Agents for Improving Eating Behavior and Decreasing Loneliness Among Community-Dwelling Older Adults: Protocol for a Randomized Controlled Trial*

*JMIR Res Protoc 2021;10(1):e22186*

*URL: <https://www.researchprotocols.org/2021/1/e22186>*

*doi: [10.2196/22186](https://doi.org/10.2196/22186)*

*PMID: [33404513](https://pubmed.ncbi.nlm.nih.gov/33404513/)*

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Protocol

# A Live Video Mind-Body Treatment to Prevent Persistent Symptoms Following Mild Traumatic Brain Injury: Protocol for a Mixed Methods Study

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## Abstract

**Background:** Every year, approximately 42 million people sustain a mild traumatic brain injury (mTBI, also known as concussion), with particularly high rates among college-aged individuals. A substantial proportion of these people (44%-64%) develop persistent symptoms that are challenging to treat, costly, and associated with significant disability. Anxiety has emerged as a risk factor for progression from acute to persistent mTBI symptoms.

**Objective:** This study aims to develop, adapt, and establish the feasibility of the *Toolkit for Optimal Recovery after Concussions* (TOR-C), an innovative mind-body program aimed at preventing persistent symptoms among young adults with mTBI and comorbid anxiety. Here, we describe the proposed study design, methodology, measurement, and treatment manuals.

**Methods:** In phase 1, we will conduct individual, live video qualitative interviews (up to n=20) with college-aged individuals with mTBI and comorbid anxiety to inform adaptation of the intervention and study procedures. In phase 2, an open pilot of the live video TOR-C (n=5) with exit interviews will be conducted to explore the initial feasibility, acceptability, and credibility of the program and to refine the study procedures. Phase 3 will involve conducting a feasibility randomized controlled trial (N=50) of the TOR-C versus a health education control (Health Enhancement for Concussions; HE-C), both delivered via live video, to establish feasibility of recruitment procedures (screening, eligibility, and enrollment) and data collection; feasibility, credibility, and acceptability of the live video TOR-C and HE-C (adherence, retention, fidelity, and satisfaction) following prespecified benchmarks; and a signal of improvement in outcomes.

**Results:** Phase 1 of the study has been approved by the Massachusetts General Hospital Institutional Review Board. Study completion is anticipated by early 2025.

**Conclusions:** We will develop and test the first mind-body intervention focused on prevention of persistent symptoms following mTBI in young adults with comorbid anxiety problems. This will allow us to establish feasibility markers in postconcussive symptoms, anxiety, disability, and fear avoidance to inform a future efficacy trial of the TOR-C versus HE-C.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/25746

(*JMIR Res Protoc* 2021;10(1):e25746) doi:[10.2196/25746](https://doi.org/10.2196/25746)

## KEYWORDS

mild traumatic brain injury; anxiety; mixed methods; intervention development

## Introduction

### Background

Every year, approximately 42 million people worldwide sustain a mild traumatic brain injury (mTBI), also known as concussion [1], with particularly high rates among college-aged individuals. Nearly all patients report physical (eg, headache), emotional (eg, irritability), behavioral (eg, insomnia), or cognitive (eg, difficulty concentrating) symptoms in the week following an mTBI [2]. Although many patients make a full recovery, a substantial proportion of patients experience persistent symptoms that can become intractable over time. Indeed, at 3 months and 1 year postinjury, up to 64% [3] and 44% [4] of patients with mTBI, respectively, continue to report 3 or more persistent symptoms [5]. Spontaneous symptom improvement is unlikely beyond this period [6]. It is therefore critical to provide early interventions to prevent symptom persistence.

Unlike moderate-to-severe traumatic brain injury (TBI), the prognosis of mTBI is not well correlated with injury severity or clinical findings [7]. Rather, symptom persistence after mTBI reflects a complex mind-body interaction, with anxiety playing a prominent role [7,8]. Anxiety may contribute to symptom persistence after mTBI by mimicking or amplifying symptoms, increasing hypervigilance and misattributions, and motivating activity avoidance [9]. These mechanisms are consistent with the fear avoidance theoretical model, which explains the transition from acute to chronic pain [10], and they provide a useful conceptualization for how anxiety causes or amplifies mTBI symptoms and leads to symptom persistence. We have previously shown that both catastrophizing and activity avoidance mediate the relationship between anxiety and postconcussion symptoms in patients with mTBI [11], supporting the applicability of the fear avoidance model to patients with mTBI.

For the substantial proportion of patients with mTBI and anxiety, current approaches are inadequate to prevent symptom persistence and disability. Accumulating evidence suggests that re-engagement in activities of daily living is healthy and promotes recovery, whereas rest and avoidance induces or maintains nonspecific symptoms and perpetuates activity avoidance [12,13]. For patients with anxiety, following recommendations for re-engagement is challenging because of maladaptive beliefs that rest is beneficial and activity is dangerous [14,15] as well as physiological manifestations of anxiety that mimic postconcussion symptoms [16]. As such, patients with anxiety and mTBI are at risk for decreased functioning across occupational, social, and recreational contexts

and for experiencing persistent symptoms [17]. To date, there are no evidence-based psychosocial interventions for patients with recent mTBI (acute and subacute periods, up to 3 months postinjury [18]) and anxiety, which are focused on breaking the cycle of avoidance and preventing symptom persistence. Thus, it is critical to develop a prevention intervention that is feasible, accepted, and efficacious.

Mind-body interventions effectively treat both individual symptoms common to mTBI (eg, headache [19], insomnia [20], and fatigue [19]) and anxiety [21]. Furthermore, they do not carry stigma that is often associated with traditional mental health referrals [22] and are well tolerated and popular among patients with neurological conditions [23]. Mind-body interventions can also be effectively delivered via live videos [24,25]. Live video represents a promising avenue for delivering preventative care for individuals with acute mTBI and anxiety, who face many barriers to in-person visits, such as symptom burden, time and cost associated with travel, decreased flexibility in scheduling, and lower access to trained providers relative to live video delivery [26]. Importantly, live video delivery enables safe participation while maintaining social distancing, in line with guidelines issued by the Centers for Disease Control and Prevention [27] and the World Health Organization [28] following the COVID-19 pandemic.

College-aged adults with mTBI and comorbid anxiety are in high need of a live video mind-body intervention for several reasons. First, mTBIs are particularly common among this population [29-31]. Second, this age group has the highest rates of anxiety symptoms (approximately 40%), even in the absence of an injury [32]. Finally, college-aged individuals prefer live video conferencing over in-person interventions [33].

### Objectives

Our team has developed a brief live video mind-body treatment, the *Toolkit for Optimal Recovery after Injury (TOR)* [34], to prevent chronic pain in people with orthopedic injuries who have high pain-related anxiety or catastrophic thinking about pain. In this study, we propose to adapt this program for the unique needs of college-aged individuals with recent mTBI (ie, in the acute and subacute stages of recovery [18]) and anxiety (*Toolkit for Optimal Recovery after Concussion; TOR-C*), and iteratively optimize it using mixed methods. Our study has 3 phases: (1) qualitative live video interviews with college-aged individuals with recent mTBIs and anxiety (n=20) to identify their treatment needs and preferences and develop the live video TOR-C and study procedures; (2) an open pilot study (n=5) with exit interviews and pretreatment and posttreatment assessments to explore the initial feasibility, acceptability, and



credibility of the live video TOR-C and study procedures; and (3) a pilot feasibility randomized controlled trial (RCT) of the TOR-C versus Health Enhancement for Concussions (HE-C), both delivered via live video (N=50), to establish the feasibility of recruitment procedures (screening, eligibility, and enrollment) and data collection as well as the feasibility, credibility, and acceptability of the live video TOR-C and education control condition (adherence, retention, fidelity, and satisfaction), following prespecified benchmarks. We hypothesize that the final version of the TOR-C will be feasible, accepted by patients, and associated with within-group improvements in postconcussive symptoms, anxiety, depression, disability, mindfulness, behavioral responses to illness, pain catastrophizing, and fear avoidance. This paper describes the study protocol.

## Methods

### Study Design

Our study design and methodology are informed by the Obesity Related Behavioral Intervention Trials (ORBIT) [35] and National Center for Complementary and Integrative Health (NCCIH) [36] models of intervention development, which emphasize the importance of iteratively optimizing interventions to establish feasibility markers before efficacy testing. Our primary outcomes will be feasibility, credibility, and acceptability markers to support a future efficacy RCT. Secondary outcomes are postconcussive symptoms, anxiety, disability, mindfulness, pain catastrophizing, behavioral responses to illness, and fear avoidance. See [Multimedia Appendix 1](#) for peer review of this research proposal by the National Institutes of Health.

### Inclusion and Exclusion Criteria

We plan to include participants aged 18 to 24 years who have been diagnosed as having uncomplicated mTBI (ie, without

intracranial abnormality) [37] 3 to 6 weeks earlier, score >8 on the Generalized Anxiety Disorder 7-Item Scale (GAD-7 scale; indicating at least mild-to-moderately elevated anxiety) [38], are fluent in English, and can participate in a live video interview (phase 1) or intervention (phase 2 and 3). Exclusion criteria include participation in mind-body or cognitive-behavioral therapy in the past 3 months, practice of mindfulness techniques >45 minutes per week on average in the past 3 months, current or previous history of complicated mTBI or moderate or severe TBI, change in psychotropic medications in the past 3 months, psychosis, bipolar disorder, active substance abuse or dependence, or pregnancy. As this is a feasibility study, we expect that these criteria may change over the course of the 3 phases to maximize feasibility markers.

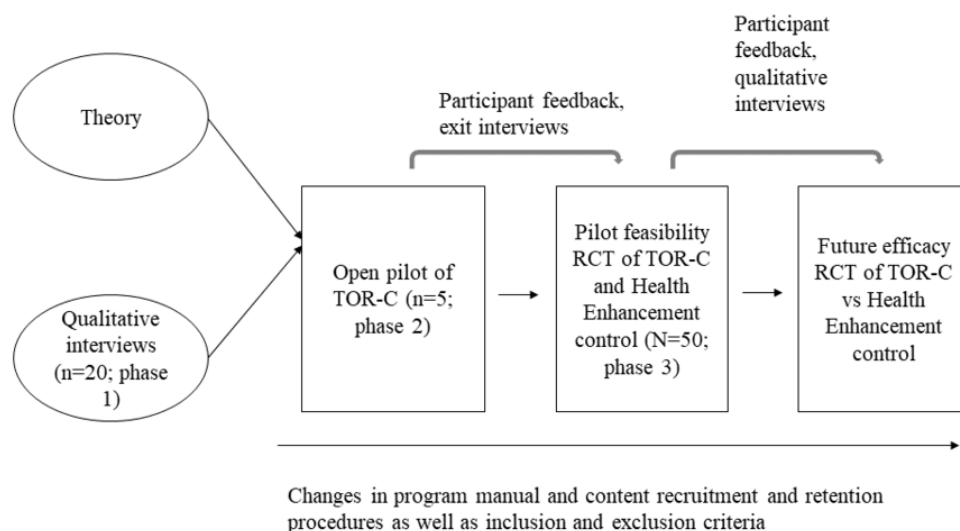
### Recruitment and Sampling

We plan to use the same recruitment procedure and eligibility criteria for all phases of the study. Some modifications may occur based on qualitative feedback from participants and lessons learned. Patients will be enrolled primarily from the sports concussion clinic at Massachusetts General Hospital. Medical staff at the concussion clinic will refer patients with uncomplicated mTBI, that is, those who show no structural abnormality [37,39]. Neuroimaging is not a requirement for study entry, and clinical neuroimaging is relatively uncommon for patients attending the concussion clinic. In each phase, the medical team will confirm diagnoses and clear patients for participation in the study. A research assistant will screen potential participants and obtain informed consent. During the restrictions of COVID-19, all recruitment procedures will be performed remotely (eg, screening conducted by telephone, informed consent forms signed and sent electronically).

### Procedure

[Figure 1](#) depicts the iterative development and testing of TOR-C.

**Figure 1.** Phases of development of the Toolkit for Optimal Recovery after Concussion. RCT: randomized controlled trial; TOR-C: Toolkit for Optimal Recovery after Concussion.



**Phase 1: Development Phase**

We will first develop a semistructured qualitative interview script to assess the specific treatment needs and preferences of young adults with mTBI. We will practice and pilot the semistructured interview over a secure video platform with 2 to 3 patients. We will subsequently administer the refined semistructured qualitative interview to 20 individuals with mTBIs to gather feedback on the intervention components and gauge treatment needs, expectations, and barriers. Specifically, the interview domains will include the following: (1) case-based scenarios of perceived effects of the injury and anxiety on function; (2) areas of need for skills training; (3) impact of the injury on activity, sports, school, work, and relationships; (4) best strategies for recruitment and retention for patients who have sustained concussions; (5) difficult situations or challenges experienced by college-aged individuals recovering from

concussions; (6) barriers to participation and adherence, including light sensitivity and comfort using screens, and strategies to address this (eg, night setting, education); and (7) specific topics they would like to learn about. Participants will be provided information about the proposed content of the adapted program (TOR-C; [Table 1](#)) to obtain their feedback on each intervention component. Skills will be modeled to ensure an accurate understanding.

Eligible patients who agree to participate and provide written informed consent will be assisted in downloading and installing the video software (Zoom). All qualitative interviews will be audio-recorded, transcribed, organized, and analyzed using the NVivo 12 qualitative statistical package (QSR International; see the *Data Analyses* section). We will use the qualitative data obtained in phase 1 to develop the TOR-C and treatment manual.

**Table 1.** Proposed adaptations to the Toolkit for Optimal Recovery after Concussion intervention.

Original Toolkit (TOR) <sup>a</sup>	Adapted content for concussion (TOR-C) <sup>b</sup>
<b>Session 1</b>	
Discuss rationale for targeting chronic pain; correct misconceptions about pain	Discuss rationale for targeting symptoms of concussion; correct misconceptions about recovery trajectory
Learn physical, emotional, and cognitive factors that can speed or slow recovery after orthopedic injury; disability spiral for chronic pain	Learn physical (eg, sympathetic nervous system), emotional, and cognitive (negative automatic thoughts) factors that are conducive to symptom persistence after concussion. Discuss the overlap in symptom presentation between anxiety and concussion. Discuss the specific role of anxiety in persistence of symptoms after acute concussion (concussion specific disability spiral) and how skills can help break this spiral. Introduce avoidance and catastrophizing as key modifiable variables in the disability spiral. Discuss how TOR-C skills directly address these to facilitate recovery. Compare and contrast the disability spiral with the recovery spiral, with catastrophizing and avoidance as key
Demonstrate relaxation strategies (diaphragmatic breathing and body scan) and their relevance to chronic pain	Provide education about the parasympathetic nervous system and relaxation; demonstrate relaxation strategies (diaphragmatic breathing, body scan) and their relevance to symptoms of concussion
Set homework: practice relaxation strategies using recordings (20 min)	Set homework: practice relaxation strategies using recordings (20 min)
<b>Session 2</b>	
Practice diaphragmatic breathing	Practice diaphragmatic breathing
Review homework; barriers to practice	Review homework; barriers to practice
Discuss bio-psychosocial model and mind-body links as they relate to pain	Discuss bio-psychosocial model and mind-body links as they relate to concussions and anxiety
Identify thoughts-feelings-behaviors-sensations related to pain; mindfulness skills for habituating to pain sensations	Identify thoughts-feelings-behaviors-sensations related to concussion and anxiety symptoms; mindfulness skills for observing thoughts-feelings-behaviors nonjudgmentally to habituate to symptoms
Identify negative or unhelpful thoughts about chronic pain; learn decision tree for negative or unhelpful thoughts regarding chronic pain	Identify negative or unhelpful thoughts about concussion and anxiety symptoms; general negative thoughts around catastrophizing and avoidance; learn decision tree for coping with negative or unhelpful thoughts regarding symptoms
Provide reframing strategies; assist patients in reframing negative or unhelpful thoughts about chronic pain symptoms	Provide reframing strategies; assist patients in reframing negative and unhelpful thoughts about concussion symptoms
Set homework: practice relaxation and mindfulness daily (new recording), complete decision tree and reframing exercises	Set homework: practice relaxation and mindfulness daily (new recording), complete decision tree and reframing exercises
<b>Session 3</b>	
Practice diaphragmatic breathing	Practice diaphragmatic breathing
Review previous material and homework; problem-solve barriers to practice	Review previous material and homework; problem-solve barriers to practice
Assist patients in identifying a problem related to chronic pain; learn and apply problem-solving skills	Assist patients in identifying a problem related to concussion symptoms; learn problem-solving skills
Learn acceptance strategies for chronic pain; assist patients in identifying when to use reframing versus problem solving versus acceptance	Learn acceptance strategies for concussion; assist patients in identifying when to use reframing versus problem solving versus acceptance
Provide rationale for return to activity via activity pacing; assist patients in setting activity goals; assist patients in applying acceptance, reframing, or problem-solving skills to achieve pacing goals	Provide rationale for return to activity via activity pacing; assist patients in setting activity goals; assist patients in applying acceptance, reframing, or problem-solving skills to achieve activity pacing goals
Set homework: practice relaxation strategies and mindfulness daily, complete decision tree exercise with options for problem solving, acceptance, and reframing; follow activity pacing protocol	Set homework: practice relaxation strategies and mindfulness daily, complete decision tree exercise with options for problem solving, acceptance, and reframing; follow activity pacing protocol
<b>Session 4</b>	
Practice diaphragmatic breathing	Practice diaphragmatic breathing

Original Toolkit (TOR) <sup>a</sup>	Adapted content for concussion (TOR-C) <sup>b</sup>
Review previous material and homework; problem-solve barriers to practice	Review previous material and homework; problem-solve barriers to practice
Review all TOR skills; and identify which skills are being used and helpful, how helpful they are, and how they can be implemented in the future to help cope with chronic pain.	Review all TOR-C skills and identify which skills are being used, how helpful they are, and how they can be implemented in the future to help cope with concussion symptoms
Interactive quiz to identify improvements, useful skills, and a plan for continued coping; continue practicing relaxation skills and mindfulness daily for 20 minutes using recordings	Interactive quiz to identify improvements patient has made, skills that are being used, skills the patient would like to continue to work on and a plan for continued coping; continue practicing relaxation skills and mindfulness daily for 20 minutes using recordings

<sup>a</sup>TOR: Toolkit for Optimal Recovery.

<sup>b</sup>TOR-C: Toolkit for Optimal Recovery after Concussion.

### Phase 2: Open Pilot of TOR-C and Exit Interviews

We will enroll and treat up to 5 patients and conduct live video qualitative exit interviews at the end of the treatment to gather detailed feedback on the intervention components, applicability of the study measures, general protocol issues, and perceptions about live video intervention delivery. Participants will complete baseline, postintervention, and 3-month postintervention follow-up questionnaires as well as weekly home practice. We will thus be able to explore the feasibility and acceptability of the TOR-C, study measures and procedures, adherence to sessions and home practice, and acceptability of the live video in this population. Each session of the TOR-C will last 45 minutes. Exit interviews will last 30 minutes and be audio-recorded and transcribed. The interviews will follow procedures similar to those described in phase 1 (eg, delivery via a semistructured interview script, qualitative analysis using NVivo 12) and be used to further refine the study manual and procedures as well as finalize the TOR-C before the pilot RCT. The analysis plan is described in the *Data Analyses* section.

### Phase 3: Feasibility RCT

After completing baseline questionnaires, eligible patients will be randomized via permuted blocks using a statistician-developed sequence to either the experimental (refined TOR-C) or control (HE-C) program in a 1:1 ratio. Participants will be blinded to intervention versus control groups. They will then be scheduled by a research assistant for their first video session. They will complete postintervention assessments after the 4-week intervention as well as at the 3-month follow-up. Both interventions will be delivered by the same mind-body clinician.

The treatment fidelity process for the RCT will follow the National Institutes of Health recommendations [40] and our previously successful clinical adherence protocol [41]. The clinicians will complete fidelity checklists after each session for both intervention and control groups and receive weekly supervision to ensure protocol adherence. To evaluate protocol fidelity for both the intervention and control, a random sample (10%) of the audio-recorded sessions will be coded by an independent coder.

### Live Video Delivery and Special Considerations for Patients With mTBI

The qualitative interview, open pilot, exit interviews, and feasibility RCT will all be delivered via a Health Insurance Portability and Accountability Act–approved video software, and all communication with participants and study staff will be performed remotely. On the basis of our previous work as well as prior research with this population and survey information from the concussion clinic at Massachusetts General Hospital [33], we anticipate that this live video format will be acceptable and well received by patients. However, we will specifically assess patients' perceptions and preferences for live video in the qualitative interview (phase 1) and exit interviews following the open pilot (phase 2). Participants will be emailed a link to install the video software after enrollment. A research assistant will conduct test calls with participants and be available to assist them with any technical difficulties or challenges that they may experience during the interviews, open pilot, or feasibility RCT. We will use procedures established in prior virtual mind-body studies [41,42].

As some patients with mTBI experience light sensitivity [43], we will assess patients' perceptions of live video delivery in phases 1 and 2. However, we do not expect this to be a barrier to live video delivery, as evidence from screen-based programs indicates that they are highly feasible and accepted by patients with mTBI, with no adverse light sensitivity issues reported [44-47]. We will consider adding educational information on light sensitivity to session 1 of the intervention, offering participants the option to use the *night setting* as a comfort measure.

### Program Structure and Modification

#### TOR-C Intervention

The original Toolkit [34] includes 4 manualized 45-min-long weekly sessions that address mind-body skills, including eliciting the relaxation response (eg, body scan, deep breathing, mindfulness), cognitive-behavioral strategies (eg, reframing), acceptance and commitment skills (eg, acceptance), and skills for returning to activity (eg, goal setting, activity pacing). [Table 1](#) presents specific adaptations that we propose to make to each module for patients with mTBI and anxiety. These proposed adaptations will inform the qualitative interviews (phase 1), and



additional refinements to the intervention will be made based on the results of our qualitative assessments.

### **HE-C (Control)**

The HE-C will be adapted from the Health Enhancement Program [48], a manualized intervention that has been successfully used in prior live video studies [49,50]. It includes 4 modules that provide educational information on the relationship between anxiety and mTBI (session 1), return to activity (session 2), roles of nutrition and sleep (session 3), and health care self-management, including access to mental health services (session 4). This control condition will be dose-, attention-, and time-matched to the TOR-C in terms of session content and home practice. Specifically, participants in HE-C will be assigned daily readings [48] for the same amount of time as those in the intervention. Participants in the TOR-C will receive HE-C information as electronic handouts. Participants in both groups will have the option to opt in to receive text messages through EZ texting [51], a communication platform, which will remind them of dates and times for scheduled sessions to maximize attendance. Our team is using EZ texting successfully in projects with other medical populations [52,53].

### **Assessments**

In phases 2 and 3, patients will complete the following battery of reliable and valid questionnaires on the internet via Research Electronic Data Capture (REDCap), a secure web-based portal at baseline, postintervention (ie, after completing the 4-week active or control intervention), and 3-month follow-up.

#### **Postconcussive Symptoms**

This will be measured using the *Post-Concussion Symptom Scale* [54], a 22-item questionnaire measuring perceived presence and severity of concussion symptoms (eg, headache, nausea, balance problems, fatigue irritability, nervousness) on a 0-6 scale. Higher scores represent worse symptoms.

#### **Anxiety and Depression**

The GAD-7 [38] is a 7-item questionnaire measuring anxiety symptoms within the past 2 weeks on a scale of 0 to 3 and will be used to ensure participants meet the criteria for anxiety symptoms. The *Hospital Anxiety and Depression Scale* [55] is a 14-item questionnaire assessing anxiety and depression in the previous week on a scale of 0 to 3 and will be used to assess changes in anxiety symptoms following the intervention and at follow-up. Higher scores represent higher anxiety.

#### **Disability**

This will be measured using the World Health Organization Disability Assessment Schedule (WHODAS) 2.0 for mTBI [56,57], a 12-item questionnaire assessing functional difficulties in various life domains (eg, participation barriers, physical activity limitations, and self-care limitations) on a scale of 0 to 4. Higher scores represent lower physical function.

#### **Fear Avoidance**

This will be measured via the *Fear Avoidance Behavior after Traumatic Brain Injury Questionnaire* [58], a 16-item questionnaire assessing beliefs about how work and physical activities affect mTBI symptoms, and whether they should be

avoided, on a scale of 0 to 3. Higher scores represent higher fear avoidance.

#### **Pain Catastrophizing**

This will be measured using the *Pain Catastrophizing Scale* [59], a 13-item questionnaire assessing one's tendency to focus on pain-related thoughts and feel helpless and hopeless due to pain on a scale of 0 to 4. Higher scores indicate higher pain catastrophizing.

#### **Mindfulness**

This will be measured via the Cognitive and Affective Mindfulness Scale-Revised, a 12-item questionnaire assessing one's ability to pay attention to the present moment in a nonjudgmental manner [60], on a scale of 1 to 4. Higher scores represent higher self-reported mindfulness.

#### **Behavioral Response to Illness**

This will be measured using the *limiting behavior* (7 items) subscale of the Behavioral Response to Illness Questionnaire [61], assessing the frequency in which participants are inactive as well as the *all or nothing behavior* (6 items) subscale, which captures one's tendency to overexert themselves. Both subscales are rated on a scale of 0 to 4, with higher scores indicating more limiting and all or nothing behavior.

#### **Treatment Satisfaction (Postintervention Only)**

This will be assessed using the *Client Satisfaction Questionnaire* [62], a 3-item questionnaire assessing the degree to which the program met the participants' needs and their satisfaction from it, on a scale of 1 to 4. Higher scores represent higher satisfaction.

#### **Treatment Credibility (After Randomization Only)**

This will be assessed using the *Credibility and Expectancy Questionnaire* [63], a 6-item questionnaire that assesses how believable, convincing, and logical patients perceive the treatment to be and the degree to which they expect to improve. Some items are scored on a scale of 1 to 9, and others are scored on an 11-point 0%-100% scale. Higher scores represent higher credibility and expectancy.

#### **Other Measures**

We will additionally collect baseline data about other factors that may influence recovery and mTBI symptom persistence, such as smoking, alcohol consumption, time since injury, and posttraumatic headache. To minimize patient burden, these data will be assessed using 1 to 2 self-report questions (eg, "how many drinks do you consume a week on average?") rather than full questionnaires. Additional information on medical history will be collected directly from patients' electronic medical records. All these data, however, will not be included in our main analyses because of the current emphasis on feasibility. Rather, they will help us better characterize the sample and provide valuable information toward a future efficacy trial using the NCCIH UG3/UH3 mechanism. It is anticipated that patients will need 20 to 30 minutes to complete the battery of questionnaires. They will also receive a prompt at the end of each questionnaire, asking them to complete unanswered fields, in effort to reduce the possibility of missing data. A blinded

research assistant who is not involved in recruitment procedures will check each questionnaire upon completion to ensure that patients do not randomly respond or acquiesce. To maintain confidentiality, patients will be identified using a specific ID. Only the unblinded research assistant and study clinicians will have access to the file connecting patients' names and study IDs.

## Data Analyses

### Phase 1 (Qualitative Interviews)

The individual qualitative interviews (phase 1) will be recorded and transcribed. They will then be analyzed using thematic content analyses following Miles and Huberman [64] in NVivo 12. We will use the framework method [65] to analyze our qualitative data and employ a primarily deductive approach [66], while also allowing flexibility to incorporate inductive themes derived directly from novel information collected during

the interviews. We will assess the reliability ( $\kappa$ ) of coding for themes and patterns in qualitative responses by 2 independent coders. The analyses will be conducted by trained clinicians and research assistants under the guidance of the research team's senior psychologist. Discrepancies will be resolved through discussion until adequate reliability is obtained ( $\kappa > 0.80$ ).

### Phases 2 (Open Pilot) and 3 (Feasibility RCT)

The primary analyses in this project will focus on establishing key quantitative feasibility benchmarks to inform future multisite RCTs. To this end, we will use frequency and proportions to assess the feasibility of recruitment and retention procedures within each group. We will additionally use proportions of patients with scores over the midpoint on the Client Satisfaction Questionnaire [62] and the Credibility and Expectancy Questionnaire to assess satisfaction and credibility, respectively. Feasibility benchmarks for these phases are detailed in Table 2.

**Table 2.** Feasibility benchmarks for phases 2 and 3.

Outcome	Acceptable	Excellent
Feasibility of recruitment	>70% of patients successfully contacted agree to participate	At least 80% of patients successfully contacted agree to participate
Credibility and expectancy	>70% of participants with score over scale midpoint	>75% of participants with score over scale midpoint
Client satisfaction score	>70% of participants with score over scale midpoint	>75% of participants with score over scale midpoint
Acceptability of treatment	>70% of participants attend 3 out of 4 sessions	>80% of participants attend 3 out of 4 sessions
Therapist adherence	>70% adherence (checklist and audio recordings)	100% adherence (checklists and audio recordings)
Adherence to homework	>70% of participants practice at least one skill on 3 days per week	>80% of participants practice at least one skill on 3 days per week
Feasibility of assessments	>70% of participants have no measures fully missing	>90% of participants have no measures fully missing
Adverse events	Minimal (see <i>Live Video Delivery and Special Considerations for Patients With mTBI</i> for light sensitivity issues)	None

Participants who drop out will be counted as not meeting applicable feasibility criteria. Benchmarks that need to be met before beginning the future fully powered RCT will include (1) >70% of participants successfully contacted agree to participate; (2) 70% of participants with a Credibility and Expectancy score and Client Satisfaction score over each scale's midpoint; (3) >70% of participants participated in at least three of four sessions; (4) >70% therapist adherence (measured via checklists and independent rater agreement on audio recordings); (5) >70% of participants practice at least one skill on 3 days per week (6) >70% of participants have no questionnaires missing; and (7) minimal adverse events. If these criteria are not met, revisions will be necessary. Benchmarks will be reported separately for the TOR-C and HE-C. These benchmarks were used previously in federally funded studies by our research team [34,52,53] and are consistent with guidelines for intervention development [35,67].

For quantitative measures, we will use descriptive statistics to characterize the sample and paired sample two-tailed *t* tests to

assess within-group changes between baseline and postintervention and between postintervention and the 3-month follow-up. Cohen *d*, including 95% CI, will be used to determine effect sizes using conventional standards (small effect sizes of 0.2 SD units, medium effect sizes of 0.5 SD units, and large effect sizes of 0.8 SD units) [68]. In line with recommendations for analyses in pilot studies [69,70], we will refrain from conducting between-group analyses of efficacy.

Analyses of the semistructured qualitative exit interviews in phase 2 will broadly follow the methods described in phase 1 above and will gather information on (1) perception of the skills taught in the program, (2) barriers and facilitators to completion of program and home practice, (3) perception of program structure and experience in the sessions, and (4) perception of the assessments.

### Power Analysis

Power analysis is not appropriate for qualitative analyses. For the individual interviews, a sample size of  $n=20$  is typically

enough to achieve saturation of themes [71]. With a sample size of N=50 in phase 3 and conservatively assuming that the feasibility criteria in Table 2 are independent, the study will have 80% power to confirm feasibility of all criteria if the expected rate of each criterion is at least 83%. Of note, we achieved greater retention in some of our other studies, including the TOR study [34] as well as previous mind-body studies using live video [41]. Importantly, as mentioned above, this power analysis is not calculated to detect group differences or significant changes in outcome measures but rather to establish feasibility.

## Results

This study is funded by the NCCIH grant #K23AT01065301A1. Phase 1 was approved by the institutional review board of the Massachusetts General Hospital. Recruitment is due to start in December 2020 for phase 1 and in September 2021 and September 2022 for phases 2 and 3, respectively. Data collection for the feasibility RCT is anticipated to be completed by September 2024, and data analysis is anticipated to be completed by early 2025.

## Discussion

Anxiety is common among college-aged individuals and has emerged as one of the strongest modifiable risk factors for progression from acute to persistent mTBI symptoms [7,8]. Identifying individuals with acute mTBI and comorbid anxiety and enrolling them in a live video mind-body program may be an effective and efficient way to prevent costly and challenging-to-treat chronic symptoms following mTBI. In this paper, we describe the steps and study procedures for developing, adapting, and establishing the feasibility of the TOR-C, the first mind-body program aimed at preventing persistent mTBI symptoms among college-aged adults with mTBI and comorbid anxiety and delivered via live video. By

applying a multimodal approach that combines mind-body skills (eg, deep breathing, mindfulness), cognitive-behavioral skills (eg, behavioral activation, reframing), and acceptance and commitment skills (eg, acceptance), the TOR-C may help break the negative cycle in which anxiety following mTBI leads to avoidance and thus perpetuates disability, symptom persistence, and further anxiety [9,10].

The results of this trial will provide important information toward a multisite RCT comparing the TOR-C with an HE-C control group. This is in line with the ORBIT [35] and NCCIH [36] intervention development models, emphasizing the importance of iteratively refining interventions and establishing feasibility benchmarks to ensure the scientific rigor of subsequent efficacy trials. This process is necessary to prevent common and negative consequences of leaping to efficacy testing before establishing feasibility, including inadequate fit of the intervention and/or procedures to the target population, lack of power to detect change, and inability to identify those who are likely to be most responsive to the intervention [72]. Moreover, processes in this study such as identifying treatment needs, preferences, perceptions, and barriers to treatment among these patients may further inform other treatments and interventions for this patient population.

In summary, this study will develop, adapt, and establish the feasibility of the TOR-C, the first mind-body intervention focused on *prevention* of persistent mTBI symptoms. It will be the first program specifically adapted and refined based on qualitative interviews to meet the unique needs, preferences, and challenges faced by this population, thus increasing its likelihood of efficacy. The results will inform a future multisite trial of TOR-C versus an HE-C control group and will potentially inform other interventions for this patient population. Future studies should also explore whether TOR-C is applicable to a wider range of patients with mTBI, including individuals across the life span.

## Acknowledgments

This work has been funded by the NCCIH grant #K23AT01065301A1.

## Conflicts of Interest

GLI has a clinical and consulting practice in forensic neuropsychology, including expert testimony, involving individuals who have sustained mild TBIs (including athletes). He has received research funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He has received research support from the Harvard Integrated Program to Protect and Improve the Health of NFLPA Members, and grant support from the National Football League. He serves as a scientific advisor for Sway Operations, LLC, Highmark, Inc., and for NanoDX® (formerly BioDirection, Inc.). EAM reports grants from Acorda Therapeutics, personal fees from Shire Human Genetic Therapies, grants from Amylyx Pharmaceuticals, grants from Mitsubishi Tanabe Pharmaceuticals America, grants from GlaxoSmithKline, personal fees from Biogen, personal fees from Novartis Pharmaceuticals, personal fees from Cerevance, personal fees from Inventram, other from Biohaven Pharmaceuticals, other from Clene Nanomedicine, other from Prilenia Therapeutics, other from Ra Pharmaceuticals, personal fees from Partners Therapeutics, personal fees from Stoparkinson Healthcare LLC, all outside the submitted work.

## Multimedia Appendix 1

Summary statement: National Institutes of Health peer review of funded grant.

[PDF File (Adobe PDF File), 284 KB - [resprot\\_v10i1e25746\\_app1.pdf](#)]

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## Abbreviations

**GAD-7:** Generalized Anxiety Disorder 7-item scale

**HE-C:** health enhancement for concussion

**mTBI:** mild traumatic brain injury

**NCCIH:** National Center for Complementary and Integrative Health

**ORBIT:** Obesity Related Behavioral Intervention Trials

**RCT:** randomized controlled trial

**TBI:** traumatic brain injury

**TOR:** Toolkit for Optimal Recovery After Injury

**TOR-C:** Toolkit for Optimal Recovery after Concussion

*Edited by T Derrick; submitted 20.11.20; this is a non-peer-reviewed article; accepted 23.11.20; published 14.01.21.*

*Please cite as:*

*Greenberg J, Singh T, Iverson GL, Silverberg ND, Macklin EA, Parker RA, Giacino JT, Yeh GY, Vranceanu AM*

*A Live Video Mind-Body Treatment to Prevent Persistent Symptoms Following Mild Traumatic Brain Injury: Protocol for a Mixed Methods Study*

*JMIR Res Protoc* 2021;10(1):e25746

URL: <https://www.researchprotocols.org/2021/1/e25746>

doi: [10.2196/25746](https://doi.org/10.2196/25746)

PMID: [33443484](https://pubmed.ncbi.nlm.nih.gov/33443484/)

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Protocol

# Mobile Health Intervention to Close the Guidelines-To-Practice Gap in Hypertension Treatment: Protocol for the mGlide Randomized Controlled Trial

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## Abstract

**Background:** Suboptimal treatment of hypertension remains a widespread problem, particularly among minorities and socioeconomically disadvantaged groups. We present a health system–based intervention with diverse patient populations using readily available smartphone technology. This intervention is designed to empower patients and create partnerships between patients and their provider team to promote hypertension control.

**Objective:** The mGlide randomized controlled trial is a National Institutes of Health–funded study, evaluating whether a mobile health (mHealth)-based intervention that is an active partnership between interprofessional health care teams and patients results in better hypertension control rates than a state-of-clinical care comparison.

**Methods:** We are recruiting 450 participants including stroke survivors and primary care patients with elevated cardiovascular disease risk from diverse health systems. These systems include an acute stroke service (n=100), an academic medical center (n=150), and community medical centers including Federally Qualified Health Centers serving low-income and minority (Latino, Hmong, African American, Somali) patients (n=200). The primary aim tests the clinical effectiveness of the 6-month mHealth intervention versus standard of care. Secondary aims evaluate sustained hypertension control rates at 12 months; describe provider experiences of system usability and satisfaction; examine patient experiences, including medication adherence and medication use self-efficacy, self-rated health and quality of life, and adverse event rates; and complete a cost-effectiveness analysis.

**Results:** To date, we have randomized 107 participants (54 intervention, 53 control).

**Conclusions:** This study will provide evidence for whether a readily available mHealth care model is better than state-of-clinical care for bridging the guideline-to-practice gap in hypertension treatment in health systems serving diverse patient populations.



**Trial Registration:** Clinicaltrials.gov NCT03612271; <https://clinicaltrials.gov/ct2/show/NCT03612271>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/25424

(*JMIR Res Protoc* 2021;10(1):e25424) doi:[10.2196/25424](https://doi.org/10.2196/25424)

## KEYWORDS

hypertension; mobile health technology; health disparities; randomized controlled trial

## Introduction

Hypertension (HTN), a major risk factor for strokes and heart attacks, is also a significant comorbidity in severe COVID-19 infections [1-3]. Unfortunately, of the estimated 86 million US adults with HTN, 46% (~40 million) have poorly controlled or uncontrolled HTN [4]. Despite widespread recognition of the health risks of HTN, suboptimal treatment of HTN remains a pernicious problem and is marked by disparities [4,5]. Rates of HTN control are worse among racial and ethnic minorities and socioeconomically disadvantaged groups, who experience a disproportionate burden of cardiovascular disease (CVD) and poor health outcomes [4,5]. According to the 2017-2018 National Health and Nutrition Exam Survey, rates of controlled HTN in Hispanic adults (36.8%) were substantially lower than in non-Hispanic white adults (45.2%) [6]. HTN is undertreated even among stroke survivors who are at significantly increased risk of recurrent stroke [7]. Many factors have been associated with suboptimal HTN control including gaps in health services, lower socioeconomic status, and limited self-care [8-10].

Self-measured blood pressure monitoring (SMBP), an aspect of self-care, is effective in lowering blood pressure (BP) and improving HTN control [11]. SMBP is recommended in guidelines on the care of patients with HTN including the Eighth Joint National Committee [1] and the American College of Cardiology [12,13]. It was also endorsed in a joint policy statement by the American Heart Association (AHA) and American Medical Association as a result of increasing utilization of telehealth visits in the COVID-19 pandemic [14].

Mobile health (mHealth) technology has emerged as an innovative way to facilitate SMBP [15,16]. Our prior pilot study with stroke survivors found that SMBP utilizing mHealth improved rates of HTN control [17]. In a randomized controlled trial (RCT), we compared usual care versus an mHealth-based model of HTN care that included automated wireless transmission of BP data to the provider team, including a clinical pharmacist, who could make responsive medication adjustments. The mHealth care model was feasible and acceptable to stroke survivors and was highly effective: 89% of participants in the mHealth group versus 58% in the usual care group ( $P=.015$ ) had their BP controlled at 3 months postrandomization. However, the generalizability of our results was limited as all the participants were stroke survivors and the majority of participants were English-speaking Caucasians, which is typical of many published studies [15]. To the best of our knowledge, there are no published studies that evaluate mHealth-based HTN care in Hmong patients.

To address these gaps, we designed an RCT, called mGlide, to evaluate whether an mHealth-based active partnership between health care teams and patients results in better HTN control than a state-of-clinical care comparison (usual care) for stroke survivors and persons at elevated risk of CVD. We are particularly interested in addressing disparities in HTN control in vulnerable patient populations in our region. Thus, our recruitment sites include federally qualified health centers (FQHCs) that predominantly serve low-income racial or ethnic minorities and immigrants, including lower socioeconomic groups and African American, Hmong, Somali, and Latino patients. The primary study aim tests the clinical effectiveness of the 6-month intervention vs usual clinical care. Secondary aims evaluate sustained HTN control rates at 12 months; describe provider experiences of system usability and satisfaction; examine patient experiences, including medication adherence and medication use self-efficacy, self-rated health and quality of life, and adverse event rates; and complete a cost-effectiveness analysis. The mGlide RCT began in late 2018, with recruitment initiated in March 2019. Our purpose in this article is to describe the design and rationale of the mGlide RCT study.

## Methods

### Study Design

mGlide is a National Institutes of Health-funded, investigator-initiated, 12-month, 2-arm RCT evaluating HTN control rates between the study intervention and clinical comparison groups. We use a PROBE (Prospective Randomized Open Blinded End-point) design. We are recruiting a total of 450 patients with uncontrolled hypertension who are either stroke survivors or primary care patients at elevated risk of CVD from the metropolitan area of Minneapolis and Saint Paul, Minnesota. The recruitment window is between March 2019 and December 2022. Individual participants are randomized to either the multilevel mGlide intervention (target  $n=225$ ) or to state-of-clinical care (target  $n=225$ ) for a 6-month intervention period, followed by a 6-month observation period. A baseline BP assessment and 2 follow-up BP assessments (at 6 months and 12 months postrandomization) are completed for each participant.

Eligibility criteria are shown in [Textbox 1](#) and in the CONSORT flow diagram ([Figure 1](#)). The University of Minnesota Institutional Review Board (IRB) approved the study protocol, and all participants provide written, informed consent.

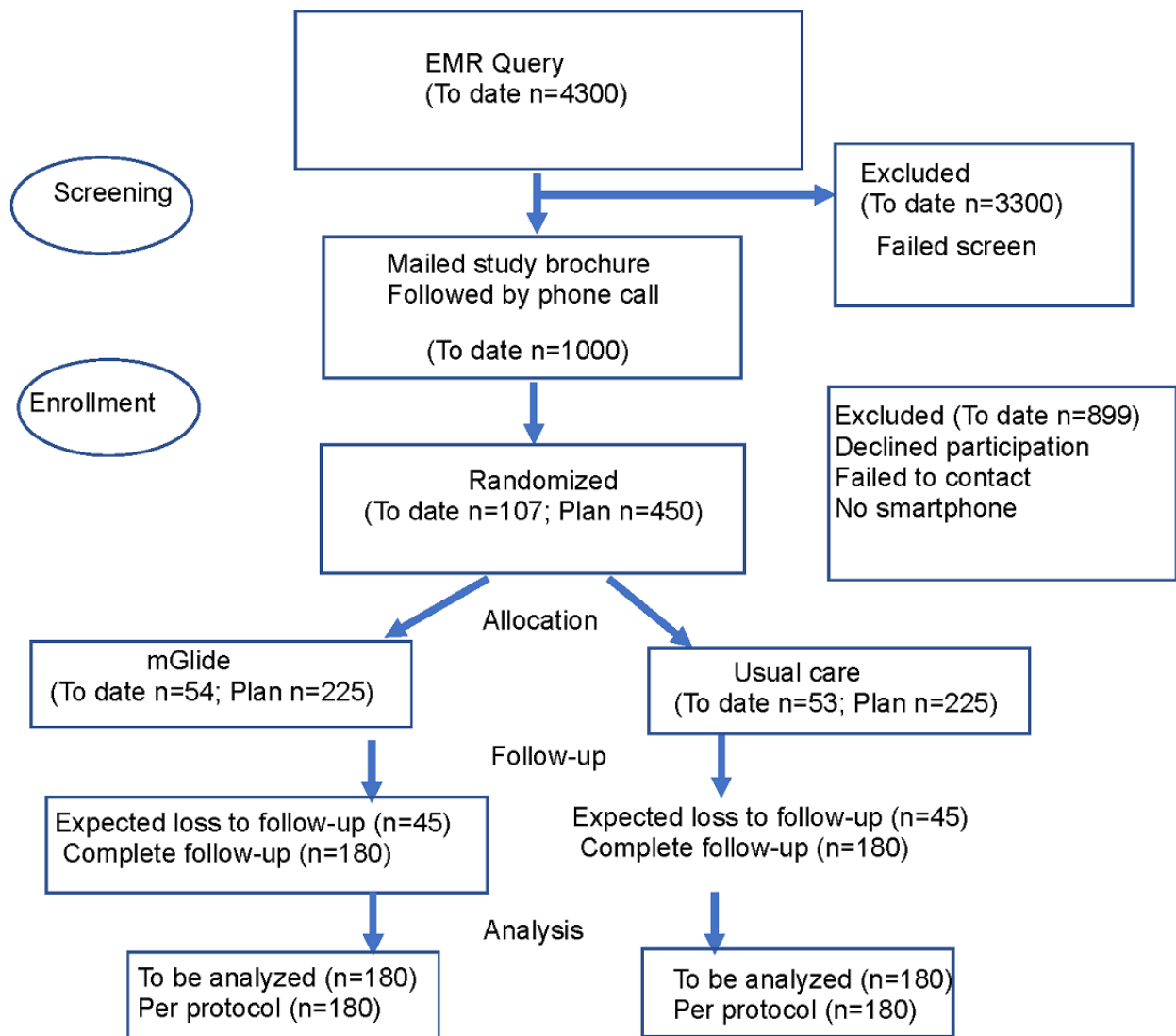
**Textbox 1.** mGlide randomized controlled trial eligibility criteria.**Inclusion criteria**

- Aged 18-85 years
- Established medical diagnosis of hypertension (HTN)
- Uncontrolled HTN during screening defined as:
  - Systolic blood pressure (SBP) >140 mm Hg at last 2 clinic visits in the 6 months prior to the screening date or
  - If a patient is discharged from the hospital in the 6 months prior to screening and does not have 2 clinic visits after hospital discharge, at least 1 SBP in last 2 hospital days >140 mm Hg or
  - If only 1 office visit and no hospitalization in last 6 months, then a single SBP in the system >150 mm Hg and SBP >140 mm Hg at an invited pre-enrollment screening visit
- Be at high cardiovascular disease (CVD) or stroke risk, defined as:
  - History of ischemic stroke or intraparenchymal hemorrhage or
  - History of established CVD disease (coronary artery disease, peripheral vascular disease) or
  - Elevated risk of stroke or CVD events as defined by the American Heart Association (AHA)/American College of Cardiology (ACC) guideline on risk stratification  $\geq 7.5\%$  over 10 years if  $\geq 40$  years old and  $\geq 10\%$  nonpooled risk calculation if  $< 40$  years old
- English, Spanish, Hmong, or Somali speaking
- Have a smartphone or mobile device (eg, iPad) that can transmit blood pressure (BP) from the BP monitor; iOS and Android compatible (iOS 7 or higher: iPhone 4 or higher, iPod touch 5th generation or higher, iPad 2nd generation or higher; Android 4.0 or higher)
- Capable and willing to comply with the entire study protocol
- Able to give voluntary written informed consent

**Exclusion criteria**

- Severe comorbid illness including end-stage kidney disease, end-stage liver disease, and life expectancy  $< 1$  year, or if medical complexity of the patient precludes clinical trial participation
- Active illicit drug use (eg, cocaine, methamphetamines, opioids, phencyclidine)
- Unable to complete study tasks, including are homeless, will leave the country, or will relocate in the next 12 months
- Serious psychiatric illness that could interfere with treatment, assessment, or compliance including significant delusional disorders such as schizophrenia and bipolar illness
- Unable or unwilling to give consent

**Figure 1.** mGlide CONSORT diagram. EMR: electronic medical record.



**Study Setting and Recruitment**

The study is conducted by the University of Minnesota, a large urban university in the upper Midwest in the United States. Study participants are community-dwelling residents within our 7-county metropolitan area recruited from (1) a large academic health system (Fairview Health System) with a stroke service

and primary care clinics; (2) university-affiliated, community-based, primary care clinics serving low-income participants and minorities (University of Minnesota Physicians clinics); and (3) 2 FQHCs: Minnesota Community Care, the largest FQHC in Minnesota, and Neighborhood Health Source, serving low-income people from ethnically diverse communities. Details are in [Table 1](#).

**Table 1.** Planned enrollment (N=450).

Site	Number of participants	Description of recruited participants
Fairview stroke service	100	Stroke survivors
Fairview primary care clinics	150	Elevated CVD <sup>a</sup> risk
UMP <sup>b</sup> primary care clinics	125	Elevated CVD risk; low income; diverse; minority
FQHC <sup>c</sup> clinics (MnCC <sup>d</sup> , NHS <sup>e</sup> )	75	Elevated CVD risk; low income; diverse; minority

<sup>a</sup>CVD: cardiovascular disease.

<sup>b</sup>UMP: University of Minnesota Physicians.

<sup>c</sup>FQHC: federally qualified health centers.

<sup>d</sup>MnCC: Minnesota Community Care.

<sup>e</sup>NHS: Neighborhood Health Source.

Eligible stroke survivors are identified from the Fairview acute stroke service and the acute rehabilitation unit. Primary care patients are identified by electronic medical record queries using the inclusion and exclusion criteria in [Textbox 1](#). Patients who have “opted out” of research are not included in the electronic medical record query (~5% of all patients). Eligible participants are mailed a study brochure and are subsequently contacted by phone. Those who express interest undergo a second screening for availability of a smartphone or mobile device and are invited for a baseline enrollment visit.

### Visit Schedule and Assessments

Each participant completes a total of 3 visits: baseline visit and 2 follow-up visits at 6 months and 12 months postrandomization. The baseline visit includes informed consent in the participant’s language, randomization into one of the 2 study arms, participant education about HTN and BP control, baseline BP measurement using a protocol [18,19], and baseline surveys. The 2 follow-up visits include assessments of the primary and secondary study outcomes. In addition, team members call participants monthly (months 1-5) and bimonthly (months 8 and 10) to identify adverse events and address any challenges. Data collection details are presented in [Table 2](#).

**Table 2.** mGlide randomized controlled trial visit schedule and assessments at baseline and follow-up.

Measures	Baseline	6-month follow-up	12-month follow-up
Demographic information	x	N/A <sup>a</sup>	N/A
Medical history	x	N/A	N/A
Health behaviors (smoking, physical activity, diet, sleep)	x	N/A	N/A
Health insurance	x	N/A	N/A
Blood pressure	x	x	x
<b>Patient-reported outcomes</b>			
Health care experiences (CAHPS <sup>b</sup> adult survey)	x	x	x
Hill-Bone Medication Adherence Scale (HB-MAS)	x	x	x
Medication and Self-Efficacy Scale - Revised (MASES-R)	x	x	x
Patient Activation Measure (PAM-10)	x	x	x
Health care utilization	x	x	x
Self-reported health status (EQ-5D-3L)	x	x	x
Technology usability (Marshfield System Usability Survey)	N/A	x	N/A

<sup>a</sup>N/A: Not applicable.

<sup>b</sup>CAHPS: Consumer Assessment of Healthcare Providers and Systems.



## Special Considerations for Recruitment

University of Minnesota researchers and community researchers from Hmong and Latino communities co-developed the informed consent and surveys in English. Subsequently, community researchers translated all participant-facing documents into Hmong, Spanish, and Somali. Each participant invited to a baseline enrollment visit works with a team member who speaks their language (Hmong, Spanish, Somali, or English).

## Randomization

Eligible and consented participants are randomized 1:1 to either an intervention mGlide arm or a state-of-clinical-care comparison arm. The randomization uses a site-specific randomization schedule and is stratified across the 4 participant groups discussed in Table 1. Randomization schedules follow from permuted blocks with randomly varying sizes to ensure approximate balance between the 2 study arms in each stratum across the trial while reducing predictability of the assignments.

## Interventions

### mGlide

The mGlide intervention has 3 components (Table 3): participant education on the importance of HTN control, training on SMBP and wireless transmission of BP, and responsive

antihypertensive medication adjustment by the pharmacist-provider team.

Each participant receives education on the importance of HTN control via an IRB-approved educational video available in English, Spanish, and Hmong. We previously developed this video through a community-engagement process led by community researchers from the Hmong and Latino communities. The study team member then trains the participant on SMBP [18] using a wireless BP monitor provided by the study and a smartphone (participant's own phone or mobile device such as iPad). The intervention participants are requested to self-monitor their BP daily with specific guidance on timing and proper technique based on the AHA recommendations [18]. The self-monitored BP is automatically transmitted to a provider REDCap database and is used for responsive antihypertensive medication adjustment. The participant BP transmission is automated and facilitated by the participant's mobile device via an app. Pharmacist teams at each clinic location access the BP data via a web-based user interface that identifies patients whose readings were out of bounds during the prior week. This user interface creates efficiencies for pharmacists reviewing the data and was developed to avoid information overload for pharmacists. Pharmacists adjust medications based on collaborative practice agreements with primary care providers (PCP) and mGlide protocols. Pharmacists adjust medications and communicate with the patient and their PCP as often as every 2 weeks or as needed to reach the BP goal.

**Table 3.** Components of mGlide intervention delivered to participants.

Component	Intervention	Comparison
Education on importance of hypertension control	Yes	Yes
Training in blood pressure self-monitoring	Yes	Yes
Daily self-monitoring	Requested	Encouraged
Automated wireless blood pressure transmission via mobile device	Yes	No
Responsive medication adjustment by pharmacy	Yes	No
Primary care follow-up as usual	Yes	Yes

Our intervention is a multilevel model with a 3-member team: frontline research team member who educates the participant and trains them on self-monitoring of BP, pharmacist who provides responsive HTN management, and PCP. This team communicates via the electronic medical record as part of clinical care.

### State-of-Clinical Care Comparison

Each study participant randomized to the clinical care comparison group receives the same education as intervention participants on the importance of HTN control via the IRB-approved educational video. The comparison group participants receive a digital BP monitor and are trained on BP self-monitoring with proper technique. Participants are encouraged to measure their BP daily and follow up with their PCP regarding their BP, as requested by the PCP as part of their clinical care. Participants, PCPs, and clinic teams are responsible for communicating as they would in usual clinical care. In other words, there is no predetermined follow-up schedule with the

PCP specified by the study, and there is no automatic transmission of participant BP readings to providers; rather, participants are responsible for sharing their BP and working with their care team to manage their BP.

## Analysis

### Outcomes

The main outcome will be the rate of HTN control at 6 months; the primary outcome will be defined as a binary indicator of uncontrolled HTN or death versus controlled HTN at 6 months. The BP is measured in-person in the clinical research center by a trained staff member who is blind to the patient's assignment. The BP is measured 4 times using a standard digital monitor using proper technique, and the average of the last 3 BP measurements denotes the BP outcome. HTN control is defined as systolic blood pressure (SBP) <140 mm Hg, which is consistent with American College of Physicians, American Association of Family Physicians, and AHA primary and

secondary stroke prevention guidelines [12,13,20]. The 2017 American College of Cardiology/AHA guidelines recommend a SBP goal of <130 mm Hg. The HTN treatment goals and target BP were discussed with the PCPs and clinical pharmacists at all sites prior to study recruitment. Everyone agreed to target a SBP goal of <140 mm Hg for intervention arm participants and requested that lower SBP goals be left to the discretion of the study pharmacists managing the patient. Study pharmacists have access to patient medical records. At 12 months, the BP outcome is assessed in the same manner as at 6 months. This allows the assessment of the secondary outcome of uncontrolled HTN or death versus controlled HTN at 12 months. Additional secondary outcomes include patient-reported medication adherence, medication use self-efficacy, self-reported health status, and quality of life that we assess with validated questionnaires at each of the 3 study visits. We ascertain participant adverse events and health care utilization during monthly phone calls during the first 6 months of the study and bimonthly in months 7-11. We also assess care providers' experience of the mGlide system usability.

### **Power and Sample Size**

Sample size was calculated to address outcomes of failure to achieve HTN control or death at 6 months and 12 months after randomization. We based sample size calculations on (1) reported 1-year stroke survivor mortality rate of 4% [21] and assuming similar mortality among primary care participants with elevated CVD risk, (2) pilot results that showed a primary outcome rate of HTN control or death at 6 months of 15% in the intervention and 50% in the comparison groups [17], and (3) a 20% attrition rate. We identified that a sample size of 450 would provide at least 85% power, with an alpha of .05 to detect a 15% effect size. We planned for a more modest intervention effect size than achieved in our pilot results due to the longer period of observation and more diverse health systems and patient populations when compared to the pilot study. Similarly, while the loss to follow-up in the pilot study was very modest at 4%, we planned for a 20% attrition rate due to the economically stressed primary care population in our low-resource health systems. Nationally reported rates of uncontrolled HTN in stroke survivors are ~50% [7]. FQHC primary care rates of uncontrolled HTN are ~38%-40% [22]. Our sample size will allow valid subgroup analysis among the subgroup of primary care patients in all low-income sites (n=200) and the stroke survivor subgroup (n=100).

### **Quality Control and Preventing Missing Data**

Data collection is standardized by the use of a detailed manual of operations. The REDCap data entry system also has built-in logic to check data at the time of entry and minimize errors. Monthly data quality reports ensure that data are validated and data entry is completed in a timely fashion. If participants drop out, we are documenting specific reasons for drop out.

### **Planned Analysis**

We will use a Cochran-Mantel-Haenszel test stratified by the randomization groups to test whether the odds of HTN control at 6 months differs between the intervention and control study arms. Statistical significance level will be set at the  $P < .05$  level.

We also will perform the same analysis at 12 months to examine if the difference between the intervention and control groups is sustained. Secondary analyses using the repeated BP assessments obtained at 6-month and 12-month visits are planned. We will use longitudinal generalized estimating equation models, with BP control modeled as a binary variable and average BP modeled continuously in separate models, with relevant covariates. Interactions will be tested to evaluate potential differential effects by baseline demographic and clinical characteristics.

We have planned for missing data. We are recording reasons for study drop out and will examine patterns of missingness. For the primary analysis, we will (multiply) impute the binary HTN control outcome. We are collecting a rich amount of covariate information on participants to inform the multiple imputation models.

We plan the following analyses to examine secondary outcomes related to system usability for care providers. The Welch  $t$  test will be used to examine the number of antihypertensive medication changes (dose adjustment, addition of new medications) per patient during the 6-month intervention period for the mGlide intervention arm. We will examine the provider mGlide experience using the Computer System Usability Questionnaire overall score as well as scores along the 3 principal factors identified on the Computer System Usability Questionnaire: System Usefulness, Information Quality, and Interface Quality. We also will collect qualitative feedback from providers using focus groups. These data will be analyzed using a qualitative framework including classic content analysis and microinterlocutor analysis [23,24].

Patient-reported outcomes (Table 2) will be examined by comparing whether there are group differences on the Patient Activation Measure [25], patient medication self-efficacy measure (Medication and Self-Efficacy Scale - Revised) [26], medication adherence (Hill-Bone Medication Adherence Scale) [27,28], self-reported health status (EQ-5D-3L) [29,30], and patient satisfaction with health systems and providers (Consumer Assessment of Healthcare Providers and Systems adult survey) [31] using a 2-sample  $t$  test separately at 6 months and 12 months after baseline. Finally, we will compare the rates of adverse events between the 2 trial arms using both adjusted and unadjusted negative binomial regression models with intervention as the key independent variable.

### **Additional Analyses**

We plan a cost-effectiveness analysis that will follow the recommendations of Cost-Effectiveness in Health and Medicine, 2nd Panel [32] to present the analysis from both the societal and health care perspectives and to include an inventory of the non-health care impacts of the mGlide intervention. We will measure effectiveness by the differences in quality-adjusted life years (as derived from the EQ-5D-3L quality-of-life weights) across the 2 trial arms. Costs will represent the intervention cost and any differences in downstream health care and other costs for the societal perspective (productivity or time, informal care, travel) across the 2 arms. We will extrapolate quality-adjusted life years and cost differences using a 10-year stochastic event model. Thus, the cost-effectiveness analysis will meld both the

trial follow-up experience of participants and their modeled experience for the remaining years, based on differences in HTN control rates between the 2 trial arms. Specifically, we will determine downstream health care utilization using a state transition (Markov) model using Monte Carlo microsimulation. Our team includes an experienced health economist (JN).

### Data Safety and Monitoring

We have convened a 5-member data safety monitoring board (DSMB) with expertise spanning the statistics of clinical trial monitoring, HTN, pharmacist-delivered care, vascular neurology, and cardiology. Following an initial meeting at study start, the DSMB meets approximately every 6 months.

## Results

Study enrollment commenced in March 2019. Through mid-March 2020, 101 participants were randomized with 52 to the mGlide arm and 49 to the state-of-clinical-care arm. In mid-March 2020, the University of Minnesota paused enrollments for non-COVID-19 research studies involving face-to-face participant contact. In response, the mGlide team developed protocols for remote enrollment including remote consent in REDCap and protocols to mirror the in-person enrollment process. We also developed a remote protocol for gathering the 6-month and 12-month follow-up data and BP measurements using Zoom. These have been approved by the IRB and the study sponsor and are currently in use. To date, we have enrolled 5 participants remotely and are completing the 6-month and 12-month follow-up visits. We will validate our remote BP measurement protocols against pre-COVID-19 in-person processes when our institution allows in-person research participant visits. The impact of COVID-19 is that the study timeline for completion of enrollment and intervention has been extended by 6 months; other possible effects on the study will be monitored.

To date, we have enrolled a total of 107 participants (54 intervention and 53 control participants). A total of 86 participants have completed their 6-month follow-up (primary BP endpoint), and 46 participants have completed their 12-month follow-up (secondary BP endpoint). Seven participants have withdrawn, and 1 participant has died. The study principal investigator reviews adverse events, and a team of 2 blinded study clinicians subsequently reviews these events. The study statisticians and DSMB review these and other study outcomes at the DSMB meetings.

## Discussion

HTN is a chronic disease requiring sustained efforts for long-term control. The mGlide RCT seeks to address the

persistent and prevalent clinical challenge of poorly controlled HTN in a diverse sample of adults at elevated risk for stroke and CVD events. The study aims are to (1) evaluate clinical effectiveness of the mGlide intervention in comparison to usual clinical care; (2) improve clinical teams' abilities to manage patients' antihypertensive medications; (3) increase patient activation, patients' satisfaction with care, and medication use self-efficacy and adherence as well as lower health care utilization; and 4) establish the cost-effectiveness of the mGlide intervention. Intervention participants monitor their BP daily with a wireless BP monitor and use their smartphone to transmit BP readings to a database automatically via an app. We then use the framework of glide paths to manage the transmitted BP data. The name of the intervention, mGlide, derives from the glide path concept of landing an airplane; an expected trajectory of BP readings is established for each patient with bounds set by guidelines and further adjusted by providers as needed. Although BP is monitored daily at home, the health care team accesses the BPs once a week and makes medication adjustments as needed, in collaboration with the patient's PCP. We believe this approach will facilitate early intervention in an efficient manner while avoiding system information overload.

The key innovation of the mGlide trial is using a mobile technology platform to facilitate better HTN control through a collaborative patient-provider partnership in limited-resource health systems. Currently, 68% of US adults use smartphones (up from 35% in 2011) [33]. The mGlide system based on mobile technology uses the patient's own smartphone. A free app allows the wireless monitor to interface with the smartphone. The app transmits the data to an online database. The database is free, and there is no patient service contract. Hence, mHealth is nimble and represents the next generation in technology. While small clinical trials have demonstrated the efficacy of mHealth in SMBP [11,15-17], we will demonstrate the feasibility of the mGlide in different clinical health systems including low-resource environments that might not be able to afford investment in telemonitoring services with an outside vendor.

Results from this study will provide evidence for the use of readily available mHealth technology for bridging the guideline-to-practice gap in HTN treatment for diverse patients in diverse health care systems. Importantly, our study is being implemented in low-resource health systems serving minority and low-income groups and thus will provide critical insights into enhancing HTN control in these elevated-risk patients who experience significant cardiovascular disparities.

## Acknowledgments

We thank the following SoLaHmo Partnership for Health and Wellness community researchers: Cecilia Martinez, Pilar de La Parra, Sandra Sedeno Revera, and Chaoching Vang. Educational videos in English, Spanish, and Hmong were created by Luis Martin Ortega MD, Kabao Vang MD, and Pao Lee Vang. mGlide RCT is funded by NIH grant R01 HL138332. A J.B. Hawley

Award from the University of Minnesota, Division of Epidemiology and Community Health funded the educational video development.

### Authors' Contributions

KL contributed to the conceptualization, methodology, investigation, writing of the original draft, supervision, project administration, and funding acquisition. TM contributed to the methodology, validation, and data curation. SW contributed to conceptualization and the methodology. JC contributed to the methodology. VO contributed to conceptualization and project administration. KC-P contributed to conceptualization and supervision. SP contributed to conceptualization, supervision, and project administration. PD contributed to the methodology. EV and TX contributed to the investigation and data curation. SE-R contributed to the writing of the original draft. All authors reviewed and edited the manuscript.

### Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review reports from the NIH.

[\[PDF File \(Adobe PDF File\), 165 KB - resprot\\_v10i1e25424\\_app1.pdf\]](#)

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## Abbreviations

**AHA:** American Heart Association  
**BP:** blood pressure  
**CVD:** cardiovascular disease  
**DSMB:** data safety monitoring board  
**FQHC:** federally qualified health centers  
**HTN:** hypertension  
**IRB:** institutional review board  
**mHealth:** mobile health  
**PCP:** primary care provider  
**PROBE:** Prospective Randomized Open Blinded End-point  
**RCT:** randomized controlled trial  
**SBP:** systolic blood pressure  
**SMBP:** self-measured blood pressure monitoring

*Edited by T Derrick; submitted 19.11.20; this is a non-peer-reviewed article; accepted 18.12.20; published 25.01.21.*

*Please cite as:*

*Lakshminarayan K, Murray TA, Westberg SM, Connett J, Overton V, Nyman JA, Culhane-Pera KA, Pergament SL, Drawz P, Vollbrecht E, Xiong T, Everson-Rose SA*

*Mobile Health Intervention to Close the Guidelines-To-Practice Gap in Hypertension Treatment: Protocol for the mGlide Randomized Controlled Trial*

*JMIR Res Protoc 2021;10(1):e25424*

*URL: <http://www.researchprotocols.org/2021/1/e25424/>*

*doi: [10.2196/25424](https://doi.org/10.2196/25424)*

*PMID: [33492231](https://pubmed.ncbi.nlm.nih.gov/33492231/)*

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Protocol

# A Tailored Web- and Text-Based Intervention to Increase Physical Activity for Latino Men: Protocol for a Randomized Controlled Feasibility Trial

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## Abstract

**Background:** Latino men in the United States report low physical activity (PA) levels and related health conditions (eg, diabetes and obesity). Engaging in regular PA can reduce the risk of chronic diseases and yield many health benefits; however, there is a paucity of interventions developed exclusively for Latino men.

**Objective:** To address the need for culturally relevant PA interventions, this study aims to develop and evaluate Hombres Saludables, a 6-month theory-based, tailored web- and text message-based PA intervention in Spanish for Latino men. This protocol paper describes the study design, intervention, and evaluation methods for Hombres Saludables.

**Methods:** Latino men aged 18-65 years were randomized to either the individually tailored PA internet intervention arm or the nutrition and wellness internet control arm. The PA intervention included 2 check-in phone calls; automated SMS text messages; a pedometer; a 6-month gym membership; access to a private Facebook group; and an interactive website with PA tracking, goal setting, and individually tailored PA content. The primary outcomes were feasibility, acceptability, and efficacy (minutes per week of total moderate-to-vigorous PA assessed via the ActiGraph GT3X+ accelerometer worn at the waist and 7-day physical activity recall at baseline and 6 months). Secondary outcomes examined potential moderators (eg, demographics, acculturation, and environmental variables) and mediators (eg, self-efficacy and cognitive and behavioral processes of change) of treatment effects at 6 months post randomization.

**Results:** This study was funded in September 2016. Initial institutional review board approval was received in February 2017, and focus groups and intervention development were conducted from April 2017 to January 2018. Recruitment for the clinical trial was carried out from February 2018 to July 2019. Baseline data collection was carried out from February 2018 to October 2019, with a total of 43 participants randomized. Follow-up data were collected through April 2020. Data cleaning and analysis are ongoing.

**Conclusions:** We developed and tested protocols for a highly accessible, culturally and linguistically relevant, theory-driven PA intervention for Latino men. Hombres Saludables used an innovative, interactive, web- and text message-based intervention for improving PA among Latino men, an underserved population at risk of low PA and related chronic disease. If the intervention demonstrates feasibility, acceptability, and preliminary efficacy, we will refine and evaluate it in a larger randomized control trial.

**Trial Registration:** Clinicaltrials.gov: NCT03196570; <https://clinicaltrials.gov/ct2/show/NCT03196570>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/23690

**KEYWORDS**

physical activity; Latino; Hispanic; men; eHealth; expert system; internet; text messaging; mobile phone; social media

## Introduction

### Background

Engaging in regular physical activity (PA) exerts health benefits, including decreases in all-cause mortality, obesity, and risk for other chronic diseases, such as cardiovascular disease, type 2 diabetes, certain cancers, obesity, hypertension, osteoporosis, osteoarthritis, depression, and dementia [1]. Compared with White non-Latino men, more Latino men do not meet national PA guidelines (49.5% vs 38.9%) for leisure time PA [2,3]. Although several studies show that disparities in overall PA are not as pronounced in Mexican American men when measuring PA objectively, overall levels of PA are still too low in this population [4-7]. Latino men are disproportionately burdened by PA-related health conditions, such as obesity and overweight status (81.8% vs 75.3%) [8] and type 2 diabetes (12.5% vs 7.5%) [9]. This lack of PA signifies a substantial public health problem. Furthermore, there is heterogeneity across Latino subgroups. National data have revealed that Cubans and Dominicans had the lowest leisure time PA levels, whereas Mexican Americans were the most active [10]. Thus, Latino men from subgroups other than Mexican Americans may be at even higher risk for inactivity.

Although several studies have demonstrated the efficacy of culturally and linguistically appropriate, individually tailored PA interventions for Latina women [11-15], PA intervention studies with Latinos have excluded male participants or had limited numbers of men [16-18]. Most PA interventions with Latinos feature activities perceived by participants as more traditionally feminine (eg, dance classes) and targeted more female-specific barriers (eg, childcare duties) [19]. Multiple systematic reviews have found that no PA interventions have specifically targeted Latino men [16-18,20]. Since the last review published in 2019 [18], 2 small PA interventions (n=45-50) with mostly Mexican American men have been published. One study included an intensive in-person intervention, which has limited scalability [21], whereas the other involved individually tailored print materials and text messages sent to participants on a tapered schedule for 6 months [22].

This study addresses the scarcity of interventions designed to increase PA specifically for diverse Latino men and uses technology to improve reach and accessibility. Computer-based, expert system-driven, theory-based interventions use participant-supplied data to generate messages tailored to the individual needs of each participant [23]. They have shown great promise for providing effective, widely available, and low-cost health promotion programs [24,25]. This approach may appeal to Latino men as it addresses barriers identified in formative research, such as lack of time, family involvement, work responsibilities, and transportation [26-28], using a technology-based (internet and cell phone) tailored intervention. Technology-based approaches can help overcome PA barriers

reported by Latinos in our formative research (eg, lack of time and transportation) and may be especially appropriate given the rapid rise in recent years in internet use among this population. In fact, as of 2019, a large majority of Latinos reported using the internet (86%) [29] and owning a cell phone (96%) [30]; smartphones accounted for 79% of cell phones [30]. Latinos are also more likely than non-Latino Whites to use their mobile devices (smartphones or tablets) to access health information [31], suggesting that technology-based PA interventions may be especially appealing to Latino men.

Recent meta-analyses (and a comprehensive review) have described the impact of web-based interventions on PA and have found small to moderate positive effect sizes [32-34]. For mobile device-based PA interventions, one meta-analysis found a moderate effect size ( $g=0.54$ ) [35]. In addition, a systematic review of texting interventions found that strong evidence exists for integrating text messages into PA trials [36]. Thus, an individually tailored, multimedia web- and text-based intervention has the potential to broadly reach Latino men at a relatively low cost, which could help reduce low PA-related health disparities.

### Objectives

The purpose of this protocol paper is to describe the study design, intervention, and evaluation methods for *Hombres Saludables*, an internet- and text-based tailored Spanish language intervention designed for an ethnically diverse population of Latino men (ie, Caribbean and Central and South American origin) to increase total PA. This intervention was adapted from our culturally and linguistically appropriate, internet-based PA intervention for Latina women, *Pasos Hacia la Salud* [14], which successfully increased and maintained total PA levels in Latina women over 12 months [15,37].

## Methods

### Overall Design

*Hombres Saludables* is a 6-month randomized controlled trial (RCT) for Latino men comparing an individually tailored, internet- and text-based PA intervention with a control group that received an attention-matched intervention about nutrition and wellness. The primary aims of the study are to determine the feasibility, acceptability, and preliminary efficacy of the intervention, as well as the recruitment, implementation, and evaluation protocols. Secondary aims include examining potential moderators (eg, demographics, acculturation, and environmental variables such as the neighborhood and socioeconomic environments) and mediators (eg, self-efficacy and cognitive and behavioral processes of change) of treatment effects at 6 months post randomization. The targeted sample size for this pilot trial is 50 Latino men.



## Design Considerations

To inform the design of this study, we conducted 8 focus groups with 38 Latino men in Rhode Island. We asked their opinions on potential design elements of this study, including website functionality, use of text messages, email and social media, and content for both the intervention and control arms of the study. All focus groups were audio-recorded, and the recordings were transcribed, translated, and subjected to several stages of analytic coding using ethnographic methods by 2 graduate students. Transcripts were initially read as texts to isolate obvious themes and then subjected to open coding to identify additional themes and actions that are relevant for further analysis. Next, transcripts were subjected to focused coding using the subdomains identified in the earlier stages. Following coding, we worked with the coded data set and the texts to create a componential analysis that identified patterns and themes. Focus group findings were discussed with the research team and used to adapt and refine recruitment and intervention materials to be culturally appropriate for the diverse target audience. Focus group results will be discussed in another paper; however, briefly, participants expressed interest in the use of text messages rather than email to deliver information and reminders during the intervention. Focus group participants also recommended the use of a private Facebook group as a forum to post intervention content for study participants and allow them to comment and post among themselves. Focus group participants expressed strong interest in a gym membership, stating that it would help with barriers of cost and motivation to exercise.

## Participants and Eligibility

Inclusion criteria were as follows: (1) self-identification as Hispanic or Latino; (2) self-identification as male; (3) age between 18 and 65 years; (4) self-reported 60 min or less of total MVPA a week; (5) had an adequate literacy level to read

study materials in Spanish, that is, scored more than 16 on the Spanish language version of the Short Test of Functional Health Literacy in Adults (S-TOFHLA) [38-40]; and (6) owned a cell phone with texting capabilities and had regular internet access via a smartphone, tablet, or computer. Eligible participants also had to agree to be assigned to either of the 2 treatment conditions.

Exclusion criteria were as follows: (1) history of myocardial infarction or angina, insulin-dependent diabetes, or hospitalization for diabetes in the past year; (2) stroke, osteoarthritis, osteoporosis, orthopedic problems, or exercise-induced asthma; (3) any other medical condition that would make MVPA unsafe; (4) hospitalization because of a psychiatric disorder in the past 3 years; (5) BMI >45; (6) planned surgery or hospitalization in the next 6 months; and (7) intake of medication that may impair PA tolerance or performance. Any questions about medical eligibility were sent to the study physician to determine eligibility. Participants who reported another family member already enrolled in another PA study being conducted concurrently by our research team were yoked during randomization to the same study arm to prevent the possibility of cross-treatment contamination.

## Theoretical Framework for the Tailored PA Internet Intervention

The computer-based, expert system-driven, individually tailored intervention was based on social cognitive theory (SCT) [41] and the transtheoretical model (TTM) [42,43]. The intervention emphasized cognitive and behavioral strategies for increasing activity levels (eg, goal setting, increasing self-efficacy, self-monitoring, problem-solving barriers, increasing social support, and rewarding oneself for meeting PA goals). Table 1 illustrates the theoretical constructs targeted by intervention activities. In addition, the intervention logic model is shown in Figure 1.

**Table 1.** Theoretical constructs of social cognitive theory and the transtheoretical model targeted by intervention components.

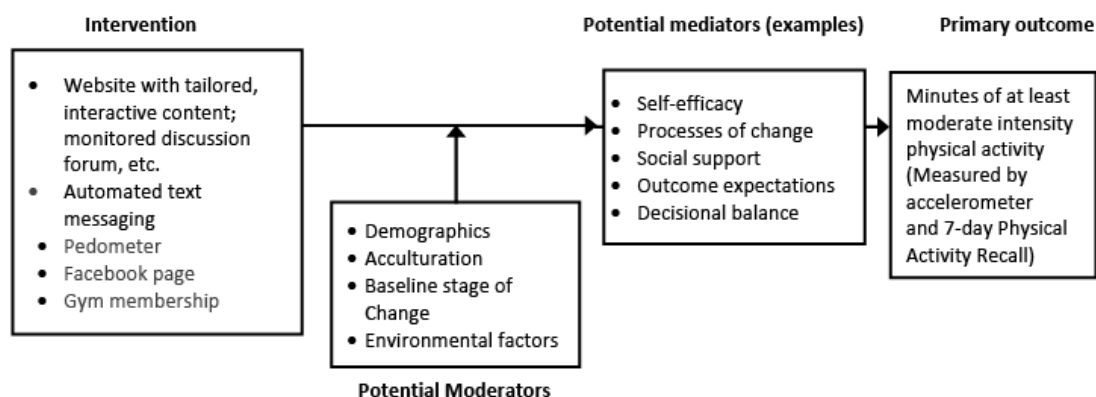
Construct (theory)	Intervention component
Self-regulation (SCT <sup>a</sup> )	<ul style="list-style-type: none"> <li>Website goal setting and PA<sup>b</sup> tracking feature allow participants to log their weekly PA goals and daily activity, including minutes of MVPA<sup>c</sup>, and to view a graph of how their actual PA compares with their goals. Participants receive a pedometer to track their daily step count</li> </ul>
Outcome expectations (SCT)	<ul style="list-style-type: none"> <li>Web-based daily and weekly exercise tips provide information about the benefits of PA. Text messages about PA benefits</li> </ul>
Stages of change and processes of change, for example, consciousness raising, social supports, and reinforcement management (TTM <sup>d</sup> )	<ul style="list-style-type: none"> <li>Participants complete monthly web-based questionnaires (stages of change and processes of change) and then receive computer-based, expert system–driven, individually tailored reports for increasing their PA based on their responses</li> </ul>
Self-efficacy (SCT and TTM)	<ul style="list-style-type: none"> <li>Participants complete monthly web-based questionnaires and then receive computer-based, expert system–driven, individually tailored reports</li> </ul>
Observational learning (SCT)	<ul style="list-style-type: none"> <li>Exercise videos in Spanish (led by diverse Latino men) let men observe peers leading exercises and allow practice, which leads to an increase in self efficacy</li> </ul>
Behavioral capability (SCT)	<ul style="list-style-type: none"> <li>Text reminders to access websites, log activity, and set goals; knowledge and skills information in concise tips, detailed tip sheets, text messages, and Facebook posts.</li> <li>Exercise videos in Spanish (led by diverse Latino men) teach skills that help participants learn to be more physically active.</li> </ul>
Reciprocal determinism (SCT)	<ul style="list-style-type: none"> <li>Information provided about the built environment: list on website of places to be active near participants' home; Facebook messages about community PA events</li> </ul>
Outcome expectations and self-efficacy and perceived barriers (SCT)	<ul style="list-style-type: none"> <li>Share motivational and culturally relevant information about benefits and how to address barriers in concise tips, detailed tip sheets, text messages, and Facebook posts.</li> <li>Exercise videos to promote self-efficacy.</li> </ul>
Social support (SCT)	<ul style="list-style-type: none"> <li>Provide social interaction and support through the online community discussion forum or on Facebook where participants can write messages and interact with each other. Concise tips, detailed tip sheets, text messages, and Facebook encourage exercising with family, spouse, friends, and coworkers</li> </ul>

<sup>a</sup>SCT: social cognitive theory.

<sup>b</sup>PA: physical activity.

<sup>c</sup>MVPA: moderate-to-vigorous physical activity.

<sup>d</sup>TTM: transtheoretical model.

**Figure 1.** Draft intervention logic model.

## Cultural Adaptations

Study materials were culturally adapted for a diverse population of Latino men. We enhanced cultural appropriateness through the following strategies using the frameworks described by Kreuter et al [44] and Resnicow et al [45]:

1. Peripheral or structural: We include appropriate physical activities, illustrations, role models, etc that are targeted for Latino men.
2. Evidential: We enhance perceived relevance by presenting evidence of the impact of a sedentary lifestyle for Latino men.
3. Constituent involving: We employ project staff who are Latino, including 1 Latino male research assistant.
4. Linguistic: We translate all study materials into Spanish that is appropriate for the Latino subgroups (eg, Dominican and Puerto Rican) in New England.
5. Sociocultural or deep structure: We incorporate cultural values and beliefs to provide context and meaning (eg, content about gender role expectations, conflicts with family time, and partner support) [12,44-53].

In designing intervention materials (eg, the web-based interface), we integrated components of the cultural dimensions theory by Hofstede, a framework for cross-cultural communication that shows the effects of the culture of a society on the values of its members and how these values relate to behavior [54]. In addition, our intervention addressed substantial PA barriers reported by Latinos in our formative research (ie, stress reduction, work and family time conflicts, lack of time, and accountability). Although similar PA barriers have been reported in non-Latino populations, in both men and women [55-58], adaptation of intervention content for cultural and linguistic relevance to Latino men was still required. Table 2 provides a description of how the intervention materials were culturally tailored.

**Table 2.** Cultural adaptations for the Hombres Saludables physical activity intervention.

Theme	Intervention modification
<b>Surface structure</b>	
Activity preferences	Focus intervention on gender-neutral and male-associated activities (eg, soccer and hiking)
Language	Translate intervention into appropriate Spanish for the diverse Latino audience
Literacy	Use qualitative methods (eg, focus groups with Latino men to review intervention materials) and low-literacy strategies (eg, Flesch Kincaid grade level less than eighth grade) to modify measures and materials to better match educational experience of participants
Role models	Provide videos, photos, and stories of diverse Latino men and families from the target population on a website
<b>Deep structure</b>	
Gender role expectations	Emphasize the need for the head of family to set a good example by being active and protect family members by exercising with them; highlight benefits of aerobic activities for men's health
Not wanting to spend money on fitness when that money should be used for family needs	Reframe PA <sup>a</sup> to include behaviors that do not require gym membership or special equipment, distribute information on low- or no-cost PA resources in the community (eg, hiking and walking trails, recreation centers, and pickup soccer games), offer a list of free Spanish or bilingual smartphone apps that provide access to exercise resources, and provide a 6-month gym membership
Perceived lack of access to culturally appropriate PA	Provide tailored community guides identifying places to do PA, including information and schedules for free and low-cost team sports at local recreation centers and community or social sports leagues; include Spanish exercise videos that are appropriate for Latino men; offer a list of free Spanish or bilingual smartphone apps that provide access to exercise resources; and provide a 6-month gym membership
<b>Barriers to PA</b>	
Stress reduction	Provide information on PA and stress reduction for stressors commonly experienced by Latino men
PA conflicts with work schedule	Provide tips for exercising at work or for transportation and on finding time with a hectic schedule; highlight low-cost local sports and activities that occur on nights and weekends
Lack of time and conflicts with family time	Augment existing content on this topic with examples that are familiar to Latino men (planning PA around family and work commitments); share Spanish exercise videos that are appropriate for Latino men; and provide membership to a gym that is open for extended hours, which helps men find time to exercise around work schedules. Provide tips and texts for getting children and family involved in PA and include specific suggestions regarding family-friendly activities (eg, easy hiking trails)
Partner support	Provide tips on eliciting social support from friends and family
Need for accountability	Provide pedometer, emphasize monthly personal reporting and feedback based on participant's reported PA (steps or minutes), provide normative feedback comparing their progress with others, send regular text messages asking about recent activity and reminding participants to log activity and answer monthly surveys, and offer private Facebook group to post progress and request support

<sup>a</sup>PA: physical activity.

## Tailored PA Internet Intervention Arm

### Website

Participants in the tailored PA internet intervention group received access to the Hombres Saludables study website. All website content was published in Spanish and adapted to be culturally and linguistically relevant for Latino men. The website was developed to be mobile phone friendly. Participants in this study arm were asked to log their minutes of MVPA each day. They were also asked to set a weekly PA goal and log it on the website. The website offered a goal setting and tracking feature to allow participants to view graphs of their actual level of PA compared with the goals they set each week. Participants were asked to complete monthly questionnaires on the study website, assessing key theoretical components of SCT and the TTM. Answers from these questions generated their individually tailored PA reports. These reports were published on the website

automatically upon completion of each monthly survey. The reports used a bank of more than 300 messages from the computer-based, expert system and offered feedback on (1) the current stage of motivational readiness for PA, (2) self-efficacy, and (3) cognitive and behavioral strategies associated with PA.

The computer-based, expert system also provided feedback on how the participant compared with individuals who are physically active based on American College of Sports Medicine guidelines [1] of engaging in the equivalent of 150 min a week of MVPA (normative feedback) and how the participant compared with their earlier responses (progress feedback) [14]. A few days after receiving the tailored report, a web-based motivation-matched PA manual based on the TTM stage of change for each participant was published on their individual website account. The manual emphasized cognitive and behavioral strategies for increasing activity levels such as goal setting, self-monitoring, problem-solving barriers, increasing



social support, and rewarding oneself for meeting PA goals (eg, nonfood rewards) [14]. Although the ultimate goal of the intervention was increasing total PA, content focused mostly on increasing leisure time-, lifestyle-, and transportation-related PA rather than occupational PA.

Other website features included resources to promote PA. Participants could access city guides containing useful information on where to be active in their city (eg, parks, bike paths, gyms, and local recreation centers), a list of free PA promotion apps participants could download on their smartphones, a series of Spanish language exercise videos found on YouTube, and concise daily and weekly tips published on the website throughout the 6-month intervention as well as detailed 2- to 3-page *tip sheets*. In the first 2 months, all participants received the following tip sheets: how to set achievable goals for PA, finding the time for PA, how to fit in short sets of PA throughout the day, and motivating yourself to be more physically active. Then, during their first monthly survey on the website, participants chose to receive up to 15 tip sheets of interest selected from a list of 20. Those tip sheets were then published on their website account throughout the intervention on a weekly or biweekly basis. Sample topics that participants could choose to receive included stretching, being active as a family, tips to exercise correctly, exercising outside, rewarding yourself for achieving your PA goals, etc. In addition, the website contained a community forum (for participants to write messages and interact with each other), an *Ask the Expert* area (where participants could ask a question and study staff post responses), and a section where participants could alert the staff if they sustained an injury during the study. Participants were also given a pedometer to help track their daily steps; alternatively, participants could choose to log daily steps using an app on their smartphone. See [Multimedia Appendix 1](#) for screenshots of the website.

### **Text Messages**

Throughout the 6 months of the intervention, participants received text messages 4 to 6 times per week. These included prompts to access new information posted on the website, such as their tailored tip sheets; reminders to log their minutes, set a weekly goal, and complete their monthly questionnaire; and texts that were informational and motivational, for example, suggestions to overcome barriers and enlist social support. Examples of the latter included: “Is lack of time a problem for you? Try waking up 15 minutes earlier to take a short 15-minute walk, and then another 15 minutes at lunchtime or in the afternoon for a second walk;” “There are many exercise videos on YouTube and in mobile apps. Look in the ‘Ways to Be Active’ section on the website for our recommendations for exercise videos and apps;” and “Remember that physical activity burns calories, improves sleep, increases your energy, and reduces stress.”

### **Facebook Group**

Participants were also given the option to join a private Facebook group where study staff posted weekly to the group with tips, quizzes, events, and information related to PA. Participants were encouraged to engage with the content, submit questions, and post comments. Each month, a random participant who had engaged with the Facebook content won a US \$25 incentive.

### **Gym Membership**

Participants also received a voucher for a free 6-month membership worth US \$60 to a local gym franchise with multiple locations. Participants who did not live in the surrounding Rhode Island or Massachusetts area received US \$60 toward the costs of a gym membership.

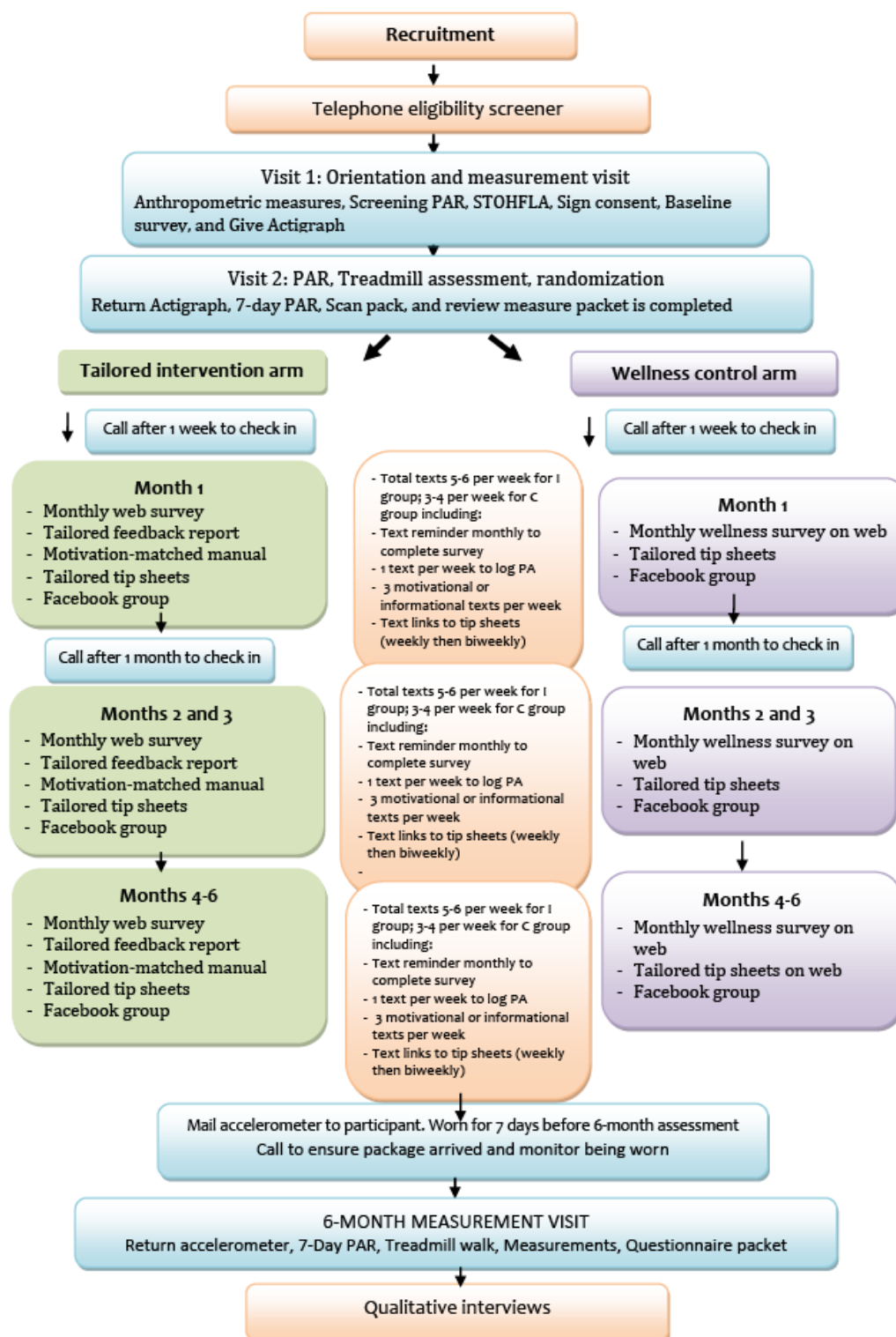
### **Check-In Phone Calls**

One week after enrolling in this study, intervention participants received a phone call from the study staff. The 5 to 10 min call ensured that all aspects of the website, Facebook, and text message alerts were functioning well, and the study staff answered any participant questions. After 1 month, the participants completed another 10 to 15 min call with study staff to review their progress and answer any study questions. A staff member supported the participants in creating a new goal for the second month of the study. If any barriers to PA arose, the staff member assisted the participants in developing solutions.

### **Attention-Matched Nutrition and Wellness Internet Group (Control Group)**

Participants randomized into the control arm received access to a Spanish language website with information on nutrition and men’s health and wellness topics unrelated to PA. The study staff guided participants through the website and set up their account. The website featured healthy recipes; app suggestions for healthy eating; and weekly tips on topics such as eating more fruits and vegetables, healthy drink choices, reducing salt intake, sleep health, prostate care, information about cholesterol, and supplements. Tip sheets on similar topics were also regularly posted on the website throughout the intervention on the same schedule as the intervention arm. Participants were asked to complete a monthly survey on the website on the same schedule as the PA arm. Survey questions asked about diet, sleep, and wellness habits. Participants completed the first survey during the baseline visit. Control arm participants also received text message alerts 3 to 4 times per week with reminders of new information on the website and helpful tips. Participants also received access to a private Facebook group that offered additional information on nutrition- and wellness-related topics. This group also received a check-in call from the study staff 1 week and 1 month after enrollment ([Figure 2](#)).

**Figure 2.** Hombres Saludables study flow diagram. C: control group; I: intervention group; PAR: physical activity recall; STOHFLA: Short Test of Functional Health Literacy in Adults.



**Feasibility Trial**

**Participant Recruitment**

We used various recruitment strategies in Rhode Island, Connecticut, and Massachusetts as well as nationally. Locally in Rhode Island, Connecticut, and Massachusetts, we advertised on Craigslist and posted flyers in local community organizations and businesses (eg, restaurants, barbershops, grocery stores,

and laundromats). We worked extensively with the local library systems and presented at local high school equivalency certificate, citizenship, and English language classes. We also attended local church groups, elementary schools, Latino men’s groups, and community organizations working with the Latino population. We visited worksites of companies with high Latino employment and posted information in college campus student centers and on student listservs at various local colleges. We

also ran paid radio ads on a local Spanish language FM radio station, performed a guest stint on a Latino radio talk show, and left study flyers and brochures with doctors' offices and health clinics. Due to a slower recruitment rate than anticipated, we also expanded recruitment efforts nationally by publishing paid ads on Facebook and Craigslist pages for different towns and cities, mainly focusing on the East Coast. Use of web-based recruitment, particularly the use of Facebook, has been shown to be an effective approach for recruiting participants in health research [59-61].

### Visit 1

A summary of the study and flow diagram is shown in Figure 2. Interested participants were screened over the phone for eligibility. Once eligibility was determined, potential participants were scheduled for their first visit. Local participants attended visits in person. Participants who lived too far away to attend in-person visits, hereafter referred to as *distance participants*, completed this visit by phone. We offered flexible scheduling for visits during weekends and weekdays and nights, both in person and via phone.

For participants attending visit 1 in person, the bilingual and bicultural research staff gave an overview of this study, described study steps and rights of participation, and answered participant questions. The participant then underwent measures to further assess eligibility, including height, weight, and waist circumference measurements; the S-TOFHLA literacy questionnaire; a brief 7-day physical activity recall (PAR) [62,63] listing the minutes of total MVPA they had done for each day of the previous week to assess their current activity level; and a basic text and web accessibility check to ensure that they were capable of using the internet and receiving text messages. A participant who did not score higher than 16 on S-TOFHLA or whose measurements calculated a BMI at 45 or higher become ineligible during this visit. Participants were also ineligible if they reported more than 60 weekly min of total MVPA. Eligible participants then signed the informed consent document. After this, they completed the baseline survey including demographic characteristics and questionnaires on PA-related psychosocial variables (stages and processes of change, self-efficacy, enjoyment, social support, stress, neighborhood cohesion, police profiling, and neighborhood safety). At the end of the visit, eligible participants received an ActiGraph wGT3X-BT accelerometer, with instructions to wear the accelerometer on their waist with a Velcro belt during waking hours for 7 consecutive days. Participants were also given a form to write down the dates and times they put on and took off the accelerometer. At the end of the visit, participants received a ClinCard, a reloadable prepaid card (similar to a debit card) for monetary incentives, and a sheet of frequently asked questions and answers about the study. We then scheduled their visit 2 to occur approximately 8 days later.

For visit 1, *distance participants* were mailed a copy of the informed consent document and a hard copy of S-TOFHLA to their home, ahead of their scheduled phone call. The study staff reviewed the informed consent document and then received verbal consent from the participants. Study staff asked these participants to self-report their height and weight. Waist

circumference measurements were not collected from distance participants. The participants completed the S-TOFHLA while on the phone with the study staff. After the phone call, the hardcopy document was mailed back to the study office. The staff member then administered the baseline survey questionnaire over the phone. For participants who had a personal computer, we offered the option to email a link for the participant to complete the survey themselves. After the phone call, eligible *distance participants* were mailed the accelerometer and a log form, as mentioned above, with instructions to wear the device for 7 consecutive days and a return envelope to mail the device and log form back immediately afterward.

### Visit 2 (PA Assessment and Randomization Session)

In-person participants returned for a second visit approximately 8 days after the first visit. They brought the accelerometer and the wear-time log form to the visit. Any participant with insufficient wear time (<3000 min over 4 days or <5 days of 600 min each) was asked to rewear the accelerometer, and the visit was rescheduled. Participants with sufficient wear time completed a 10-min treadmill walk to demonstrate moderate-intensity PA (3-4 miles per hour). Heart rate and rate of perceived exertion were documented throughout the treadmill walk by the study staff. The goal of the walk was to help improve the accuracy of participants' self-report of their PA by providing a real-time demonstration of a 10-min bout of moderate-intensity PA with no breaks. The protocol for this demonstration was developed by Dr Marcus and has been used in earlier studies [11-13,64]. Participants then completed a 7-day PAR [62,63]. If participants reported more than 60 min of total MVPA in bouts lasting 10 min or more, they became ineligible.

Participants were then randomized to 1 of the 2 Spanish language internet and text message-based conditions: tailored PA intervention arm or nutrition and wellness control arm. Group assignment was determined using a permuted block randomization procedure with small randomly sized blocks. Randomization was stratified by the TTM stage of change [42,43] to ensure an equal distribution of treatment assigned across levels of motivational readiness for PA.

At the end of visit 2, the study staff helped participants in the tailored PA intervention arm to set up their personalized website account. The study staff also set up a bookmark to the page on the participant's smartphone to aid easy access to the website and then provided thorough instructions on using all sections of the website. In the final phase of the visit, the study staff helped the participants set a personalized exercise goal and create a detailed PA plan for their first week. The staff members and the participants discussed potential barriers to completing this goal and how to overcome those barriers. The staff members walked the participants through these goal-setting steps and how to record their minutes of MVPA and goal on the website to ensure that the participants were able to complete these steps independently throughout the 6-month intervention.

At the end of the visit, the staff members reviewed the study goals and expectations and asked the participants to do the following:

1. Try to do MVPA for at least 10 min at a time, with no breaks.
2. Track how much exercise they perform each day and log the time on the website.
3. Wear the pedometer every day and log the steps on the website.
4. Review and revise the exercise goal each week to work up to 150 min of MVPA each week by the end of 6 months in the study.
5. Complete the monthly questionnaire on the website.

*Distance participants* completed visit 2 by phone and were guided through the same steps by the study staff. The visit was broken into 2 parts. Part 1 was completed on the day immediately after 7 consecutive days of accelerometer wearing. A staff member gave the participant a detailed explanation of what MVPA feels like, including examples of activities at this level. The staff member then completed the PAR by phone. The participant was instructed to return the accelerometer by mail, with a preaddressed envelope. Once the device was received back at the office, the study staff reviewed the data to ensure sufficient wear time and then scheduled part 2 of the visit by phone. In part 2, the *distance participant* was randomized into one of the study arms using the same randomization procedure as local participants, and then, the staff member guided the participant through the website and other study components by phone.

### Study Incentives

For participants traveling to our office for in-person visits, we offered a US \$10 incentive to aid with the cost of transportation and a monthly US \$5 incentive to aid with cell phone and data costs. Participants were also compensated for their time at evaluation time points, receiving US \$25 for completing their second visit and US \$50 for completing the 6-month assessment visit. In addition, participants received US \$10 for returning their accelerometer at visit 2 and at the 6-month visit. Each time the participants completed a monthly web-based questionnaire, they also received a US \$10 incentive. Local participants received a voucher for a free 6-month gym membership worth US \$60, and distance participants received US \$60 toward the cost of a gym membership. Those in the PA intervention arm received the gym membership at the start of the study, whereas those in the control arm received the membership (or financial equivalent) at the 6-month follow-up.

### 6-Month Visit

At the end of the 6-month intervention, participants were contacted again to set up their final assessment visit. Participants were mailed an ActiGraph accelerometer and asked to wear it for 7 complete days, following the baseline protocol. Participants were scheduled for their assessment visit on day 8 after they started wearing their monitor. *Distance participants* mailed the device back to our office on day 8 and conducted the visit with the study staff by phone.

At the start of the visit, the study staff reviewed the ActiGraph wear data to ensure that it was worn for sufficient time. Any participant with insufficient wear time was asked to rewear the accelerometer, and the visit was rescheduled. Participants then

completed the same survey measures from the baseline assessment, with some additional process evaluation questions. Height, weight, and waist circumference were recorded again, followed by a 10-min treadmill walk (for in-person participants) and the PAR assessment. Finally, after the 6-month visit, the study staff conducted brief semistructured qualitative interviews with study participants who agreed to complete this interview.

## Measures and Outcomes

### Demographics

Demographic questions at baseline assessed age, education, race, ethnicity, income, employment status, marital status, household size, country of birth, Hispanic subgroup, and years lived in the United States. In addition, the Brief Acculturation Scale [65] asked 4 questions about languages used in different contexts.

### PA Outcomes

The primary outcome measure is total PA, as measured by an accelerometer (ActiGraph wGT3X-BT). All participants were asked to wear an accelerometer for 7 days to measure their movement and intensity of activity. The minimum acceptable wear time is 5 days, with at least 600 min daily, or 4 days, with at least 3000 min total. The daily and weekly minutes of MVPA were calculated with Actilife software, using a minimum cutoff point of 1952 [66] to define the moderate-intensity PA and a minimum activity bout of 10 min, as current recommendations suggest that MVPA activities should last at least 10 min at a time [67,68]. Accelerometers have been validated with both total energy expenditure [69] and heart rate telemetry [70].

A self-reported measure of total weekly PA was also included as an outcome measure of MVPA. Using the 7-day PAR [62,63], an interviewer asked participants about moderate, hard, and very hard activities that they might have engaged in during each morning, afternoon, and evening over the past week. The 7-day PAR has repeatedly shown acceptable internal consistency, reliability, and concurrent validity with objective measures of PA [71-75], along with sensitivity to changes [72,73] in both moderate and intensive levels of PA [74,75]. In addition, the 7-day PAR demonstrated test-retest reliability among Latino participants [76]. The 7-day PAR data were assessed to overlap with accelerometer wear to corroborate the self-reported data.

### Psychosocial Variables

Readiness to change, self-efficacy, and processes of change were also assessed as psychosocial constructs related to PA. The 5-item PA stages of change questionnaire determines whether a participant is in the precontemplation, contemplation, preparation, action, or maintenance stage of PA change. This measure has demonstrated reliability and concurrent validity with measures of self-efficacy and current activity levels [77,78]. The 40-item processes of PA change measure asks participants how often (never, seldom, occasionally, often, or repeatedly) they engage in various cognitive and behavioral strategies associated with behavior change [79]. The measure contains 5 behavioral subscales (counterconditioning, helping relationships, reinforcement management, self-liberation, and stimulus control) and 5 cognitive subscales (consciousness raising, dramatic relief,



environmental re-evaluation, self-re-evaluation, and social liberation). A 5-item self-efficacy measure was included to assess confidence in one's ability to exercise in various situations on a 5-point scale, ranging from not at all confident to extremely confident [77]. In addition to being administered at baseline and at 6-month follow-up, the readiness to change, self-efficacy, and processes of change measures were administered on a monthly basis via the website to help generate the computer-based, expert system feedback reports for the intervention group.

Additional psychosocial measures related to PA included social support, PA enjoyment, perceived stress, and perceived quality of life. The social support measure (social support for exercise) [80] included 2 sets of 14 items (1 set for friends and 1 set for family) related to the frequency with which friends or family members provided social support for PA over the past 3 months, with response options including none, rarely, a few times, often, very often, or does not apply. The Physical Activity Enjoyment Scale [81] measures the level of enjoyment that a person derives from engaging in PA. Using a scale of 1 to 7, participants were asked to rate their feelings on 18 items about their enjoyment of PA (eg, a rating of 1 means *I find it pleasurable* and a rating of 7 means *I find it unpleasurable*). The Perceived Stress Scale [82,83] is a widely used, validated instrument composed of 10 items to measure perceived stress in the past month, with a 5-point scale, where 0 means never and 4 means very often. The perceived quality of life was measured using a single item modified from the 26-item World Health Organization Quality of Life measure [84]. Participants were asked to rate their quality of life as excellent, very good, good, or poor.

### **Neighborhood Measures**

Measures of neighborhood safety, neighborhood social cohesion, neighborhood police attitudes, and fear of police were also administered. Neighborhood safety was assessed with a single item [85] asking participants if they felt safe in their neighborhood all of the time, most of the time, some of the time, or none of the time. The Neighborhood Social Cohesion [86] scale is a reliable, validated set of 4 items asking participants to rate their level of agreement with statements about their neighborhood. Neighborhood police attitudes were assessed with 7 items asking whether police activities in the neighborhood (eg, stopping too many people on the street without a good reason, stopping people because of the color of their skin, being rude to people they stop, and disrespecting women when they stop them) were a big problem, some problem, or no problem [87,88]. Fear of police was assessed with 2 questions that asked if the participant agrees or disagrees (strongly agree, agree, neither agree nor disagree, disagree, and strongly disagree) with the following statements [87]: Are you sometimes afraid that police will stop you and threaten to arrest you when you are completely innocent? and Are you sometimes afraid that police will stop and threaten to arrest one of your children, or a younger member of your family, when they are completely innocent? On the basis of our earlier work [89], a new neighborhood police attitude question developed by our team was included to ask how worried a participant was that police would stop them if they were exercising in their neighborhood. Response options

to this question included not at all worried, somewhat worried, and very worried.

### **Built Environment Measures**

To assess built environment factors that influence PA, including land use characteristics, sidewalks, shoulders and bike lanes, street characteristics, and quality of the pedestrian environment, we used Objective Neighborhood Audits using Google Street View [90-92] and the Active Neighborhood Checklist (ANC) [93]. We used a 0.5-mile buffer around participants' homes. We used Google Street View to conduct the ANC audit, which has demonstrated excellent reliability with in-person audits and audits comparing new, archived, and commercial imagery [91,94].

### **Control Group Measures**

For the nutrition and wellness control arm, a wellness questionnaire assessed knowledge regarding the men's wellness topics presented in the control materials. We also assessed pre and post fruit and vegetable intake using the National Cancer Institute's *Eating at America's Table All Day Screener* [95].

### **Process Evaluation**

Standardized protocols were used in training staff to conduct all study visits. All PAR questionnaires were reviewed for errors before data entry. To ensure receipt of treatment, phone calls were conducted 1 week and 1 month post randomization to ensure proper use of the pedometer and self-monitoring on the website. Participants who were not completing their PA logs or their monthly web-based questionnaires were also contacted. To measure fidelity and dose of treatment implementation—and to provide insight into participant usage—the website captured the number of log-ins and views of each page or link; how much time participants spent on the website; and what participants entered on the website, that is, goals, discussion board posts, *Ask the Expert* submissions, etc; data were tracked by user selections and time stamped accordingly. Receipt of text messages was assessed by the text messaging system, and Facebook participation was measured by counting participants' engagement such as likes, comments, and posts.

### **Feasibility**

Our main feasibility measure is a participant retention rate of 80% or more. To inform a future study, we also measured time to recruit 50 participants, what proportion of recruited participants were eligible and reasons for ineligibility, the yield of various recruitment methods, and baseline process data (proportion of eligible participants who completed study visits, length of visits, time range from initial recruitment to randomization, visits attempted and completed on different days, duration of visit, refusals, and interviewer notes on surveys). Six-month visit process data included duration of the visit, the proportion of randomized participants completing the study, and those who refused or were dropped from the study along with reasons for dropping as well as participants we were unable to reach for follow-up.

### **Acceptability**

In the 6-month follow-up survey, participants completed questions regarding their overall level of satisfaction with the

intervention (*In general how satisfied were you with the intervention?*); their satisfaction with each component of the intervention; the degree to which these components were accessed, read, and/or used; and how helpful they were. We also conducted a poststudy qualitative interview with the study participants to explore how they found out about the study and why they joined, their perceptions about various study protocols (recruitment, visits, treadmill walk, incentives, etc) and individual components of the intervention (eg, website components, text messages, Facebook, and gym membership), and thoughts on ideas for future interventions. Qualitative interviews were digitally recorded, with the recordings sent to a professional company for transcription and translation into English. The transcribed responses to each interview question are being thematically coded by graduate students using similar methods as the focus groups described above.

### Power Analysis

Our sample size estimates were based on results from 2 of our completed studies with accelerometer data for Latina participants [12,15]. In addition, in a small pilot [19], the mean change from baseline to 6 months in MVPA from the subsample of male participants who were given accelerometers was 76.4 min per week (SD 113.5) for the intervention versus 15.0 min (SD 22.6) for the control. Although the effect size ( $d=0.75$ ) was large, the subsample was small ( $N=9$ ) and, thus, must be considered with caution. In our recently completed intervention with Latinas [15], the mean change in total MVPA was 42.5 min per week (SD 81.8) for the intervention versus 9.0 min (SD 45.7) for the control, yielding an effect size of  $d=0.51$ . With 25 participants randomized to each arm, we expected to have at least 43% power to detect differences in accelerometer-measured MVPA between conditions at 6 months, assuming an effect size of  $d=0.51$  and 75% power if  $d=0.75$ , using a two-tailed significance  $\alpha$  of .05. The web-based program for Latinas had a slightly higher effect size; therefore, this was a conservative estimate. Although we do not expect to achieve statistically significant group differences in this pilot study, we will determine the effect size achieved between groups and use these data to estimate the sample size needs for a future RCT.

### Planned Analyses

The primary aim of this study is to determine the feasibility, acceptability, and preliminary efficacy of the tailored PA intervention. We will consider the intervention feasible if at least 80% of the randomized participants are retained at the 6-month follow-up. The intervention will be considered acceptable if at least 80% of participants completing the 6-month follow-up respond favorably (*satisfied* or *very satisfied*) to the question *In general how satisfied were you with the intervention?* on the 6-month follow-up survey. We also asked more questions about intervention and study acceptability on the 6-month survey and the poststudy qualitative interviews described earlier. The main efficacy outcome was minutes per week of total MVPA, as measured by accelerometer data and PAR self-report, assessed at baseline and 6 months after baseline. The hypothesis is that participants in the PA intervention condition will have greater increases in minutes of

total MVPA from baseline to post intervention (6 months) than participants in the control condition.

As a preliminary step, we will assess potential between-group differences in baseline characteristics (demographics and baseline PA level) using graphical methods and nonparametric and parametric tests as appropriate (eg, the Wilcoxon rank sum test for skewed data,  $t$  tests for normally distributed continuous data, and chi-square tests for categorical data). Any variables not balanced by randomization will be controlled for as covariates in subsequent analyses if they are correlated with the outcome (eg, minutes per week of MVPA) at a modest  $P<.10$  level. We will estimate the preliminary efficacy of intervention compared with control using a generalized linear model in which we regress minutes per week of objectively measured MVPA at 6 months on the treatment assigned, baseline value of the outcome, and potential confounders (including those variables not balanced by randomization). To avoid the effects of outliers, we apply a normalizing transformation (if necessary) to the outcome before analysis. Should this transformation not adequately bring the data toward normality, we will model the median outcome (instead of the mean) using a quantile regression model.

Modeling is performed using a likelihood or quasi-likelihood-based approach and, thus, makes use of all available data (intent-to-treat sample) to produce consistent estimates of the regression parameters. Our goal is to estimate effect sizes, rather than strict statistical hypothesis tests. A similar modeling strategy will be used to estimate effects on self-reported minutes per week of MVPA.

Potential moderators will be examined using a similar analytic approach to that described earlier. For example, the total PA at 6-month follow-up (as measured by the accelerometer) will be regressed simultaneously on each moderator (eg, neighborhood PA environment profiles), as determined by latent class analysis, treatment assignment, and the interaction between the 2. If the interaction term is nonzero, we will conclude that there is evidence for a potential moderator. Models will also control for potential confounders of the association, including baseline PA and any variables unbalanced between arms. Our interest is in estimating effect sizes for conditional effects rather than strict statistical hypothesis testing.

## Results

This study was funded in September 2016. Initial institutional review board approval was received in February 2017. Focus groups and intervention development were conducted from April 2017 to January 2017. Recruitment for the clinical trial was carried out from February 2018 to July 2019. Baseline data collection was carried out from February 2018 to October 2019, with a total of 43 participants randomized. Follow-up data were collected through April 2020. Data cleaning and analysis are ongoing, and we expect study results to be published in summer 2021.

## Discussion

### Importance of the Study

PA is a critical health behavior known to promote health and prevent the onset of chronic diseases and mortality [1,96,97]. Previous research indicates that Latino men are underserved with respect to inclusion in interventions designed to increase PA [16-18]. Therefore, this study addresses these research gaps by specifically targeting diverse subgroups of underserved Latino men (ie, Caribbean and Central and South American) and engaging them in the intervention design [10,98]. This engagement is critical as (1) the majority of PA research with Latino men to date has involved mainly Mexican Americans [21,55], and these results may not generalize to other Latino men subgroups, and (2) there may be additional cultural considerations for retention of non-Mexican Latino men and their perceived acceptability of a PA intervention [10,18,98]. As such interventions remain untested with diverse Latino men, we designed this novel tailored web- and text-based PA intervention and piloted it in a feasibility RCT with these diverse groups of Latino men. If the results of the pilot study provide support for feasibility, acceptability, and preliminary efficacy, then a larger, fully powered efficacy RCT will be tested with diverse Latino men.

The Hombres Saludables study leverages theories of behavior change and low-cost, technology-based intervention delivery mechanisms that demonstrate high reach with Latinos, most of whom use the internet and own a cell phone [29,30], although future research should consider that internet usage for health-related purposes may vary by the Latino subgroup [98]. These theoretical and technological components have demonstrated efficacy in other populations [32-34], including Latinas [11-15,37]. For Latino men, however, studies documenting the efficacy and effectiveness of such low-cost interventions are lacking [16-18]. In the limited intervention research that does exist, 98% of the 48 participants in one study identified as either Mexican or Mexican American. The intervention focused on weight loss, not specifically PA, and involved weekly in-person individual sessions with a bilingual, bicultural Hispanic male lifestyle coach, which, although effective in increasing leisure time PA, raises cost, replicability, and scalability concerns [21]. Another small study with 45 Latino participants (mostly Mexican American) delivered a 6-month intervention wherein participants received a baseline counseling session and then individually tailored PA print materials and text messages. Intervention participants increased their total MVPA significantly more than the control group [22]. Thus, the findings from the Hombres Saludables study will contribute to intervention research by providing preliminary evidence of how integration of theories of health behavior change with internet and text-based intervention components may impact PA among diverse Latino men, a disparity group with low levels of leisure time PA [2,10].

With regard to the intervention dose and components of the study design, literature findings indicate that interventions averaging 12.7 weeks in duration (ranging from 2 to 52 weeks) yield small but significant increases in PA [32] and that daily

text messaging has been associated with increases in PA [99]. However, in the systematic review and meta-analysis citing the duration and effectiveness of web- and text-based interventions, the overwhelming majority of studies were with White non-Latino adults [32]. The Hombres Saludables intervention will provide preliminary effect sizes of a 6 month web- and text-based intervention for diverse Latino men that uses less frequent text messaging than the daily text messaging identified in the PA literature [32,99]. Our findings, if supported via additional research, could help inform the study design for future interventions that involve text messages, including (and perhaps beyond) PA interventions targeted to diverse Latino men.

In addition, achieving the study aims will provide evidence for potential mediators and moderators of PA, which remain underexamined in Latino men. The mediators in this study are based on theoretical constructs (eg, self-efficacy and social support) associated with increases in PA among Latina women and other racial or ethnic subgroups [11-15,28,77]. Although, well-established evidence points to the effects of these mediators on PA, this study provides preliminary evidence as to whether these mediators explain changes in PA among diverse Latino men.

Although the intervention focuses mostly on changing the psychological, behavioral, and economic barriers to PA, we will explore potential moderating effects of individual and environmental factors on PA. At the individual level, we will examine whether important demographics (eg, age, country of origin, marital status, and education), acculturation, or baseline stage of change (based on TTM) impact changes in PA among Latino men. At the neighborhood level, we will explore walkability and social conditions, which have not been reported in PA intervention studies with Latino men. Although many studies explore associations of neighborhood walkability with PA (including studies with Latinos) or as a potential moderator of intervention efficacy [100-104], associations between other neighborhood social conditions and PA remain unanswered. This study will provide preliminary evidence for some of these unanswered questions. For example, this intervention will examine whether perceived neighborhood-based police profiling impacts PA among Latino men. In previous qualitative studies with disparity groups, neighborhood race and gender-based police profiling is cited as a potential barrier to PA for racial or ethnic minority men [89,105]. Consequently, this study seeks to build upon the limited available evidence for Latino men by exploring the potential moderating effects of these individual and environmental variables in a PA-focused pilot RCT.

### Study Limitations and Strengths

Although the strengths of this study are numerous, a few potential challenges exist. Recruitment and retention of Latinos in PA interventions are often challenging [106], and it is possible that there are unforeseen confounding factors that may impact the study results. However, the purpose of this pilot RCT is to determine the feasibility, acceptability, and preliminary efficacy of the intervention. Although contamination is often a concern when implementing interventions, we do not expect this to be a significant problem. If members of the same family participated, they were yoked together. In addition, the PA



Facebook group membership was accessible only to participants in the PA intervention, and the web- and text message-based components were tailored to each participant. Despite these potential limitations, the Hombres Saludables study aims to increase PA among diverse Latino men by engaging them in a culturally appropriate, low-cost, and easily accessible internet and cell phone-based intervention. The intervention also provided economic incentives, including a gym membership, to overcome the cost barriers associated with PA. To our

knowledge, no studies have included all the combined intervention components that are incorporated into the Hombres Saludables study. We expect that this study will demonstrate preliminary efficacy and lead us to implement a larger RCT in the future. This intervention has the potential to be scalable and to reach and engage a large number of diverse Latino men, a disparity group with respect to PA and related chronic diseases and mental health [1,2,8-10,18].

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## Acknowledgments

This study was funded by the National Heart Lung and Blood Institute #R34HL128067.

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## Conflicts of Interest

None declared.

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### Multimedia Appendix 1

Screenshots of the Hombres Saludables website.

[[DOCX File, 2247 KB](#) - [resprot\\_v10i1e23690\\_app1.docx](#) ]

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### Multimedia Appendix 2

Peer review of study grant proposal.

[[PDF File \(Adobe PDF File\), 153 KB](#) - [resprot\\_v10i1e23690\\_app2.pdf](#) ]

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## Abbreviations

**ANC:** Active Neighborhood Checklist  
**MVPA:** moderate-to-vigorous physical activity  
**PA:** physical activity  
**PAR:** physical activity recall  
**RCT:** randomized controlled trial  
**SCT:** social cognitive theory  
**S-TOFHLA:** Short Test of Functional Health Literacy in Adults  
**TTM:** transtheoretical model

*Edited by G Eysenbach; submitted 19.08.20; peer-reviewed by R Joseph, K Mateo; comments to author 20.10.20; revised version received 20.11.20; accepted 24.11.20; published 29.01.21.*

*Please cite as:*

Gans KM, Dulin A, Palomo V, Benitez T, Dunsiger S, Dionne L, Champion G, Edgar R, Marcus B  
*A Tailored Web- and Text-Based Intervention to Increase Physical Activity for Latino Men: Protocol for a Randomized Controlled Feasibility Trial*  
*JMIR Res Protoc* 2021;10(1):e23690  
URL: <http://www.researchprotocols.org/2021/1/e23690/>  
doi: [10.2196/23690](https://doi.org/10.2196/23690)  
PMID: [33512327](https://pubmed.ncbi.nlm.nih.gov/33512327/)

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Protocol

# Repeated Transcranial Magnetic Stimulation for Improving Cognition in Patients With Alzheimer Disease: Protocol for a Randomized, Double-Blind, Placebo-Controlled Trial

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## Abstract

**Background:** Alzheimer disease has no known cure. As existing pharmacologic interventions only modestly slow cognitive decline, there is a need for new treatments. Recent trials of repetitive transcranial magnetic stimulation (rTMS) have reported encouraging results for improving or stabilizing cognition in patients diagnosed with Alzheimer dementia. However, owing to small samples and lack of a well-controlled double-blind design, the results to date are inconclusive. This paper presents the protocol for a large placebo-controlled double-blind study designed with sufficient statistical rigor to measure the efficacy of rTMS treatment in patients with Alzheimer dementia.

**Objective:** The objectives are to (1) recruit and enroll up to 200 eligible participants, (2) estimate the difference in treatment effects between active treatment and sham treatment, (3) estimate the difference in treatment effects between two doses of rTMS applications, (4) estimate the duration of treatment effects among responders to active rTMS treatment, and (5) estimate the effect of dementia severity on treatment outcomes among patients receiving active rTMS treatment.

**Methods:** We have designed our study to be a double-blind, randomized, placebo-controlled clinical trial investigating the short- and long-term (up to 6 months) benefits of active rTMS treatment at two doses (10 sessions over 2 weeks and 20 sessions over 4 weeks) compared with sham rTMS treatment. The study will include patients aged  $\geq 55$  years who are diagnosed with Alzheimer disease at an early to moderate stage and have no history of seizures and no major depression. The primary outcome measure is the change in the Alzheimer Disease Assessment Scale-Cognitive Subscale score from pretreatment to posttreatment. Secondary outcomes are changes in performance on tests of frontal lobe functioning (Stroop test and verbal fluency), changes in neuropsychiatric symptoms (Neuropsychiatric Inventory Questionnaire), and changes in activities of daily living (Alzheimer Disease Co-operative Study-Activities of Daily Living Inventory). Tolerability of the intervention will be assessed using a

modification of the Treatment Satisfaction Questionnaire for Medication. We assess participants at baseline and 3, 5, 8, 16, and 24 weeks after the intervention.

**Results:** As of November 1, 2020, we have screened 523 individuals, out of which 133 were eligible and have been enrolled. Out of the 133 individuals, 104 have completed the study. Moreover, as of November 1, 2020, there has been no serious adverse event. We anticipate that rTMS will considerably improve cognitive function, with effects lasting up to 3 months. Moreover, we expect rTMS to be a well-tolerated treatment with no serious side effect.

**Conclusions:** This protocol design will allow to address both the rTMS active treatment dose and its short- and long-term effects compared with sham treatment in large samples.

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

**International Registered Report Identifier (IRRID):** DERR1-10.2196/25144

(*JMIR Res Protoc* 2021;10(1):e25144) doi:[10.2196/25144](https://doi.org/10.2196/25144)

## KEYWORDS

repetitive transcranial magnetic stimulation; Alzheimer disease; double blind; treatment; placebo controlled; randomized

## Introduction

### Background

Dementia is a growing problem in our society as life expectancy increases. The leading cause of dementia, Alzheimer disease, has no cure, with current treatment options limited to slowing the progression of cognitive impairment. Recent small-scale clinical trials of high-frequency repetitive transcranial magnetic stimulation (rTMS) have shown some improvement in the cognitive abilities of patients with mild to moderate Alzheimer disease [1-15], with effects that diminish over a period of 2 to 3 months [8].

Cholinesterase inhibitors are the current treatment mainstay for Alzheimer disease. These medications increase the excitability of cells that respond to acetylcholine. The most commonly used medication, donepezil, shows some benefits in 20% to 60% of patients [16], but a substantial and marked benefit in only 2.3% of patients [17]. A long-term follow-up study of donepezil showed no significant benefit compared with placebo for improving or preventing declines in activities of daily living among patients with Alzheimer disease [18]. Moreover, some patients discontinue these drugs owing to severe side effects [16,17]. Thus, better treatments are needed. A few recent studies have suggested that modulating cortical excitability through noninvasive brain stimulation using rTMS is a promising approach to treatment, either alone or in addition to cholinesterase inhibitors [1-15].

rTMS is a noninvasive nonpharmacological technique that is quick to administer and relatively easy for patients to tolerate, with no lasting side effects. It is a procedure in which a series of electric currents are pulsed through a coil placed on the scalp; they produce a time-varying magnetic field [19] that passes through the skull to the brain, wherein a small current is induced in the underlying cortical tissue. Low-frequency pulses (<5 Hz) seem to decrease cortical excitability through the well-described process of long-term depression, while high-frequency pulses (10-20 Hz) seem to increase cortical excitability and synaptic plasticity through long-term potentiation mechanisms [20-22]. Long-term potentiation has a role in synaptic plasticity and is regarded as one of the central cellular mechanisms of learning and memory [23]. rTMS at either low or high frequency has

been studied as a potential treatment for a wide variety of neurological and neurodegenerative disorders (eg, depression, Alzheimer disease, Parkinson disease, and stroke). Currently, the use of rTMS is only approved for the treatment of major depressive disorders.

### Development of the Protocol

A few studies [1-8], including some from our team, have explored the possibility of rTMS as a treatment for Alzheimer disease in small samples (<45) with similar protocols, that is, high-frequency rTMS applied bilaterally to the dorsolateral prefrontal cortex (DLPFC). The assessments used in these studies mostly included Mini-Mental State Examination (MMSE) and Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog; some only used performance on an object/action naming task). They all reported some improvements over the course of treatment. Not every study had a sham-treated control group. Only one of these studies investigated the durability (up to 3 months) of the treatment among responders. None of these studies reported any adverse effect of the treatment.

To date, such studies have yielded conflicting results, which may be due in part to methodological limitations, such as a small sample size and the lack of a well placebo-controlled double-blind design. We aim to address these limitations in a large sample clinical trial investigating the efficacy of rTMS treatment and the duration of its effects. We will also explore the characteristics of responders and nonresponders.

Previous studies of rTMS in patients with Alzheimer disease used different rTMS protocols (ie, different areas of stimulation, duration and frequency of stimulation, coil type, number of pulses, and intertrain interval), without directly addressing their suitability for Alzheimer disease. The most important parameters of rTMS treatment are stimulation frequency and the location targeted by this stimulation. Many previous studies of rTMS treatment in the context of Alzheimer disease have used high-frequency (10-20 Hz) stimulation bilaterally to the DLPFC in order to increase cortical excitability. The DLPFC plays an important role in executive functions, such as planning, organization, and decision-making, with a well-established key role in working memory. Dementia commonly affects these

cognitive processes, and it is related in part to DLPFC dysfunction [24]. Other studies have stimulated the Broca area, Wernicke area, parietal somatosensory association cortex, right frontal gyrus, right superior temporal gyrus, parietal P3/P4, posterior temporal T5/T6, and precuneus, and combinations thereof with varying degrees of success [9-15]. The only large study so far used neuroAD therapy applied over 6 weeks to six sites (three at a time and alternating across days). This study claimed a considerable improvement (ie, 31.7% had a 0-4 ADAS-Cog improvement for active treatment compared with 15.4% for sham treatment) in people with Alzheimer disease and baseline Montreal Cognitive Assessment (MoCA) scores less than 30 [14]. Weiler et al have reviewed the extant literature up to 2018 [25].

Individuals with Alzheimer disease may have profound impairment of metabolic interactions between neurons and astrocytes owing to an abnormal glutamate-glutamine (Glx) cycle [26]. Application of high-frequency rTMS to the left DLPFC area has been shown to increase Glx levels and normalize the Glx cycle [27]. High-frequency rTMS also increases cerebral blood flow and glucose metabolism in stimulated and remote brain regions [28], as well as reduces intracortical inhibition at the stimulation site [29]. High-frequency rTMS applied to the right DLPFC area has been shown to alleviate anxiety symptoms [30], which are considerably higher in patients with Alzheimer disease at mild to moderate stages than age-matched healthy controls [27,28,31,32]. Enhanced synaptic plasticity has been suggested as a potential mechanism for the effects of high-frequency rTMS [21].

Cortical excitability is observed following repetitive high-frequency stimulation [33,34]. Long-term potentiation-like changes in synaptic strength are widely presumed to be a mechanism of learning and memory. It has been shown that 100-Hz magnetic stimulation induces long-term potentiation effects in rat hippocampal slices [35], while related synaptic enhancement has been reported in cortical structures following 10 to 20-Hz stimulation [36,37]. High-frequency rTMS can considerably upregulate brain-derived neurotrophic factor (BDNF) levels [38], which decline within the hippocampus in patients with Alzheimer disease [39]. BDNF levels are affected by neuronal activity and long-term potentiation, which regulate these plasticity-related neurotrophins. Moreover, rTMS is a modifier of inhibitory neuron function. In hippocampal slices, 10-Hz stimulation reduces gamma aminobutyric acid (GABA)ergic synaptic strength in principal neurons. This supports models and mechanisms involving GABAergic synapses modulating the overall inhibitory/excitatory balance [40].

Building on this promising body of research, we chose to apply high-frequency rTMS bilaterally to the DLPFC. We speculated that this would benefit people with Alzheimer disease via enhanced blood flow and glucose metabolism, synaptic plasticity, and improved connectivity. Either side of the DLPFC will likely activate the basal forebrain cholinergic complex, which has projections over most of the cortex and has connectivity via GABAergic inputs to the midbrain regions. New studies have shown a link between GABAergic dysfunction

and cognitive function [41-43]. Consequently, the increased excitability of these less GABA-suppressed areas in the brain of patients with Alzheimer disease may allow for increased response in not only cortical regions but also midbrain regions, which are important as major sources of cholinergic, serotonergic, and norepinephrinergic inputs to many regions of the brain.

The other parameters of rTMS treatment selected for this clinical trial, such as the number of pulses, intertrain intervals, and the duration of treatment, are rather arbitrary within a range [44]. They were selected from among specific parameters with demonstrated effectiveness in the extensive rTMS literature on Alzheimer disease [1-15], and depression as a depressive symptom is often comorbid with Alzheimer disease [45].

The intertrain interval in this trial was selected for its efficiency and safety profile as documented in international guidelines for the use of high-frequency rTMS [46,47]. Alternative stimulation protocols, such as theta-burst stimulation [44], are more efficient, but were not selected for study because there is only limited evidence for their effectiveness in Alzheimer dementia.

As for the choice of coil, there are only a few options. Double cone and H coils are used for reaching deep areas of the brain (up to 5-cm penetration), but they have not been used in Alzheimer treatment studies owing to the uncomfortable facial twitches that they may cause during high-frequency stimulation. As nearly all the studies cited herein use the figure-8 coil, this configuration was chosen. Pulses of both figure-8 and round coils penetrate only to the neocortex close to the skull surface of the brain.

### Choosing rTMS Parameters

The investigation of rTMS as a potential treatment for Alzheimer disease presents many challenges. Among these challenges is the multitude of parameters that may impact the efficacy of treatment, including, but not limited to, (1) the target area of stimulation, (2) the total number of pulses, which is also correlated with the duration of the treatment, (3) the frequency of the pulses, (4) the intensity of the pulses (percentage of the resting motor threshold [RMT]), and (5) the protocol of delivery of the pulses (train length, intertrain interval, etc).

Guerra et al considers managing the many variabilities in noninvasive brain stimulation studies [44]. To date, there is no study that can provide convincing answers as to what the optimum parameters are. For a tabularized review on the used rTMS parameters, please refer to a previous report [25]. Thus, we are still at the stage of pilot studies to determine an optimum protocol for Alzheimer rTMS treatment. One main constraint is the number of eligible study participants. This limits the number of protocols to be tested if we desire to have a high statistical power in our outcome measures. This study has endeavored to select reasonable and justifiable values for each of these parameters, mainly based on our previous pilot studies [8,48], which were themselves based on previous work in the field.



## Study Goal, Objectives, and Hypotheses

The overall goal of this study is to compare the efficacy of high-frequency active versus placebo rTMS for the treatment of cognitive impairment among people with mild to moderate Alzheimer dementia. The specific objectives and hypotheses of the study are as presented below.

First, estimate the difference in treatment effects among patients treated with active as compared with placebo high-frequency rTMS applied bilaterally to the DLPFC. Hypothesis 1 (H1) is as follows: better cognitive performance will be seen in patients randomly assigned to the active treatment group compared with those assigned to the placebo group.

Second, estimate the difference in treatment effects for patients receiving 4 weeks of rTMS versus 2 weeks of rTMS. Hypothesis 2 (H2) is as follows: four weeks of rTMS will be more effective than 2 weeks of rTMS in improving cognitive function.

Third, estimate the duration of treatment effects among responders to active rTMS, where response is defined as improvement in the ADAS-Cog of  $\geq 3$  points. Hypothesis 3 (H3) is as follows: treatment effects will still be detectable 8 weeks postintervention, although not necessarily at 16 and 24 weeks postintervention.

Fourth, estimate the effect of dementia severity on treatment outcomes among patients receiving active rTMS. Hypothesis 4 (H4) is as follows: the effect size will be greater in participants with a clinical dementia rating (CDR) of 1 than in those with a CDR of 2.

## Experimental Design

This is a randomized, double-blind, placebo-controlled clinical trial of rTMS for the treatment of cognitive impairment in patients stratified by severity of Alzheimer dementia. Participants with probable Alzheimer disease will be recruited from the three sites contributing to the study (Winnipeg, Montreal, and Melbourne), and will be randomly assigned to either a 2-week, 4-week, or sham high-frequency rTMS treatment. Standard cognitive assessments will be performed before and after treatment, as well as at scheduled follow-up visits up to 6 months after the end of the intervention. Participants will be blind to the type of treatment (active vs placebo). Assessors will be blind to both the type and duration (2 vs 4 weeks) of treatment.

## Methods

### Recruitment

Recruitment for this study will be performed at all three sites. Patients with probable Alzheimer disease at mild to moderate stages will be recruited. The target recruitment rate of patients at each site is estimated to be approximately 25 per year, with a target total recruitment of 300 participants across all sites.

All potential participants must have been diagnosed with mild or moderate stage Alzheimer disease by their referring physician or one of our study doctors. The screening doctor will complete an eligibility assessment with the potential participants to confirm their suitability to participate in the study. This

assessment will use the CDR [49] and MoCA [50] to assess the severity of dementia. In addition, they will complete the Cornell Scale for Depression in Dementia (CSDD) [51] to assess for comorbid depression. The screening doctor will also consider various inclusion and exclusion criteria.

The inclusion criteria are as follows (all must be met): age  $>55$  years; MoCA score between 7 and 25; CDR score of 1 to 2; CSDD score of 18 or less to rule out moderate to severe depression; diagnosis of probable mild or moderate Alzheimer disease as confirmed by the treating neurologist, geriatrician, or psychiatrist, and/or by the study coinvestigators; and use of a stable dose or no dose of an acetylcholinesterase inhibitor for at least 3 months prior to study entry with no plans to change medication for the duration of the study. If a participant decides to discontinue an Alzheimer disease-related medication (ie, a cholinesterase inhibitor), he/she will wait a minimum of 6 weeks prior to the start of the rTMS treatment.

The exclusion criteria are as follows (any of the following): psychiatric conditions/disorders or current neurological or medical disorders, other than Alzheimer disease, that could interfere with cooperative participation (eg, severe agitation and prominent anxiety); diagnosis of intellectual disability; impaired vision or hearing severe enough to impair performance in cognitive tests; exclusive diagnosis of other forms of dementia (including posterior cortical atrophy); primary psychiatric disorders (eg, schizophrenia and bipolar affective disorder) or current and/or unstable neurological, systemic, or medical disorders (eg, liver disease, congestive heart failure, and severe chronic obstructive pulmonary disease [COPD]) that may impair cognition or the ability to complete the required study procedures; use of benzodiazepines and zopiclone during the study and preceding 2 weeks; use of high doses of antipsychotics (based on clinical judgement) that may impair cognition during the study and preceding 2 weeks, or situations where changes in antipsychotic doses can reasonably be anticipated; participation in a clinical trial with any investigational agent within 2 weeks prior to study enrolment; current substance abuse disorder; history of epileptic seizures or epilepsy; contraindication for receiving TMS treatment according to a TMS questionnaire; inability to adequately communicate in English at Manitoba and Australia sites and either English or French at the Montreal site; previous treatment with rTMS within the past 3 months; and any plans to change medication for Alzheimer disease, mood disorders, or pain during the study. Neuropsychiatric symptoms that are considered secondary to Alzheimer disease are not considered in the exclusion criteria, except where they would make it difficult to comply with study requirements, as described above.

Following the initial screening process, we will obtain a magnetic resonance imaging (MRI) scan of the participant's head. An MRI scan is required by the neuronavigation software in order to position the TMS coil accurately over the target brain region. If a clinical MRI scan already exists, which is suitable for our needs (adequate resolution and coverage to identify and locate internal and external reference points used by the software), we will obtain it from the medical records. If there is no previous clinical MRI scan or the previous MRI scan is

not adequate for our research purposes, we will schedule and pay for a research MRI scan to be completed for the participant.

Before performing the MRI scan, we will ask participants if they have any implants, devices, or objects that can be hazardous to them and/or may interfere with the scan. If they express any concerns, we will consult with the MRI clinic and/or ask them to consult with their family doctor. If we still cannot retrieve a valid MRI scan, a reference head model will approximate the participant's anatomy.

When a scan is performed for the purpose of this study, the following scanning parameters will be used: T1-weighted scan; voxel resolution, 1 mm<sup>3</sup>; matrix, 256×256; and field of view, 25.6 cm (to match the matrix and resolution). The tip of the nose and both ears are required to be included in the scan.

If patients have any medical implants, devices, or objects that could be hazardous to them during the rTMS treatments, we will ask them to consult with their family doctor and provide their doctor's confirmation via a written document that rTMS can be safely applied for their continuation in the study.

Prior to study participation, all patients and their primary caregivers will be required to sign an informed consent form approved by the ethics board of each site of the study.

### Randomization

Once enrolled in the study, each participant will be assigned to a treatment group (either sham or active, as well as either 2 or 4 weeks of treatment), using stratified block randomization (block size of 3). There will be four distinct stratification blocks using two levels for two factors (age and severity) as follows: age ≥70 years, CDR=1; age ≥70 years, CDR=2; age <70 years, CDR=1; age <70 years, CDR=2.

Group assignment will be determined using an automated algorithm. The only person who will know the group assignment for a given participant is the rTMS administrator at each site who provides the age and CDR data for the algorithm and informs the participant of the duration of treatment. Blinding of the site coordinator will be broken only when necessary to ensure patient safety, that is, in case of a serious adverse event where clinical follow-up is necessary.

### Treatment Protocol

Patients in both the active and sham treatment groups will undergo daily (5 days/week) rTMS treatment. Each treatment will apply 25 trains of rTMS pulses bilaterally to the DLPFC. Each train will have a duration of 1.5 s, and pulses will be applied at 20 Hz (for a total of 30 pulses per train). The intertrain interval will be 10 seconds. Thus, there will be a total of 1500 pulses delivered to the brain per day (25×30=750 per side), resulting in a total of 30,000 pulses applied over the course of 4 weeks of treatment (20 sessions) or 15,000 pulses for 2 weeks of treatment (10 sessions). Each TMS treatment session will take approximately 10 to 25 minutes. Any missed treatment sessions will be made up on the following day, with a minimum 30-minute break between sessions.

The pulses will be applied at 90% to 100% of the RMT of each participant. The RMT, which will be measured for each

hemisphere before the first treatment, is determined by applying single TMS pulses over the primary motor cortex and observing the lowest intensity at which it causes an involuntary twitch of the participant's contralateral thumb. The specific process involves setting the intensity of the stimulator at 65% to 75% of the maximum intensity and adjusting the coil location over the primary motor cortex until the "hotspot" for activating the involuntary twitch is found. Then, the intensity is lowered in 1% decrements to find the lowest intensity at which an involuntary twitch can be clearly observed in three consecutive pulses. The intensity of treatment will be 90% to 100% of the RMT, unless the participant is having trouble tolerating the treatment, in which case treatment at an intensity of 90% of the RMT will be used for the first session and increased to the full dose of 100% by the end of the first week of treatment.

The location of the DLPFC will be determined using the BrainSight 2 navigation system [52] for TMS. The right and left DLPFCs of each participant will be localized using their own MRI scan, and the coil location and direction will be specified using the BrainSight software at Talairach coordinates (x, y, z) = (-50, 30, 36). The coil will be held at approximately 45 degrees relative to the horizontal axis, but this will be measured approximately rather than specified exactly using the neuronavigation software.

To prevent unblinding, a Magstim sham coil will be used for sham treatments. This coil provides the same sound and tactile sensory experience as the real coil, but it attenuates the strength of the induced electrical field in the brain well below the threshold required to stimulate neurons. In addition, during treatment, only the participant and the research personnel designated to administer the rTMS will be present (no caregiver).

### Outcome Measures

Each participant will attend six assessment days in total as follows: baseline (week 0) and week 3, week 5, week 8, week 16, and week 24 posttreatment sessions. At each assessment day, three assessments will be given to the participant in the following fixed sequence: ADAS-Cog, verbal fluency test, and Stroop test. Only the patient and the research personnel designated to administer assessments will be in the room during assessments. At the baseline and week 5 and week 16 posttreatment assessments, additional caregiver assessments will be performed. Alzheimer Disease Co-operative Study-Activities of Daily Living Inventory (ADCS-ADL) and Neuropsychiatric Inventory Questionnaire (NPI-Q) assessments will be performed at each of these visits (in that order), while the Treatment Satisfaction Questionnaire for Medication (TSQM) will only be used at the week 5 assessment. These outcome measures must be administered to the same caregiver at each visit. If a participant is accompanied to an assessment visit by someone other than their usual caregiver, the assessor will contact the usual caregiver by phone to complete these assessments.

All assessments will be performed on a Monday or the first working day of the week. Note that the specific dates of the last three assessments (the follow-up assessments) will be adjusted based on whether the participant is in a 2-week or 4-week

treatment group. An assessor will be assigned to each participant. That same assessor must perform all of the six assessments with the assigned participant. Deviations should be justified (changes in staff, assessor illness, etc), and an explanation will be documented in the assessment notes.

As participant schedules are often busy, we can adjust the specific dates of the assessments within ranges (Table 1). If no assessment is possible within these windows, the assessment will be skipped and the data point will be missing from the analysis (with the exception of the baseline assessment, which will require rescheduling the treatment).

The primary outcome measure will be the change in patient scores from baseline on the ADAS-Cog assessment, as that is

the most common standard test used in dementia clinical trials. Alternate forms of the ADAS-Cog word lists will be used at each visit to avoid possible practice effects. The secondary outcome measures will be the change in the scores from baseline of the proximal measures Stroop test [53] and verbal fluency test, as well as the distal measures NPI-Q and ADCS-ADL. We will also assess the tolerability of the rTMS treatment by the TSQM [54], which will be completed by patients and their primary caregivers posttreatment.

At each site, the above assessments will be administered by a study research assistant (RA) blinded to the group assignment of the patients. The RAs involved in administering treatment or assessments will not be involved in any of the statistical data analyses.

**Table 1.** Date adjustments for assessments.

Assessment	Range of possible dates
Baseline	Up to 1 week before the first treatment
Week 3	+/- 1 day of the ideal date
Week 5	+/- 1 week of the ideal date, but after the final treatment
Week 8	+/- 1 week of the ideal date
Week 16	+/- 2 weeks of the ideal date
Week 24	+/- 2 weeks of the ideal date

## Safety Considerations

Before enrolling in the study, all participants will be screened for possible rTMS contraindications (seizure history, brain lesions, metallic implants, etc). Participants will be asked at each visit if they have experienced any adverse effects from the treatment. Any reported adverse events or effects will be recorded, and treatment will be suspended at the discretion of the study physicians if the adverse effect is considered to be serious (ie, life threatening or requiring hospitalization or medical treatment). The participant's self-assessment of any pain or discomfort from the treatment will also be recorded at every visit.

A data and safety monitor board (DSMB) will oversee the study to ensure that proper safety procedures are followed and that adverse effects of the treatment are properly documented. If adverse effects are discovered that warrant a review or investigation before proceeding with the study, the DSMB will have the authority to initiate such a review. The DSMB will also ensure that the study does not deviate from the intended protocol.

## Ethical Considerations and Follow-Up

Following the 24-week posttreatment assessment, participants will be informed of their assigned treatment group. Patients randomized to the sham treatment will be offered 2 weeks or 4 weeks of active treatment. The patients and/or their family can choose the duration of treatment. Any participant who experiences an adverse effect will be followed up by a study physician until the adverse effect has resolved.

## Data Management

Study data (participant medical and demographic data, treatment records, and assessment results) will be maintained on a password-protected database accessible only to active research team members, with access to specific information, such as group assignment, and assessment results restricted based on the individual's assigned role in the study. Regular backups of the database will be performed and stored on a secure server. Identifying information (name, phone number, address, etc) will not be stored on the same system as the study data and will only be accessible to staff members who need to contact participants.

## Statistical Analysis

### Sample Size Estimation

The sample size for the hypothesis that one group's mean is statistically significantly different from the other (assuming two equally sized groups, which is the case in this study) can be calculated using the following formula [55]:

$$N = \frac{2(Z_{\alpha} + Z_{\beta})^2 \sigma^2}{d^2}$$

where  $Z_{\alpha}$  is the upper tail critical value in the standard normal distribution at the  $\alpha$  level of significance (it is 1.96 and 2.58 for 5% and 1% significance levels, respectively),  $Z_{\beta}$  is the normal deviate at  $1-\beta$  power with  $\beta$  of type II error (it is 0.84 and 1.28 for 80% and 90% power, respectively), and  $\sigma$  and  $d$  are the standard deviation and difference of means of the two groups, respectively. The calculated  $N$  is the number of subjects in each group.

Using the above formula with a significance level of .05 (corrected using the Bonferroni adjustment for three treatment



groups), an expected difference of 3 points on the ADAS-Cog score (derived from a study by Rabey et al [7], which also used ADAS-Cog as a primary outcome measure), a standard deviation of 4.9 points (derived from the results of our own pilot study [8]), and a power level of 80%, the minimum sample size is estimated to be 63 participants per group (189 in total). Allowing for 10% drop out, we will need to enroll at least 208 patients in the study to achieve this power.

### ***Analysis of the Results***

Baseline characteristics will be assessed between the active and sham treatment groups by descriptive statistics, as well as formal statistical tests. Baseline differences between the two groups, if any, will be adjusted for in the final statistical analyses. All assessment scores will be checked for normality of distribution to determine the choice of either parametric or nonparametric methods. Bartlett statistic will be used to assess the homogeneity of variances, and Levene [56] or Brown-Forsythe [57] tests, which are less sensitive to departures from normality, may also be used. In all instances, a  $P$  value  $<.05$  will be considered significant.

To test H1 and H2 (the efficacy of rTMS treatment), two-factor (active vs sham) repeated (pre-post treatment) analysis of variance (ANOVA) will be used to investigate the effect of treatment before and after the 4-week block of treatment. The dependent variable will be the change in the ADAS-Cog score (primary outcome measure). Testing H3 will be similar to the tests of H1 and H2, but the two factors will be the two durations of treatment.

For secondary outcome measures, a two-factor ANOVA will also be used in the same way as described above, but a Hochberg test [58] will be applied to correct for multiple comparisons.

The last-observation-carried-forward method will be used in the case of missing data or premature termination.

To test H4 (the durability of rTMS treatment), repeated measure ANOVA will be used among responders (those who show improvement in the ADAS-Cog score of  $\geq 3$  points over the course of treatment [3] in both groups) to investigate the duration over which the improvement may last. Post-hoc follow-up methods, such as Dunnett [59] and Tukey [60] tests, will be applied as needed. In addition, a mixed regression model will be developed to predict the response variable at each assessment visit of the active treatment group (both treatment arms separately). The independent variables will be patients' current age and the severity of Alzheimer disease (as measured by the CDR).

To test H5 (the correlation of treatment effect and severity), we will run regression and correlation analyses between the severity of Alzheimer disease (the MoCA and CDR scores) at baseline and the change in the ADAS-Cog score. The correlation coefficient (either the Pearson or Spearman correlation coefficient, whichever is more appropriate) and its statistical significance will be determined. Sensitivity of the regression and correlation analyses with respect to the data distribution will be assessed. Influential observations and outliers, if any, will be identified.

The above statistical analysis will also be repeated for secondary outcome measures after correcting for multiple comparisons. In addition, covariate analysis will be performed in an appropriate manner. Covariance balance (or imbalance) is checked with the ANOVA test when there are three or more groups or by the  $t$  (or the approximate  $Z$ ) test when there are only two groups. For the ANOVA test, we will first check the satisfaction of ANOVA assumptions (such as normality of distribution and equality of variances). If any violation is found, transformations will be made before the ANOVA test. If covariance imbalance is statistically significant, the final data analysis will be adjusted for covariance imbalance (eg, by the use of regression analysis with these imbalanced covariates as explanatory variables).

### **Quality Assurance**

A designated study coordinator will travel and visit the study sites approximately three times per year to ensure that each site is adhering to the study protocol. They will also ensure that the three sites are consistent in the details of implementing the study protocol, such as RMT measurement and assessment techniques.

Before the study starts, after the RAs are hired, the principal investigator (PI) and co-PIs at each site will have an online meeting to go through the protocol and procedure entirely. All the RAs will be trained and will fully practice their specific tasks before the study starts. If there is any issue of ambiguity raised during this meeting, the PI and co-PIs of the sites may schedule a follow-up meeting to discuss the issue and ensure the group is in agreement on the intended protocol.

The study coordinator's job is to ensure that the three sites are synchronized in terms of adherence to the protocol. Before the first visit of the site coordinator, the PIs of each site will meet virtually by video conferencing to go over the details of the protocol and how they plan to ensure the staff at each site will be trained to perform the protocol in exactly the same manner at every site. The first visit of the coordinator will be during the first months of the study when the treatment of the first block of patients starts. During each visit, the study coordinator will attend at least one treatment and one assessment to be able to evaluate the procedures and flag any inconsistencies across the sites. In addition, the coordinator is responsible to oversee the overall data management in the main server located in Manitoba, as well as monitor and communicate across the three sites on an ongoing basis to ensure compliance with the protocol at every site.

All outcome assessment data will be uploaded and saved on the PI's Biomedical Engineering (BME) server in Manitoba, which is a secure server that is being administered by a dedicated computer engineer. A standard routine of anonymization will be in place to assign a code to each patient and ensure the safety and security of patient data.

A process of cross-validating data entry will be established between the three sites. All assessment scores will be recorded in the study database along with scanned copies of the supporting assessment documents. Assessors will check the scoring and data entry performed by other assessors (Winnipeg assessments will be checked by Melbourne, Melbourne



assessments will be checked by Montreal, and Montreal assessments will be checked by Winnipeg). The purpose of this is to ensure data quality by catching and correcting errors, as well as requiring site assessors to communicate regularly about assessment scoring guidelines.

### Ethics

All participants (or their caregivers in cases where the caregivers are legal representatives acting on behalf of the participants) will read and sign an informed consent form before being enrolled in the study. A trained RA will discuss the study and the consent form with the participants and their caregivers prior to signing and answer any questions they may have. Participants may withdraw from the study at any time without being required to offer an explanation.

The consent forms and the overall study protocol must be approved by the local ethics board for each site of the study prior to the commencement of the study.

### Plausible Side Effects

There are some known and expected side effects of rTMS treatment, which will be mentioned in the consent forms to inform participants of the study. The most common side effects of rTMS are as follows: (1) headache (usually mild) following rTMS application that is believed to be due to muscle tension and (2) toothache and pain in the eye, scalp, and neck that are all reported to be mild and temporary following rTMS application. The more serious side effect of rTMS is the risk of seizures in people with a history of epilepsy or in people who have an increased risk of seizures. For this reason, we will screen carefully to exclude those with a history of seizures or increased risk of seizures.

### Interim Analysis and Plausible Changes to the Protocol

We will run an interim analysis after enrollment of 150 participants and after at least 100 of them have finished at least 16 weeks of the study. Through the interim analysis, we will try to answer the question of whether the trial is likely to reach its objective if continued to the planned maximum sample size and/or whether the treatment protocol should be modified, for example, in case a disease-modifying therapy is discovered in the course of the study. In case of the latter, the team will write an amendment to the funding agency and then, upon their approval, will submit the amendment to the ethics board for the modified protocol and will inform the participants.

To ensure the double-blind nature of the study is not compromised by the interim analysis, all eligible data to be included in the analysis will be randomly assigned as P1, P2, P3, etc by the PI. Only the PI and one main coordinator will have access to the master file that associates the P1, P2, etc labels to the codes of the study subjects. The data will be analyzed by a RA blinded to that data under the supervision of our collaborator statistician (XW), who will also remain blind to the group identity within the data. The arms of the intervention will be named randomly as G1, G2, G3, and G4 by the PI to avoid any bias.

## Results

### Recruitment and Enrollment

As of November 1, 2020, we have screened 523 individuals, out of which 133 were eligible and have been enrolled. Out of the 133 individuals enrolled and randomized to the intervention groups, 104 have completed the study and 20 have discontinued the study or have withdrawn for various reasons at various stages of the study. Data of some withdrawn individuals who completed the study up to week 8 or 16 are still usable for analysis. Three individuals withdrew because they found the treatment uncomfortable, nine withdrew with no reason given, and eight were withdrawn by the site PI. Out of the eight withdrawn by the site PI, two were withdrawn for safety reasons as they developed some illnesses, although they were not related to the rTMS treatment, four were noncompliant (changed their medication during the study) or found the rTMS pulses unbearable, and two could not finish the treatment due to pandemic lockdown.

Recruitment and enrollment have been slower than initially anticipated, and the pandemic has slowed these even further. Before the pandemic, the realistic recruitment rate was one per month.

### Adverse Events

We have developed a series of detailed questions to mark any plausible adverse effect of the treatment, and the series is used consistently among the different sites of the study. As of November 1, 2020, there has been no serious adverse event. However, 89 of the participants reported expected adverse events as described in the Plausible Side Effects section above. Twelve participants reported some unexpected adverse events, which were most likely unrelated to the rTMS treatment. The reported events were increased blood pressure on one day, a nightmare, vivid dreaming, sleeping trouble, disorientation, blurry vision, and unsteadiness on the feet for a few minutes. All reported cases were temporary and reported on only one day. All issues resolved without medication. All adverse events have been described in detail in quarterly DSMB reports.

### Minor Deviations From the Treatment Protocol

For those participants finding rTMS pulses painful, we will administer pulses lower than 90% to 100% of the RMT threshold in the first three sessions of treatment and slowly increase the value to 90% of the RMT for the rest of the sessions.

## Discussion

Overall, the study has been continuing as expected. In general, participants have found the rTMS treatment tolerable and have been compliant to the study protocol. One interesting fact is that we found our participants eager to continue the study even during the pandemic. However, the study has become slow because of the lockdowns imposed by the universities and health authorities.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Funding agency reviews of the proposal.

[[PDF File \(Adobe PDF File\), 105 KB - resprot\\_v10i1e25144\\_app1.pdf](#)]

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## Abbreviations

- ADAS-Cog:** Alzheimer Disease Assessment Scale-Cognitive Subscale
- ADCS-ADL:** Alzheimer Disease Co-operative Study-Activities of Daily Living Inventory
- ANOVA:** analysis of variance
- BDNF:** brain-derived neurotrophic factor
- CDR:** clinical dementia rating
- CSDD:** Cornell Scale for Depression in Dementia
- DLPFC:** dorsolateral prefrontal cortex
- DSMB:** data and safety monitor board
- GABA:** gamma aminobutyric acid
- Glx:** glutamate-glutamine



**MoCA:** Montreal Cognitive Assessment  
**MRI:** magnetic resonance imaging  
**NPI-Q:** Neuropsychiatric Inventory Questionnaire  
**PI:** principal investigator  
**RA:** research assistant  
**RMT:** resting motor threshold  
**rTMS:** repetitive transcranial magnetic stimulation  
**TMS:** transcranial magnetic stimulation  
**TSQM:** Treatment Satisfaction Questionnaire for Medication

*Edited by G Eysenbach; submitted 19.10.20; peer-reviewed by A Benussi, W Myung; comments to author 31.10.20; revised version received 06.11.20; accepted 24.11.20; published 08.01.21.*

*Please cite as:*

*Moussavi Z, Rutherford G, Lithgow B, Millikin C, Modirrousta M, Mansouri B, Wang X, Omelan C, Fellows L, Fitzgerald P, Koski L*

*Repeated Transcranial Magnetic Stimulation for Improving Cognition in Patients With Alzheimer Disease: Protocol for a Randomized, Double-Blind, Placebo-Controlled Trial*

*JMIR Res Protoc 2021;10(1):e25144*

*URL: <http://www.researchprotocols.org/2021/1/e25144/>*

*doi: [10.2196/25144](https://doi.org/10.2196/25144)*

*PMID: [33416500](https://pubmed.ncbi.nlm.nih.gov/33416500/)*

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Protocol

# Program for Healthier School Cafeterias in Rio Grande do Sul, Brazil: Protocol for a Community-Based Randomized Trial

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## Abstract

**Background:** School cafeterias can promote poor eating habits, as these retail outlets have a variety of foods considered to be nonnutritive and unhealthy. However, despite the need for effective preventive strategies, there is still disagreement on the best approach due to the lack of evidence on interventions to prevent and treat obesity in the school settings.

**Objective:** We aim to verify the efficacy of an educational intervention program to improve the hygienic conditions and the composition of the menu offered in school cafeterias in the state of Rio Grande do Sul, Brazil.

**Methods:** We will conduct a randomized, parallel, two-arm, community-based controlled study. Elementary and high schools, both public and private, in the State of Rio Grande do Sul, Brazil, that have a cafeteria will be eligible. Schools will be recruited and randomly assigned to the intervention (n=27) or control (n=27) group. The intervention group will receive an educational intervention program based on the guidelines issued by the Ministry of Health of Brazil, consisting of a 160-hour distance-learning qualification course, for 10 weeks, and using the Moodle platform and WhatsApp app. The intervention targets the owners and people in charge of the cafeterias, food handlers, principals, vice principals, teachers, pedagogical coordinators, dietitians, representatives of students' parents, and students over 16 years old. Meanwhile, the control group will receive only a printed copy of the book containing the guidelines used. The efficacy of the intervention will be determined by the hygienic conditions of the cafeteria and the composition of the menu offered, also considering the levels of processing of food sold. All outcomes will be analyzed as intention-to-treat and per-protocol. We will use covariance analysis or a generalized linear model for continuous data and ordinal logistic regression for ordinal categorical data. The level of statistical significance considered will be  $P < .05$  for a 95% CI.

**Results:** This project was funded in early 2018. We administered the intervention program in 2019. All data have already been collected, and we are analyzing the data. The results are expected in 2021.

**Conclusions:** To our knowledge, this may be the first randomized controlled study in school cafeterias held in Brazil. The results will provide evidence for the formulation of public food and nutritional security policies and for the development of effective strategies to provide safe and healthy school meals.

**Trial Registration:** Brazilian Clinical Trials Registry RBR-9rrqhk; <https://ensaiosclinicos.gov.br/rg/RBR-9rrqhk>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/22680

(*JMIR Res Protoc* 2021;10(1):e22680) doi:[10.2196/22680](https://doi.org/10.2196/22680)

**KEYWORDS**

school health services; healthy diet; pediatric obesity; schools; snacks

## Introduction

Childhood obesity has been recognized as one of the greatest public health challenges of the 21st century, according to the World Health Organization [1]. By 2016, 18% of children and adolescents aged 5 to 19 years were overweight or obese worldwide [1]. Data from the Global Burden of Disease Study indicate that more than 70 countries have doubled their prevalence of obesity between 1980 and 2015, with an increase to 112 million obese children worldwide [2].

In Brazil, access to food in the school environment can occur through school meals provided by the Brazilian National School Feeding Program (PNAE - Programa Nacional de Alimentação Escolar) as well as through school cafeterias (ie, a facility within the educational establishment that aims at providing food to the school community upon payment). Data from the 2015 Brazilian National School Health Survey report that the percentages of foods considered unhealthy consumed by Brazilian students are high. The consumption of sweets, ultra-processed snacks, soft drinks, and fried snacks was 41.6%, 31.3%, 26.7%, and 13.7%, respectively [3]. The same survey revealed that these items are mostly unhealthy, nutrient-poor, and unsuitable for health promotion at school.

Studies indicate that school cafeterias end up promoting unhealthy eating habits [4,5]. A high prevalence of foods with low nutritional quality marketed in these places was identified in several observational studies in Brazil [4,6-8], as well as in other countries [9-12]. Given this scenario, evidence indicates that school interventions can have an impact on the prevention or treatment of obesity, with changes in the nutritional status and eating behavior of children and adolescents [13-17]. There is some evidence of effective interventions for better school meals; however, several systematic reviews reveal heterogeneous, low-quality studies with methodological deficiencies and very small effect sizes [12,18-23]. Moreover, few studies have addressed intervention strategies to improve the food environment of school cafeterias [10,24-27]. In addition, the maintenance of long-term effects is not yet known, and large-scale interventions can pose a considerable challenge, limiting their impact on nutrition and public health [18,26,28-30].

According to local government regulations, school food service employees must undergo food safety training [31,32]. The involvement of the entire school community in the development of these interventions is promising for the promotion of an adequate and healthy diet [33,34]. However, studies report that insufficient training appears to be a barrier to adequate food security practice [35]. Review studies suggest that food safety education training is effective for improving the knowledge of food handlers, but more evidence is needed to improve behavior change [36,37].

To the best of our knowledge, there has been no randomized controlled trial conducted in school cafeterias in Brazil. Addressing this gap, we have been developing an educational intervention program with a multicomponent strategy to improve the hygienic conditions and composition of the menu offered in school cafeterias in the state of Rio Grande do Sul, Brazil.

## Methods

This protocol is reported in accordance with the statement of the Consolidated Standards of Reporting Trials (CONSORT) [38] and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [39]. We will conduct a randomized, parallel, two-arm, community-based controlled study in school cafeterias in the state of Rio Grande do Sul, Brazil. The Research Ethics Committee of the Federal University of Rio Grande do Sul (report 89504618.9.0000.5347) approved this project, which was registered in the Brazilian Platform of Clinical Trials under the code RBR-9rrqhk on April 30, 2018 (Universal Trial Number U1111-1213-1614).

### Recruitment and Eligibility Criteria

A total of 330 schools will be assessed for eligibility to participate in the study. The definition of these schools will be obtained through data from the Education Department of the State of Rio Grande do Sul [40]. Confirmation or updates of the existing data will be verified by phone calls to all schools. We will invite to participate elementary and high schools of the public and private sectors located in the Cidania Noroeste Colonial region, State of Rio Grande do Sul, Brazil, which total 36 municipalities according to the last official census [41].

Schools will be eligible to participate if they have a school cafeteria and they show interest in participating in the research upon signature of a consent form. Schools with exclusive care for children with special needs will be excluded, as they require a different standard of care. Schools will not be excluded based on other characteristics such as size, socioeconomic indicators, and others. Eligibility criteria will be applied prior to randomization.

Eligible schools will be personally invited to participate in the study by the research team. This strategy will be used to ensure the desired sample size. The school principal will sign a consent form for participation. In the case of outsourced cafeterias, we will request the consent of its owner. Each school will nominate its representatives to participate in the study. The principal will be responsible for obtaining the consent of the nominated members.

### Sampling

The sample size calculation was based on primary outcomes. For a significance level of 5% and statistical power of 90% to detect an effect magnitude ( $d$ ) of 0.90, 54 schools will be needed, considering 27 for the intervention group and 27 for the control group. We considered a 10% sample loss to estimate an increase in the sample size. The estimated number of participants required to achieve the study objectives was also based on the study by Nathan et al [24], which aimed at examining whether a theoretically conceived multicomponent intervention was effective in enhancing the implementation of a healthy cafeteria policy in Australian primary schools. The sample size calculation was performed using the Power and Sample Size software (HyLown Consulting LLC, Atlanta, GA).

### Randomization and Allocation

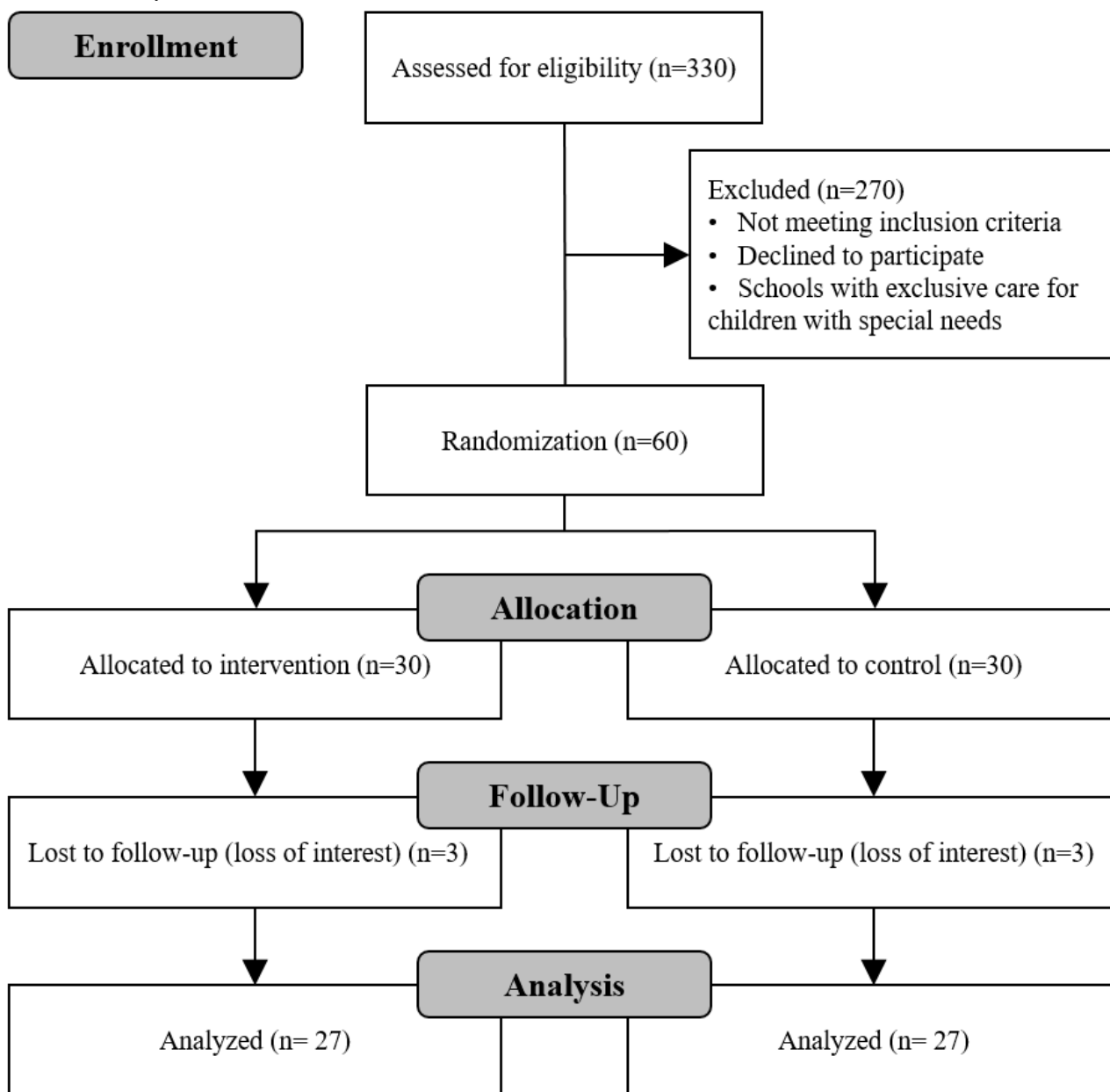
Randomization will use a minimization process [42] to balance the number of schools between the 2 groups. This approach ensures an excellent balance between groups for several prognostic factors, even in small samples. According to Egbewale [43], the minimization process makes the evaluated groups similar in important characteristics, mainly in trials that involve a small sample and have several prognostic factors to be balanced [38,44]. This procedure decreases the chances of significant discrepancies in baseline prognostic factors that may occur at random [45]. Minimization also controls the imbalances in baseline variables more efficiently than simple randomization, since, in small samples, simple randomization can produce a biased and misleading effect [43,46].

To maintain the balance between groups and prevent disproportionate distribution from occurring, 4 predictors of

interest for the allocation will be considered: city, cafeteria administration (school-owned versus outsourced), school scope (public versus private), and the number of students (<500 students versus ≥500 students). An independent researcher will perform the randomization by minimization using a computer-generated technique in SPSS 26 (IBM Corp, Armonk, NY), avoiding possible influence on the allocation. The randomization unit will be schools with cafeterias.

As it will be an educational intervention, the researchers in charge of administering the interventions and assessing the outcomes will not be able to be blinded. Therefore, to avoid interference between the control and intervention groups, blindness will be arranged for the statistician in charge of data randomization and analysis. Participant flow during each stage of the study can be seen in the estimated study flowchart in Figure 1.

Figure 1. Planned study flowchart.





## Intervention Group

After completing randomization at baseline, schools located in the intervention group will be invited to participate in the “Healthy Cafeteria: we support this idea!” Program (*Cantina Saudável: a gente apoia essa ideia!* originally in Brazilian Portuguese). This is an educational intervention consisting of a 160-hour asynchronous distance-learning qualification course using the Moodle platform. Each school from the intervention group will also have a support group on WhatsApp (Facebook Inc, Menlo Park, CA), including all the participants enrolled by the school. The course will have a duration of 10 weeks, with a workload of 16 hours per week.

The target audience of the intervention will be the owners and people in charge of the cafeterias, food handlers, principals, vice principals, teachers, pedagogical coordinators, dietitians, representatives of students’ parents, and students over 16 years old. Each week, a course module will be available on a distance-learning platform through lectures, texts, videos, and activities. Moreover, a discussion forum will be developed for each module to encourage learning, share experiences, provide support, and instigate community interaction. In each module, we will provide practical activities to be held in school cafeterias. Our teaching strategy will implement context-based and problem-solving activities. The modules will be made available in stages, so that the workload is fulfilled according

to the plan. In addition, the modules will be available until the end of the course, and it is not necessary to meet fixed hours and deadlines for most course activities. This flexibility of distance learning allows participants to adapt their studies according to their routine.

The principal of each school in the intervention group will receive 2 phone calls during the intervention: the first one in the 4th week and the other in the 7th week. Both calls will be for support and follow-up for the intervention program. Calls will last approximately 5 minutes, and we will ask the director if their participants need any instructions or assistance. In addition, participants will be able to chat with a tutor throughout the intervention via chat using the Moodle platform and WhatsApp. These strategies will be used to avoid participant drop-outs.

The material used as a basis for developing the education intervention will be the book “Manual das cantinas escolares saudáveis: promovendo a alimentação saudável” (Guide of the Healthy School Cafeteria: Promoting the Healthy Food), developed by the Ministry of Health of Brazil [47]. This document guides the implementation of the school cafeterias throughout Brazil. The material was adapted according to the characteristics of the region of Brazil where the courses will be developed. The course will consist of 8 modules, depicted in [Textbox 1](#).

**Textbox 1.** Components of the intervention program for a healthier school cafeteria.

## Module 1 - Starting the healthy school cafeteria

- Goals
  - To present relevant information about the health of children and adolescents
  - To study how schools and cafeterias can promote healthy and proper eating
  - To understand the importance of implementing healthy school cafeterias and reasons to change
  - To get to know the current laws that provide for regulation in the supply of food in school cafeterias
- Intervention items and components
  - Expository classes, using slides, with an introduction of the theme and concepts for implementing a healthy cafeteria in the school setting
  - Current legislation regulating the supply of food in school cafeterias in Brazil
  - A video with a report on the law of cafeterias in southern Brazil
  - Hands-on activity: participants are instructed to check what is sold at school

## Module 2 - What is healthy eating?

- Goals
  - To get to know the concept of adequate and healthy eating
  - To learn what is healthy eating based on the Brazilian Population Food Guide
- Intervention items and components
  - Expository class, using slides, on the importance of healthy eating in schools and the concept of adequate and healthy eating
  - Videos about the concept of healthy eating
  - Indication of a film about the childhood obesity epidemic
  - Hands-on activities: participants are instructed to classify food sold in the cafeteria based on the concepts learned, create a campaign to encourage the consumption of healthy foods in school (eg, “buy 10 healthy items, get the 11th item for free”; “collect and exchange your points for products”). In addition, teachers are instructed on how to apply the concepts of healthy eating in the classroom

## Module 3 - Cafeteria and industrialized foods

- Goals
  - To get to know the effects of the consumption of industrialized foods on the student's health
  - To learn how to choose foods by reading labels and nutritional information
- Intervention items and components
  - Expository class, using slides, on industrialized foods and their effects, involving the reading of food labels
  - Educational videos that teach the participant to choose healthy foods by reading the labels
  - Suggesting an app to aid in healthy choices: Desrotulando
  - Hands-on activity: participants are instructed to remove from the cafeteria foods they consider unhealthy

## Module 4 - Healthy snacks

- Goals
  - To provide suggestions for healthy and creative snacks to be offered in school cafeterias
- Intervention items and components
  - Expository class, using slides, with suggestions for healthy and creative snacks
  - A video about healthy snacks at school
  - eBook with healthy recipes for school cafeterias
  - Hands-on activity: participants are instructed to develop a menu with healthy snack options for the cafeteria.

**Module 5 - Food hygiene**

- Goals
  - To learn about the importance of adopting good practices in food handling to ensure the sanitary quality and safety of food sold in the school cafeteria
- Intervention items and components
  - Expository class, using slides, about food hygiene
  - Videos on food handler hygiene and the correct way to sanitize vegetables and fruits
  - Hands-on activities: participants are instructed to record a video sanitizing their hands, take a selfie wearing a hygiene cap, and draw up a poster to prohibit unauthorized people from entering the cafeteria.

**Module 6 - Food and nutrition education**

- Goals
  - To present educational strategies and activities to promote adequate and healthy eating in the school setting
- Intervention items and components
  - Expository class, using slides, about food and nutrition education activities
  - A video addressing the importance of promoting adequate and healthy eating in the school curriculum
  - Hands-on activity: participants are encouraged to develop a food and nutrition education activity based on the content learned.

**Module 7 - How to profit from healthy school cafeterias and successful experiences**

- Goals
  - To present strategies on how to profit from the sale of healthy foods and show successful experiences in planning and implementing the healthy school cafeteria
- Intervention items and components
  - Expository class, using slides, on strategies to profit from healthy school cafeterias
  - Videos showing successful experiences in the implementation of a healthy school cafeteria
  - Hands-on activity: participants are instructed to create a healthy recipe with a creative name and disseminate it to the school community.

**Module 8 - Schedule of activities and how to keep the school cafeteria healthy**

- Goals
  - To propose a schedule of actions that must be carried out for the school to implant and maintain a healthy school cafeteria
- Intervention items and components
  - Expository class, using Microsoft PowerPoint, with actions that must be performed in school for the implementation and maintenance of the healthy school cafeteria
  - Hands-on activity: participants are encouraged to reflect on the changes made in the cafeteria (positive and negative points) during the intervention, including what still needs to be improved and what goals will be set to keep the school cafeteria healthy.

All components of the program will be offered to all participants in the school community because the content of the program does not require specific knowledge or prior training, meeting the requirements of the book on which it was based [47]. No payment nor refund will be made for cafeterias and schools to participate in the study. Local law does not allow individuals to participate in research for remuneration [48]. Schools that agree to participate will be aware of the need for the participants to dedicate time and adapt their work routine during the intervention period. Although the course includes 160 hours, this number of hours does not refer only to attending classes,

but rather considers engagement in all activities necessary for the intervention process, such as talking to the school staff and performing the proposed tasks and assignments. At baseline and after follow-up, cafeterias will receive feedback on their performance, and the situation will be assessed.

There was a post hoc change in the protocol of this study in relation to what was originally planned in the trial registry. Initially, we stipulated that the intervention program would be delivered in 160 hours over 20 weeks, therefore, with a workload of 8 hours per week. It was also foreseen that the course would have 140 hours in distance mode and 20 hours of in-person

mode. However, in new planning, we defined that the program would be delivered only in the distance mode and in a shorter period of time, with a weekly workload of 16 hours over 10 weeks. We justify this because of the limited funding available and the considerable geographical distance between the locations of participating schools.

**Control Group**

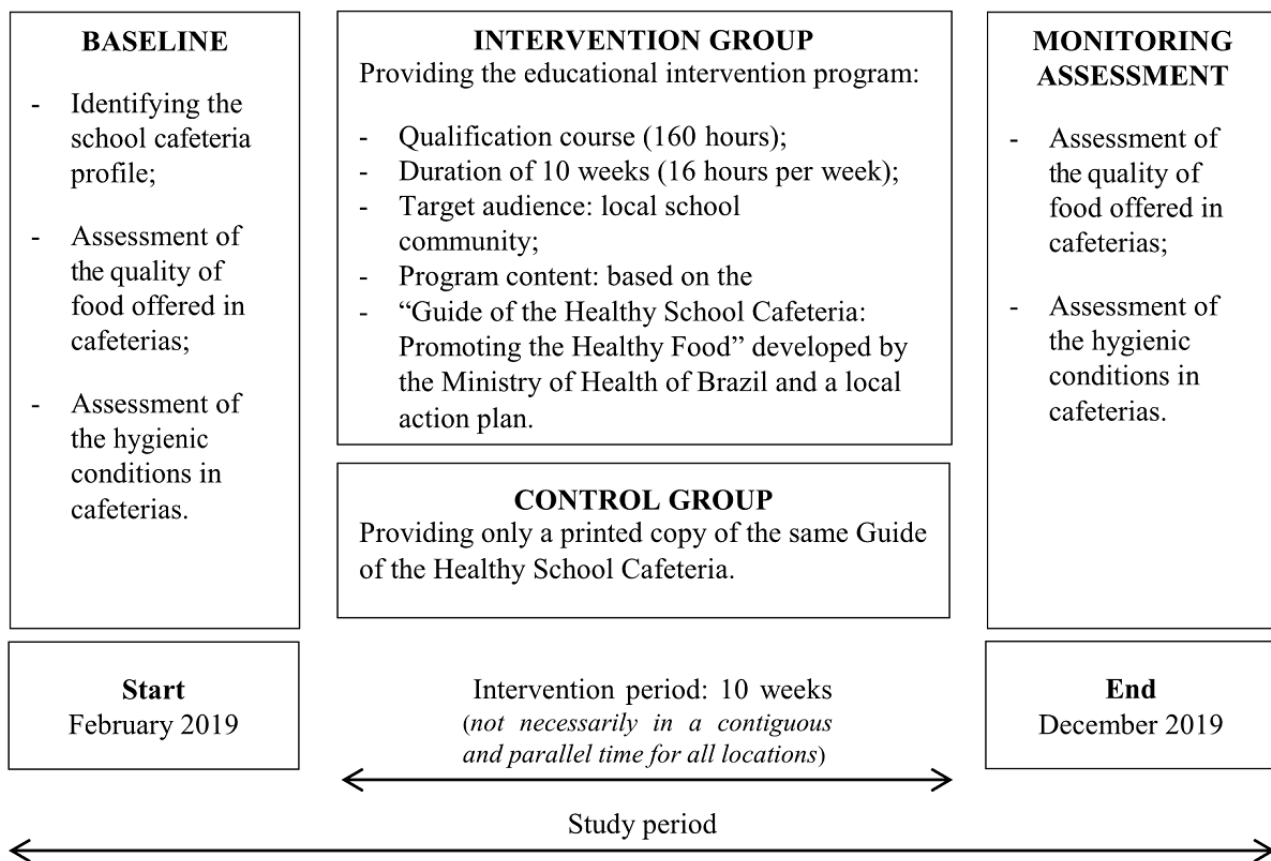
The control group will not receive any type of active intervention. After data collection is completed at baseline, schools from the control group will receive a printed copy of the book “Guide of the Healthy School Cafeteria: Promoting

the Healthy Food” developed by the Ministry of Health of Brazil [47]. At baseline and after follow-up, cafeterias will receive feedback on their performance, and the situation will be assessed.

**Data Collection and Management**

The study will be conducted in 3 stages, depicted in Figure 2. Data to assess outcomes will be collected at baseline and after follow-up. Not all interventions will be carried out in a contiguous and parallel time for all locations since the schools to be selected may be very distant geographically, and this will require more effort and time from researchers.

Figure 2. Study overview.



Researchers responsible for collecting data on site will be previously trained and will receive a guidance manual with information on the collection order, data completeness, researcher’s characterization and identification, behavior, actions, language, and guidelines on the observation of hygienic conditions. The investigation of the profile of school cafeterias will be carried out through a cross-sectional assessment using a printed questionnaire with the owners or people in charge of the school cafeterias and the school directors. This characterization of the study population will be done at the beginning of the study, simultaneously with the data collection of baseline variables, and it will be carried out before randomization by the researcher tasked with the collection of outcome measures. The data on the profile of the school and the cafeteria will be collected through a face-to-face interview with the principal and head of the cafeteria, respectively, using a printed demographic questionnaire.

The questionnaire for collecting demographic data will be based on studies by Giacomelli [49] and Porto et al [50]. The following information will be included: characterization of the school, type of management, educational stage, number of students, presence of school meals, type of cafeteria management, number of people working in the cafeteria, opening hours, number of snacks served, place of production of snacks, aspects involved with the choice of food offered, presence of other types of sale within the school, and presence of a dietitian. The questions related to the composition of the menu offered in school cafeterias according to the level of food processing will be based on the recommendations of the Food Guide for the Brazilian Population [51] and on the studies by Wolfenden et al [52] and Williams et al [25]. Meanwhile, the questions related to hygienic conditions will be obtained from the assessment frameworks already developed and validated by the Brazilian Health Regulatory Agency, which is equivalent to the US Food and Drug Administration [31,53]. Data entry from all instruments



will be performed in parallel and with redundant copies to verify the integrity and concordance of collected data.

We will analyze the fidelity and dose of the intervention based on the reports of participants' usage of the Moodle platform. This includes access logs with the day and time that the participant accessed the platform, all actions performed, list of activities and assignments, number and history of views, the fulfillment of activities, dwell time, and other information. In addition, participation will be verified based on the history of submitted assignments and participation in the discussion forums. The assessment of the feasibility and acceptance of the intervention will be measured based on the changing effects of the assessed outcomes, usage reports of Moodle, and an assessment of the participants' acceptance and their perception of the course, through an online retrospective questionnaire ([Multimedia Appendix 1](#)) applied at the end of the program.

### Outcome Measures

We aim to verify the efficacy of an educational intervention program to improve the hygienic conditions and the composition of the menu offered in school cafeterias in the state of Rio Grande do Sul, Brazil. The efficacy of the intervention will consider 2 primary outcomes: (1) composition of the menu offered (percentages of fresh, processed, and ultraprocessed foods) and (2) assessment of hygienic conditions concerning good practices in handling food. The secondary outcome will be a score calculated according to the level of processing of food sold. These variables will be collected at baseline and immediately after the intervention.

#### Primary Outcomes

The assessment of the impact of the intervention on the composition of the menu offered in school cafeterias will be based on similar Australian studies [25,54]. The assessment of the school cafeteria menu composition will be determined by counting all items sold and the percentages of food classified according to the level of industrial processing proposed by the Food Guide for the Brazilian Population [51] and Monteiro et al [55]. A modified version of these references was used for this research. Group 1 (*Ffresh*) includes fresh foods, minimally processed and culinary preparations without the addition of culinary ingredients (salt, sugar, oils, fats, or other ingredients). Group 2 (*Fprocess*) includes processed foods and culinary preparations with culinary ingredients. Group 3 (*Fultra*) includes ultraprocessed foods. The culinary ingredients group proposed by Brazil [31] was excluded from the classification because the cafeterias do not sell these foods in isolation. Two properly trained dietitians will carry out this assessment using pen and paper. In case of divergence, a third dietitian will be consulted.

Good practices in food handling are a set of procedures that food services implement to ensure food quality to the consumer, minimizing possible harm to health, especially that caused by foodborne diseases. In this sense, there is a need to assess and classify the food sold according to the characteristics that include the amount of microbial and chemical contamination [56]. To collect data regarding hygienic conditions, we will use an instrument that has been validated by the National Health Surveillance Agency [57], which is based on Brazilian

legislation, Regulatory Ordinance 817, published on May 10, 2013, by the Ministry of Health [56]. This legislation is composed of 51 items from 9 categories: water supply; building structure; cleaning of facilities, equipment, furniture, and utensils; control of vectors and urban pests; food handlers; raw material, ingredients, and packaging; food preparation; storage, transport, and display of prepared food; and liability, documentation, and registration.

The assessment of the hygienic conditions of the cafeterias consists of a continuous scoring system that ranges from 0 (less severe) to 2498.89 (more severe). The score will be assigned when the evaluated cafeteria does not meet some of the requested requirements, so the higher the score, the greater the number of nonconformities verified and the worse the performance of the establishment [58]. The scores for each of the 51 items checked will be defined based on risk criteria, in order to identify those that have the most direct impact on the quality of food and on the health of consumers. In the score, the Impact Index will be used, representing the importance in the prevention of foodborne diseases, as well as the Factor Load of the items, as validated by the National Health Surveillance Agency [57]. This assessment will take place through an onsite inspection carried out by a trained dietitian using a printed checklist.

#### Secondary Outcome

To assess the impact of the intervention on the food sold in the cafeteria, we have prepared a score that can be calculated based on the frequency of food available for sale and its classification according to the level of industrial processing proposed by Brazil [51] and Monteiro et al [55]. This score was developed due to the lack of a standard method for analyzing food in the school environment [59] and was also based on similar Australian studies [25,26]. Therefore, in addition to evaluating the composition of the menu offered in primary outcomes, we also chose to develop an equation that uses the frequency of each type of food but makes these variables continuous for a secondary outcome.

After data collection, all types of food and drinks sold in the cafeterias will be classified according to their level of processing. In the second stage, for each cafeteria, the frequency of items available in each category will be counted, multiplied by the standardized weight for the Group of fresh foods, Group of processed foods, and Group of ultraprocessed foods, which are +1, 0, and -1, respectively, as they are healthy, neutral, and unhealthy, respectively.

Equation (1) is used to calculate the score of the cafeteria for the level of food processing, where *Ffresh* = frequency of fresh food items; *Fprocess* = frequency of processed foods; *Fultra* = frequency of ultraprocessed foods; *n* = total number of items sold in the cafeteria, achieved by multiplying the frequency of food in each category by its corresponding weight, added to the values and dividing by the total number of items sold in the cafeteria. The score formula  $50R + 50$  is used to obtain scores for each establishment.



The score can vary on a scale of 0 to 100 points, where 50 is the midpoint. Thus, a cafeteria that offers healthy (fresh) and unhealthy (ultraprocessed) food in equal quantities will receive an average score of 50 points and will be considered a neutral cafeteria. Cafeterias that reach a score below 50 points have a greater predominance of ultraprocessed foods (ie, a greater offering of unhealthy foods). In summary, higher scores reflect better food quality in the school cafeterias.

### Statistical Analysis

We will consider the 2 primary outcomes and the secondary outcome: composition of the menu offered (ordinal categorical data), assessment of hygienic conditions concerning good practices in handling food (continuous variables), and the score for the level of processing of food sold (continuous variables). The baseline characteristics of the school and the cafeteria will be presented in conventional descriptive statistics. Continuous variables will be presented as means and standard deviations for symmetric data or medians and interquartile ranges for asymmetric data, while categorical variables will be presented as frequencies and percentages. All outcomes will be analyzed as intention-to-treat and per-protocol. The intention-to-treat analysis will include all participants according to their original group assignment, regardless of what happened later. The per-protocol analysis will consider only those participants who comply with the protocol in terms of eligibility, interventions, and evaluation of results [38]. Unadjusted and adjusted estimates allowing for the potential confounding effects of all minimization factors will be presented for primary and secondary endpoints. Multiple imputation will be used to deal with missing data [60].

For the analysis of continuous data (hygienic conditions and level of processing of food sold), analysis of covariance or a generalized linear model with an appropriate link function will be used, depending on the data characteristics. The outcomes

will be assessed by comparing the mean changes (delta) between baseline and follow-up values between the groups, adjusting for the baseline value of the outcome. For the analysis of ordinal categorical data (menu composition and percentages of each type of food), we will use an ordinal logistic regression model to assess between-group differences at follow-up, adjusting for the baseline value of the outcome. All data will be analyzed using the statistical software SPSS 26.0 (IBM Corp, Armonk, NY) and R Software 3.5.0 (R Development Core Team). The statistical level of significance considered will be  $P < .05$  for a confidence interval of 95%.

### Results

This project started receiving funds in early 2018. The educational program was developed in 2018. We administered the intervention program in 2019. All data have already been collected, and we are analyzing the data. In 2020, to ensure ethical and opportunity principles, we offered the educational program to schools from the control group that expressed interest after completion of follow-up. The results are expected in 2021.

### Discussion

This protocol presents a description of the methods to be used to assess the effect of an intervention for the implementation of healthy school cafeterias, ensuring the accuracy of the study and allowing its reproducibility. To our knowledge, this may be the first randomized controlled study in school cafeterias held in Brazil. After the completion of this study, it will be possible to determine whether the proposed educational intervention program is able to improve the menu offered and hygienic conditions of school cafeterias. The results will provide evidence for the formulation of public nutritional and food security policies and for the development of efficacy strategies to provide safe and healthy school meals.

### Acknowledgments

The National Council for Scientific and Technological Development of Brazil (CNPq) and the Ministry of Science, Technology and Innovation of Brazil funded this project with grant number 442730/2016-0 (Multimedia Appendix 2). The authors are solely responsible for designing and performing this study and all its analyses, for drafting and editing the manuscript, and for the final content. The authors would like to thank the support of the researchers ACB De Marchi, BS Acosta, B Steffler, CT Bohrer, ÉV Vargas, GVS Leal, OAT Figueredo, and RL Leal.

### Conflicts of Interest

None declared.

#### Multimedia Appendix 1

Retrospective questionnaire applied at the end of the intervention program.

[PDF File (Adobe PDF File), 93 KB - [resprot\\_v10i1e22680\\_app1.pdf](#)]

#### Multimedia Appendix 2

Peer review report from the grant agency.

[PDF File (Adobe PDF File), 1774 KB - [resprot\\_v10i1e22680\\_app2.pdf](#)]

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*Edited by G Eysenbach; submitted 20.07.20; peer-reviewed by R Wyse, T Delaney; comments to author 21.08.20; revised version received 12.10.20; accepted 20.10.20; published 19.01.21.*

**Please cite as:**

Balestrin M, Brasil CCB, Bellei EA, Kirsten VR, Wagner MB

Program for Healthier School Cafeterias in Rio Grande do Sul, Brazil: Protocol for a Community-Based Randomized Trial

*JMIR Res Protoc* 2021;10(1):e22680

URL: <http://www.researchprotocols.org/2021/1/e22680/>

doi: [10.2196/22680](https://doi.org/10.2196/22680)

PMID: [33464219](https://pubmed.ncbi.nlm.nih.gov/33464219/)

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Protocol

# The Current State and Diagnostic Accuracy of Digital Mental Health Assessment Tools for Psychiatric Disorders: Protocol for a Systematic Review and Meta-analysis

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## Abstract

**Background:** Despite the rapidly growing number of digital assessment tools for screening and diagnosing mental health disorders, little is known about their diagnostic accuracy.

**Objective:** The purpose of this systematic review and meta-analysis is to establish the diagnostic accuracy of question- and answer-based digital assessment tools for diagnosing a range of highly prevalent psychiatric conditions in the adult population.

**Methods:** The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) will be used. The focus of the systematic review is guided by the population, intervention, comparator, and outcome framework (PICO). We will conduct a comprehensive systematic literature search of MEDLINE, PsychINFO, Embase, Web of Science Core Collection, Cochrane Library, Applied Social Sciences Index and Abstracts (ASSIA), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for appropriate articles published from January 1, 2005. Two authors will independently screen the titles and abstracts of identified references and select studies according to the eligibility criteria. Any inconsistencies will be discussed and resolved. The two authors will then extract data into a standardized form. Risk of bias will be assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, and a descriptive analysis and meta-analysis will summarize the diagnostic accuracy of the identified digital assessment tools.

**Results:** The systematic review and meta-analysis commenced in November 2020, with findings expected by May 2021.

**Conclusions:** This systematic review and meta-analysis will summarize the diagnostic accuracy of question- and answer-based digital assessment tools. It will identify implications for clinical practice, areas for improvement, and directions for future research.

**Trial Registration:** PROSPERO International Prospective Register of Systematic Reviews CRD42020214724; [https://www.crd.york.ac.uk/prospero/display\\_record.php?ID=CRD42020214724](https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020214724).

**International Registered Report Identifier (IRRID):** DERR1-10.2196/25382

(*JMIR Res Protoc* 2021;10(1):e25382) doi:[10.2196/25382](https://doi.org/10.2196/25382)

**KEYWORDS**

diagnostic accuracy; digital mental health; digital questionnaire; meta-analysis; psychiatry; systematic review

## Introduction

Mental health disorders represent the leading cause of disability worldwide, with over a third of the world's population being affected by a mental health condition in their lifetime [1]. Despite the well-documented economic and global burdens of mental disorders and the wide range of existing evidence-based treatments, mental health conditions remain largely underdiagnosed or misdiagnosed and undertreated [2,3], even in high-income countries [4,5]. Critically, the challenges associated with identifying and treating mental health disorders are multifaceted and present with a combination of patient, provider, and system-level barriers. With increasing pressure on mental health care budgets and the overwhelming growing burden of mental health disorders globally [6], prevention strategies and improvements in early identification are essential.

In this regard, digital technologies may offer an innovative and cost-effective way to improve and develop mental health care detection and diagnosis. In fact, digital assessment tools have the potential to support health care professionals in the recognition of mental health symptoms and patient-specific treatment needs. Furthermore, the use of digital technologies could help alleviate the load on the health care system by reducing the number of in-person appointments and providing patients with subclinical or mild mental health symptoms with self-help strategies and psychoeducation [7]. Digital solutions for psychiatry also have the potential to lessen some of the barriers associated with disclosing mental health difficulties in person, such as shyness and discomfort, as well as issues related to stigma and discrimination. Furthermore, such technologies can overcome geographical barriers to health seeking and treatment and can facilitate the engagement of conventionally hard-to-reach groups.

Studies have revealed the acceptability and efficacy of digital platforms for improving the reach, quality, and impact of mental health care [8], and patients have been found to value the ease of access and empowerment that can be obtained via the use of a digital platform [9]. Importantly, research has demonstrated that patients have a strong interest in using digital technologies to help monitor their mental health [10,11] and are more likely to report severe symptoms on technology platforms than in a face-to-face meeting with a health care professional [11]. Despite the benefits and potential identified by global and national organizations, such as the World Health Organization (WHO), the National Health Service (NHS), and the US Department of Health and Human Services [12], the implementation of these technologies in public and private mental health care services has been slow.

This may be, in part, due to resistance from medical professionals and public policy makers who may be unaware of how to best integrate the technologies into standard care practices. An area that has received less resistance is that of the digitalization of psychiatric questionnaires, with studies demonstrating comparable interformat reliability relative to traditional pen-and-paper questionnaires [13,14]. While the digitalization of existing psychiatric questionnaires is ongoing, the development of more sophisticated question- and

answer-based digital solutions for psychiatry, including the use of audio and video [15,16] and personalized user journeys via dynamic question selection [17], represents a promising ground for further innovation.

Critically, while digital psychiatric questionnaires and other technology-based tools are likely to play an important role in the future of mental health care, little attention and effort have been put into establishing their diagnostic accuracy. To this end, there is a need for a comprehensive appraisal of the current state and diagnostic accuracy of digital solutions for screening and diagnosing mental health conditions. We aim to conduct a systematic review and meta-analysis of available question- and answer-based digital mental health tools for a range of psychiatric conditions in the adult population and to evaluate their diagnostic accuracy. Implications for clinical practice, policy making, development, and innovation will be provided. Additionally, potential routes for improving and facilitating blended care (ie, the combination of traditional and digital services) will be investigated, and directions for future research will be identified.

## Methods

### Overview

This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020214724). The protocol was developed to comply with the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [18]. In line with the PRISMA checklist recommendations, the focus of the systematic review is guided by the population, intervention, comparator, and outcome framework (PICO). This review will involve literature search, article selection, data extraction, quality appraisal, data analysis, meta-analysis, and data synthesis. Protocol amendments will be tracked and reported in the final publication.

### Eligibility Criteria

We aim to conduct a systematic review and meta-analysis of available question- and answer-based digital mental health assessment tools for a range of psychiatric conditions in the adult population and to evaluate their diagnostic accuracy. To do this, the below-mentioned PICO framework will be used.

### Population

The scope of this research includes a comprehensive range of highly prevalent psychiatric conditions that are typically diagnosed and treated in primary and/or secondary care settings (see [Multimedia Appendix 1](#) for an overview of the lifetime prevalence and patient impact of the concerned conditions). The population will include adults who have been assessed for the presence of any of the following mental health conditions: mood/affective disorders (eg, bipolar disorder and depressive disorders/dysthymia), anxiety disorders (eg, generalized anxiety disorder, social anxiety disorder/social phobia, and panic disorder), trauma and stress-related disorders (eg, posttraumatic stress disorder, acute stress disorder, and adjustment disorder), neurodevelopmental disorders (eg, attention-deficit/hyperactivity disorder and autism spectrum disorders), eating disorders (eg,



anorexia nervosa and bulimia nervosa), personality disorders (eg, borderline personality disorder and emotionally unstable personality disorder), substance-related disorders (eg, alcohol use disorder and substance use disorder), obsessive-compulsive disorder, insomnia, and schizophrenia. In consultation with a psychiatrist (SB) and given their relevance for the assessment of the above-listed psychiatric conditions, the following transdiagnostic symptom domains will also be included: self-harm, suicidality, and psychosis.

Studies comprising age ranges, where the mean age falls within 18 to 65 years, will be included. The review will focus on both clinical and community-based samples of any gender, severity of mental health concern, ethnicity, and geographical location.

### Intervention

Interventions of interest include question- and answer-based digital diagnostic tools completed by an individual that a health care professional might use to reach a mental health diagnosis. This can comprise pen-and-paper psychiatric questionnaires that have been digitalized and digital assessment tools that are intended to aid in clinical decision-making, including script-based automated conversational agents (ie, chatbots). The format of delivery can include computerized or web-based interventions delivered either offline or online via a computer, tablet, or smartphone.

### Comparator

No specific comparator is required for studies to be included in this systematic review and meta-analysis.

### Outcomes

The primary objectives are to identify the types of question- and answer-based digital assessment tools used in mental health care and to assess their diagnostic accuracy (eg, sensitivity and specificity).

### Study Design

We will consider any study design for the assessment.

### Search Strategy

We will search the following databases: MEDLINE, PsychINFO, Embase, Web of Science Core Collection, Cochrane Library, Applied Social Sciences Index and Abstracts (ASSIA), and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Other potentially eligible trials or publications will be identified by hand searching the reference lists of retrieved publications, systematic reviews, and meta-analyses. Grey literature (eg, unpublished theses, reports, and conference presentations) will also be identified by hand. Keywords and subject headings related to digital technologies, assessment tools, and diagnostic accuracy outcomes were identified in a preliminary scan of the literature and chosen in consultation with a medical librarian (EB). Key terms for the most common mental health conditions were taken from the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 and International Classification of Diseases (ICD)-11 (or DSM-IV and ICD-10 for older publications) diagnostic manuals and chosen in consultation with a psychiatrist (SB). In addition to these, notable symptom domains, such as self-harm, suicidality, and psychosis, were included in the search terms on the basis of their relevance in psychiatric assessments. The search terms that will be included in this review are grouped into four themes and are presented in [Table 1](#), with search strategies presented in [Multimedia Appendix 2](#). For simplicity, while we will not specifically search for conditions, such as generalized anxiety disorder, separation anxiety disorder, and histrionic personality disorder, these will be captured by our broader search strategy terms (ie, “anxiety disorder” and “personality disorder”). If additional relevant keywords or subject headings are identified during any of the electronic searches, we will modify the electronic search strategies to incorporate these terms and document the changes.

**Table 1.** Search terms.

Category	Keywords/subject headings (in the title or abstract)
Digital technology	“Application” OR “chatbot” OR “computer” OR “conversational agent” OR “device” OR “digital” OR “e-health” OR “e-mental health” OR “electronic” OR “internet” OR “mHealth” OR “m-health” OR “mobile” OR “online” OR “PC” OR “phone” OR “smart” OR “tablet” OR “telehealth” OR “telemedicine” OR “text messaging” OR “web” OR “algorithm” OR “software”
Assessment tool	“Assessment” OR “diagnostic” OR “mood diary” OR “PHQ” OR “PHQ-9” OR “GAD” OR “GAD-7” OR “questionnaire” OR “screening” OR “tool” OR “test” OR “The Computerized Adaptive Test for Mental Health” OR “CAT-MH” OR “e-PASS” OR “WSQ” OR “TAPS” OR “Nview” OR “ada” OR “doctorlink” OR “clinicom”
Mental health	“Depression” OR “major depressive disorder” OR “MDD” OR “dysthymia” OR “bipolar” OR “anxiety disorder” OR “generalised anxiety disorder” OR “generalized anxiety disorder” OR “GAD” OR “panic disorder” OR “social anxiety disorder” OR “social phobia” OR “attention-deficit/hyperactivity disorder” OR “attention deficit hyperactivity disorder” OR “ADHD” OR “autism spectrum disorders” OR “ASD” OR “insomnia” OR “eating disorders” OR “anorexia nervosa” OR “bulimia nervosa” OR “obsessive compulsive disorder” OR “OCD” OR “schizophrenia” OR “psychosis” OR “alcohol abuse” OR “alcohol addiction” OR “substance abuse” OR “substance addiction” OR “drug abuse” OR “drug addiction” OR “post-traumatic stress disorder” OR “PTSD” OR “acute stress disorder” OR “adjustment disorder” OR “personality disorder” OR “borderline personality disorder” OR “BPD” OR “emotionally unstable personality disorder” OR “EUPD” OR “self harm” OR “self-harm” OR “suicidality”
Diagnostic accuracy	“Accuracy” OR “sensitivity” OR “specificity” OR “receiver operating characteristic” OR “ROC” OR “area under the curve” OR “AUC” OR “AUROC” OR “positive predictive value” OR “PPV” OR “negative predictive value” OR “NPV” OR “precision” OR “recall” OR “true positive rate” OR “TPR” OR “true negative rate” OR “TNR” OR “agreement rate” OR “validity”

## Inclusion Criteria

Owing to the recent developments in the digitalization of existing psychiatric questionnaires and the rapid growth in digital assessment tools for the screening and diagnosis of mental health conditions, only studies published in the last 15 years (from January 2005) will be included. Studies that evaluate at least one question- and answer-based digital assessment tool to screen or diagnose one or more mental health conditions covered by this review will be included. Any gender, severity of mental health concern, ethnicity, and geographical location will be included. Any study design will be included.

## Exclusion Criteria

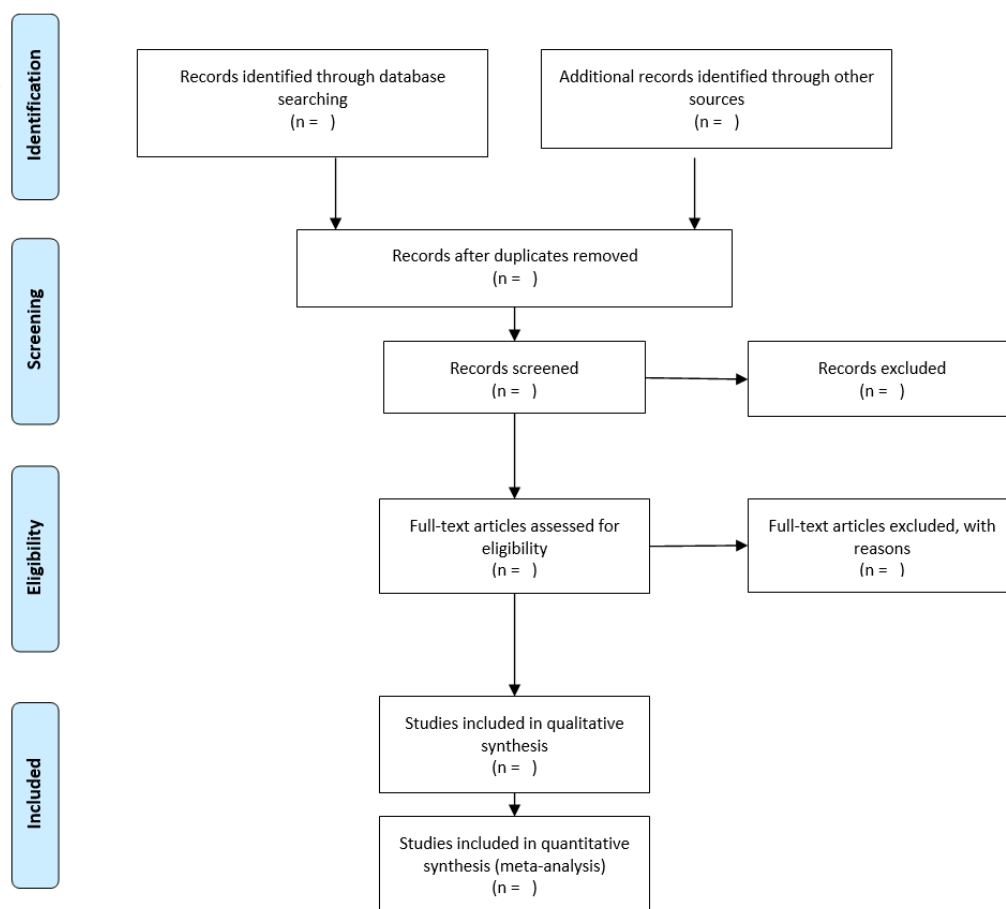
Studies of digital assessment tools that are not exclusively question and answer based, such as blood tests, imaging techniques, monitoring tools, genome analysis, accelerometer devices, and wearables, will also be excluded. Specific subgroups, such as pregnant women, refugees/asylum seekers, prisoners, and those in acute crisis/admitted to emergency services will be excluded. Studies on tools used to identify mental health disorders in physical illnesses (eg, cancer) will also be excluded. We will also exclude studies on somatoform disorders and specific phobias as these are less frequently diagnosed in primary care and rarely present in secondary care. In addition, studies on tools used to identify neuropsychiatric disorders (eg, dementias) or any disorders that are due to

clinically confirmed temporary or permanent dysfunction of the brain are outside the scope of the current review. Studies on digital assessment tools used to predict the future risk of developing a mental health disorder will also be excluded.

## Screening and Article Selection

All articles identified from the database searches will be stored in the systematic review software Rayyan, which will be used to eliminate any duplicates. Two independent reviewers will screen the titles and abstracts of all the studies. To decide whether an article should be examined further, independent reviewers will assess their eligibility against the inclusion criteria. Publications will be labelled as “exclude,” “include,” or “maybe.” For an article to be included, both reviewers must label it as “include.” An article will be excluded if both reviewers label it as “exclude.” Articles labelled as “maybe” or any disagreements will be discussed until a consensus is reached. All exclusions will be documented. The screening process will be piloted and tested by the reviewers on a subset of 100 studies, after which the review will continue. The full text of the “included” articles will then be examined by the two independent reviewers in order to determine final eligibility, with any disagreements being resolved by a third reviewer. All reasons for full-text exclusions will be recorded. A PRISMA flow diagram will be used to record the details of the screening and selection process so that the study can be reproduced (Figure 1).

**Figure 1.** PRISMA flow-chart template of the search and selection strategy.



## Data Extraction

Two independent reviewers will examine the full text of all the papers included in the final selection to extract the predetermined outcomes. Outcomes will be extracted into a predetermined standardized electronic data collation form, and they will include (1) publication details: author(s) and date; (2) study design and methodology: sample size(s), sample characteristics (mean age, proportions of males and females, ethnicity, and geographical location), recruitment and sampling procedures, main psychiatric diagnosis, and how psychiatric diagnosis was established/confirmed; (3) index test (ie, the digital assessment tool) and reference standard (ie, assessment by a psychiatrist and standardized structured and semistructured diagnostic interviews based on the DSM-5 and ICD-11 criteria, or DSM-IV and ICD-10 for older publications, such as the Composite International Diagnostic Interview [19] and the Structured Clinical Interview for DSM-5 Disorders [20]); and (4) outcomes of interest: measure of diagnostic accuracy.

Disagreements will be resolved by discussion, and if consensus cannot be reached, a third reviewer will be consulted.

## Quality Appraisal: Risk of Bias and Applicability

Following the final selection of studies, two independent reviewers will assess risk of bias and applicability of all included studies using the Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2 [21]). The checklist consists of the following four key domains: patient selection, index test, reference standard, and flow of participants through the study and timing of the index tests and reference standard. Each of these domains has a subdomain for risk of bias, while the first three have a subdomain for concerns regarding applicability. The subdomains about risk of bias include signaling questions to guide the overall judgement about whether a study is likely to be biased or not. Studies that are judged as “low” on all domains relating to bias or applicability are classed as having “low risk of bias” or “low concern regarding applicability.” On the other hand, studies judged as “high” or “unclear” in one or more domains may be deemed as “at risk of bias” or as having “concerns regarding applicability.”

In the event of a disagreement, the reviewers will discuss before consulting a third reviewer. A table will be created summarizing the risk of bias and applicability of all included studies.

## Data Analysis and Synthesis

The data analytic strategy was developed in consultation with a statistician. We will conduct a descriptive analysis to summarize the extracted data, with studies grouped by target mental health condition (eg, bipolar disorder).

Where possible and in line with the recommendations in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [22], we will construct bivariate random-effects meta-analyses to determine the meta-analyzed sensitivity and specificity of each digital assessment tool and all digital assessment tools collectively per target mental health condition. Summary receiver operating characteristic (sROC) curves with

accompanying 95% CIs for each digital assessment tool and for all digital assessment tools collectively per condition will be calculated using hierarchical sROC curve meta-analysis methods.

Between-study variance as a result of heterogeneity for each digital assessment tool and all digital assessment tools collectively per target mental health condition will be assessed using Higgins  $I^2$  statistic (0%-25%, might not be important; 25%-50%, might represent low heterogeneity; 50%-75%, might represent moderate heterogeneity; 75%-100%, high heterogeneity [23]). To explore the potential sources of heterogeneity, meta-regression analyses using potential predictive covariates will be conducted where possible. In order to explore potential sources of heterogeneity, QUADAS-related factors, such as participant selection, will be used as predictive covariates in the meta-regression analyses. Further, if sufficient data are available, the effects of the following modifiers will be assessed: (1) reference standard (assessment by a psychiatrist, and standardized structured and semistructured diagnostic interviews based on the DSM-5 and ICD-11 criteria, or DSM-IV and ICD-10 for older publications, are considered the gold standard, but these can vary considerably; thus, separate analyses per reference standard will be conducted); (2) population (inpatient or noninpatient); (3) national context (Western or non-Western); (4) gender (male or female); and (5) mode of delivery (smartphone, tablet, or computer).

Importantly, in the event of overlapping populations across studies, subgroup analyses (excluding the smaller studies with shared populations) will be conducted in order to quantify the impact of these on the overall results. Finally, publication bias will be explored by employing the Begg test [24] and Egger test [25] for each digital assessment tool and all digital assessment tools collectively per target mental health condition. Analyses will be conducted in R (R Foundation for Statistical Computing) in consultation with a statistician. Any amendments to the data analytic strategy will be tracked and reported in the final publication.

## Results

The systematic review and meta-analysis commenced in November 2020. Findings are expected by May 2021. This work has been funded by Stanley Medical Research Institute (SMRI; grant number: 07R-1888) and Psycomics Ltd.

## Discussion

A comprehensive systematic review of the literature and meta-analysis will provide a better understanding of the current state of digital assessment tools for mental health and their diagnostic accuracy. Based on the data, we will identify implications for clinical practice, policy making, development, and innovation. Additionally, potential routes for improving and facilitating blended care (ie, the combination of traditional and digital services) will be investigated, and directions for future research will be identified.

## Acknowledgments

This review has been funded by Stanley Medical Research Institute (SMRI; grant number: 07R-1888) and Psyomics Ltd. We would like to thank the Department of Pure Mathematics and Mathematical Statistics at the University of Cambridge for assisting with the development of the data analytic strategy.

## Authors' Contributions

NMK and TSS conceived the study topic and designed the review protocol. EJB developed the search strategies. NMK and TSS prepared the first draft of the protocol with revisions from EJB, BS, EF, JB, JT, and SB.

## Conflicts of Interest

SB is a director of Psynova Neurotech Ltd and Psyomics Ltd. NMK, TSS, EF, and SB have financial interests in Psyomics Ltd. The other authors have no conflicts to declare.

### Multimedia Appendix 1

Prevalence and patient impact of the concerned psychiatric conditions.

[DOCX File, 46 KB - [resprot\\_v10i1e25382\\_app1.docx](#)]

### Multimedia Appendix 2

Search strategies.

[DOCX File, 20 KB - [resprot\\_v10i1e25382\\_app2.docx](#)]

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## Abbreviations

**DSM:** Diagnostic and Statistical Manual of Mental Disorders

**ICD:** International Classification of Diseases

**PICO:** population, intervention, comparator, and outcome

**PRISMA-P:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol

**QUADAS-2:** Quality Assessment of Diagnostic Accuracy Studies-2

**sROC:** summary receiver operating characteristic

*Edited by G Eysenbach; submitted 30.10.20; peer-reviewed by M Gottschalk, M Behzadifar; comments to author 13.11.20; revised version received 23.11.20; accepted 24.11.20; published 08.01.21.*

*Please cite as:*

Martin-Key NA, Schei TS, Barker EJ, Spadaro B, Funnell E, Benacek J, Tomasik J, Bahn S

*The Current State and Diagnostic Accuracy of Digital Mental Health Assessment Tools for Psychiatric Disorders: Protocol for a Systematic Review and Meta-analysis*

*JMIR Res Protoc* 2021;10(1):e25382

URL: <http://www.researchprotocols.org/2021/1/e25382/>

doi: [10.2196/25382](https://doi.org/10.2196/25382)

PMID: [33416508](https://pubmed.ncbi.nlm.nih.gov/33416508/)

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Protocol

# Technology-Supported Guidance Models Stimulating the Development of Critical Thinking in Clinical Practice: Protocol for a Mixed Methods Systematic Review

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## Abstract

**Background:** Critical thinking is an essential skill that nursing students need to develop. Technological tools have opened new avenues for technology-supported guidance models, but the challenges and facilitators of such guidance models, as well as how they stimulate the development of critical thinking, remain unclear.

**Objective:** We developed a protocol for a mixed methods systematic review to investigate the use of technology-supported guidance models that stimulate the development of critical thinking in nursing education clinical practice.

**Methods:** A convergent integrated design following the Joanna Briggs Institute Manual for Evidence Synthesis will be employed. A pair of authors will select the articles by screening titles and abstracts, and the methodological quality of the articles included in the review will be assessed by a pair of authors according to checklists for specific study designs. The data will be extracted using the standardized Joanna Briggs Institute mixed methods data extraction form and following a convergent integrated approach. The thematic synthesis for data transformation will be used.

**Results:** Development of a comprehensive systematic search strategy was completed in October 2020. The database searches were performed on October 21, 2020. As of January 2021, analysis and synthesis is ongoing. Completion of this review is expected by January 2021.

**Conclusions:** By combining evidence from studies with varied methodological approaches, the results should provide broad insight into the use of technology-supported guidance models for clinical practice in nursing education with a focus on the development of nursing students' critical thinking. The results of this mixed methods systematic review can also be used to develop or improve current technology-supported guidance models for clinical practice in nursing education.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/25126

(*JMIR Res Protoc* 2021;10(1):e25126) doi:[10.2196/25126](https://doi.org/10.2196/25126)

**KEYWORDS**

critical thinking; technology; guidance models; nursing education; clinical practice

## Introduction

### Background

Critical thinking is an essential element of the skill set of all health professionals as it enables them to address complex problems and make informed evidence-based decisions [1,2].

This is especially true in the nursing profession as nurses provide complex, prolonged care to a diverse group of patients [3]. Thus, critical thinking is a prerequisite for being able and enabled to provide safe qualified care [4,5], and it is a key component of undergraduate nursing students' emerging competencies [6,7]. Clinical practice is an essential part of the nursing curriculum [8] and is the setting best suited to developing nursing students' necessary skills, such as critical thinking, for their future role as nurses [7].

Critical thinking is a broad concept, and terms such as clinical decision making, analytical thinking, creative thinking, problem solving, reflective thinking, diagnostic reasoning, and clinical judgement are often used interchangeably to describe critical thinking [9]. Nursing has often adopted definitions of critical thinking that are different from those used in other disciplines [10]. In the consensus definition of critical thinking, cognitive skills such as information seeking, knowledge transformation, logical reasoning, and application of standards are highlighted [11].

In addition to cognitive skills, self-awareness, creativity, and risk taking are also deemed important [10]. According to Facione [12], critical thinking is a judgement that is purposeful and self-regulatory and that results in a process of interpretation, analysis, evaluation, and inference.

Clinical practice is an ideal context in which to develop critical thinking [5,13]. This skill is facilitated by a nurse preceptor (a registered nurse working in clinical practice) who, by posing questions, examining problems, and contemplating different ways of thinking about a patient's situation, stimulates the development of students' critical thinking [14,15]. Other strategies to stimulate critical thinking among nursing students involve the use of problem-based learning, case-based learning, and concept mapping [9]. A guidance model (a framework of procedures, meetings, and cooperation) between health care and educational institutions is also often used to facilitate the acquisition of nursing students' competencies in clinical practice [16].

Novel technologies afford new opportunities for supporting nursing students in clinical practice and developing their critical thinking [17,18], but the use of educational technologies in nursing education lacks a solid evidence base [19], and a wide range of technological tools has been adopted without clear recommendations about their use in nursing education [20].

In a meta-analysis, Ismail et al [17] reviewed available research on how technological tools, such as mobile technology, might improve nursing students' critical thinking. Most of the studies in that meta-analysis [17] reported that the use of mobile technology improved critical thinking but that the actual effectiveness of mobile technology in the development of critical

thinking remains unclear. Mobile apps incorporate several strategies, such as cooperative learning and problem-based learning, but the mobile apps and strategies in the meta-analysis were not situated in the clinical education and guidance of nursing students.

Another study, conducted by Lee et al [19], reviewed the use of mobile technology in nursing education and noted that mobile technology is still immature in this field; technology is often used for quickly accessing evidence-based information, submitting various requirements to educational institutions, and communicating with nurse educators, yet its potential to support the development of competencies is unclear.

Regarding guidance models, Jayasekara et al [21] identified 4 clinical educational models used in clinical practice: the clinical education unit model, the standard facilitation model, the collaborative clinical placement model, and the mentor-arranged clinical placement model. None of these approaches includes the use of technological tools.

In conclusion, the existing systematic reviews and meta-analyses are limited to the development of critical thinking in nursing education (both in and outside clinical practice) without the use of technological tools [9,22,23]. Consequently, a systematic literature review is needed that focuses on critical thinking as a competency and on its development in clinical practice in nursing education through guidance and the use of technology. This focus can be informed by evidence from various types of studies; therefore, a mixed methods systematic review is appropriate. Mixed methods systematic reviews are suitable for answering complex questions because the methodology allows the inclusion, integration, and discussion of qualitative, quantitative, or mixed methods primary studies [24]. To the best of our knowledge, no earlier reviews or protocols of reviews have appraised existing studies on technology-supported guidance models that aim to stimulate critical thinking among nursing students in clinical practice.

### Aim

This study outlines a mixed methods systematic review with an overall aim of synthesizing available knowledge about various technology-supported guidance models that employ technological tools in clinical practice to stimulate the development of critical thinking among nursing students.

### Review Questions

Which technology-supported guidance models are used to stimulate the development of critical thinking in the context of clinical practice in nursing education?

What is known about the challenges and facilitators of such technology-supported guidance models?

## Methods

### Design

This mixed methods systematic review will be guided by the Joanna Briggs Institute Manual for Evidence Synthesis and will have a convergent integrated design [24]. The convergent integrated design involves the transformation, integration, and



synthesis of data from primary qualitative, quantitative, or mixed methods studies [24]. The reporting of this systematic mixed methods review protocol is guided by the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist [25].

## Eligibility Criteria

We will include evidence that addresses preregistration or undergraduate nursing students in clinical practice; further details on the inclusion and exclusion criteria are provided in [Table 1](#).

**Table 1.** Inclusion and exclusion criteria.

Criterion	Inclusion	Exclusion
Study population	Preregistration nursing students or undergraduate nursing students	Nursing students studying at the master's or PhD degree level; postregistration nursing students; student paramedics; students of midwifery, physiotherapy or occupational therapy; medical students; dental students
Phenomenon of interest	Technological tools used in clinical practice and technology-assisted guidance models or technology-supported guidance models or guidance models or mentoring or tutoring or preceptorship in clinical practice or clinical educational models	Technology-assisted guidance models; clinical educational models; guidance models; mentoring, tutoring, or preceptorship outside clinical practice, in clinical labs and as a preparation for clinical practice; simulation or technology use in conjunction with simulation.
Context	Clinical practice in hospitals, nursing homes, community health care, or other health care institutions and settings	Outside clinical practice, such as in classes for preparation for clinical practice, simulation sessions and training in a clinical laboratory
Type of study	Qualitative, quantitative, and mixed methods studies using experimental, quasi-experimental, or nonexperimental design published in peer-reviewed journals	Any type of systematic or nonsystematic review, non-peer-reviewed articles, conference proceedings, comments or opinion articles, official guidelines, national nursing curriculums, editorials, abstracts and doctoral theses
Type of outcome	Critical thinking, clinical decision making, analytical thinking, creative thinking, problem solving, reflective thinking, diagnostic reasoning, clinical judgement	All other outcomes

## Search Strategy

A systematic, comprehensive search strategy will be built through an initial search in MEDLINE and CINAHL by an experienced research librarian, the first author, and the last author using subject terms, Medical Subject Heading terms, CINAHL headings, and text words. The search strategy includes terms chosen based on an initial search and discussion within the review team. The search will be limited to publications in English, Slovak, Hungarian, Czech, Spanish, Portuguese, Finnish, Norwegian, Swedish, and Danish. To capture the studies most relevant to current and emerging technologies in nursing education, the search strategy will be limited to articles published from January 1, 2010 through December 31, 2020.

The search strategy will be tested and retested [26] in the initial databases before it is peer reviewed by a second research librarian. The search strategy will then be applied to CINAHL, Cochrane Trials, Embase, ERIC, MEDLINE, PsycINFO, and Web of Science. An example of the MEDLINE search strategy is provided in [Multimedia Appendix 1](#).

In addition, forward and backward reference searches will be conducted. A search for unpublished studies and other grey

literature will not be included. The rationale for not conducting a search for grey literature is the lack of a standard, accepted systematic procedure for such searches [27]. This lack of a standard procedure, combined with the surfeit of sources of grey literature, could produce a search with unsystematic and random results.

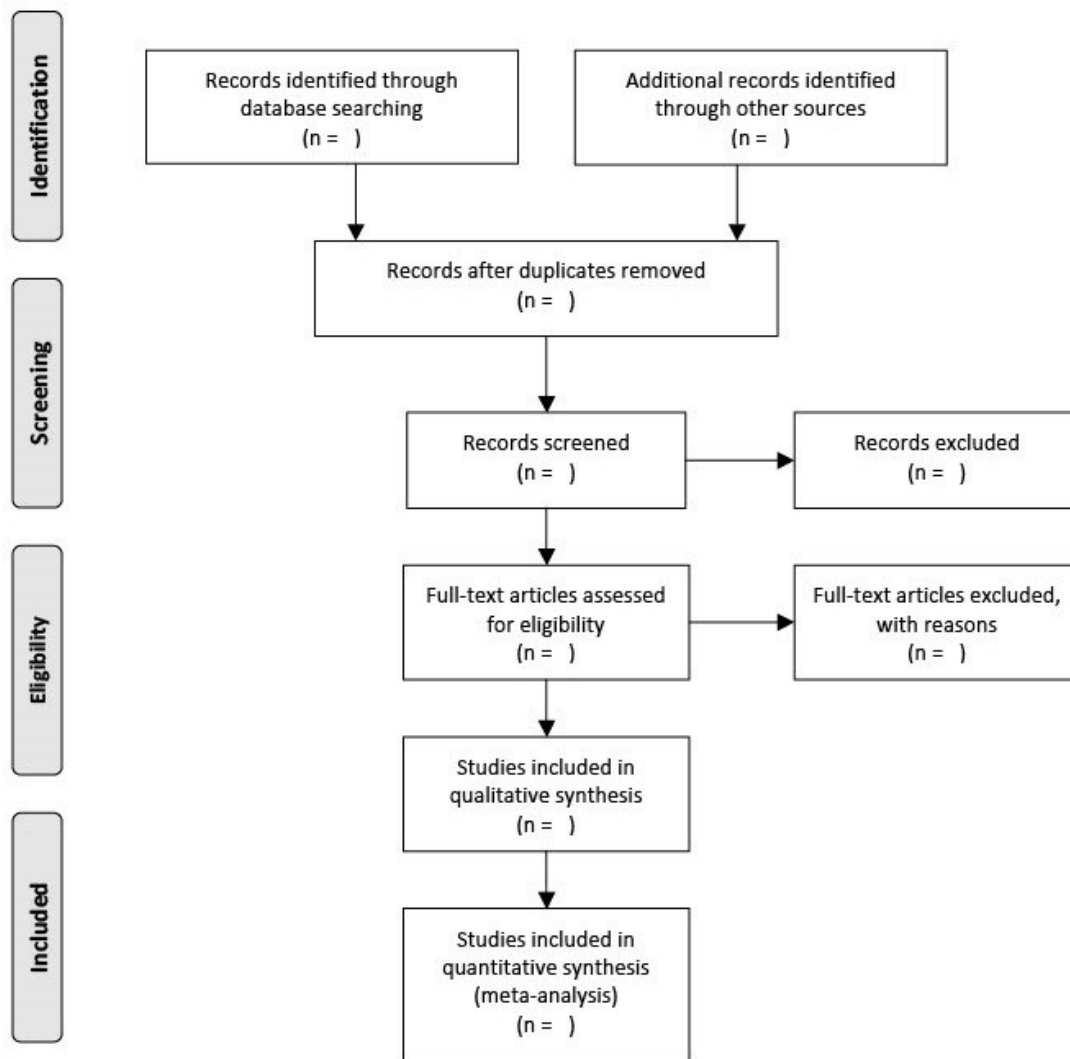
## Data Management

Records will be managed through EndNote (Clarivate Analytics) [28], and Rayyan (Qatar Computing Research Institute) [29] will be used to facilitate the screening, blinding, organization, and storage of the publications for the study selection process.

## Selection Process

Titles and abstracts will be screened independently by pairs of authors (AAGN and JZ, ERG and MF, MHL and CS-L, SAS and MTS) based on the inclusion and exclusion criteria for the review. From this selection, the full-text articles will be assessed independently by pairs of authors against the inclusion and exclusion criteria for the review. The final decision on whether to include or exclude articles will be made by consensus between the team of authors. An overview of the selection process that will be used is shown in a PRISMA [30] flow diagram ([Figure 1](#)).

Figure 1. PRISMA [29] flow diagram of the selection process that will be used.



### Assessment of Methodological Quality

Studies eligible for inclusion will be critically assessed for their methodological quality. The critical assessment will be conducted by pairs of authors (AAGN and JZ, ERG and MF, MHL and CS-L, SAS and MTS) according to checklists specific to the study design. The tools used to assess the methodological quality of the studies are shown in Table 2. If required, authors will be contacted for additional data or to provide missing data. During the review process, if a pair of authors disagrees on the

assessment of the methodological quality of the articles, either the disagreement will be resolved by discussion between the pair, or another author (the first or last author) will independently appraise the quality of the study.

All studies, regardless of the results of the assessment of methodological quality, will be included in the data extraction and synthesis, but the results of the assessment of methodological quality will be elaborated on in discussion, and the results will be displayed in appropriate tables.

Table 2. Checklist for the assessment of methodological quality.

Type of study	Checklist or tool
Cohort studies	Joanna Briggs Institute Checklist for Cohort Studies [31]
Case-control studies	Joanna Briggs Institute Checklist for Case Control Studies [32]
Qualitative studies	Joanna Briggs Institute Checklist for Qualitative Research [33]
Cross-sectional studies	Appraisal Tool for Cross-Sectional Studies [34]
Mixed methods studies	Mixed Methods Appraisal Tool [35]
Quasi-experimental studies	Joanna Briggs Institute Checklist for Quasi-Experimental Studies [36]
Randomized controlled trials	Cochrane Risk-of-Bias Tool [37]

## Data Extraction and Data Items

Quantitative and qualitative data will be extracted by pairs of authors (AAGN and JZ, ERG and MF, MHL and CS-L, SAS and MTS) from studies that meet the inclusion criteria using the standardized Joanna Briggs Institute mixed methods data extraction form and following a convergent integrated approach [24]. The extracted data will include population, phenomenon of interest, type of study, methods, context, time period and outcomes. Quantitative data will include percentage or average (for descriptive studies) and significant and nonsignificant results (for analytical studies). Qualitative data will include themes and subthemes with, for example, supporting quotations from participants. Qualitative data will be assigned a level of credibility (unequivocal, credible, or not supported) according to the Joanna Briggs Institute Manual for Evidence Synthesis [24].

## Outcomes

The primary outcome is critical thinking, as defined by Facione [12], as well as synonyms of the term *critical thinking*, as defined in Table 1.

## Data Transformation, Synthesis, and Integration

To facilitate combining qualitative and quantitative data, quantitative data will first be transformed into qualitized data. The process of qualitizing data refers to converting quantitative data into themes through textual description of quantitative data in relation to the review question [24]. This will be accomplished by thematic analysis [24]. NVivo (version 12; QSR

International) [38] will be used to store and synthesize data. We will use thematic synthesis for data synthesis and integration. Qualitized and qualitative data are assembled according to similar meanings [24]; coding themes are coded and codes are grouped by similarity to develop encompassing themes that will answer the review question. In that manner,

## Confidence in the Cumulative Evidence

According to the Joanna Briggs Institute Manual for Evidence Synthesis, the assessment of the certainty of evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) is not recommended for mixed methods systematic reviews [24].

## Results

A comprehensive systematic search strategy was developed by a research librarian in MEDLINE and CINAHL and reviewed by a second research librarian (completed in October 2020). Initial database searches were performed on October 21, 2020, and resulted in 7307 publications. After the removing 3861 duplicates, we began screening the titles and abstracts of 3446 publications in addition to conducting manual searches and contacting researchers in this field. From the results of this selection, we will assess the full-text articles. We anticipate that the review will be completed by January 2021. Table 3 provides a detailed timeline of the stages of this mixed methods review. The results should clarify the feasibility and reliability of the technological guidance models used in clinical nursing education.

**Table 3.** Timeline of completion of the stages of mixed methods review.

Stage of the review	Date of completion
Building a comprehensive search strategy	October 2020
Application of the search strategy in databases	November 2020
Screening search results from databases	November 2020
Assessment of methodological quality	December 2020
Data extraction	December 2020
Data transformation, synthesis, and integration	January 2021

## Discussion

### General

In this mixed methods systematic review, we will discuss the contribution of technology to guidance models that are employed in nursing education clinical practice settings, focusing on the stimulation and development of critical thinking among nursing students.

### Significance of the Results

Technology is an important part of nursing education that has the potential to significantly improve it, especially in clinical practice [18]. Earlier research shows that various technological tools have been implemented in nursing education with varied degrees of use, but their implementation and use in nursing clinical practice sometimes appear unsystematic [20]. This

study's results will enable the improvement of current or the further development of new technology-supported guidance models, which may benefit nursing students, nurse educators, and health care institutions.

### Limitations of the Review

One of the limitations of this study is the exclusion of unpublished studies and other grey literature. Such material can potentially benefit a systematic review, but the challenges of searching for grey literature and including its findings [27] outweigh its benefits for this study. By choosing a mixed methods systematic review with an integrated convergent design, however, we have facilitated a comprehensive synthesis of peer-reviewed empirical evidence. This approach makes possible broad novel insight into the use, challenges, and facilitators of technology-supported guidance models in nursing clinical practice [24].

## Acknowledgments

This study is financed by Lovisenberg Diaconal University College and Diku Norwegian Agency for International Cooperation and Quality Enhancement in Higher Education. The funding body has no involvement in any part of the process of this protocol or the final manuscript of the review.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Example of the MEDLINE search strategy.

[[DOCX File , 17 KB - resprot\\_v10i1e25126\\_app1.docx](#) ]

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*Edited by G Eysenbach; submitted 19.10.20; peer-reviewed by IV George, C Mather, I Shubina; comments to author 10.11.20; revised version received 22.11.20; accepted 24.11.20; published 19.01.21.*

*Please cite as:*

Zlamal J, Gjevjon ER, Fossum M, Solberg MT, Steindal SA, Strandell-Laine C, Larsen MH, Pettersen FS, Nes AAG  
*Technology-Supported Guidance Models Stimulating the Development of Critical Thinking in Clinical Practice: Protocol for a Mixed Methods Systematic Review*  
*JMIR Res Protoc* 2021;10(1):e25126  
URL: <http://www.researchprotocols.org/2021/1/e25126/>  
doi: [10.2196/25126](https://doi.org/10.2196/25126)  
PMID: [33464214](https://pubmed.ncbi.nlm.nih.gov/33464214/)

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Protocol

# Risk Factors and Prevalence of Dilated Cardiomyopathy in Sub-Saharan Africa: Protocol for a Systematic Review

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## Abstract

**Background:** Cardiomyopathies, defined as diseases involving mainly the heart muscles, are linked to an estimated 5.9 of 100,000 deaths globally. In sub-Saharan Africa, cardiomyopathies constitute 21.4% of heart failure cases, with dilated cardiomyopathy (DCM) being the most common form. The etiology of DCM is heterogeneous and is broadly categorized as genetic or nongenetic, as well as a mixed disease in which genetics interact with intrinsic and environmental factors. Factors such as age, gender, family history, and ethnicity are nonmodifiable, whereas modifiable risk factors include poor nutrition, physical inactivity, and excessive alcohol consumption, among others. However, the relative contribution of the different risk factors to the etiology of DCM is not known in sub-Saharan Africa, and the prevalence of DCM among heart failure patients has not been systematically studied in the region.

**Objective:** The aim of this review is to synthesize available literature from sub-Saharan Africa on the prevalence of DCM among patients with heart failure, as well as the literature on factors associated with DCM. This paper outlines the protocol that will be followed to conduct the systematic review.

**Methods:** A limited search of the PubMed database will be performed to identify relevant keywords contained in the title, abstract, and subject descriptors using initial search terms “heart failure,” “cardiomyopathy,” and “sub-Saharan Africa.” These search terms and their synonyms will then be used in an extensive search in PubMed, and will address the first research question on prevalence. To address the second research question on risk factors, the terms “heart failure,” “cardiomyopathy,” and “cardiovascular risk factors” in “Sub-Saharan Africa” will be used, listing them one by one. Articles published from 2000 and in the English language will be included. Indexed articles in PubMed and Embase will be included, as well as the first 300 articles retrieved from a Google Scholar search. Collected data will be organized in Endnote and then uploaded to the Rayyan web app for systematic reviews. Two reviewers will independently select articles against the inclusion criteria. Discrepancies in reviewer selections will be resolved by an arbitrator. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for reporting systematic reviews will be applied. A map of sub-Saharan Africa with colors to show disease prevalence in each country will be included. For quantitative data, where possible, odds ratios (for categorical outcome data) or standardized mean differences (for continuous data) and their 95% CIs will be calculated.

**Results:** The primary outcomes will be the prevalence of DCM among patients with heart failure and cardiovascular risk factors associated with DCM in sub-Saharan Africa. The literature search will begin on January 1, 2021, and data analysis is expected to be completed by April 30, 2021.

**Conclusions:** This review will provide information on the current status of the prevalence and associated factors of DCM, and possibly identify gaps, including paucity of data or conflicting results that need to be addressed to improve our understanding of DCM in sub-Saharan Africa.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/18229

(*JMIR Res Protoc* 2021;10(1):e18229) doi:[10.2196/18229](https://doi.org/10.2196/18229)

## KEYWORDS

dilated cardiomyopathy; cardiomyopathy; heart failure; cardiovascular risk factors; sub-Saharan Africa

## Introduction

### Background

An interesting phenomenon is unfolding in sub-Saharan Africa due to globalization and urbanization. The region traditionally plagued with infectious diseases is currently facing a double burden of disease as evidenced by the rise of noncommunicable diseases, mainly cardiovascular diseases (CVDs) [1]. The increase in CVD incidence has resulted in a growing burden of heart failure in sub-Saharan Africa [2], a trend that is expected to increase over time [3].

Cardiomyopathies, which are diseases affecting mainly the heart muscles, are a common cause of heart failure worldwide, and represent a significant cause of morbidity and mortality. In 2010, cardiomyopathies were estimated to cause mortality in up to 5.9 of 100,000 individuals globally and most likely are underdiagnosed [4,5]. In sub-Saharan Africa, a contemporaneous systematic review and meta-analysis of the etiology of heart failure performed by Agbor et al [6] showed that cardiomyopathies (all forms) constituted 21.4% (18.2%-40.2%) of all heart failure cases, second only to hypertensive heart disease as a cause of heart failure. Among the different types of cardiomyopathies, dilated cardiomyopathy (DCM) is by far the most common in sub-Saharan Africa [7-9].

DCM is defined as the presence of left or biventricular dilatation and contractile dysfunction in the absence of abnormal loading conditions (such as hypertension or valve disease) or coronary artery disease that is sufficient to cause global contractile impairment [10]. The etiology of DCM is diverse and heterogeneous, including genetic mutations, infections, and autoimmunity, although in most instances the etiology cannot be completely identified [5]. The European Society of Cardiology (ESC) classifies DCM as familial or nonfamilial, in which familial cases usually have a genetic cause [11]. However, the American Heart Association classifies DCM as genetic, acquired, or mixed [12]. A revised definition of DCM by the ESC Working Group on Myocardial and Pericardial Diseases highlighted the heterogeneous nature of the disease that can broadly be grouped as genetic or nongenetic, although there are some circumstances in which a genetic predisposition interacts with intrinsic or environmental factors to form a clinical picture seen in DCM [13]. The presence of nonmodifiable cardiovascular risk factors such as family history, age, ethnicity, and gender, as well as modifiable risk factors such as hypertension, diabetes, tobacco use, physical inactivity, poor nutrition, excessive alcohol consumption, high cholesterol, and

obesity increase the probability of developing CVD and heart failure [14,15].

However, the relative contribution of the different risk factors to the etiology of DCM is not known in sub-Saharan Africa, and the prevalence of DCM among heart failure patients has not been systematically studied in the region.

With the increasing recognition of DCM as a heterogeneous and diverse disease [11,12,16], it is important to understand the contribution of the different cardiovascular risk factors to the clinical presentation of DCM. Identifying risk factors associated with DCM may bring about insightful management consequences, including medical counseling directed to patients and their relatives to avoid or manage the modifiable risk factors so as to halt or prolong the course of DCM. This review will systematically study the available data published from 2000 onward to capture the current situation in sub-Saharan Africa with regard to the risk factors and prevalence of DCM in patients with heart failure. This time period has been selected to reflect the current definitions of DCM [11-13].

### Aim of This Review

The aim of this review is to determine the prevalence of DCM and its associated risk factors among patients with heart failure in sub-Saharan Africa.

### Review Questions

The specific review questions to be addressed are: (1) What is the prevalence of DCM in patients with heart failure in sub-Saharan Africa? (2) What are the associated risk factors for DCM in patients with heart failure in sub-Saharan Africa?

## Methods

### Inclusion Criteria

All full-text articles from observational studies (cross-sectional, cohort, retrospective, or prospective) that meet the search criteria, published in the English language from January 1, 2000 to December 31, 2020 will be included in this review.

### Exclusion Criteria

This review will exclude case reports, editorials, comments or expert opinions, as well as letters of study subjects due to lack of peer review. In addition, articles published in a language other than English will be excluded. Qualitative studies will also be excluded.



## Search Strategy

A limited search of PubMed will be performed to identify relevant keywords contained in the title, abstract, and subject descriptors. The initial search terms will be “heart failure,” “cardiomyopathy,” and “sub-Saharan Africa”; these search terms and their synonyms will then be used in an extensive search in PubMed. This search will be applied to answer question 1 on prevalence. Thereafter, a search will be performed to answer question 2 using the terms “heart failure,” “cardiomyopathy,” and the risk factors of interest, which are age, gender, ethnicity, family history, hypertension, diabetes, tobacco use, physical inactivity, poor nutrition, excessive alcohol consumption, high cholesterol, and obesity, in “sub-Saharan Africa.” Filters will be added to narrow down to articles published from 2000 and in the English language. Indexed articles in PubMed and Embase will be included. Taking into account that some journals in Africa may not be indexed in PubMed, searches in Google Scholar will also be performed, and the first 300 articles will be included. The detailed search terms following the PICO (Patient/Population/Problem, Intervention/Prognostic Factor, Comparison, Outcome) format are as follows:

P: “heart failure” [MeSH Terms] OR (“heart” [All Fields] AND “failure” [All Fields]) OR “heart failure” [All Fields] in “Sub-Saharan Africa” OR “Africa” OR “Saharan” OR ((Angola OR Burundi OR DRC OR Cameroon OR Central Africa Republic OR Chad OR Republic of Congo OR Equatorial Guinea OR Gabon OR Kenya OR Nigeria OR Rwanda OR Sao Tome and Principe OR Tanzania OR Uganda OR South Sudan OR Eritrea OR Ethiopia OR Botswana OR Comoro OR Lesotho OR Madagascar OR Malawi OR Mauritius OR Mozambique OR Namibia OR Seychelles OR South Africa OR Swaziland OR Zambia OR Zimbabwe OR Benin OR Mali OR Burkina Faso OR Cape Verde OR Ivory Coast OR Gambia OR Ghana OR Guinea OR Guinea Bissau OR Liberia OR Niger OR Mauritania OR Senegal OR Sierra Leone OR Togo))).

I: (“cardiovascular system” [MeSH Terms] OR (“cardiovascular” [All Fields] AND “system” [All Fields]) OR “cardiovascular system” [All Fields] AND (“risk factors” [MeSH Terms] OR (“risk” [All Fields] AND “factors” [All Fields]) OR “risk factors” [All Fields])).

C: “age” OR “gender” OR “family history” OR “hypertension” OR “diabetes” OR “tobacco use” OR “physical inactivity” OR “poor nutrition” OR “excessive alcohol consumption” OR “high cholesterol” OR “obesity”.

O: “cardiomyopathy, dilated” [MeSH Terms] OR (“cardiomyopathy” [All Fields] AND “dilated” [All Fields]) OR “dilated cardiomyopathy” [All Fields] OR (“dilated” [All Fields] AND “cardiomyopathy” [All Fields]).

## Risk of Bias and Study Quality

Identified studies that meet the inclusion criteria will be assessed independently for methodological validity by two reviewers prior to inclusion in the final analysis using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) assessment tool, version for cohort-type studies (see [Multimedia Appendix 1](#)) [17].

## Data Collection

Full copies of articles identified by the search, and considered to meet the inclusion criteria based on their title, abstract, and subject descriptors will be obtained for data synthesis. The collected data will be organized in Endnote reference manager and subsequently uploaded to the Rayyan web app for systematic reviews to allow for adequate sorting [18]. Two reviewers will independently select articles against the inclusion criteria. Discrepancies in reviewer selections will be resolved by a third author (arbitrator) prior to the selected articles being retrieved. A data extraction tool will be developed specifically for quantitative research data extraction based on the work of the Cochrane Collaboration and the Centre for Reviews and Dissemination, as shown in [Multimedia Appendix 2](#). Two reviewers will independently perform data extraction. In cases of missing data, the corresponding authors of the study will be approached once by email.

## Data Synthesis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews will be applied [19]. A flow diagram will be used to illustrate the literature search and article selection process, and a table will be compiled to provide an overview of the articles included in the review along with their characteristics. Furthermore, a map of sub-Saharan Africa with colors to show disease prevalence in each country will be included. For quantitative data, where possible, odds ratios (for categorical outcome data) or standardized mean differences (for continuous data) and their 95% CIs will be calculated from the data generated by each included study.

## Results

The outcome measures will include the prevalence of DCM and cardiovascular risk factors associated with DCM among patients with heart failure in sub-Saharan Africa. The anticipated or actual start date is January 1, 2021 and the anticipated completion date is April 30, 2021.

## Discussion

As CVDs are on the rise in sub-Saharan Africa [1,4,15], there is an urgent need to obtain more insight into the characteristics of the underlying pathologies in the region. It is currently unclear how heterogeneous or homogenous data on prevalence and risk factors for DCM are in sub-Saharan Africa, since previous reviews from the region addressed the prevalence and etiology of heart failure [2,6] or cardiomyopathies in general [9,16]. Likewise, it is unclear what paucity of data do exist regarding DCM in the region. To the best of our knowledge, no previous review is available with exclusive focus on DCM as an entity of heart failure in sub-Saharan Africa. We will discuss the literature on DCM in sub-Saharan Africa, describing the current status of DCM based on prevalence and cardiovascular risk factors, thus identifying gaps that need to be addressed to improve our understanding of DCM, with the overall goal to improve the prevention and management of this condition.

## Conflicts of Interest

None declared.

### Multimedia Appendix 1

ROBINS-I tool.

[[PDF File \(Adobe PDF File\), 933 KB - resprot\\_v10i1e18229\\_app1.pdf](#)]

### Multimedia Appendix 2

Data extraction tool adapted from the Cochrane Collaboration tool.

[[PDF File \(Adobe PDF File\), 272 KB - resprot\\_v10i1e18229\\_app2.pdf](#)]

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## Abbreviations

**CVD:** cardiovascular disease

**DCM:** dilated cardiomyopathy

**ESC:** European Society of Cardiology

**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses

*Edited by G Eysenbach; submitted 18.02.20; peer-reviewed by A Ibrahim Abushouk, M Nichols; comments to author 21.08.20; revised version received 15.10.20; accepted 20.10.20; published 21.01.21.*

*Please cite as:*

*Fundikira LS, Chillo P, van Laake LW, Mutagaywa RK, Schmidt AF, Kamuhabwa A, Kwesigabo G, Asselbergs FW Risk Factors and Prevalence of Dilated Cardiomyopathy in Sub-Saharan Africa: Protocol for a Systematic Review* *JMIR Res Protoc* 2021;10(1):e18229

URL: <http://www.researchprotocols.org/2021/1/e18229/>

doi: [10.2196/18229](#)

PMID: [33475522](#)

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Protocol

# Efficacy and Safety of Medicines Targeting Neurotrophic Factors in the Management of Low Back Pain: Protocol for a Systematic Review and Meta-analysis

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## Abstract

**Background:** Low back pain (LBP) is the leading cause of years lived with disability worldwide. Most people with LBP receive the diagnosis of nonspecific LBP or sciatica. Medications are commonly prescribed but have limited analgesic effects and are associated with adverse events. A novel treatment approach is to target neurotrophins such as nerve growth factor (NGF) to reduce pain intensity. NGF inhibitors have been tested in some randomized controlled trials (RCTs) in recent years, showing promise for the treatment of chronic LBP; however, their efficacy and safety need to be evaluated to guide regulatory actions.

**Objective:** The aim of this study is to evaluate the efficacy and safety of medicines targeting neurotrophins in patients with LBP and sciatica.

**Methods:** In this systematic review, we will include published and unpublished records of parallel RCTs and the first phase of crossover RCTs that compare the effects of medicines targeting neurotrophins with any control group. We will search the CENTRAL, MEDLINE, Embase, CINAHL, ClinicalTrials.gov, EU Clinical Trials Register, and WHO International Clinical Registry Platform databases from inception. Pairs of authors will independently screen the records for eligibility, and we will independently extract data in duplicate. We will conduct a quantitative synthesis (meta-analysis) with the studies that report sufficient data and compare the medicines of interest versus placebo. We will use random-effects models and calculate estimates of effects and heterogeneity for each outcome. We will assess the risk of bias for each study using the Cochrane Collaboration tool, and form judgments of confidence in the evidence according to GRADE recommendations. We will use the PRISMA statement to report the findings. We plan to conduct subgroup analyses by condition, type of medication, and time point. We will also assess the impact of a potential new trial on an existing meta-analysis. Data from studies that meet inclusion criteria but cannot be included in the meta-analysis will be reported narratively.

**Results:** The protocol was registered on the Open Science Framework on May 19, 2020. As of December 2020, we have identified 1932 records.

**Conclusions:** This systematic review and meta-analysis will assess the evidence for the efficacy and safety of NGF inhibitors for pain in patients with nonspecific LBP and sciatica. The inclusion of new studies and unpublished data may improve the precision of the effect estimates and guide regulatory actions of the medications for LBP and sciatica.



**Trial Registration:** Open Science Framework; <https://osf.io/b8adn/>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/22905

(*JMIR Res Protoc* 2021;10(1):e22905) doi:[10.2196/22905](https://doi.org/10.2196/22905)

## KEYWORDS

back pain; analgesics; drug therapy; monoclonal antibodies; nerve growth factor; review; meta-analysis; antibodies; pain; back; growth factor; disability; sciatica

## Introduction

Low back pain (LBP) is the most prevalent musculoskeletal condition globally and the leading cause of years lived with disability [1,2]. Approximately 5%-10% of people with LBP have radiating pain that follows a dermatomal pattern, which leads to the diagnosis of sciatica [3]. For 90% of people with LBP, the nociceptive source cannot be reliably identified, and the condition is classified as nonspecific LBP [4,5]. A substantial number of people with nonspecific LBP and sciatica (28%) experience severe levels of disability [2], and 65% of individuals still have some level of continuing or fluctuating pain 3 months after the first episode [6,7].

Analgesic medicines are commonly prescribed for LBP [8,9]. There is widespread use of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, skeletal muscle relaxants, opioid analgesics, antidepressants, benzodiazepines, and antiepileptic drugs (eg, gabapentin) for all types of acute and chronic LBP [8]. These medicines have different proposed biological targets. Acetaminophen and NSAIDs likely exert their analgesic and anti-inflammatory actions by reducing prostaglandin synthesis [10]. Opioids mimic the actions of endogenous opioid peptides by interacting with presynaptic receptors; this interaction reduces neuronal excitability and inhibits nociceptive neurotransmitters in the central nervous system [11]. Antidepressants often involve reuptake inhibition of neurotransmitters involved in descending inhibition transmission of pain [12]. Gabapentin and pregabalin decrease the release of nociceptive transmitters by binding to calcium channels at different parts of the central nervous system [13]. In general, these medicines have limited analgesic effects and are often associated with negative side effects [14]. For example, opioids are associated with constipation, nausea, vomiting, itching, and somnolence, and only a minority of people have substantial pain relief [15-17]. Accordingly, research has focused on the investigation of other mechanisms and novel analgesic agents for chronic pain [18].

Neurotrophins constitute a group of structurally related proteins that include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), neurotrophin-3, and neurotrophin-4 [19,20]. These molecules are expressed at different levels in the peripheral and central nervous system after injury, inflammation, or exposure to a noxious stimulus, and contribute to the persistence of pain [19,21,22]. Preclinical studies have demonstrated that levels of NGF are elevated in a variety of chronic pain conditions (eg, interstitial cystitis, prostatitis, arthritis, pancreatitis, chronic headaches, cancer pain, diabetic neuropathy, sciatica, and other noncancer pain) [23-25].

Experimental studies have demonstrated that NGF and BDNF can maintain peripheral and central pain sensitization [22,26].

Approaches have been developed to target neurotrophins, including anti-NGF agents, which are in the most advanced phases of clinical testing. NGF inhibitors (or anti-NGF) are considered biological agents because they are harvested from a living system instead of being synthesized chemically as is the case for conventional analgesics [27]. Biologic drugs are relatively large molecules, which may have more precise mechanisms compared to conventional medicines and result in fewer adverse effects compared to opioids [27]. However, biologic agents interfere with key molecules in the human physiology, which may produce adverse effects [28]. Anti-NGF medicines have been tested in some chronic pain conditions, particularly LBP and osteoarthritis [23,25,29]. Anti-NGF medicines are commonly administered to people with chronic pain via multiple subcutaneous and intravenous injections, delivered at least 1 week apart [30,31]. Anti-NGF medicines may target novel mechanisms for pain relief and reduce some of the risks associated with opioids, such as medication addiction, misuse, dependence, and other side effects [18]. Anti-NGF medicines have not yet received approval from the US Food and Drug Administration (FDA), although the FDA recently accepted regulatory submission for tanezumab, an anti-NGF medicine, to treat patients with osteoarthritis [32]. The goal date for the FDA to make a decision is December 2020. The last systematic review with a meta-analysis that investigated the effect of anti-NGF medicines for LBP was published in 2014 [30]. Since then, several randomized controlled trials (RCTs) with large numbers of participants have been conducted. Therefore, this systematic review will evaluate the effect and safety of medicines targeting neurotrophins in patients with LBP.

## Methods

### Protocol Registration and Design

The protocol for this review is registered on the Open Science Framework ([osf.io/b8adn](https://osf.io/b8adn/)). This protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) reporting guidelines [33,34].

### Eligibility Criteria

#### Study Design

We will include published and unpublished records of parallel RCTs and the first phase of crossover RCTs that compare the effect of medicines targeting neurotrophins with any control group. We will include secondary records of included trials (reporting additional results from the same trial) when authors

provide additional results on outcomes or time points of interest. We will not include enriched-enrollment or cluster RCTs, or observational studies. We will include records reported in any language, except those for which a translator cannot be obtained.

### **Participants**

We will include studies on adults aged 18 years or over diagnosed with LBP or sciatica of any duration. LBP is defined as a primary area of pain between the 12th rib and gluteal fold with or without leg pain [35]. Sciatica is defined as radiating pain in one leg combined with a positive result on one or more neurological tests indicating nerve root tension or neurological deficit [3]. We will consider the following pain duration: acute (from the first episode to 6 weeks), subacute (from 6 weeks to 12 weeks), and chronic (12 weeks or more) [36]. We will include studies that randomized participants with heterogeneous pain conditions (eg, hip osteoarthritis and LBP) only if we are able to obtain separate data for participants with LBP. Participants may be experienced or naïve to the trial intervention. We will exclude interventions that are combined with surgery; however, studies that investigated the effect of medicines targeting neurotrophins to prevent surgical/operative interventions will be included in the review. We will exclude LBP that is attributed to a specific pathology other than sciatica, such as infection, neoplasm, metastasis, inflammatory disease (eg, ankylosing spondylitis), or fractures.

### **Interventions**

For this review, we will include any type of agent designed to target neurotrophins for the management of LBP. We expect to identify a larger number of medicines that target NGF than those targeting other neurotrophins. The medicines do not need to be listed on the World Health Organization Anatomical Therapeutic Chemical system or licensed for current use, because biologic drugs are new to the management of pain and still need to show their efficacy and safety. Medicines may be delivered as monotherapy or combination therapy via any route of administration (eg, subcutaneous, epidural, oral, intravenous). We will consider separate doses given that biologic agents are not FDA-approved and there may be a dose-response effect.

### **Comparators**

We will include studies comparing the effect of a medicine targeting neurotrophins to any of the following interventions: (1) placebo/sham medicine, (2) waiting list or no treatment, (3) another dose or type of medicine targeting neurotrophins, and (4) other medicines. We will not exclude studies that assign nonpharmacological cointerventions to one or more of the intervention arms. We define the placebo intervention as any drug intervention that does not contain an active ingredient. We consider that waiting list or no treatment includes continuation of usual care or being placed on a waitlist.

### **Outcome Measures**

#### **Primary Outcomes**

The primary outcomes are pain intensity and safety. Pain intensity reported in the lower back can be measured by any self-report scale such as the visual analog scale (VAS), numeric rating scale (NRS), or a rating scale within a composite measure

of pain (eg, McGill Pain Questionnaire). We will assume that ordinal scales exhibit continuous properties [37].

Safety is defined as the number of participants who experience an adverse effect during the treatment period [38].

#### **Secondary Outcomes**

The secondary outcomes include leg pain, back-specific function, and harm. Leg pain is defined as pain intensity in the leg due to sciatica as measured by any self-report scale. Leg pain has been used as a separate outcome for sciatica in previous studies [39].

Back-specific function can be measured by any self-report scale such as the Roland Morris Disability Questionnaire (RMDQ), Oswestry Disability Index (ODI), or a rating scale within a composite measure (eg, LBPRS-DI) [40].

Harm is defined as the number of participants who experience a serious adverse effect during the treatment period. A serious adverse event is defined according to the USA FDA as any event that results in death, is life threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, may have caused a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage [38].

#### **Time Points of Outcomes Measures**

We will consider outcomes measured at the time point closest to (1) 4 weeks, (2) 12 weeks, (3) 24 weeks, and (4) 48 weeks after randomization, regardless of the number of injections administered in the study.

### **Search Strategy**

We will search the following electronic databases from inception to present: MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, EU Clinical Trials Register, and WHO International Clinical Trial Registry Platform. We will manually search the reference lists of included studies and previous reviews to identify additionally eligible studies.

We will combine terms related to RCTs, LBP, and spinal disorders, and interventions of interest as recommended by the Guideline for Systematic Reviews in the Cochrane Back and Neck Pain Group [41] and Cochrane Handbook [42]. We reviewed previous studies and conducted a preliminary search to inform the search terms for drugs that target neurotrophic factors. The search strategy for MEDLINE (Ovid) is detailed in [Multimedia Appendix 1](#).

### **Study Selection and Management**

We will upload the records to Covidence [43], which will apply an automatic deduplication function to remove remaining duplicate records. Two reviewers will independently screen studies for title and abstract eligibility. We will retrieve full texts of all records where exclusion could not be determined from title and abstract screening. Two reviewers (RR and one or more reviewers) will independently screen the full text of these records for eligibility. Reviewers will give reasons for exclusion, and disagreements will be resolved through discussion or arbitration from a third author (JM) if required.

We will search and identify related records (eg, other journal articles, conference abstracts, and trial registries). We will link related records for each included trial and follow this order for data extraction: (1) journal article of the trial, (2) conference abstract, (3) trial registration, (4) other records. We will summarize the search process using an adapted PRISMA flow diagram [44].

### Data Management and Extraction

Two reviewers (RR and one or more reviewers) will independently extract and enter data from the included trials into standardized Microsoft Excel spreadsheets. Disagreements between reviewers will be resolved through discussion or arbitration from a third author (JM) if necessary.

We will extract data for (1) trial characteristics, including country, setting, number of trial sites, sample size, and study duration; (2) participants, including diagnosis, duration of LBP, age, male/female ratio, arm-level pain intensity at baseline (mean and SD), and experience or naivety with the trial intervention; (3) interventions, including medicine tested, control, duration of intervention, dosage regimen, routes of administration, and usage of rescue medication; and (4) outcomes, including type and dimensions of the scale/measure and the time from randomization at which the outcome data were measured. For adverse events, we will extract the definition used in each study, and extract the type and number of adverse events in each intervention group.

If studies report more than one measure for pain, we will prioritize extraction in the following order: 100-mm VAS, 10-cm VAS, 11-point NRS, rating scale for pain intensity from a composite measure of pain (eg, McGill Pain Questionnaire), ordinal scale. If studies report more than one measure for function, we will prioritize extraction in the following order: ODI, RMDQ, rating scale for functional ability from a composite measure, ordinal scale. For both pain intensity and function, we will preferentially extract the outcome score and measure of variance at the end of treatment (or closest time point) for each group, followed by the change from baseline and measure of variance. If data are not available for each trial arm, we will extract the between-group statistics at the end of treatment. We will consider a minimally important difference of 10 mm (100-mm VAS) between groups [45]. We will extract data from graphs only if the extraction from tables, text, or after contacting authors is not possible. We will manage data in Microsoft Excel and conduct the analyses in R (version 4.0.3) [46].

### Missing Data

We will contact a trial's corresponding author up to three times via email to request missing data, which will be considered unobtainable if no reply is received within 6 weeks. If data for outcomes of pain and function are not presented in an appropriate form for meta-analysis (such as median and range instead of SDs, standard errors, *t* statistics, or *P* values), we will attempt to impute these using established methods [47,48]. We will conduct sensitivity analyses for pain at end of treatment if we impute missing data for either of these outcomes.

### Assessing Risk of Bias

Two reviewers (RR and one or more reviewers) will independently appraise the risk of bias for each trial using the Cochrane risk of bias tool described in Cochrane Handbook 5.1.0 [41,49]. We will resolve disagreements through discussion or arbitration from a third author (JHM). The Cochrane risk of bias tool assesses the following domains: selection, performance, attrition, detection, reporting, and other sources of bias (eg, conflict of interest, baseline imbalance between groups) [41]. Each domain will receive one of the following judgments: low risk, high risk, or unclear risk of bias. Reviewers will judge items at the study level, which prioritizes information regarding the primary outcome (pain intensity and safety).

### Data Synthesis

We will conduct a quantitative synthesis (meta-analysis) for studies that report sufficient data and compare the medicine targeting neurotrophins versus placebo. We will convert different instruments that measure pain and the associated estimate of precision into a single, most familiar instrument [45]. The meta-analysis will use random-effects models in R [46]. Results will be presented in forest plots. Data from studies that we are not able to use in the quantitative analysis or data from other comparisons (eg, anti-NGF versus tramadol) will be reported narratively.

### Subgroup Analysis

Subgroup analysis will be conducted by condition (sciatica or chronic LBP), duration of pain (acute or chronic), type of medication (eg, anti-NGF versus placebo or only a type of anti-NGF such as tanezumab versus placebo), time point (4 weeks, 12 weeks, 24 weeks, and 48 weeks after the first dose), risk of bias (removing studies classified as having a high risk of bias), and number of participants (excluding studies with less than 10 participants per group).

### Assessment of Heterogeneity

We will evaluate the presence of heterogeneity in the meta-analysis using the *Q* statistic ( $\alpha < 10\%$ ). The magnitude of heterogeneity will be assessed using the estimate of between-study variance ( $\tau^2$ ). We will calculate 95% prediction intervals for pooled effects and interpret prediction intervals spanning greater than 15 points on a 0 to 100 scale on either side of the pooled effect as indicative of important heterogeneity [50]. The distributions of the effect sizes in forest plots will be inspected visually and the  $I^2$  value will be calculated to indicate the proportion of observed variance due to heterogeneity. Important heterogeneity will be investigated using meta-regression, subgroup analysis, or sensitivity analysis (depending on the availability of data).

### Sensitivity Analysis

We will assess the influence on the effect estimates of the following factors: studies where the definition of the condition is not clear, studies where measures of variance have been imputed, and studies where treatment effects are presented as medians [41,49].



## Extended Funnel Plot

We will construct an extended funnel plot to explore the potential impact of a new trial on the meta-analysis and evaluate whether performing a new trial is worthwhile [51,52].

## Confidence in Cumulative Evidence

Two reviewers (RR and one or more reviewers) will assess the quality of evidence and strength of recommendations. We will use the Grading of Recommendations Assessment Development and Evaluation (GRADE) [53] working group methodology to grade the recommendations. Once this systematic review is limited to include RCTs only, the quality of evidence will be classified as “high” (further research is very unlikely to change our confidence in the estimate of effect) and possibly downgraded to “moderate” (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), “low” (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or “very low” (any estimate of effect is very uncertain) [53]. The recommended domains will be assessed using arbitrary percentages that have been used in previous systematic reviews [50].

For risk of bias, we will downgrade the quality of evidence recommendations by one level if >25% but <50% of the participants in our analysis were included in trials that we evaluated to be at “high” risk of bias, and we will downgrade the recommendations by two levels if >50% of the participants were from trials we evaluated to be at “high” risk of bias. For inconsistency, we will downgrade the quality of evidence recommendations by one level if we identify significant heterogeneity. We will assess heterogeneity using the between-study variance parameter ( $\tau^2$ ) and the proportion of study variance not due to sampling error ( $I^2$ ). For indirectness,

the downgrade will be related to the characteristics of participants in the study. Studies may include participants with sciatica and nonspecific LBP. We will only downgrade the evidence quality if the differences are considered sufficient to make a difference in outcome. For imprecision, we will downgrade the quality of evidence recommendations by one level if the total number of participants is <400 or based on the width of the confidence intervals (for continuous variables as pain intensity and function) by crossing either the null or the threshold for a clinically meaningful effect (10 points on a 0 to 100 scale), and by two levels if the interval spans both. For dichotomous variables (eg, safety), we will downgrade the recommendations by one level if the interval spans the null. For publication bias, we will downgrade the quality of evidence recommendations by a single level if we strongly detect publication bias. We will assess publication bias by visually assessing a funnel plot and by performing a sensitivity analysis. The strength of recommendations will be graded as strong or weak.

## Results

The protocol was registered in Open Science Framework (osf.io/b8adn) on May 19, 2020. As of December 2020, we have identified 1932 records.

## Discussion

There has been a growing number of RCTs investigating the effect of medicines designed to inhibit the nociceptive effect of NGF for osteoarthritis and LBP. This systematic review with meta-analysis will assess the evidence for the efficacy and safety of NGF inhibitors for pain in patients with nonspecific LBP and sciatica. The inclusion of new studies and unpublished data may improve the precision of the effect estimates and guide regulatory actions of the medication for LBP and sciatica.

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## Authors' Contributions

RRNR, MCF, and MAW developed the review protocol. RRNR drafted the manuscript, and all authors read and approved the final manuscript.

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## Conflicts of Interest

None declared.

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Multimedia Appendix 1

Search terms.

[[DOCX File, 17 KB - resprot\\_v10i1e22905\\_app1.docx](#)]

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## Abbreviations

**BDNF:** brain-derived neurotrophic factor  
**FDA:** US Food and Drug Administration  
**GDNF:** glial cell-derived neurotrophic factor  
**GRADE:** Grading of Recommendations Assessment Development and Evaluation  
**LBP:** low back pain  
**NGF:** nerve growth factor  
**NRS:** numeric rating scale  
**NSAID:** nonsteroidal anti-inflammatory drug  
**ODI:** Oswestry Disability Index  
**PRISMA-P:** Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols  
**RCT:** randomized controlled trial  
**RMDQ:** Roland Morris Disability Questionnaire  
**VAS:** visual analog scale

*Edited by G Eysenbach; submitted 18.08.20; peer-reviewed by J Bailey, J Vermeir, S Yusif; comments to author 18.11.20; revised version received 22.11.20; accepted 01.12.20; published 22.01.21.*

*Please cite as:*

Rizzo RRN, Ferraro MC, Wewege MA, Cashin AG, Leake HB, O'Hagan ET, Jones MD, Gustin SM, McAuley JH  
*Efficacy and Safety of Medicines Targeting Neurotrophic Factors in the Management of Low Back Pain: Protocol for a Systematic Review and Meta-analysis*  
*JMIR Res Protoc* 2021;10(1):e22905  
URL: <http://www.researchprotocols.org/2021/1/e22905/>  
doi: [10.2196/22905](https://doi.org/10.2196/22905)  
PMID: [33480861](https://pubmed.ncbi.nlm.nih.gov/33480861/)

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Protocol

# Tui Na for Chronic Nonspecific Low Back Pain: Protocol for a Systematic Review and Meta-analysis

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## Abstract

**Background:** Chronic nonspecific low back pain (CNLBP) is one of the most common complex pain conditions, and it is strongly associated with high rates of disability. Even though several studies on Tui na for CNLBP have been reported, to our knowledge there has been no systematic review of the currently available publications.

**Objective:** This study aims to develop a protocol for a systematic review and meta-analysis that will evaluate the effectiveness and safety of Tui na therapy for patients with CNLBP.

**Methods:** An electronic literature search of PubMed, Embase, MEDLINE, Cochrane Library, Springer, Scopus, World Health Organization International Clinical Trials Registry Platform, Physiotherapy Evidence Database (PEDro), Clarivate Analytics, and Chinese biomedical databases (the China National Knowledge Infrastructure, Wan-fang database, Chinese Scientific Journals Database, and Chinese Biomedical Literature Databases) will be conducted. Studies will be screened by two reviewers independently based on titles and abstracts, followed by a full-text reading with eligibility criteria. Randomized controlled trials involving Tui na for patients with CNLBP will be reviewed. The primary outcomes of the study are improvement of pain, analgesic medication reduction, improvement of functional disability, and degree of satisfaction with the intervention. A secondary outcome is any adverse event of Tui na intervention. Methodological quality and risk of bias will be assessed with the Cochrane Collaboration Risk of Bias Tool. If studies are sufficient, a meta-analysis of the effectiveness will be performed. If possible, we will evaluate publication bias using funnel plots. If substantial heterogeneity between studies is present, and there are sufficient studies, subgroup analyses will be conducted to explain the study findings.

**Results:** The review database searches will be initiated in December 2020, with findings expected by January 2021.

**Conclusions:** This protocol will establish a framework of a high-quality literature synthesis on the impact of Tui na treatment in patients with CNLBP. The proposed review will determine whether Tui na is effective and safe for CNLBP patients.

**Trial Registration:** PROSPERO CRD42020166731; [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=166731](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=166731)

**International Registered Report Identifier (IRRID):** PRR1-10.2196/20615



**KEYWORDS**

Tui na; Tuina; low back pain; protocol; systematic review

## Introduction

Chronic low back pain (CLBP) is one of the most common causes of disability and work absence, affecting 4.2% to 19.6% of individuals, placing a heavy burden on global health care services [1]. About 90% of CLBP patients do not have a clearly identifiable cause of pain, which is classified as chronic nonspecific low back pain (CNLBP) [2,3], a diagnosis based on the exclusion of a certain cause or pathology. CNLBP refers to pain and discomfort located below the costal margin and above the inferior gluteal fold that is not attributed to recognizable or known specific pathology, with (or without) referred leg pain for more than 3 months [4,5]. It is a complex and extremely frequent disorder closely associated with high rates of disability [2]. The symptom onset, recovery, and clinical outcomes of CNLBP are influenced by biological, psychological, and social factors, and therefore its management is complicated and multimodal [6].

Currently, there is not a universally accepted evidence-based treatment approach that has been recommended for patients with CNLBP [7]. Previous clinical practice guidelines focused on relieving pain and pain-related functional disability and relied heavily on pharmacotherapy reduction [6]. Long-term use of analgesics, especially opioids, has been associated with psychological distress like depression and increased risk for other health issues such as falls, fractures, and sexual dysfunction. Thus, current practice is focusing less on pharmacotherapy due to increasing concerns regarding limited efficacy and increased risk. Therefore, nonpharmacological therapies are recommended for CNLBP in current guidelines [8]. This shift in focus has resulted in growing attention on the role that complementary and alternative medicine (CAM) treatments may play [9]. Tui na therapy is one CAM modality that has been widely accepted, especially in Asia [10]. Kong et al [11] reviewed the efficacy of Tui na for LBP and found that it appeared to be an effective therapy. However, to our knowledge, no systematic review and meta-analysis or review protocol relevant to Tui na for CNLBP has been published.

There are many studies on Tui na for patients with CNLBP [11-16]. However, due to nonstandard measurement, nonuniform outcomes, and other factors, these individual studies do not provide sufficient evidence for the impact of Tui na in patients with CNLBP [13,17]. In some countries, Tui na is not even included in the guidelines for the treatment of LBP [18]. Thus, the question of whether Tui na is effective and safe for the management of CNLBP is an important one. A review to help assess the efficacy and safety of Tui na in CNLBP management is therefore important and timely. This paper aims to provide a protocol for a systematic review and meta-analysis on the evidence of Tui na therapy for patients suffering from CNLBP. The primary objective of this review is to identify the effectiveness of Tui na treatment among people with CNLBP.

In addition, we will investigate the safety of Tui na in this setting.

## Methods

This protocol was developed to adhere to the PRISMA-P 2015 (Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols 2015) [19]. This study will be conducted in accordance with the PRISMA guidelines [20].

### Study Selection Criteria

The PICOS (patient, intervention, comparison, outcome, and study design) framework will be used to inform the eligibility criteria of studies [21,22]. Studies will be excluded if they meet any of the following criteria: (1) duplicate studies; (2) nonrandomized controlled trials; (3) literature reviews; (4) case reports; (5) studies comparing different types of Tui na; and (6) animal experiments.

### Types of Studies

Any randomized controlled trial (RCT) involving Tui na therapy in the treatment group for patients with CNLBP will be included in this study.

### Participants

Adults (aged 18 years and older) who were diagnosed with chronic, nonspecific (with no diagnosable underlying pathology) LBP will be included in this study. There are no limits on race, gender, age, nationality, etc.

### Intervention

All trials evaluating Tui na intervention will be included. Experimental intervention can be any type of Tui na or Tui na combined with other therapies.

### Comparison

Different control interventions such as no-treatment control, placebo, and other currently used interventions (such as health education, behavior therapy, acupuncture, moxibustion, physical therapies, medications, and gentle touch) will be included.

### Outcomes

Primary outcomes will include improvement of pain, reduction in analgesic medication, improvement of functional disability, and degree of satisfaction with the intervention. A secondary outcome will be any adverse events (AEs) associated with Tui na.

### Search Strategy

An electronic literature search will be applied to the following databases: PubMed, Embase, MEDLINE, Cochrane Library, Springer, Scopus, World Health Organization International Clinical Trials Registry Platform, Physiotherapy Evidence Database (PEDro), Clarivate Analytics, and Chinese biomedical databases (the China National Knowledge Infrastructure,

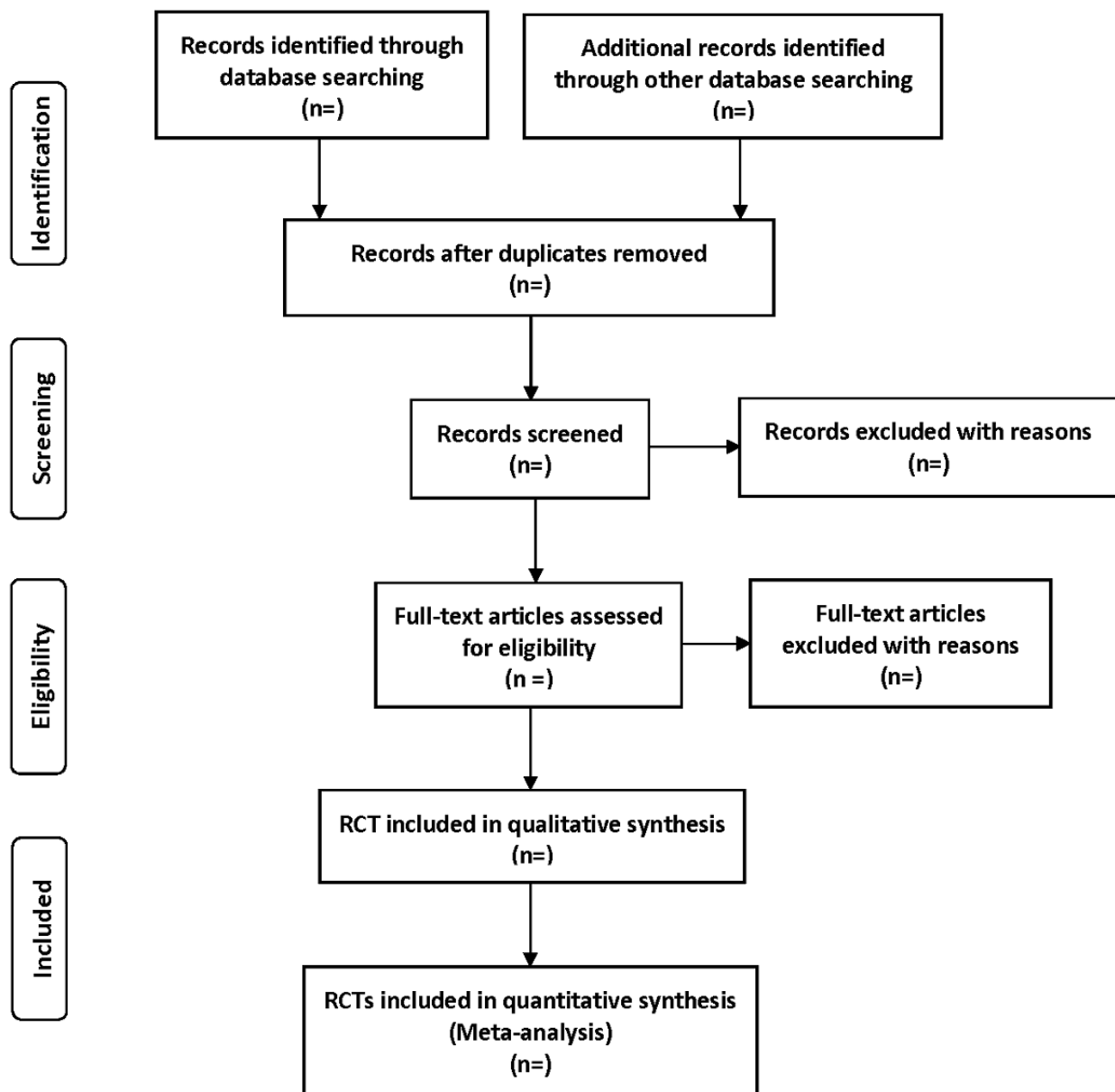
Wan-fang database, Chinese Scientific Journals Database, and Chinese Biomedical Literature Databases), from database inception to December 2020, limited to English and Chinese language only. Peer-reviewed journal articles and reference lists of final included studies, as well as grey literature including conference proceedings, dissertations, and white papers, will be used to help identify all applicable studies for inclusion.

The comprehensive literature search will be designed and carried out by an experienced librarian at Mayo Clinic, Rochester campus, with input from the study's principal investigator. Controlled vocabulary and keywords will be used to search for publications describing the effect and safety of Tui na on patients with CNLBP.

## Study Selection

The results of the literature search, including the abstract and citation, will be imported into EndNote X9 (Thomson Reuters Clarivate Analytics), and duplicate studies will be removed prior to the literature screening. Two authors will screen titles and abstracts on inclusion criteria independently. Publications that are not relevant or do not meet the inclusion criteria will be removed. The whole selection process will be presented in the PRISMA flowchart of [Figure 1](#). Any selection divergence will be resolved by the consensus between the two authors or by consulting the original corresponding author.

**Figure 1.** PRISMA diagram of identified studies.



## Methodological Quality and Risk of Bias Appraisal

To ensure reliability, the risk of bias of each study included in our study will be assessed independently by two authors using the special assessment tool recommended by the Cochrane Collaboration [23], including selection, performance, attrition, detection, reporting, and other biases. An assessment disagreement between the two authors will be discussed between the two authors or by involving a third reviewer until a consensus is reached. Any discrepancies will be resolved through discussion or by involving a third reviewer.

## Data Extraction

Important data associated with our study will be extracted from the included studies using a designed and piloted data collection Excel spreadsheet (Microsoft Corp) by two authors independently. Data will include characteristics of the studies including the first author, published year, sample size, population, and outcome measurement, and detailed information about the interventions such as observation group, control group, provider, frequency, efficacy, AEs, and follow-up.

## Adverse Event Severity

The AE severity is evaluated with the Common Terminology Criteria for Adverse Events (CTCAE) [24]. The CTCAE Scale uses Grades 1 through 5 as follows: Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE), Grade 4 (life-threatening or disabling AE), and grade 5 (death AE). Disagreements will be resolved by discussions. If necessary, the corresponding author will be contacted for clarification.

## Assessment of Reporting Bias

Funnel plots will visually reveal the publication bias if the number of included trials for data analysis is sufficient (a minimum of 10 trials). Egger and Begg tests will be carried out to check the asymmetry of the funnel plot. A symmetric funnel plot represents a low risk of reporting bias, while a dissymmetric funnel plot represents a high risk.

## Data Synthesis

Descriptive analysis or meta-analysis will be conducted according to the interventions, the measurements, and heterogeneity levels. Quantitative findings will be descriptively reported. Continuous variables are analyzed using mean difference and 95% CI, while dichotomous variables will be analyzed using odds ratio. If outcome measure scales are different, the standardized mean difference and 95% CI will be calculated. Study heterogeneity will be calculated within each pairwise comparison by  $Q$  test and  $I^2$  statistic; higher values indicate higher heterogeneity.  $I^2=0\%$  indicates no heterogeneity;  $I^2<25\%$  indicates low,  $25\%<I^2<50\%$  indicates moderate, while  $50\%<I^2<75\%$  indicates substantial, and  $75\%<I^2<100\%$  indicates considerable heterogeneity [25]. If at least 2 included trials are sufficiently homogenous in terms of study design, comparator, and outcome measurement, a meta-analysis will be performed using a random-effects model. Review Manager software (RevMan 5.3) provided by the Cochrane Collaboration will be applied for the meta-analysis. If substantial heterogeneity between studies is present and there are sufficient RCTs,

subgroup analyses will be performed to explain clinical heterogeneity effects on study intervention, pain intensity, and measurement tool.

## Ethics and Dissemination

The proposed review will only synthesize previous publications. No research ethics committee review approval is required. Results from this study will be disseminated as a peer-reviewed journal article and presented in conferences.

## Results

This protocol has been registered on PROSPERO (CRD42020166731) on April 28, 2020 [26]. The review database searches will be initiated in October 2020. The literature search strategy is presented in Figure 1. Study results will be submitted for publication in January 2021.

## Discussion

By means of the proposed systematic review, we intend to assess the impact of Tui na in CNLBP. Tui na therapy is a very common, convenient, noninvasive, and relatively inexpensive therapy that has historically been used successfully to treat low back pain [11]. However, Tui na is still not included in the guidelines for the treatment of LBP in most countries, especially those using the mainly Western form of medicine, though other manual therapies are gaining acceptance (eg, chiropractic) [18]. In regard to CNLBP, the evidence is still unclear, preventing its successful adoption into the list of potential treatment options. Thus, the need for this proposed review is clear; to our knowledge, it will be the first to objectively synthesize the currently available publications and evaluate the effect and safety of Tui na for CNLBP patients.

Recognizing that missing data could introduce greater uncertainty and possible bias in estimating the effect of experimental treatment in our meta-analysis, two authors will independently screen, select, and evaluate the data. Any divergence for missing information or unclear information (eg, on study methods or results) will be resolved by consensus between the two authors or by consulting the original corresponding author.

Given the narrowness of our research question, it is possible that only a few RCTs could be included in the proposed systematic review. It is our hope that even should this occur, the research results can still be valuable as a summary of currently available evidence, which may provide some preliminary guidance to inform existing low back pain practice and future research. Finally, to broaden our data and to minimize publication bias, we will conduct the electronic search for studies in both Chinese and English. In the future, as new evidence is made available, the systematic review and meta-analysis is planned to be updated every 1 to 3 years.

This protocol intends to provide a framework of evidence on Tui na therapy for patients with CNLBP that can be used by health care providers worldwide. It is also intended to lay the foundation for future Tui na studies with greater attention

focused on remedying deficits found in many of the current studies.

## Acknowledgments

The authors thank Prof Tay Boon Keng, the previous Chairman, Medical Board, International, SingHealth, for his initial study proposal of Tui na treatment for low back pain. This work has been supported by The HEAD Foundation, Singapore. Their support is gratefully acknowledged.

## Authors' Contributions

BAB contributed to the study conceptualization, investigation, and funding acquisition. JY, ZC, ST, and YT curated the data. JY and AD analyzed the data. JY, XZ, and QM developed the study methodology. BAB, JC, and CICT contributed to project administration and supervision. JY, XZ, and LS contributed to software. JY, JSB, XZ, and QM wrote the original draft of the manuscript. BAB, JC, CICT, JSB, MAJ, CZ, and KCPC reviewed and edited the manuscript.

## Conflicts of Interest

None declared.

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## Abbreviations

**AE:** adverse event

**CAM:** complementary and alternative medicine

**CLBP:** chronic low back pain

**CNLBP:** chronic nonspecific low back pain

**CTCAE:** Common Terminology Criteria for Adverse Events

**PRISMA-P:** Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols

**RCT:** randomized controlled trial

*Edited by G Eysenbach; submitted 24.05.20; peer-reviewed by AR Safarpour, J Li; comments to author 07.07.20; revised version received 06.09.20; accepted 15.12.20; published 27.01.21.*

*Please cite as:*

Yang J, Brault JS, Jensen MA, Do A, Ma Q, Zhou X, Shen L, Zhao C, Cheong KCP, He K, Guo Y, Chen Z, Tang S, Tang Y, Tan CIC, Chen J, Bauer BA

*Tui Na for Chronic Nonspecific Low Back Pain: Protocol for a Systematic Review and Meta-analysis*

*JMIR Res Protoc* 2021;10(1):e20615

URL: <http://www.researchprotocols.org/2021/1/e20615/>

doi: [10.2196/20615](https://doi.org/10.2196/20615)

PMID: [33502327](https://pubmed.ncbi.nlm.nih.gov/33502327/)

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Proposal

# A Bayesian Network Decision Support Tool for Low Back Pain Using a RAND Appropriateness Procedure: Proposal and Internal Pilot Study

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## Abstract

**Background:** Low back pain (LBP) is an increasingly burdensome condition for patients and health professionals alike, with consistent demonstration of increasing persistent pain and disability. Previous decision support tools for LBP management have focused on a subset of factors owing to time constraints and ease of use for the clinician. With the explosion of interest in machine learning tools and the commitment from Western governments to introduce this technology, there are opportunities to develop intelligent decision support tools. We will do this for LBP using a Bayesian network, which will entail constructing a clinical reasoning model elicited from experts.

**Objective:** This paper proposes a method for conducting a modified RAND appropriateness procedure to elicit the knowledge required to construct a Bayesian network from a group of domain experts in LBP, and reports the lessons learned from the internal pilot of the procedure.

**Methods:** We propose to recruit expert clinicians with a special interest in LBP from across a range of medical specialties, such as orthopedics, rheumatology, and sports medicine. The procedure will consist of four stages. Stage 1 is an online elicitation of variables to be considered by the model, followed by a face-to-face workshop. Stage 2 is an online elicitation of the structure of the model, followed by a face-to-face workshop. Stage 3 consists of an online phase to elicit probabilities to populate the Bayesian network. Stage 4 is a rudimentary validation of the Bayesian network.

**Results:** Ethical approval has been obtained from the Research Ethics Committee at Queen Mary University of London. An internal pilot of the procedure has been run with clinical colleagues from the research team. This showed that an alternating process of three remote activities and two in-person meetings was required to complete the elicitation without overburdening participants. Lessons learned have included the need for a bespoke online elicitation tool to run between face-to-face meetings and for careful operational definition of descriptive terms, even if widely clinically used. Further, tools are required to remotely deliver training about self-identification of various forms of cognitive bias and explain the underlying principles of a Bayesian network. The use of the internal pilot was recognized as being a methodological necessity.

**Conclusions:** We have proposed a method to construct Bayesian networks that are representative of expert clinical reasoning for a musculoskeletal condition in this case. We have tested the method with an internal pilot to refine the process prior to deployment, which indicates the process can be successful. The internal pilot has also revealed the software support requirements for the elicitation process to model clinical reasoning for a range of conditions.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/21804

(*JMIR Res Protoc* 2021;10(1):e21804) doi:[10.2196/21804](https://doi.org/10.2196/21804)

## KEYWORDS

back pain; decision making; Bayesian methods; consensus

## Introduction

Back pain is a prime example of the general increase in long-term musculoskeletal conditions. It has been deemed a leading cause of years lived with disability worldwide, and health care costs for treating back pain are escalating [1]. Some low back pain (LBP) cases are associated with injuries that will self-resolve, but there are a considerable number of people who live with disabling LBP. It is difficult to predict who will have a favorable outcome and who will not. Meta-analyses have consistently shown that treatment outcomes for musculoskeletal conditions are partial [2]. Studies have shown that clinicians may not recognize complexity when assessing these patients [3], and efforts made to improve diagnosis via pattern recognition or analytical approaches [4] have limited success. An artificial intelligence (AI) decision support tool that overcomes one or more of these issues would greatly improve the referral of LBP patients to the correct treatment care pathway, and the approach would be generalizable to other musculoskeletal conditions.

The potential of AI systems to address some of these issues has been recognized by The Digital Framework for Allied Health Professionals in the United Kingdom [5], which highlights the priority to develop digitally mature systems, improve outcomes, and limit variation in service delivery. Similarly, in 2019, Her Majesty's Government announced a £250 million investment in AI development in the UK National Health Service [6] for such purposes. However, many of these techniques are data driven and thus require large error-free data sets that must, crucially, also contain outcome results. Unfortunately, while there is an abundance of data within the musculoskeletal health care system, access is severely restricted and most of the data are unrefined, often being free text or hand written without the necessary outcomes. Furthermore, studies have found that clinicians are skeptical about the ability of AI to perform at the human level [7], and patient and public involvement forums have highlighted a mistrust of black box systems. Successful adoption of AI therefore requires combining clinical evidence, patient data, and expert opinion to mirror the clinical reasoning process and provide transparency regarding how predictions have been reached.

An LBP decision support tool to guide the treatment of patients has been developed with an expert-opinion Delphi-consensus approach in the Netherlands [8], with some success, although there was a suggestion that the results could be further improved with AI and machine learning techniques [9]. The previous authors particularly highlight the limitations of traditional multivariate regression models and suggest that a Bayesian network (BN) would take into account more clinical aspects of

assessment. A BN is a probabilistic model that offers an ideal approach for modeling clinical reasoning as it is capable of combining expert opinion with available evidence to provide probabilistic outcomes for a given scenario [10]. These outcomes can be continuously updated to ensure the most recent clinical knowledge is being used [11] and provide explanations of the predictions arrived at [12].

In order to support clinicians in their decision making, we envisage a BN that can predict a patient's response to a given treatment or course of action when they first present with LBP (ie, in a primary care setting). In order to do this, we must first characterize the types of LBP possible, and the associated risk factors, signs, and symptoms. We propose eliciting a BN that predicts the probability of a patient having a certain LBP-related presentation and, subsequently, how likely they are to improve in response to a course of action. To be clear, this focus on characterization rather than diagnosis was deliberately taken owing to the lack of accurate diagnostic labels for the majority of people with LBP [13], but the BN was designed to identify patients with serious diagnoses, such as nerve root pain and cauda equina syndrome, where these can be identified. For reasons mentioned above, the clinical knowledge base of our BN must be elicited from experts [14,15]. We also believe that it is important not to constrain the type of LBP considered but use expert opinion to guide our focus. In this paper, we outline a protocol for a BN elicitation process that aims to balance the construction of a complex expert-driven model for the treatment of LBP while minimizing the elicitation burden placed on participants. We also describe a pilot study of this process, which highlights the subsequent results that informed the main protocol, discuss the overall methodology, and consider future implementation of the AI tool.

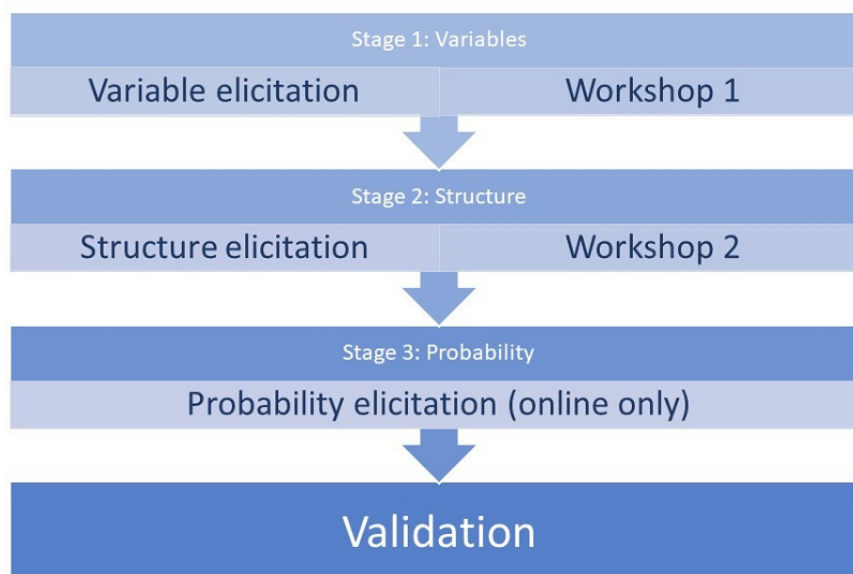
## Methods

### Design

A BN is comprised of the following three components: (1) variables, quantities of interest, such as age, BMI, and the presence/absence of a condition; (2) structure, the dependence of variables on each other, for instance, the condition may be more prevalent in the elderly but the BMI makes no difference; (3) probabilities, quantification of the structure, for example, the probability of having a condition given the person is of a certain age.

We therefore divide the elicitation process into three distinct stages related to those components plus a final stage intended as a rudimentary validation of the output from the process (Figure 1).



**Figure 1.** Study procedure.

The overall elicitation method will be a combined Delphi and RAND appropriateness procedure [10]. Participants will first answer questions individually online before contentious results are discussed together in a face-to-face workshop. We have chosen this strategy because related methods have been used with success in previous musculoskeletal studies [8,16-18], and it combines individual tasks and group discussions to explore biases [19]. We acknowledge that further rounds of discussion may help with consensus, but time constraints render this infeasible.

Ethical approval was sought from the Queen Mary University of London, and approval was granted by the Queen Mary Ethics of Research Committee (reference: QMREC2018/48027).

### Participants and Recruitment

Clinicians will be recruited via clinical networks, word of mouth, and social media. There is no definitive number of participants recommended for this style of study. However, for face-to-face workshops, an optimum number of attendees has been suggested to lie between seven and 15 [19]. This number of participants is thought to represent a range of views and promote discussion, without becoming too onerous to manage and facilitate in a workshop setting. We will include extended scope/advanced practitioner physiotherapists (covering orthopedics, rheumatology, neurosurgery, and general musculoskeletal triage services), general practitioners with a special interest in musculoskeletal conditions, and sports medicine doctors. We will exclude clinicians who do not regularly manage patients with LBP or do not hold current professional registration. Participants will be provided with information about the research and be asked to provide informed written consent prior to taking part.

### Data Management

Participants will not be identified in any reports or publications of the results. Any information held by the project team in

relation to participants will be kept confidential and managed in accordance with the Data Protection Act, the General Data Protection Regulation (GDPR), the UK Policy Framework for Health and Social Care Research, and the conditions of the Research Ethics Committee.

### Elicitation Process

#### Stage 1: Variable Elicitation

Ad hoc building of the BN causal structure is prone to biases and modeling error, which can lead to overly complex models that are not repeatable in later studies [20]. To mitigate this potential issue and to form concepts familiar to the clinical participants, we have constructed a conceptual model where potentially relevant factors in the assessment and treatment of LBP will be grouped into either “risk factors,” “signs and symptoms,” or “judgement factors.” A list of potential treatments will also be elicited. The categories have been connected in the fashion as shown in Figure 2 to form a “skeleton causal diagram,” which approximates the clinical reasoning process. This is necessary for the model functionality and makes the elicitation process recognizable for participants.

Conventional appropriateness scoring usually relies on a Likert scale [19]; however, it is anticipated that participants will have considerable time constraints and the number of potential variables will render the task unfeasible. We will therefore use a placement and ranking procedure. At the start, participants will see many example variables chosen by the research team (Figure 3) (reasons behind this decision are presented in the Results section). They can also create new variables. They will then be asked to place them into one of the three categories of their choosing and order the three associated lists so the variables they deem most important for the assessment of patients with LBP appear at the top. Unfortunately, this setup does create the risk of anchoring biases, but we hope this will be mitigated when the variables are voted on in the workshop.

Figure 2. Skeleton causal diagram involving the categories of variables to be considered.

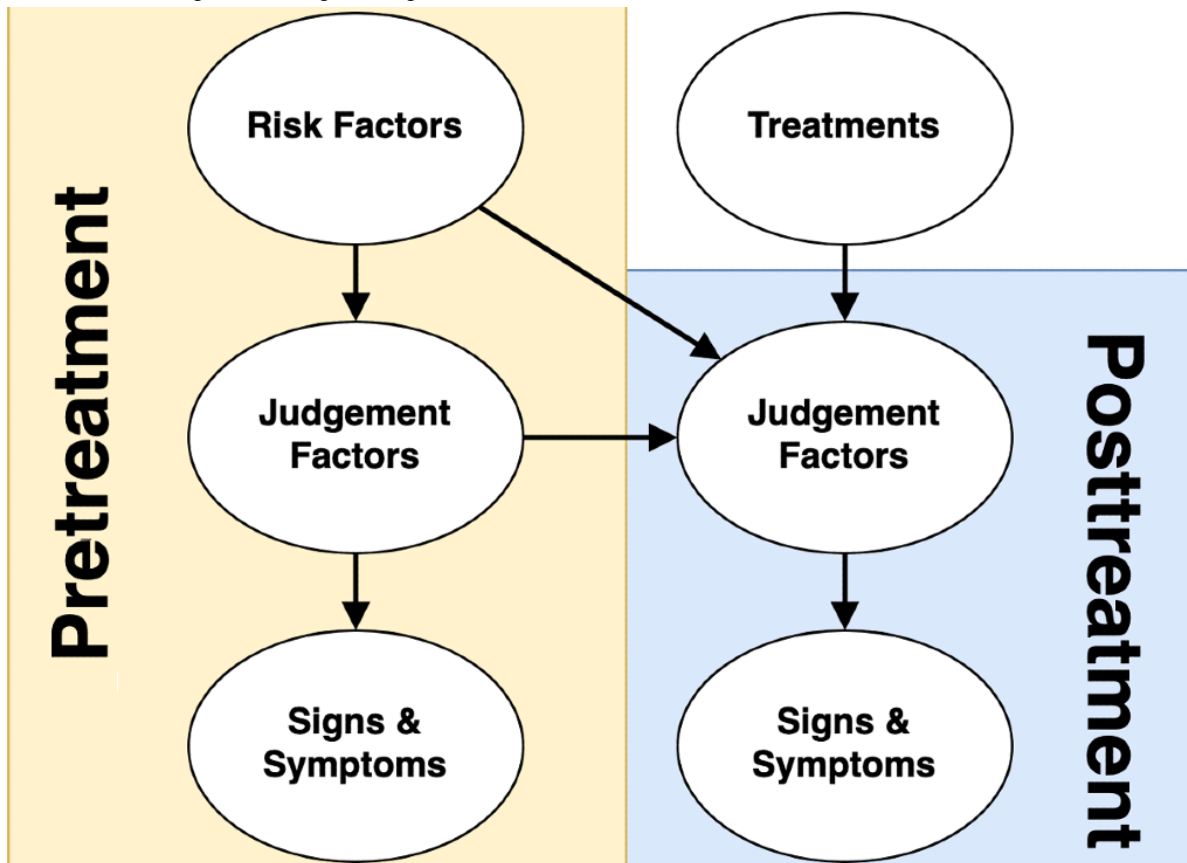
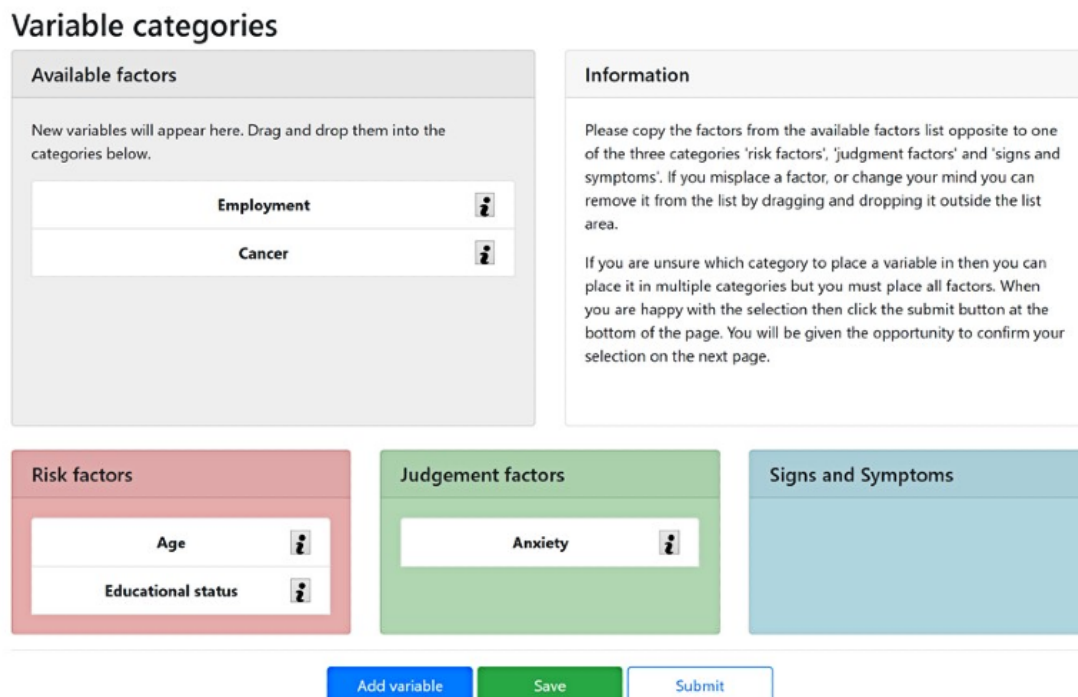


Figure 3. Mockup of the online interface for stage 1 of the process.



To aid their understanding, participants will be given explanatory information about what constitutes risk factors, signs and symptoms, and judgement factors (Table 1), as well as many example variables from the prepopulated lists. Additionally, the meaning of each variable will be clarified by

giving a question that could be answered to find out the value of the variable (such as “What is the patient’s anxiety level?”) and indication of the mode and units of measurement of the variable to ensure consistent responses.

**Table 1.** Categories of variables in the Bayesian network.

Category name <sup>a</sup>	Definition
Risk factor	These are pre-existing factors that might raise (or lower) the chances of the patient having a certain judgement factor or characterization of low back pain. They may also have an effect on the efficacy of the treatment but, crucially, are factors (like age and demographics) that cannot be changed by the treatment.
Signs and symptoms	These are factors that arise as a consequence of the patient having certain conditions or judgement factors. In contrast to risk factors, signs and symptoms are factors that may change or respond to treatment.
Judgement factors	These are clinical reasoning factors or the characterization of the patient's low back pain. They are the factors that are likely to be unmeasurable with a Patient Reported Outcome Measure or test, but which help a clinician reason about prognosis or likelihood of recovery.

<sup>a</sup>Explanatory information about each type of variable will be made available to participants in order to inform the categorization of factors from the prepopulated lists and those created in the elicitation.

Each variable will be included in a particular category if more than 80% of participants allocate it. From those participants, we will take the median normalized rank (0 if placed at the bottom of the list and 1 at the top) to give an indication of preference for inclusion, which will be further adjusted by an interpercentile range (IPR) measure to measure consensus (more consensus will result in less adjustment of the median value). The top-placed variables will be selected for the face-to-face stage. We anticipate around 50 variables can be taken forward without overburdening participants, but we reserve some clinical judgement to decide on the exact number. Suggested variables from the online elicitation will be consolidated by the working team, and those judged by the clinical team to be duplicates will be removed.

After the online session, a face-to-face workshop will be held, in which participants will use the same tool. Misconceptions or differences in understanding will be clarified by the research team. A member of the research team will facilitate discussion of the variables that do not have consensus via use of open-ended questions. The face-to-face workshops will be video recorded to capture the discussions and enable postworkshop checking and clarification. The participants will then be given the opportunity to categorize and rank the variables for a second time, on the basis of the discussion. We anticipate that the mixture of not allowing new variables, the refined interface,

and having numerous variables fixed in categories will reduce the elicitation burden while still maintaining an opportunity for group discussions, according to the conventional RAND process.

### **Stage 2: Structure Elicitation**

The second stage seeks to connect individual variables linking risk factors to judgement factors, and judgement factors to signs and symptoms. This will be achieved by grids (Figure 4). In the online elicitation, participants will be presented with a blank grid and asked to give each relationship a strength score between 0 and 3 in the appropriate cell. The definitions of the scores are as follows: 0, no relationship; 1, *X sometimes* has a *small* effect on *Y*; 2, *X sometimes* has a *large* effect on *Y* or *X always* has a *small* effect on *Y*; and 3, *X always* has a *large* effect on *Y*, and they reflect the nuances of the BN probabilities.

We will again use the median and an 80% IPR as descriptive statistics. To make the workshop manageable (but still allow for discussion), we will fix the median score of those variables with an IPR of 1 or less (ie, the cells in the grids cannot be edited), and all others will be edited again by the participants following discussions. A subsequent overall score will be taken from the workshop for each relationship in a similar manner to the overall score in stage 1. We will then only keep the strongest relationships to form the structure of the BN, and any variables not connected to others will be discarded.

**Figure 4.** An example grid for stage 2. Relationship strengths are placed in the cells. The definitions of the scores are as follows: 0, no relationship; 1, X sometimes has a small effect on Y; 2, X sometimes has a large effect on Y or X always has a small effect on Y; and 3, X always has a large effect on Y.

		Judgement Factors															
		Onset	Severity – Pain	Severity – Loss of function	Severity – Paraesthesia	Severity – Stiffness	Irritability	Source/structure (primary)	Process	Fear Avoidance	Catastrophising	Anxiety	Depression	Impact on work	Impact on family	Impact on leisure	Masquerading condition
Signs and Symptoms	Bilateral paraesthesia	3	1	2	3	0	0	3	3	1	1	1	1	1	1	1	3
	Leg pain	3	1	2	2	1	2	3	3	2	2	1	1	1	1	1	2
	Gait disturbance	3	1	3	2	1	1	3	3	1	1	1	1	1	1	1	3
	Physical capacity	2	1	2	1	1	1	1	1	2	2	2	1	2	2	2	0
	Distress	1	2	2	0	0	1	1	1	3	3	3	3	2	2	2	0
	Stiffness/loss of range	1	1	2	0	3	0	3	3	2	1	1	1	1	1	1	0
	Bladder dysfunction	1	0	1	0	0	0	3	3	0	0	0	0	0	0	0	3
	Bowel dysfunction	1	0	0	0	0	0	3	3	0	0	0	0	0	0	0	3
	Saddle anaesthesia	1	0	0	3	0	0	3	3	0	0	0	0	0	0	0	3
	Weight loss	1	0	0	0	0	0	2	2	0	0	0	0	0	0	0	3
	Deformity	1	2	2	0	2	1	3	1	2	2	2	0	1	1	1	2
	Anxiety	1	2	2	2	2	1	1	3	3	3	3	3	3	3	3	0
	Depression	1	2	2	2	2	1	1	1	3	3	3	3	3	3	3	0
	Sexual dysfunction	1	0	0	0	0	0	3	3	0	0	0	0	0	2	0	3
	Referred pain	2	2	1	1	1	1	3	3	2	2	1	1	1	1	1	3
	Sleep disturbance	3	2	1	1	1	2	3	3	0	0	2	2	1	1	1	1
	Night pain	1	2	1	1	1	2	2	3	1	1	1	1	1	1	1	1
	24 hour pattern	1	0	0	0	0	2	2	3	0	0	0	0	1	1	1	3
	Duration or chronicity	0	0	1	0	0	0	2	2	2	2	2	2	2	2	2	3
	Inflammatory signs	3	0	0	0	3	0	3	3	0	0	0	0	0	0	0	1
	UMN/LMN signs	0	0	0	0	0	0	3	3	0	0	0	0	0	0	0	3
	Blood tests/imaging (to maybe put in risk factors)	0	0	0	0	0	0	2	3	0	0	0	0	0	0	0	2
	Palpation	1	2	0	2	3	3	3	0	0	0	0	0	0	0	0	0
	AND - SLR/slump	1	1	1	2	0	2	3	3	0	0	0	0	0	0	0	0
	Decreased coordination	0	0	2	0	0	0	3	3	0	0	0	0	0	0	0	3

**Stage 3: Probability Elicitation**

The third stage seeks to endow the BN structure with quantitative probabilities for making predictions. Crucially, although cognitive biases appear in all stages, the probability elicitation is particularly susceptible because of the quantitative nature and known issues with probability estimation [21,22]. Cognitive bias training will therefore be given prior to starting

the third stage. This will include questions from unrelated fields that are susceptible to biases likely to arise within the elicitation, such as recall bias and confusion of inverse probabilities [21,22]. A brief explanation of how the bias may lead to systematic deviations in the estimates will be presented for each question (Figure 5). Moreover, we will word questions so that participants are aware of the target population and are thinking about frequency estimates, rather than individual patients (Figure 6).

**Figure 5.** Examples of questions to be given in the cognitive bias training.

**Cognitive biases**

A cognitive bias is a systematic pattern of deviation from norm or rationality in judgment. These have a large effect in elicitation exercises such as this one, as it means the given answers will deviate in a systematic manner from the 'true' answer.

The psychological explanation for the existence of these biases is that we tend to rely on mental shortcuts, known as heuristics, rather than a more logical reasoned argument.

For example, take the following question:

Q. Which occurs more frequently in the English dictionary: Words that begin with the letter "K" or words for which "K" is the third letter?

Tversky and Kahneman argued that when confronted with this question, people will use an *availability heuristic*, meaning people equate the frequency of something with how easily it comes to mind. In this case words beginning with "K" are more easily thought of, however there are in fact three times more words with "K" in the third position Hence, using this availability heuristic leads to a systematic recall bias.

Many of these biases have been recorded, which arise due to one or more different heuristics. A selection of relevant ones are listed below:

Recall bias

Base rate fallacy

Conjunction fallacy

Affect-induced biases

Confusion of the inverse

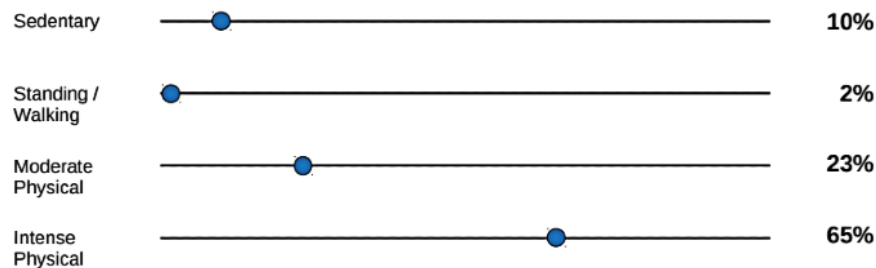
Anchoring



The variables in the BN can be binary (eg, true and false), labeled, that is, nominal with states without any order (eg, muscle, tissue, and tendon), or ranked, that is, ordinal with states with increasing or decreasing order (eg, high, medium, and low). Additionally, some variables (eg, age) will be independent of others (known as prior variables), whereas others will be dependent (eg, the prevalence of a condition may be influenced by the age of a patient).

For binary and labeled variables, sliders will be used to allow participants to assign probabilities individually to each state. For example (Figure 6), the question “What proportion of people work in the described type of job?” has a series of nominal answers, which can be represented with individual percentages adding up to 100. In contrast, ranked variables have a smooth distribution, so participants will be asked to estimate the most likely value and the extent of the variation around that value [23].

**Figure 6.** Example of direct probability elicitation for the question “What proportion of people work in the described type of job?”.



For independent (prior) variables, a simple question similar to that in Figure 6 will suffice, whereas for conditional variables, the states of related variables will be needed, for example, “What is the probability of a patient having a fracture *given* that they have an *age* of 80+ and experienced *trauma*?”

For binary/labeled variables, the answers from the probability elicitation will be combined using logistic regression and generalized noisy OR [23] techniques to generate the probability tables for each variables. For ranked variables, we will use the answers to estimate a truncated normal distribution [24]. This reduces the number of parameters compared with other methods [25,26] and so has the advantage of avoiding overfitting, but certain nuances of the relationships are missed. Outlying answers will be identified using an IPR-based metric and removed so as not to bias the regression approach.

#### Stage 4: Validation

A subset of clinical experts will be asked to give their judgement regarding the decision-making process for a number of given scenarios, which will then be compared against the model output, otherwise known as “face validity” [27]. Further validation will likely be required to establish the efficacy of the BN in practice; however, this is outside the scope of the study.

#### Internal Pilot

A much reduced version of the above protocol has already been conducted in an internal pilot study with three clinical colleagues (AH, CKJ, and DM) from Queen Mary University of London, who regularly treat patients with LBP. This was to test whether a suitable model could feasibly be constructed within a framework where the elicitation burden was not too high.

They completed all three stages of the elicitation process. During and after each stage of the process, a discussion took place regarding overall impressions of the stage in order to learn lessons and refine the process. These discussions captured clinical perspectives on the design of the questions and elicitation, feedback on what may or may not be acceptable to clinical participants, and appropriate redesign to ensure that the

requirements for the modeling process were still being met. The differences in methods are discussed below, with lessons learned reserved for the subsequent Results section.

#### Stage 1: Variable Elicitation

The creation, placement, and ranking of variables were performed individually in Word documents (Microsoft Corp), with no suggested variables available from the start. Responses were collated by the computer science team and then discussed in a workshop meeting to form consensus regarding the categorization and definition of variables. Because of limited participant numbers, a final ranking was obtained via the discussion.

#### Stage 2: Structure Elicitation

This stage was performed as described in the main protocol, except for definitions of the relationship strength. Owing to limited participants, the mean and SD were used as descriptive statistics instead. A simpler definition of relationship strength (Table 1) was also used, with 0, 1, 2, and 3 simply described as “none,” “weak,” “medium,” and “strong,” respectively.

#### Stage 3: Probability Elicitation

Clinical colleagues were first asked to complete example questions based on the methods reported previously [26,28] on paper and provide their feedback. This guided the development of a primitive online tool to automatically generate the questions and record answers. Despite basic methods for easing the elicitation, the number of variables, states, and connections led to upwards of 700 questions. Completion was only feasible by splitting the questions among the three clinical members of the team and avoiding subsequent workshop discussions. Unfortunately, elicitation of probabilities associated with the treatments was abandoned owing to the volume of questions and the scope of the BN restricted to predicting judgment factors prior to treatment.

## Results

### Overview

The below text documents the outcomes of the pilot study that influenced the subsequent makeup of the described protocol. We discuss each stage separately.

#### Stage 1: Variable Elicitation

Many variables were suggested, with most having similar definitions that could be combined easily, and there was general agreement about inclusion. However, the following issues became apparent:

- Using Word documents to collate the results was cumbersome. It was also felt that the crude method could adversely affect the engagement of participants.
- There was some misunderstanding regarding the categories and how they fitted into the BN.
- There was misunderstanding and poor explanation of computer science terminology, particularly what was meant by “definition” and “states” of a variable.
- Discrepancies arose in choosing categories for certain variables. For example, “depression” could be considered a risk factor for LBP, a sign and symptom in cases where depression was a result of LBP, or a judgement factor where depression was thought to be the main driver of the patient’s condition.
- There was no formal quantitative procedure for ranking the variables.
- The time taken to discuss all the suggested variables was too long.

The use of an online interface has been influenced by the issues described. We have decided to present the participants with a number of prepopulated variables based on the pilot study together with a review of relevant literature [29-31]. This is to help them understand the terminology, allow us to gather better statistics, and reduce elicitation burden. In addition, this would highlight the difficulty in placing certain variables (eg, the “depression” example above). One of the prepopulated examples will highlight this issue to allow the participants to decide on the best handling of these variables. As described in the methods, participants will still be given the ability to add as many variables as they deem appropriate to help avoid biasing results toward the pilot.

#### Stage 2: Structure Elicitation

The process of filling in the grids to define relationships was understandable and streamlined; however, the main issue concerned the time burden, arising as a result of too many variables passed from stage 1. The following issues were also identified:

- The mean and SD measure frame consensus in terms of averaged values and so can be affected by outliers, which is not suitable for the full study.
- Similar to stage 1, the Excel files were cumbersome to manage and made preserving anonymity difficult to avoid potential biases.

- The wording of the relationships (none to strong) did not convey the nuances of the relationships between variables that could occur in the BN.

Again, the decision to use an online interface came from these issues of data collection, engagement of the participants, and anonymity of responses. For the main protocol, we have updated the definition of the relationships and introduced more appropriate statistical measures.

#### Stage 3: Probability Elicitation

The use of the online interface was, in general, a success, making the acquisition of data more streamlined and user friendly. This success, along with issues identified in previous stages of the pilot, was the reason for our decision to transfer all stages of the process online. However, beyond the sheer number of questions, we identified the following issues:

- Cognitive biases were mentioned but not adequately explained or motivated, and relevant examples were not included.
- Numerous issues with the questions and online interface were raised, including (1) eliciting the distributions required different questions depending on the variable type; (2) incorrect/strange wording of the questions; (3) questions about individual probabilities rather than frequency estimates (the former is more cognitively challenging); (4) lack of information about the related variables was not included, meaning participants had to refer elsewhere, thus slowing the process down; and (5) technical terminology displayed for ranked variables, such as “mean” and “variance,” was not very intuitive.

As mentioned in the protocol, we have introduced targeted cognitive bias training to help overcome those specific issues. Interface issues will also be addressed during development. The main issue is the elicitation burden, and the pilot has shown that any follow-up workshop would be too time consuming for participants. Therefore, instead, possible outlying answers will be identified using an IPR-based metric and removed so as not to bias the regression approach.

#### Stage 4: Informal Validation

Following the probability elicitation, a tentative BN was constructed using the AgenaRisk software [32] and compared against fictitious case study scenarios. This was in order to check whether the process was capable of returning a suitable model that would be meaningful to clinicians. The scenarios represented patients presenting with signs of serious underlying pathology, inflammatory pathology, and nonspecific LBP. The BN appeared to reason in a similar qualitative manner to that which the clinicians would expect.

## Discussion

### LBP Clinical Reasoning

We believe we have created a process that compliments the clinical reasoning process familiar to domain experts by reflecting our mathematical variables into distinct recognizable categories and asking them to describe how variables within those categories are related. Enumerating probability

relationships is an area in which we anticipate experts will be least comfortable; those values are often implicitly known but almost never explicitly expressed in clinical practice. We have attempted to mitigate this by identifying common cognitive biases [21,22] and designing the elicitation to reduce the burden.

Giving this structure to the elicitation and subsequently the BN will provide confidence to future users about the “reasoning” performed by the tool. We hope the role of clinicians within the process will help alleviate concerns among users about its technical nature. Second, the structure is relatable and can be interrogated by the end user to understand the outcomes from the tool. Additionally, although the overall BN outline (Figure 2) has been designed specifically for this project, we believe it to represent clinical reasoning in a broad array of musculoskeletal conditions.

### Methodology for Eliciting Expert Opinion

There exists a wealth of literature concerning the elicitation of BNs and associated probabilities [14,15,24-28]. However, we are not aware of previous attempts to elicit comparably sized BNs with such limited time constraints on experts. To increase the chances of success, many of the individual components will use tried and tested methods, such as Noisy OR [23] and ranked node approximation [24]. Nevertheless, combining them all together in this fashion poses a major challenge.

Using the Delphi/RAND methodology [10] will help mitigate biases via group discussion and give participants an opportunity to reach a consensus. Considering an approach from the report by Ritchie et al [33], the discussion will need to remain flexible enough to explore in depth the contentious issues raised by the participants, with open questioning to avoid bias from the team that has already piloted the method. Additionally, there will

likely need to be exploration of divergent views, drawing attention to elicited themes where participants have disagreed.

The very basic validation process already conducted gives encouragement that this method is viable for the purpose of eliciting a clinical reasoning BN for LBP; however, the study team recognizes the inherent bias in conducting an internal validation. As mentioned, our Delphi/RAND process has been designed to help remove such biases, but it still remains to be seen whether the process conducted with external experts will yield a clinically credible BN.

### Other Uses for the Methodology

This methodology, should it be successful in the main study, could provide a new framework for developing decision support for other musculoskeletal problems and for other complex interventions in medicine. Additionally, it could provide a learning tool for aspiring expert clinicians to confront their cognitive biases, as it did for the pilot study colleagues.

### Conclusion

We propose a protocol for developing a complex expert-driven BN decision support tool while minimizing the elicitation burden on experts, who, as professional clinicians, have limited time to offer. A basic version of the elicitation method has been internally tested with a small group of clinician researchers in a pilot study, which has yielded credible results. The proposed protocol aims to establish consensus among users by using appropriate scoring metrics and subsequent workshops to draw consensus in a Delphi-like process. This will establish the content of the model as well as the inclusion of probability values to enable scenario testing. The initial skeleton BN, derived from the internal pilot, performed well enough with simple validation to suggest that a robust BN may be achievable from implementation of the protocol.

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### Acknowledgments

This report represents independent research arising from a Predoctoral Clinical Academic Fellowship, Adele Hill (ICA-PCAF-2018-01-137) supported by the National Institute for Health Research and Health Education England. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health. This work was supported by the CAP-AI program funded through the European Regional Development Fund and Barts Charity. This work was supported by an Institutional Links grant (ID 352394702) under the Turkey-Newton-Katip Çelebi Fund partnership. The grant is funded by the UK Department of Business, Energy and Industrial Strategy (BEIS) and The Scientific and Technological Research Council of Turkey (TUBITAK, ID 217M518) and delivered by the British Council. For further information, please visit [www.newtonfund.ac.uk](http://www.newtonfund.ac.uk).

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### Authors' Contributions

AH was the main author of this protocol. CHJ was the author of the data analysis and provided overall technical advice and review. CKJ provided methodology advice. WM supervised the technological aspects of this protocol. BY and CTS have advised on numerous aspects of the probability elicitation and provided peer review of the project. DM is the supervisor of this project and provided quality review.

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### Conflicts of Interest

None declared.

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## Abbreviations

- AI:** artificial intelligence  
**BN:** Bayesian network  
**IPR:** interpercentile range  
**LBP:** low back pain

*Edited by G Eysenbach; submitted 07.07.20; peer-reviewed by N Fenton, J Lurie; comments to author 15.08.20; revised version received 01.09.20; accepted 10.11.20; published 15.01.21.*

*Please cite as:*

Hill A, Joyner CH, Keith-Jopp C, Yet B, Tuncer Sakar C, Marsh W, Morrissey D

*A Bayesian Network Decision Support Tool for Low Back Pain Using a RAND Appropriateness Procedure: Proposal and Internal Pilot Study*

*JMIR Res Protoc* 2021;10(1):e21804

URL: <http://www.researchprotocols.org/2021/1/e21804/>

doi: [10.2196/21804](https://doi.org/10.2196/21804)

PMID: [33448937](https://pubmed.ncbi.nlm.nih.gov/33448937/)

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Protocol

# A Mindfulness-Based Brain-Computer Interface to Augment Mandala Coloring for Depression: Protocol for a Single-Case Experimental Design

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## Abstract

**Background:** The regular practice of mindfulness has been shown to provide benefits for mental well-being and prevent depression relapse. Technology-mediated interventions can facilitate the uptake and sustained practice of mindfulness, yet the evaluation of interactive systems, such as brain-computer interfaces, has been little explored.

**Objective:** The objective of this paper is to present an interactive mindfulness-based technology to improve mental well-being in people who have experienced depression. The system, Anima, is a brain-computer interface that augments mandala coloring by providing a generative color palette based on the unfolding mindfulness states during the practice. In addition, this paper outlines a multiple-baseline, single-case experimental design methodology to evaluate training effectiveness.

**Methods:** Adult participants who have experienced depression in the past, have finished treatment within the last year, and can provide informed consent will be able to be recruited. The Anima system, consisting of 2 tablets and a nonintrusive mental activity headband, will be delivered to participants to use during the study. Measures include state and trait mindfulness, depression symptoms, mental well-being, and user experience, and these measures will be taken throughout the baseline, intervention, and monitoring phases. The data collection will take place in the form of a questionnaire before and after each mandala-coloring session and a semistructured interview every 2 weeks. Trial results will be analyzed using structured visual analysis, supplemented with statistical analysis appropriate to single-case methodology.

**Results:** Study results will offer new insights into the deployment and evaluation of novel interactive brain-computer interfaces for mindfulness training in the context of mental health. Moreover, findings will validate the effectiveness of this training protocol to improve the mental well-being of people who have had depression. Participants will be recruited locally through the National Health Service.

**Conclusions:** Evidence will assist in the design and evaluation of brain-computer interfaces and mindfulness technologies for mental well-being and the necessary services to support people who have experienced depression.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/20819

(*JMIR Res Protoc* 2021;10(1):e20819) doi:[10.2196/20819](https://doi.org/10.2196/20819)

## KEYWORDS

brain-computer interface; mental well-being; depression; mindfulness; mandala coloring

## Introduction

### Background

Recent developments in interventions for depression and the prevention of its relapse have focused on applying mindfulness-based strategies, which aim to shift the focus of attention away from the negative content of thought to nonjudgmentally observe the mind processes [1-3]. It has been long suggested that recovered patients with depression should be trained in mindful self-awareness to counter rumination and reduce the risk of future relapses [4]. Mindfulness, with its origins in Buddhist traditions, has been defined in Western psychology as a process of deliberate, nonjudgmental self-regulation of attention to the present moment-to-moment experience without being distracted by thoughts of the past or future [5]. Landmark examples of psychology programs that aim to improve mental and physical health are the mindfulness-based stress reduction [6], mindfulness-based cognitive therapy [7], and mindfulness-based art therapy (MBAT) [8] programs. The underlying mechanisms of mindfulness training have also been widely investigated, and there is an agreement in the literature that mindfulness is a metacognitive attentional process that is concerned with how individuals relate to the content of their thoughts [9]. This specific relational process is believed to reduce the ruminative aspects of depression by altering the way individuals view their own process of thought [4,10,11].

MBAT is based on the self-regulation theory and integrates mindfulness skills and aspects of art therapy into an 8-week, gender-segregated, supportive group therapy format [12,13]. The overall goal is to provide specific skills for cultivating self-regulation of attention and affect in a format that is not confined to verbal processing alone. It provides a foundation for understanding reactions to perceptions of physical and emotional well-being. A common activity in MBAT is the coloring of mandalas for self-awareness, self-expression, conflict resolution, and healing [14]. Mandalas, originally from Tibetan Buddhism, were introduced into psychotherapy by Carl Jung [15]. He suggested that the act of drawing mandalas had a calming and healing effect on its creator, while simultaneously facilitating psychic integration and personal meaning in life [16]. The mandala functions as a symbolic representation of emotionally laden and conflicting material, yet at the same time provides a sense of order and integration to this material [17-23].

Our research draws from previous scientific investigation of the benefits of mandala coloring for mental health [24] and previous studies we conducted exploring this practice and its impact on well-being with the general population [25,26]. The approach presented in this paper differs from previous MBAT programs, as it is an individual self-care approach that uses interactive technology, which we named Anima, to decrease depressive symptoms and increase mental well-being in people who have experienced depression in the past. Anima is a mindfulness-based technology that was designed and developed after an exploratory study with experts on the practice of mandalas, in which we found that people used mandalas as a self-care tool for their mental well-being (paper submitted for

publication). Experts described how the coloring of the mandala allowed for the expression of affective and mental states that would otherwise be difficult to communicate. We found that the colors used during coloring were used to express such underlying emotions, and they served as emotional cues in the final mandala to facilitate reflection on their experiences. Therefore, mandala coloring seemed to support both attention and emotion regulation strategies [27]. Furthermore, the coloring process of the mandala was seen as a kinetic mindfulness training that allowed for the practice of acceptance and reappraisal when, for example, a coloring mistake happened. With this in mind, Anima is a brain-computer interface that generates an adaptive color palette to foster awareness on one's mental states, and it is tailored to one's experience and interests as an aid to augment mandala coloring.

### Theoretical Framework

It has been shown that mindfulness practice and the development of mindfulness expertise is closely linked to increased awareness of the body and its sensations [28-31], which has been found to be beneficial for mental well-being in people with depression [1,5,32]. Despite the broad range of practices to train mindfulness, most interactive systems have focused on static guided meditation [33-35]. Our work builds on the practice of mandala coloring [21,36-38] as an alternative, less-explored approach to supporting focused-attention mindfulness training [39]. Originated in Buddhist traditions as a meditation aid, mandalas are a type of sacred geometry that represents harmony, wholeness, and the self [15]. Always starting from an epicenter, mandalas grow in concentric structures consisting of circles and layers that represent different aspects of the Tibetan Buddhist universe. Mandalas were brought to Western traditions by Carl Jung, who was the first to use the mandala as a therapeutic tool [14]. He found that the drawing of a mandala had a calming and healing effect on its creator by eliciting structure within the person's thoughts and ultimately creating a meditative state [40]. Ever since, mandalas have been used in art therapy to facilitate the emergence of inner experiences and feelings, which are expressed both consciously and unconsciously through art materials and the use of colors [21,38,41].

During the practice of mandala coloring, individuals need to focus on the coloring process, as the complex design provided by the mandalas requires a high concentration level. Small areas have to be colored with small and conscious movements [9,31,42], which in turn facilitates grounding in the present moment [42,43]. In contrast to static practices, such as sitting meditation, traditional movement-based mindfulness practices tend to rely on physical tools to restrict one's motion, such as copper funnels for sand mandalas [44], Baoding balls [45], or prayer wheels [46]. These tools are generally used as aids for grounding in the present moment while engaging in controlled, slow, and continuous movements [45]. Some of these traditional meditation artifacts have also influenced the design of mindfulness technologies, such as the Spheres of Wellbeing [47] or the Channel of Mindfulness [48]. In the case of mandala coloring, the tools that facilitate the mindfulness training would be the art materials used for coloring the geometry. Despite the increasing human-computer interaction and psychological interest in the role of art or craft materials [24,49-51] and

technology for well-being [35,52-56], there is still a lack of systems that use art materials as active interaction cues. Further, designs inspired by movement-based mindfulness practices such as mandala coloring are still limited despite their potential to offer distinctive interactions for fostering the experience of an embodied self [28,33,36].

Recently, brain-computer interfaces (BCIs) have also been used to support the self-regulation of attention during mindfulness practices. For instance, MeditAid is an interactive system that uses neurofeedback during mindfulness sitting meditation to support the self-regulation of attention [57]. In this case, adaptive aural entrainment is controlled by the user's brain activity and their mindfulness state. Similarly, PsychicVR introduced an element of playfulness to the experience of sitting meditation, as it allows users to interact with the virtual environment [58]. Another example is Inner Garden, in which one's internal state is projected in a sand terrain that can be modified by shaping the sand [59]. These are some key illustrations of how BCIs have been used to differently augment mindfulness practices to enhance self-regulation processes. We argue that there is a less-explored design space, in which BCIs could be used to also augment movement-based mindfulness practices such as mandala coloring to foster mental well-being.

### Research Questions and Aims

The main objective of this research is to evaluate the impact of a novel mindfulness-based interactive technology (ie, Anima) on the mental well-being of people who have experienced depression.

The main research questions we seek to answer are the following: (1) To what extent can the materialization of brain activity using Anima facilitate the training of a mindfulness state for people who have depression? (2) To what extent does exposure to the training program positively influence the training of acceptance, self-awareness, and regulation of attention and emotions? (3) Does the use of Anima decrease depressive symptoms and increase mental well-being for people who have experienced depression?

The primary outcome is increased mental well-being after the study in comparison to baseline. The secondary outcomes are improved acceptance, self-awareness, and self-regulation of attention and emotional strategies and increased trait mindfulness at the end of the study.

### Anima: A Brain-Computer Interface for Mandala Coloring With a Generative Color Palette

According to Jung, the psychotherapist that introduced mandala coloring to Western culture, the anima represents the inner personality, which allows the individual to bring attention toward unconscious parts of the self [55]. Previous research has

shown that colors play an important role in mandala-coloring practices for well-being [24,38]. In this context, colors are used to better understand one's affective states while coloring the mandala by materializing current emotions onto colors or using colors to achieve the desired state. Furthermore, the practice of mandala coloring has been widely used in spiritual and mental well-being practices to facilitate the training of mindfulness [24,38]. Our Anima prototype aims to bring the attention inwards by materializing intangible processes (ie, mindfulness states) to facilitate the monitoring of mindfulness practice, such as mandala coloring. Building on work showing that mandala coloring fosters nonjudgmental focused attention [33,60], we sensitively designed Anima to augment the practice of mandala coloring by giving access to colors that represent one's mindfulness states in real time. The design was also inspired by traditional coloring and its interaction with the materials, which are placed within reach, there when needed, yet peripheral.

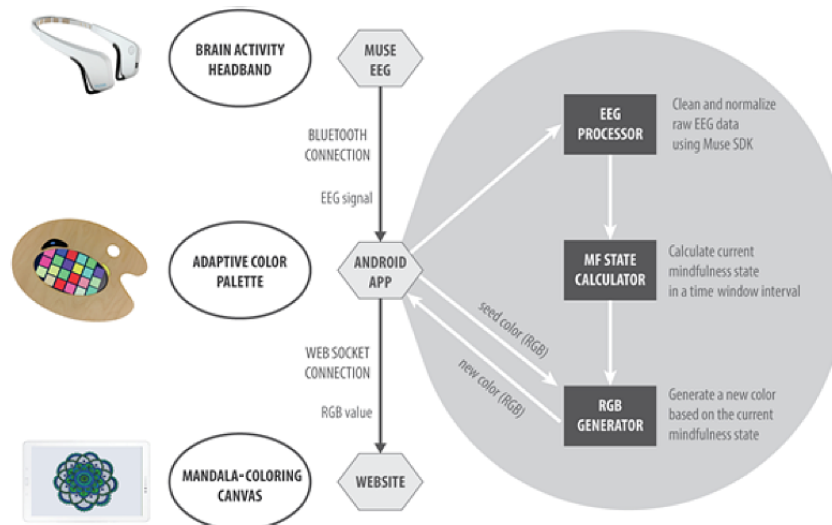
Anima consists of 3 main components that have been carefully designed to fulfill a specific goal during its use (Figure 1): a brain activity headband, an adaptive color palette, and a mandala-coloring canvas. First, a brain activity headband is used to unobtrusively sense the electroencephalography (EEG) data, from which the mindfulness states of the person coloring the mandala are extracted. We will use Muse (Interaxon Inc) [61], a commercial unobtrusive brain activity headband that has been shown to provide valid and reliable measurements of event-related brain potentials in real time [62,63]. Previous work has also linked each of these brain waves with specific mental states [64], particularly during mindfulness training, from which mindfulness states can be clearly identified [13,65].

Second, the adaptive color palette is used as a peripheral interface to monitor the practice, as it provides new colors that are generated based on the current mindfulness state. The color palette is a hybrid object consisting of a tablet enclosed in a bespoke, wooden painter palette that adaptively provides a generative set of 22 colors from the user's brain activity via an Android app we developed. The palette aims to subtly reflect the mental states involved in the unfolding mandala-coloring practice and to explore the ways that such materializations of mental states support mindfulness practice. When a color is selected from Anima's generative palette (by tapping it), the canvas automatically loads it to color the digital mandala.

Finally, the canvas aims to recreate the traditional practice of mandala coloring to train focused attention. The canvas used to color the mandala consists of a tablet that displays a mandala from a website we developed and can be colored using a stylus. The color selected from the palette's Android app is automatically sent to the mandala canvas using web sockets, and it becomes available for coloring immediately.



**Figure 1.** This diagram shows an overview of the system by describing the 3 components of Anima (ie, brain activity headband, adaptive color palette, and mandala-coloring canvas) and their integration. EEG: electroencephalogram; MF: mindfulness; RGB: red, green, and blue; SDK: software development kit.



## Methods

### Single-Case Experimental Design

In this study, we will follow the well-established methodology of a single-case experimental design (SCED). A SCED is an experimental research design in which an individual case serves as its own control, and the dependent variable measured is analyzed for each individual case and is not averaged across groups or across participants. This methodology emphasizes intensive repeated observations of a particular participant to demonstrate precise control over targeted behavior and includes a family of methods in which each participant serves as his or her own control [66]. There is an assortment of single-case designs. Dallery et al [67] discussed the purpose of each design as well as the similarities and differences between designs to evaluate novel technology-based health interventions. Following their assessment, this study will follow a combined approach of the multiple-baseline design and changing criterion design.

The multiple-baseline experimental design is a SCED in which a treatment is successively administered over time to different participants for different behaviors or in different settings. That is, in multiple-baseline designs, multiple AB data series are compared, and the introduction of the intervention is staggered across time. Comparisons are made both between and within data series. Adding phase repetitions increases the power of the statistical test, similar to adding participants in a traditional group design [68]. The number and timing of the repetitions can vary depending on the outcomes of the intervention. Among the characteristics of this design, effect replication across series is regarded as the characteristic with the greatest potential for enhancing internal and statistical conclusion validity.

The changing criterion design is a SCED in which a baseline phase is followed by successive treatment phases in which some

criterion or target level of behavior is changed from one treatment phase to the next. The participant must meet the criterion of the treatment phase before the next treatment phase is administered. Thus, the changing criterion design is used to determine the effects of an independent variable when the final version of the target behavior cannot be emitted initially. Experimental control is demonstrated by the repeated changes in the dependent measure as the criterion is changed [69]. The steps in the changing criterion design must be large enough to clearly show the effects of the independent variable but not so large that the participant cannot meet the changed criterion. The critical element of changing criterion designs is the systematic introduction of a criterion level of performance over successive phases so that the behavior is essentially shaped into a final level, with each change in behavior occurring concurrently with the change in criterion. Experimental control is established by the simultaneous co-occurrence of both.

To sum up, the flexibility of SCED allows for greater freedom to ask innovative questions about novel treatments and has been widely used as an initial research design for testing innovative research in, for example, behavioral sciences [65] or novel technologies for health [67]. This methodology does not need a control group, as each participant acts as control during the baseline [68,70]. Although SCED is typically associated with low population validity, which is a subcategory of external validity, the external validity can be strengthened by generalizing across behaviors, participants, and settings [68,70].

### Study Setting

This training intervention will be carried out in the homes of eligible consenting participants. Participants will be asked to color a mandala using Anima (Figure 2) a total of 3 times a week, as described below, in their preferred quiet space in their house and during the evening if possible (ie, after work or other daily routines).

**Figure 2.** A person using Anima. While wearing the electroencephalography headband, colors based on the current mental states are generated on the wooden palette and can be used to color the digital mandala.



## Measures

Following previous studies evaluating the effect of mindfulness-based programs for health in general and depression in particular [71] (ie, MBAT [12,72], mindfulness-based cognitive therapy [7,73], and mindfulness-based stress reduction [74]), several instruments have been chosen to assess the dependent variables from the research questions.

### Mindfulness

For state mindfulness [75], the Toronto Mindfulness Scale (TMS) was designed to assess mindfulness as a “quality maintained when attention is intentionally cultivated with an open, non-judgmental orientation to experience” [76]. The original TMS measures mindfulness as a state-like quality and not as a trait. The administration of the TMS requires that a brief mindfulness exercise precede self-administration of the instrument, and the TMS items assess the quality of that experience. The TMS is composed of 2 subscales, curiosity and decentering, and a total TMS score is not reported. Exploratory factor analysis suggested a 2-factor structure for the TMS, and this was supported by confirmatory factor analyses. The TMS has evidence of internal consistency, with the Cronbach  $\alpha$  ranging from .86 to .91 and a Cronbach  $\alpha$  of .85 and .87 for curiosity and decentering, respectively. Correlations for the decentering subscale with most of the other measures of mindfulness ( $r=0.20$  to  $0.74$ ) were stronger than the correlations between the curiosity subscale and these measures ( $r=0.10$  to  $0.54$ ) [77]. Curiosity and decentering were positively correlated with absorption, awareness of surroundings, reflective

self-awareness, and psychological mindedness. As hypothesized, only curiosity was correlated with awareness of internal states and self-consciousness ( $r=0.41$  and  $r=0.31$ , respectively), and only decentering was correlated with openness and cognitive failures ( $r=0.23$  and  $r=-0.16$ ). Decentering is posited to be a major outcome of mindfulness-based cognitive therapy and a mechanism that enables patients to be resilient to depressive thoughts, and patients with depression have lower levels of decentering compared with healthy controls [78].

For trait mindfulness [75], the Mindful Attention Awareness Scale (MAAS) was created to specifically capture attention and awareness in daily life [32]. It is a 15-item scale designed to assess a core characteristic of dispositional mindfulness, that is, open or receptive awareness of and attention to the present moment’s experiences. The scale shows strong psychometric properties (Cronbach  $\alpha=.89$ ) and has been validated with college students [79-81] and community [32] and cancer [82] patient samples.

Research has shown that the MAAS taps into a unique quality of consciousness that is related to and predictive of a variety of self-regulation and well-being constructs. It has also been found that the greater the change in mindfulness, the greater the reduction in depressed mood and the extent to which participants deal with difficulties through rumination and avoidance [83,84].

### Depression Symptoms

The Beck Depression Inventory second edition (BDI-II) is a 21-item scale and one of the most widely used self-report

measures of depression [85], with well-established psychometric properties (Cronbach  $\alpha$  ranging from .83 to .96) [86].

### ***Mental Well-Being***

The Warwick-Edinburgh Mental Well-being Scale (WEMWBS) [87] is designed to capture a broad conception of well-being, including affective-emotional aspects, cognitive-evaluative dimensions, and psychological functioning. The scale consists of 14 items, each answered on a 5-point scale ranging from “none of the time” (1) to “all of the time” (4), and it is scored by summing all the items into a total well-being score (range of 14-70). The total score is the summation of all the items, with higher scores indicating greater well-being. The WEMWBS was assessed in the United Kingdom with 9 focus groups, one with mental health service users [88]. The Cronbach  $\alpha$  is .91 for this scale.

### ***Acceptance and Reflection***

Private self-consciousness and the subordinate constructs of self-reflection and insight are key factors in the self-regulatory process underpinning the creation of behavior change in both clinical and nonclinical environments, and they can be assessed with the Self-Reflection and Insight Scale (SRIS) [89]. The SRIS self-reflection factor analysis correlated positively with anxiety and stress but not with depression and alexithymia, while the insight factor analysis was negatively correlated with depression, anxiety, stress, and alexithymia and positively correlated with cognitive flexibility and self-regulation. The coefficient  $\alpha$  was .91 for the self-reflection scale and .87 for the insight scale.

### ***Emotional State***

The Self-Assessment Manikin (SAM) is a widely used nonverbal pictorial assessment technique used to obtain self-assessments of emotional state on the dimensions of affective valence, arousal, and dominance [90]. Each dimension is represented by one item that shows a picture of a manikin in 5 grades. Valence is operationalized by a manikin showing a negative or positive affective state, arousal is operationalized by a manikin being more or less energetic, and dominance is operationalized by showing a rather small (feeling of less dominance) or large manikin (feeling of much dominance). Despite the small item number, several studies indicate sufficient reliability of the SAM [60,91].

### ***User Experience***

User experience will be measured indirectly by how often participants use the prototype and directly during the interviews and using the User Experience Questionnaire (UEQ) after each session [92]. The average Cronbach  $\alpha$  value for the English version of the UEQ is .79, which makes the reliability of the questionnaire sufficiently high. This measure has been evaluated in different scenarios [93], and a benchmark has been developed to facilitate the interpretation of user experience evaluations using UEQ [94]. In this study, we will use the short version (UEQ-S) [95], which has Cronbach  $\alpha$  values between .81 and .85, as filling out the UEQ takes between 3 and 5 minutes, which might be too long to do after each session, deteriorating user experience.

### ***Data Collection***

The study will have 3 phases (as shown in Figure 3): baseline, intervention, and monitoring. Following the multiple-baseline design, the duration of the baseline will vary depending on the participant, but the intervention phase will always last 8 weeks, and the monitoring phase will be 4 weeks. During the baseline and monitoring phases, participants will be asked to complete the trait measurements of trait mindfulness (ie, MAAS), depression symptoms (ie, BDI-II), mental well-being (ie, WEMWBS), and acceptance and reflection (ie, SRIS). These questionnaires will be filled in 3 times a week, and the total time expected for completing them all is about 34 minutes.

The intervention phase will last 8 weeks for all participants, starting at different points in time. Every week, they will be asked to practice mandala coloring using Anima 3 times. Each session will last between 70 and 75 minutes, as shown in Figure 4, and is divided into 4 stages: premeasurements and postmeasurements (marked in pale green), EEG data collection (marked in blue), and mandala coloring (marked in yellow). Instruments measuring trait will be completed once a week and distributed during the 3 weekly sessions (marked in darker green). All data will be collected using digital versions of each questionnaire on the tablet used as a canvas for mandala coloring.

Further, a short face-to-face semistructured interview will take place every 2 weeks with each participant to check that the technology is working and to gather qualitative data on their experience, both for the evaluation of user experience with Anima and for their mandala-coloring practice evolution.

**Figure 3.** Timeline of the protocol, starting with N weeks of baseline per participant, followed by 8 weeks of intervention and 4 weeks of postintervention monitoring.

Week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
0	Obtain informed consent. Screen potential participants by inclusion and exclusion criteria.						
N		Checkpoint		Checkpoint		Checkpoint	
1 + N	Face-to-face interview. Set up technology and necessary training.						
		Mandala 1		Mandala 2		Mandala 3	
2 + N		Mandala 4		Mandala 5		Mandala 6	
3 + N	Face-to-face interview						
		Mandala 7		Mandala 8		Mandala 9	
4 + N		Mandala 10		Mandala 11		Mandala 12	
5 + N	Face-to-face interview						
		Mandala 13 (i)		Mandala 13 (ii)		Mandala 13 (iii)	
6 + N		Mandala 14 (i)		Mandala 14 (ii)		Mandala 14 (iii)	
7 + N	Face-to-face interview						
		Mandala 15 (i)		Mandala 15 (ii)		Mandala 15 (iii)	
8 + N		Mandala 16 (i)		Mandala 16 (ii)		Mandala 16 (iii)	
9 + N	Face-to-face interview						
		Checkpoint		Checkpoint		Checkpoint	
10 + N		Checkpoint		Checkpoint		Checkpoint	
11 + N		Checkpoint		Checkpoint		Checkpoint	
12 + N		Checkpoint		Checkpoint		Checkpoint	

**Figure 4.** Triweekly mandala-coloring sessions during the intervention phase (in blue in Figure 3). To evaluate the effect of mandala coloring, data collection in each session will include pre- and post-EEG and measurements of emotional state (ie, SAM), mindfulness state (ie, TMS), and user experience (ie, UEQ-S). Trait measurements will be collected once a week. Hence, questionnaires will be distributed during the 3 sessions: BDI-II for depression symptoms in the first session, MAAS for trait mindfulness and WEMWBS for mental well-being in the second session, and SRIS for acceptance and reflection in the third session. BDI-II: Beck Depression Inventory second edition; EEG: electroencephalography; MAAS: Mindful Attention Awareness Scale; SAM: Self-Assessment Manikin; SRIS: Self-Reflection and Insight Scale; TMS: Toronto Mindfulness Scale; UEQ-S: User Experience Questionnaire short version; WEMWBS: Warwick-Edinburgh Mental Well-being Scale.

(1)										
SAM	EEG setup	EGG (pre)	Color selection	Mandala coloring	EEG (post)	TMS	UEQ-S	SAM	BDI-II	
1 min	3 min	3 min	3 min	30-40 min	3 min	5 min	1 min	1 min	10 min	
~70 min										
(2)										
SAM	EEG setup	EGG (pre)	Color selection	Mandala coloring	EEG (post)	TMS	UEQ-S	SAM	MAAS	WEMWBS
1 min	3 min	3 min	3 min	30-40 min	3 min	5 min	1 min	1 min	7 min	7 min
~75 min										
(3)										
SAM	EEG setup	EGG (pre)	Color selection	Mandala coloring	EEG (post)	TMS	UEQ-S	SAM	SRIS	
1 min	3 min	3 min	3 min	30-40 min	3 min	5 min	1 min	1 min	10 min	
~70 min										

### Data Analysis

The most common method of data analysis in SCEDs consists of conducting a visual analysis to determine intervention effects, as long as the baseline phase has been stable [68,70]. In this case, the stability of a measure is assessed by the consistency in the pattern of change in a dependent measure in each phase of a design. The more stable or consistent changes in a dependent measure are in each phase, the higher the internal validity of the research design. Furthermore, a measure can have a change in level or a change in trend, and the larger the magnitude of change (ie, size of the change in a dependent measure observed between phases of design), the greater the internal validity of the research design.

Although there are no specific guidelines for using statistical methods for analyzing SCED data, repeated measurements have been commonly used to evaluate the autocorrelation of sequential observations of the data. However, because of the nature of the SCED method, missing data can occur. Therefore, multilevel modeling and autoregressive moving average methods can be used to overcome these challenges.

## Results

### Ethics Approval

This study is currently in the process of being submitted to the National Health Service (NHS) to be reviewed by a research ethics committee (Integrated Research Application System number: 262687). Given the current situation and the NHS



dealing with a global pandemic, as of summer 2020, we understand that this process may be delayed.

We now detail the sample and recruitment process for the study.

### Inclusion Criteria

All adults in the community who (1) are aged between 18 and 60 years, (2) have been diagnosed with mild to moderate depression in the past, (3) have finished treatment within the last year, and (4) are not currently being treated or on a waiting list for psychotherapy for any kind of mental health problem will be initially selected for the study. Further, in order to be included in the study, people will need to (1) show readiness to change, (2) show willingness to engage in self-care, (3) have an interest in interactive mindfulness practices, (4) have internet at home, and (5) have basic knowledge of how to use interactive technology (eg, regular usage of a smartphone, knowing how to connect two devices using Bluetooth).

### Exclusion Criteria

People with (1) motor impairments in the upper part of the body; (2) a major depressive disorder, bipolar disorder, or psychotic disorder based on the Diagnostic and Statistical Manual of Mental Disorders fifth edition criteria; (3) suicidal risk; or (4) a history of a major depressive disorder in the past 6 months according to Kupfer's model [96] will be excluded. It is also known that medication, drugs, and alcohol can highly affect brain activity [97]. Therefore, people with signs of alcohol misuse (ie, drinking more than 14 units a week) [64] and people undergoing a long-term medication treatment will be excluded. Finally, people who have actively engaged in mindfulness practices for the past year (ie, any type of meditation, yoga, tai chi, or qigong) or who score higher than 4 in the MAAS will be excluded from the study, as the number of years of meditation practice is positively related to the MAAS [32]. Likewise, people who have colored mandalas or adult coloring books more than once a week for the past 6 months will be excluded.

### Sampling

The method followed in this study is the well-established purposeful sampling method [98], which involves identifying and selecting individuals from a specific population group. In our case, this is people who have recovered from a depressive

episode recently and have an interest in mindfulness (detailed description in "Inclusion Criteria" section).

Single-case experimental designs emphasize intensive repeated observations of a particular subject to demonstrate precise control over the targeted behavior [70]. Therefore, these designs usually select a limited number of individuals and collect a considerable amount of data per participant [67]. Based on previous work following SCED methodology [70], the estimated sample size for this study is 15 people.

### Recruitment

Participants of this study will be recruited through the Lancashire Care NHS Foundation Trust and will be able to withdraw at any time without justification. This provider will pass the invitation on to eligible residents so they can consider whether they would like to release their contact details to the research group. This study will only include participants who can provide their own informed consent. The service provider handing on the invitation will know whether the person can provide his or her own consent to participate as part of their service agreement with the resident.

### Discussion

This study follows the ethical guidelines and requirements by the European Union, Lancaster University, and the NHS. In terms of data collection and protection, Lancaster University will be the data controller for any personal information collected as part of this study under the General Data Protection Regulation. Further information about how Lancaster University processes personal data for research purposes and about individual data rights can be found on their webpage [99].

This protocol has been designed alongside a clinical psychologist with expertise in biofeedback from the AffecTech consortium. It was later iterated with the study support service from the National Institute for Health Research Clinical Research Network in the North West. The technology used in this study, Anima, has already been evaluated with the general population in 2 different settings: a public engagement event with mental health professionals in Lancashire and a workshop with people with experience coloring mandalas for mindfulness training and mental well-being (ie, they had been coloring mandalas at least monthly for the last year).

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### Acknowledgments

This work has been supported by AffecTech: Personal Technologies for Affective Health, Innovative Training Network, which is funded by the H2020 People Programme (Marie Skłodowska-Curie GA No. 722022).

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### Conflicts of Interest

None declared.

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Multimedia Appendix 1

Peer-review reports (1).

[PDF File (Adobe PDF File), 127 KB - [resprot\\_v10i1e20819\\_app1.pdf](#) ]

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## Multimedia Appendix 2

Peer-review reports (2).

[\[PDF File \(Adobe PDF File\), 165 KB - resprot\\_v10i1e20819\\_app2.pdf \]](#)**References**

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## Abbreviations

**BCI:** brain-computer interface  
**BDI-II:** Beck Depression Inventory second edition  
**EEG:** electroencephalography  
**MAAS:** Mindful Attention Awareness Scale  
**MBAT:** mindfulness-based art therapy  
**NHS:** National Health Service  
**SAM:** Self-Assessment Manikin  
**SCED:** single-case experimental design  
**SRIS:** Self-Reflection and Insight Scale  
**TMS:** Toronto Mindfulness Scale  
**UEQ:** User Experience Questionnaire  
**WEMWBS:** Warwick-Edinburgh Mental Well-being Scale

*Edited by G Eysenbach; submitted 01.06.20; peer-reviewed by B Johansson, L Guo; comments to author 15.07.20; revised version received 19.08.20; accepted 10.11.20; published 18.01.21.*

*Please cite as:*

Daudén Roquet C, Sas C

*A Mindfulness-Based Brain-Computer Interface to Augment Mandala Coloring for Depression: Protocol for a Single-Case Experimental Design*

*JMIR Res Protoc* 2021;10(1):e20819

URL: <http://www.researchprotocols.org/2021/1/e20819/>

doi: [10.2196/20819](https://doi.org/10.2196/20819)

PMID: [33459604](https://pubmed.ncbi.nlm.nih.gov/33459604/)

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Protocol

# Improving Patient Prioritization During Hospital-Homecare Transition: Protocol for a Mixed Methods Study of a Clinical Decision Support Tool Implementation

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## Abstract

**Background:** Homecare settings across the United States provide care to more than 5 million patients every year. About one in five homecare patients are rehospitalized during the homecare episode, with up to two-thirds of these rehospitalizations occurring within the first 2 weeks of services. Timely allocation of homecare services might prevent a significant portion of these rehospitalizations. The first homecare nursing visit is one of the most critical steps of the homecare episode. This visit includes an assessment of the patient's capacity for self-care, medication reconciliation, an examination of the home environment, and a discussion regarding whether a caregiver is present. Hence, appropriate timing of the first visit is crucial, especially for patients with urgent health care needs. However, nurses often have limited and inaccurate information about incoming patients, and patient priority decisions vary significantly between nurses. We developed an innovative decision support tool called *Priority for the First Nursing Visit Tool* (PREVENT) to assist nurses in prioritizing patients in need of immediate first homecare nursing visits.

**Objective:** This study aims to evaluate the effectiveness of the PREVENT tool on process and patient outcomes and to examine the reach, adoption, and implementation of PREVENT.

**Methods:** Employing a pre-post design, survival analysis, and logistic regression with propensity score matching analysis, we will test the following hypotheses: compared with not using the tool in the preintervention phase, when homecare clinicians use the PREVENT tool, high-risk patients in the intervention phase will (1) receive more timely first homecare visits and (2) have decreased incidence of rehospitalization and have decreased emergency department use within 60 days. Reach, adoption, and implementation will be assessed using mixed methods including homecare admission staff interviews, think-aloud observations, and analysis of staffing and other relevant data.

**Results:** The study research protocol was approved by the institutional review board in October 2019. PREVENT is currently being integrated into the electronic health records at the participating study sites. Data collection is planned to start in early 2021.

**Conclusions:** Mixed methods will enable us to gain an in-depth understanding of the complex socio-technological aspects of the hospital to homecare transition. The results have the potential to (1) influence the standardization and individualization of nurse decision making through the use of cutting-edge technology and (2) improve patient outcomes in the understudied homecare setting.

**Trial Registration:** ClinicalTrials.gov NCT04136951; <https://clinicaltrials.gov/ct2/show/NCT04136951>

**International Registered Report Identifier (IRRID):** PRR1-10.2196/20184

**KEYWORDS**

clinical decision support system; homecare agencies; rehospitalization; RE-AIM framework; PREVENT; effective implementation

## Introduction

### Background

Each year, more than 5 million patients are admitted to the approximately 12,000 homecare agencies across the United States [1-3]. Registered nurses (RNs) make several critical decisions before and during homecare admission, including identifying patients at risk for poor outcomes who might benefit from early interventions. However, there are no rigorously developed standards to assist in making these important decisions.

In this study, we focus on patients admitted to homecare from hospitals because their recent acute exacerbation makes them likely to be in urgent need of timely care, and they constitute up to 70% of all homecare recipients [3,4]. Nationwide evidence shows that about 20% of homecare patients are rehospitalized during the up to 60-day homecare episode [1,5], with as many as 68% of these rehospitalizations occurring within the first 2 weeks of services [4,6-9]. The Medicare regulations require a visit within 48 hours of referral to homecare, but for many patients, this may be too late. A growing body of evidence shows that a significant portion of rehospitalizations may be prevented by timely and appropriately targeted homecare services [4,8,10,11]. Patient prioritization at the time of transition to homecare services is a critical key to better patient outcomes.

The first homecare visit, usually conducted by an RN, is one of the most critical steps of the homecare episode [12,13]. This start of care visit includes an assessment of the patient's capacity for self-care, medication reconciliation, an examination of the home environment, and a discussion regarding whether a caregiver is present and able to help. A unique care plan is created based on this evaluation of the patient's needs [14]. Hence, appropriate timing of the first visit is crucial, especially for patients with urgent health care needs. However, recent research by our team showed that nurses have very limited and often inaccurate information about incoming patients due to lack of information exchanges between care settings and lack of standards about the necessary information needed for patient prioritization [12-15]. Often operating with limited information, resources, and time [13], nurses must decide how to prioritize the patient's first homecare visit.

Some studies have examined solutions for improving patient prioritization in a postacute care setting. For example, one study from Canada developed a method called Method for Assigning Priority Levels (MAPLe) to assist case managers in determining the relative priority that should be attached to patients when postacute care referrals are made [16]. However, the MAPLe system is not specific to homecare, and it prioritizes patients irrespective of the care setting. Another study from the United States has developed a tool that helps prioritize patients discharged to skilled nursing facilities [17]. None of the existing studies have developed prioritization tools specific to homecare.

### Objectives

Our team has developed an innovative clinical decision support system (CDSS) called *Priority for the First Nursing Visit Tool* (PREVENT) to assist nurses in prioritizing patients in need of immediate first homecare nursing visits [18]. PREVENT was developed with rigor, using a strong theoretical foundation (transition theory) [19] and methodology for eliciting experts' decisions to create clinical decision support tools [20]. PREVENT was constructed using data mining, regression modeling, and expert homecare nurses' ratings of example patients who were transitioned from hospital to homecare. The goal was to identify key patient characteristics that are essential to support early homecare admission decision making. Overall, more than 70 patient demographic and clinical characteristics (eg, comorbidities, level and availability of social support, and detailed functional status) were considered for inclusion in the final prediction model from which PREVENT was developed. The final PREVENT CDSS uses 5 factors (including the number of medications, number of comorbid conditions, presence of a wound, presence of a comorbid condition of depression, and patient's functional status) to produce a recommendation on whether a specific homecare patient should be prioritized for the first homecare nursing visit. See [Multimedia Appendix 1](#) [16-18,21-23] for more information about the methods for PREVENT CDSS development.

We completed a pilot efficacy study [9] to measure the efficacy of PREVENT, conducted at a large urban hospital in Brooklyn, New York. In collaboration with the Visiting Nurse Service of New York (VNSNY), we enrolled 176 patients admitted to homecare from the hospital during April and May 2016. In the control phase (n=90 patients), we calculated the PREVENT priority score but did not share the score with the homecare admission staff who influence visit scheduling. In the experimental phase, the PREVENT score was shared with the homecare admission staff (n=86 patients). During this phase, patients identified as high priority received their first homecare nursing visit about a half-day sooner as compared with the control phase (1.8 days vs 2.2 days;  $P=.09$ ). Rehospitalizations from homecare decreased by almost 50% (9.4% point reduction) when comparing the control (21.1%) and experimental phases (11.7%), with a significant difference between the rehospitalization (survival analysis) curves (log-rank  $P=.03$ ). We acknowledge that this pilot study had a relatively small sample size and potentially insufficient adjustment for background variables. However, these results were promising in that high-priority patients received their first homecare visit sooner and overall rehospitalization rates were lower.

This manuscript presents our methodology for examining PREVENT's impact on patient outcomes via a larger and more rigorous effectiveness trial. Our specific study aims are as follows:



1. Evaluate the effectiveness of the PREVENT tool on process and patient outcomes. We will test the following hypotheses using survival analysis and logistic regression with propensity score matching: compared with not using the tool in the preintervention phase, when homecare clinicians use the PREVENT tool, high-risk patients in the intervention phase will receive more timely first homecare visits and have decreased incidence of rehospitalization and have decreased emergency department use within 60 days of hospital discharge.
2. Explore PREVENT's reach and adoption by the homecare admission staff and describe the tool's implementation during homecare admission. Aim 2 will be assessed using mixed methods incorporating homecare admission staff interviews, think-aloud simulations [24], and analysis of staffing and other relevant data.

## Methods

### Mixed Method Approach

We are using an embedded mixed methods design. We will conduct a pre- and postintervention trial of PREVENT's integration into clinical practice using homecare admissions from two New York City urban hospitals serving diverse racial and ethnic populations. We will use quantitative methods, including logistic regression and survival analysis, to evaluate the effects of the tool on process and patient outcomes. We will utilize qualitative methods integrated with quantitative methods to gain an in-depth insight into technology adoption and implementation.

### Setting

On the basis of our consultations with New York-Presbyterian (NYP) hospitals' leadership and our goal of exploring the

effectiveness of the PREVENT system in different settings and among sites serving an ethnically diverse population, we will conduct the study at 2 NYP hospitals: (1) NYP Hospital/Columbia University Irving Medical Center (large academic medical center), a 745-bed adult academic medical center providing emergency, primary, and specialty care in all the major fields of medicine, and (2) NYP Allen Hospital (small community hospital), a 196-bed community hospital serving northern Manhattan, Riverdale, and other communities in the Bronx. As a homecare site, we will use VNSNY—the largest not-for-profit home health agency in the United States serving up to 48,500 patients and health plan members daily.

### Conceptual Model

The study is guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework. The RE-AIM was adopted [25] to specifically focus on real-world implementation of clinical informatics interventions, such as CDSS. Since its adoption, RE-AIM has been successfully applied in numerous studies of health information technology evaluations [26]. The components of this framework are as follows: *reach* of the intervention to a representative proportion of the target population, *effectiveness* of the intervention, *adoption* of the intervention across a broad and representative proportion of settings, *implementation* details, and *maintenance* of the intervention after implementation. In each phase of implementation, we will use the mixed methods approach for data collection and analysis to identify barriers and facilitators of the PREVENT implementation. Table 1 summarizes the RE-AIM dimensions with the associated definitions of each component, questions that need to be addressed in each component, and the associated analytic methods to answer those questions.

**Table 1.** Reach, Effectiveness, Adoption, Implementation, and Maintenance framework dimensions in this study.

RE-AIM <sup>a</sup> dimension and definition	Questions relevant to this study and aims addressed	Analytic methods	Data sources
Reach (individual level): Absolute number, proportion, and representativeness of individuals who participate in the intervention.	1. Were patients for whom PREVENT <sup>b</sup> was calculated representative of all the eligible patients? ( <i>Aim 2</i> )	<i>Quantitative analysis:</i> Comparison of patient demographic and clinical characteristics within the study (preintervention vs intervention groups), and between the study period and annual data (method: <i>t</i> tests or chi-square tests, when applicable).	VNSNY <sup>c</sup> data repository (including OASIS <sup>d</sup> ) [27]
Individuals who participate in the intervention.	2. What proportion of admission staff eligible to use the PREVENT actually used it? ( <i>Aim 2</i> )	<i>Quantitative analysis:</i> Estimation of how many admission staff used PREVENT out of total eligible admission staff members.	Data from VNSNY admission units
Efficacy or effectiveness (individual level): Impact of an intervention on important outcomes, including potential negative effects.	3. What is the effect of PREVENT on process outcomes? ( <i>Aim 1</i> )	<i>Quantitative analysis:</i> Estimation of PREVENT's effect on timing of the first homecare visit (method: survival analysis).	VNSNY data repository (including OASIS)
Efficacy or effectiveness (individual level)	4. What is the effect of PREVENT on patient outcomes? ( <i>Aim 1</i> )	<i>Quantitative analysis:</i> Estimation of PREVENT's effect on incidence and time to rehospitalization and ED <sup>e</sup> use within 30 and 60 days (method: logistic regression and survival analysis).	VNSNY data repository (including OASIS) +RHIO <sup>f</sup> (health service use data in New York)
Adoption (setting and/or organizational level): Absolute number, proportion, and representativeness of settings and intervention agents (people who deliver the program) who are willing to initiate a program.	5. What are the characteristics of the settings that decided to adopt PREVENT? ( <i>Aim 2</i> )	Quantitative analysis: Description of the VNSNY and two referring hospitals in terms of location, staffing, and patient population (method: descriptive summary).	VNSNY staffing data and hospitals staffing data; VNSNY data repository
Adoption (setting and/or organizational level)	6. How well did the goals of PREVENT fit with the values and expectations of the practice settings? ( <i>Aim 2</i> )	Qualitative analysis: Identification of the strategic plans and potential other incentives (such as CMS <sup>g</sup> readmission reduction program) related to PREVENT (method: descriptive summary).	VNSNY and NYP <sup>h</sup> strategic plans; information about potential other incentives
Implementation (setting and/or organizational level): Setting level—intervention agents' fidelity to the various elements of an intervention's protocol, including consistency of delivery as intended and the time and cost of the intervention; individual level—clients' use of the intervention strategies.	7. How many admission staff members used PREVENT? ( <i>Aim 2</i> )	Quantitative analysis: Description of the number of admission staff members who used PREVENT (method: descriptive statistics).	VNSNY data repository
Implementation (setting and/or organizational level)	8. What was the user satisfaction with PREVENT? ( <i>Aim 2</i> )	Quantitative analysis (method: summary statistics).	Administration of the 12 item End-User Computing Satisfaction Instrument
Implementation (setting and/or organizational level)	9. Did users perceive PREVENT as easy to use? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Postintervention interviews
Implementation (setting and/or organizational level)	10. Did users perceive PREVENT as useful? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Postintervention interviews
Implementation (setting and/or organizational level)	11. Was there sufficient leadership support? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Administration of open-ended questions during think-aloud simulations and postintervention interviews

RE-AIM <sup>a</sup> dimension and definition	Questions relevant to this study and aims addressed	Analytic methods	Data sources
Implementation (setting and/or organizational level)	12. What workflow adjustments needed to be made to streamline PREVENT into routines of daily clinical practice? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Research team experience; administration of open-ended questions during think-aloud simulations and postintervention interviews
Implementation (setting and/or organizational level)	13. What support, resources, and outside collaborations were needed to implement PREVENT? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Research team experience; agency description of PREVENT electronic integration process
Implementation (setting and/or organizational level)	14. What technical infrastructure was required to implement the CDSS <sup>i</sup> ? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Research team experience; agency description of PREVENT electronic integration process
Implementation (setting and/or organizational level)	15. What user training and support services were needed by PREVENT users? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Research team experience; data from think-aloud simulations and postintervention interviews
Implementation (setting and/or organizational level)	16. What were the potential barriers to successful PREVENT implementation and how were they addressed? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Research team experience; administration of open-ended questions during think-aloud simulations and postintervention interviews
Implementation (setting and/or organizational level)	17. Did homecare admission staff agree with PREVENT recommendations? ( <i>Aim 2</i> )	Quantitative analysis: Comparison of PREVENT recommendations with actual homecare admission staff decisions to provide priority visits and comparison of patient characteristics between cases that disagree versus agree with PREVENT recommendations (method: <i>t</i> tests or chi-square tests, when applicable).	Service use and patient data from VNSNY data repository
Implementation (setting and/or organizational level)	18. Did homecare admission staff agree with PREVENT recommendations? ( <i>Aim 2</i> )	Qualitative analysis (method: thematic analysis).	Administration of open-ended questions during think-aloud simulations and postintervention interviews and follow-up calls to assess disagreements
Maintenance: Setting level—extent to which intervention becomes institutionalized or part of the routine organizational practices; individual level—long-term effects of a program on outcomes for 6 or more months after the most recent intervention contact.	Beyond the scope of this study	Beyond the scope of this study	Beyond the scope of this study

<sup>a</sup>RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

<sup>b</sup>PREVENT: Priority for the First Nursing Visit Tool.

<sup>c</sup>VNSNY: Visiting Nurse Service of New York.

<sup>d</sup>OASIS: Outcome and Assessment Information Set.

<sup>e</sup>ED: emergency department.

<sup>f</sup>RHIO: Regional Health Information Organization.

<sup>g</sup>CMS: Centers for Medicare & Medicaid Services

<sup>h</sup>NYP: New York-Presbyterian.

<sup>i</sup>CDSS: clinical decision support system.

## Study Intervention: PREVENT

The PREVENT tool will be integrated with the hospitals' electronic health record (EHR) via a locally developed system called iNYP, which integrates with the EHR and provides advanced data review capabilities of all EHR data. iNYP is a Java-based service-oriented web app that builds on Columbia University's 25-year history of clinical information system

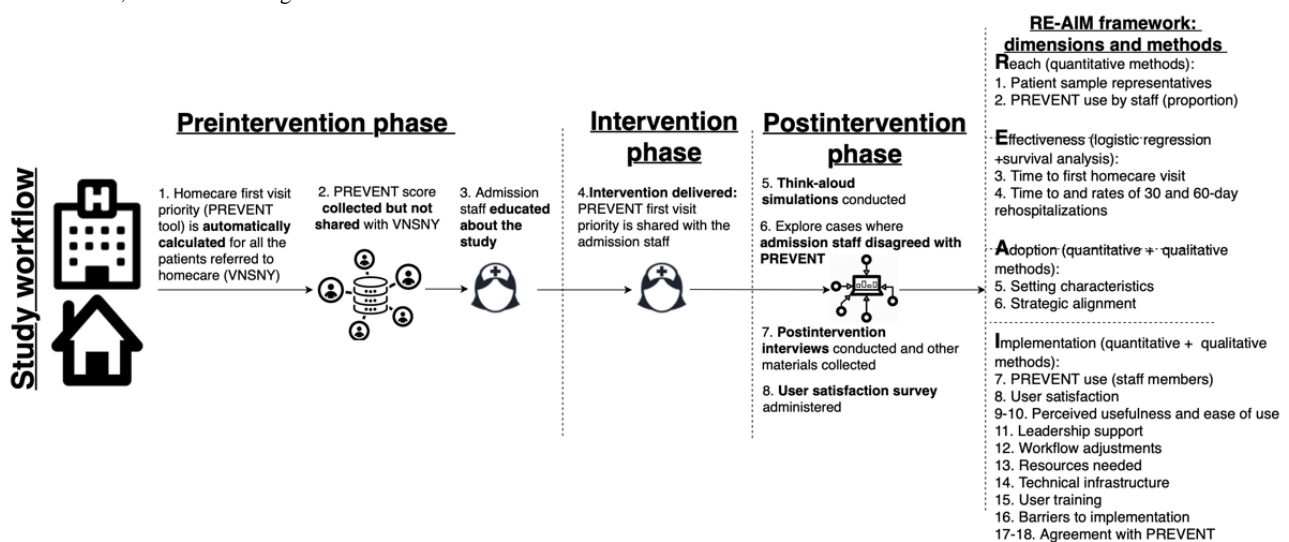
innovation [28,29]. iNYP is available as a custom tab within the commercial hospital EHR (supplementing the native results review capabilities) and is also accessible from a web browser or a mobile device. iNYP is widely used by most clinicians alongside the EHR, including the homecare admission staff. The PREVENT score will be calculated automatically from EHR data that populate the patient discharge summary or other parts of the EHR. We have cross-mapped the elements (eg,

number of medications and comorbid conditions) needed for the calculation of the PREVENT score to confirm that the required elements are readily available in the EHR system. VNSNY admission staff will receive an auto-populated field within the homecare referral containing the PREVENT recommendation about visit priority, presented as high priority and medium or low priority. Before any data collection, we will test the accuracy of the PREVENT score on the first 50 priority calculations and correct the EHR integration if any mistakes are found.

### Standard VNSNY Patient Admission Workflow

During our preliminary work, we determined that the scheduling and assignment unit assumes responsibility for patient admission to the VNSNY. The unit comprises several admission staff members who are involved in the admission processes, including intake coordinators, clinical associate managers, and schedulers.

**Figure 1.** Study workflow and design. PREVENT: Priority for the First Nursing Visit Tool; RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance; VNSNY: Visiting Nurse Service of New York.



### Preintervention Phase

During this phase of the study, 3 research activities will be implemented. First, the PREVENT priority score will be automatically calculated for all the patients referred to VNSNY from the 2 hospitals (step 1). Second, the PREVENT score (and priority recommendation based on the score) will be collected but not shared with homecare admission staff over about 3 months (see the *Sample Size Calculation* section; step 2). Third, after the preintervention phase data are collected, the study team will conduct several 30-min educational sessions for the admission staff about the development and validation of PREVENT and this study (step 3). We will work with the VNSNY scheduling and assignment unit management to identify all the VNSNY staff eligible (15-20 staff) to be exposed to PREVENT's recommendations during the study. We will ensure that each eligible admission staff member undergoes at least one educational session about the study workflow.

### Intervention Phase

To minimize periodical and time effects, the intervention phase will start at both hospitals on the same date. The PREVENT recommendation will be shared with the homecare intake

Homecare admission starts with standard homecare referral signed by the referring physician.

The referrals are passed to the intake coordinators (administrative staff) who enter the referral information into the VNSNY EHR system. Next, clinical field managers give patients a welcome call and coordinate the general start of care dates. After that, schedulers identify the date of a first homecare nursing visit. Each geographic location (based on city boroughs and street addresses) is served by several admission staff members.

### Study Workflow

The workflow of PREVENT implementation consists of 3 phases: preintervention phase, intervention phase, and postintervention phase. Figure 1 provides an overview of these phases.

coordinators for about 3 months (step 4). The intake coordinator will enter the PREVENT recommendation into the *special recommendations* field of the VNSNY EHR system. This field stores information about any special programs or services patients should receive in homecare, such as recommendations for frontloading of visits. Next, clinical field managers and schedulers will incorporate the PREVENT priority recommendations in their processes related to visit scheduling and patient prioritization. The field clinician will then conduct the first nursing visit. For cases where patient prioritization was not possible, we will ask the admission staff to document why a priority visit could not happen (such as the patient refused or short staffing; step 5).

### Postintervention Phase

After completion of data collection, we will continue to share the results of the PREVENT recommendation for approximately 4-6 weeks. During this period, four evaluation activities will be conducted. First, we will use the *Postintervention simulation guide* (see *Study Instruments* section) to conduct think-aloud simulations with admission staff who were exposed to the CDSS (step 6). Second, concurrently with the think-aloud simulations, we will continuously assess cases where admission staff did not



implement PREVENT recommendations (step 7). We will compare patient characteristics between cases that disagreed versus agreed with PREVENT recommendations. We want to identify additional factors that PREVENT might have missed when assessing a patient’s priority for a visit. Once saturation in responses is achieved and we have a solid number of cases for quantitative disagreement comparisons (about 100 cases of disagreement), we will discontinue sharing the PREVENT recommendation. Third, we will anonymously distribute the End-User Computing Satisfaction Instrument using a secure web-based survey platform (Qualtrics [30]; step 8). Fourth, we will conduct in-person interviews using the *Postintervention phase interview guide* with the same respondents who participated in the observations (step 9).

**Study Instruments**

Qualitative interviews and think-aloud simulations will be guided by two robust interview guides we will develop for this study. The guides will incorporate aspects of the RE-AIM framework dimensions as questions. The guides are as follows: (1) postintervention simulation guide (think-aloud protocol) and (2) postintervention phase interview guide. Each interview guide will include semi-structured open-ended questions to be answered by the admission staff. The *Postintervention phase interview guide* will include questions about PREVENT’s perceived usability and ease of use, leadership support, workflow adjustments, adequacy of training sessions, and barriers to implementation such as any changes the respondent made to his or her regular workflow to use PREVENT’s recommendations.

The End-User Computing Satisfaction Instrument [31-33] will be used to quantitatively measure satisfaction. The 12 item instrument measures concepts such as accuracy and ease of use and has been used to evaluate many types of applications, including decision support. A score of 54 corresponds to the 70th percentile. Any concept scoring less than the 70th

percentile from either user group will guide future tool revision. See [Multimedia Appendix 2 \[31-33\]](#) for more information on the study instruments.

**Methods for Study Aim 1: Evaluate the Effects of PREVENT on Process and Patient Outcomes**

**Sample Size Calculation**

In this study, we will calculate the PREVENT scores for all patients referred to VNSNY from the 2 hospitals (see study setting) in a 3 month period during the preintervention phase (scores not shared) and a 3 month intervention phase (scores shared) for an estimated total of 2094 patients and 1508 high-priority patients, respectively. This calculation is based on the pilot study rehospitalization decrease. [Multimedia Appendix 3](#) presents the minimum detectable difference between high-priority intervention group patients and preintervention high-priority patients.

**Data Sources**

Patient characteristics will be extracted from the Outcome and Assessment Information Set (OASIS), a standardized assessment tool designed to collect nearly 100 items related to a recipient’s functional status, clinical status, and service needs during a homecare episode. Mandated by CMS since 1999, OASIS is the most comprehensive national data set for homecare patient assessment and outcomes. Data were collected upon admission, every 60 days, if transferred to an inpatient facility, and at discharge. OASIS data will be extracted from the VNSNY EHR and supplemented with additional data such as language spoken and residence county. [Table 2](#) shows the details of the variables and the sources of the data.

The first visit timing will be extracted from the VNSNY administrative database. In this study, we will examine the impact of PREVENT’s recommendation on the time from the patient’s hospital discharge to the first homecare nursing visit.

**Table 2.** Conceptual domains, measures, and data sources.

Domain	Measures	Data sources
Socio-economic factors	Age, sex, race and ethnicity, language, caregiver support, living arrangements, language spoken, and residence county	OASIS <sup>a</sup> /VNSNY <sup>b</sup> EHR <sup>c</sup>
Clinical factors	Primary and background diagnoses, limitations in functioning, cognitive status, depressive symptoms, behavioral problems, wounds, pain, sensory status, elimination status, and medications	OASIS/VNSNY EHR
Health outcomes	Time from hospital discharge to first homecare visit, rehospitalizations, and ED <sup>d</sup> visits	Regional Health Information organization/ VNSNY EHR

<sup>a</sup>OASIS: Outcome and Assessment Information Set.

<sup>b</sup>VNSNY: Visiting Nurse Service of New York.

<sup>c</sup>EHR: electronic health record.

<sup>d</sup>ED: emergency department.

**Rehospitalization Data**

Most often when patients are rehospitalized, they return to the same facility as the initial hospitalization. In this study, it would be the NYP system. We will have access to these data. See [Multimedia Appendix 4](#) for more information about rehospitalization data.

**Quantitative Analysis Methods**

We will use survival analysis methods and logistic regression to estimate the effect of the CDSS on process and patient outcomes. As this is an observational study, we will also conduct propensity score matching (1:1 matching) of high-risk patients between the preintervention and intervention phases using the greedy nearest neighbor algorithm [34,35]. See [Multimedia](#)

[Appendix 5](#) [34,35] for more information about the quantitative methods used in this study.

### **Methods for Study Aim 2: Explore PREVENT's Reach and Adoption by the Homecare Admission Staff and Describe the Tool's Implementation During Homecare Admission**

To explore PREVENT's reach and adoption of the proposed study, we will match qualitative and quantitative analyses of the collected data to gain an in-depth understanding of the topic. [Table 1](#) provides a description of the RE-AIM aspects, specific questions, analytical methods, and data sources for these analyses.

#### **Think-Aloud Method**

Think-aloud methodology is a standard approach to elicit data about cognitive reasoning that occurs during a problem-solving task [24,36]. The think-aloud method will help answer questions about operational support (ie, 11-12, 15-16, and 18), as specified in [Table 1](#). This methodology will be implemented to observe patient admission in a simulated environment with 20 comprehensive and diverse case scenarios of patient admissions (10 high-priority cases and 10 low or medium-priority cases). See [Multimedia Appendix 6](#) [24,36] for more information about the think-aloud methodology.

#### **Qualitative Analysis Method**

Thematic analysis is a qualitative descriptive approach for identifying, analyzing, and reporting themes within data [37,38]. Researchers will use this approach to analyze data collected during the postintervention interviews and think-aloud simulations. The study research assistant will transcribe each interview into a text file. A different member of the study team will validate portions of transcriptions (20-30%) for quality. We will use qualitative analysis software (NVivo [39]) to implement the analysis. See [Multimedia Appendix 7](#) [37-40] for more information.

#### **Mixed Methods Analysis**

This mixed methods analysis will match qualitative (for exploring the PREVENT's reach and adoption) and quantitative (to evaluate the effects of PREVENT on process and patient outcomes) findings to provide context so as to gain an in-depth understanding of our experimental results. The qualitative findings will supplement the quantitative findings. For example, to understand aspects of CDSS implementation related to PREVENT's use and user satisfaction, we will match findings from qualitative questions #9 and 10 ([Table 1](#)) with findings from quantitative questions #7 and 8. Similarly, to understand aspects of CDSS adoption related to setting characteristics and strategic alignment of PREVENT with the setting's goals, we will match the findings from questions #5 and 6.

## **Results**

The study research protocol was approved by the institutional review board in October 2019. Currently, the study team is working on integrating the PREVENT CDSS into hospital and homecare EHRs. The study team is also analyzing information on patients who are currently being admitted to the VNSNY to

create a framework for statistical analysis of this study's findings. These activities are necessary to conduct study aims 1 and 2. Data collection is planned to start in early 2021.

## **Discussion**

### **Principal Findings**

In this study, we introduced a rigorous methodology for evaluating the implementation of an innovative CDSS, PREVENT, which was developed to assist in determining which patients should be prioritized for the first homecare nursing visit [18] (more details on the PREVENT tool are presented in [Multimedia Appendix 1](#)). This methodology was built on the RE-AIM framework and mixed methods approaches, incorporating homecare admission staff interviews, think-aloud simulations [24], and analysis of staffing and other relevant data. By following the methodology's steps, we will be able to explore the reach and adoption of PREVENT by the homecare admission staff; describe the implementation phase; identify the potential barriers for implementation; and improve the perceived value (usefulness) and familiarity (ease of use) of PREVENT from the schedulers', clinicians', and administrative staffs' perspectives. In addition, by exploring the technical infrastructure and the process of clinician decision making, we will be able to adjust the workflow and smoothly integrate PREVENT with the EHR system for automated computation of the first homecare nursing visit priority for individual patients.

Overall, our approach for the evaluation of PREVENT as a CDSS implementation consists of 3 major phases: preintervention, intervention, and postintervention phases. It is crucial to measure the efficacy of the CDSS in improving health care outcomes using controlled experimental methods. In the preintervention phase, we will identify the eligible staff for exposure to the CDSS and conduct training to educate them about using the CDSS. The research team will also explore and evaluate the existing infrastructure and workflow of decision making and prepare a rigorous plan for the integration of the CDSS with the clinical workflow.

In the intervention phase, the trained admission staff will be exposed to the CDSS intervention. Monitoring and tracking the staff's use of the CDSS recommendations and the extent to which the recommendations are overridden is essential to develop appropriate mechanisms to measure CDSS usability and adjust the infrastructure and workflow to meet the needs of administrative staff.

For the postintervention phase, the core step is to evaluate the implementation of the CDSS using appropriate instruments and tools to generate a clear picture of the barriers and facilitators for CDSS uptake and effectiveness. Tools such as qualitative interviews, think-aloud simulations, and End-User Computing Satisfaction Instrument will help the research team measure staff satisfaction and agreement with the CDSS and perceived CDSS usability and ease of use. Other important factors to be evaluated in this phase are access to resources and adjustment of workflow and technical infrastructure.

## Strengths, Limitations, and Alternatives to the Methodology

We considered several options for the study design. We could have used a stepped wedge cluster randomized trial [41]. One prerequisite for such a design is the ability to randomize the intervention among clearly defined clusters of hospital units or homecare agencies. In this study, homecare admission staff consists of 3 types of professionals (intake coordinators, clinical associate managers, and schedulers), some of whom work together on a constant basis in the same office. Thus, isolating selected admission staff is challenging, with a high risk of contamination.

Another option was to conduct a randomized controlled trial of PREVENT. This study design would require randomization at the patient level such that PREVENT recommendations would be shared for half of the randomly selected patients but not the others. Similar to the stepped wedge cluster design challenge, clear randomization would be unlikely due to contamination. The proposed quasi-experimental pre-post design (with propensity score matching) is similar to our pilot efficacy study [9] and addresses the contamination challenge of the abovementioned approaches. By matching patients in the preintervention and intervention phases based on their propensity score, we will account for potential differences in these 2 patient groups, which we were not always able to do in the pilot study. This design, guided by the RE-AIM framework, is preferable for an effectiveness study of real-world CDSS implementation.

Additional study limitations include the relatively limited generalizability of study findings, as the study involves 2 hospitals in a large academic hospital system in New York City. In addition, our ability to draw causal inferences is somewhat limited in quasi-experimental pre-post study designs.

## Innovation and Impact

Our study is innovative in the seamless use of CDSS and patient-centeredness:

- Our work is focused on building and evaluating one of the first evidence-based CDSS for homecare in the United States. The majority of hospitals and many homecare agencies across the nation use some type of EHR [42]. Tools such as PREVENT are becoming increasingly important in the effort to standardize care among agencies and avoid negative patient outcomes.
- For decades, the homecare industry has promoted providing the first nursing visit close to hospital discharge as an effective strategy to prevent hospitalizations. PREVENT will provide the first CDSS in homecare to assist agencies with implementing this important intervention.
- PREVENT will help highlight unique patient characteristics to support person-centered care. Our work is intended to change the paradigm in homecare by implementing 3 out of 4 key characteristics of the homecare agency of the future recently identified by the Institute of Medicine report *The Future of Home Health Care* [43]. The 3 characteristics are the agency being *patient and person centered*, *seamlessly connected*, and *technology enabled*.

Study results may have the potential to (1) standardize and individualize nurse decision making by using cutting-edge technology and (2) improve patient outcomes in the understudied homecare setting.

## Conclusions and Recommendations

This manuscript presents a protocol of a CDSS PREVENT study aimed at improving the outcomes of patients admitted to homecare services. We strongly encourage other researchers who study the effects of CDSS in clinical practice to apply similar mixed qualitative and quantitative methodologies in their studies. The application of mixed methods can enable researchers to gain an in-depth understanding of the complex socio-technological aspects of CDSS use in clinical practice. In turn, such comprehensive understanding can improve long-term effective use of CDSS in clinical settings.

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## Acknowledgments

Research reported in this publication was supported by the National Institute of Nursing Research of the National Institutes of Health under Award Number R01NR018831. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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## Conflicts of Interest

KB and MT are co-inventors of a decision support tool called “Priority for the First Nursing Visit Tool” (PREVENT), which under governing University policy is Clinical Trial intellectual property being studied in this research (“I Interest”). The intellectual property is assigned to the University of Pennsylvania.

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### Multimedia Appendix 1

Development of the Priority for the First Nursing Visit Tool.  
[DOCX File, 16 KB - [resprot\\_v10i1e20184\\_app1.docx](#) ]

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### Multimedia Appendix 2

Study instruments.  
[DOCX File, 15 KB - [resprot\\_v10i1e20184\\_app2.docx](#) ]

## Multimedia Appendix 3

Minimum detectable difference between high priority intervention group patients versus pre-intervention high priority patients.  
[DOCX File , 15 KB - [resprot\\_v10i1e20184\\_app3.docx](#) ]

## Multimedia Appendix 4

Rehospitalization data.

[DOCX File , 18 KB - [resprot\\_v10i1e20184\\_app4.docx](#) ]

## Multimedia Appendix 5

Quantitative analysis methods.

[DOCX File , 14 KB - [resprot\\_v10i1e20184\\_app5.docx](#) ]

## Multimedia Appendix 6

Think-aloud methodology.

[DOCX File , 14 KB - [resprot\\_v10i1e20184\\_app6.docx](#) ]

## Multimedia Appendix 7

Qualitative analysis methods.

[DOCX File , 15 KB - [resprot\\_v10i1e20184\\_app7.docx](#) ]

## Multimedia Appendix 8

Peer-Review Reports from National Institute of Health.

[PDF File (Adobe PDF File), 250 KB - [resprot\\_v10i1e20184\\_app8.pdf](#) ]

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## Abbreviations

**CDSS:** clinical decision support system

**EHR:** electronic health record

**MAPLe:** Method for Assigning Priority Levels

**NYP:** New York-Presbyterian

**OASIS:** Outcome and Assessment Information Set

**PREVENT:** Priority for the First Nursing Visit Tool

**RE-AIM:** Reach, Effectiveness, Adoption, Implementation, and Maintenance

**RN:** registered nurses

**VNSNY:** Visiting Nurse Service of New York

*Edited by G Eysenbach; submitted 12.05.20; peer-reviewed by R Pryss, S Sabarguna; comments to author 20.06.20; revised version received 25.07.20; accepted 08.08.20; published 22.01.21.*

*Please cite as:*

*Zolnoori M, McDonald MV, Barrón Y, Cato K, Sockolow P, Sridharan S, Onorato N, Bowles K, Topaz M*

*Improving Patient Prioritization During Hospital-Homecare Transition: Protocol for a Mixed Methods Study of a Clinical Decision Support Tool Implementation*

*JMIR Res Protoc* 2021;10(1):e20184

URL: <https://www.researchprotocols.org/2021/1/e20184>

doi: [10.2196/20184](https://doi.org/10.2196/20184)

PMID: [33480855](https://pubmed.ncbi.nlm.nih.gov/33480855/)

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Protocol

# Long-Term Morbidity and Health After Early Menopause Due to Oophorectomy in Women at Increased Risk of Ovarian Cancer: Protocol for a Nationwide Cross-Sectional Study With Prospective Follow-Up (HARMOny Study)

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## Abstract

**Background:** BRCA1/2 mutation carriers are recommended to undergo risk-reducing salpingo-oophorectomy (RRSO) at 35 to 45 years of age. RRSO substantially decreases ovarian cancer risk, but at the cost of immediate menopause. Knowledge about the potential adverse effects of premenopausal RRSO, such as increased risk of cardiovascular disease, osteoporosis, cognitive dysfunction, and reduced health-related quality of life (HRQoL), is limited.

**Objective:** The aim of this study is to assess the long-term health effects of premenopausal RRSO on cardiovascular disease, bone health, cognitive functioning, urological complaints, sexual functioning, and HRQoL in women with high familial risk of breast or ovarian cancer.

**Methods:** We will conduct a multicenter cross-sectional study with prospective follow-up, nested in a nationwide cohort of women at high familial risk of breast or ovarian cancer. A total of 500 women who have undergone RRSO before 45 years of age, with a follow-up period of at least 10 years, will be compared with 250 women (frequency matched on current age) who have not undergone RRSO or who have undergone RRSO at over 55 years of age. Participants will complete an online questionnaire on lifestyle, medical history, cardiovascular risk factors, osteoporosis, cognitive function, urological complaints, and HRQoL. A full cardiovascular assessment and assessment of bone mineral density will be performed. Blood samples will be obtained for marker analysis. Cognitive functioning will be assessed objectively with an online neuropsychological test battery.

**Results:** This study was approved by the institutional review board in July 2018. In February 2019, we included our first participant. As of November 2020, we had enrolled 364 participants in our study.

**Conclusions:** Knowledge from this study will contribute to counseling women with a high familial risk of breast/ovarian cancer about the long-term health effects of premenopausal RRSO. The results can also be used to offer health recommendations after RRSO.

**Trial Registration:** ClinicalTrials.gov NCT03835793; <https://clinicaltrials.gov/ct2/show/NCT03835793>.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/24414

(*JMIR Res Protoc* 2021;10(1):e24414) doi:[10.2196/24414](https://doi.org/10.2196/24414)

## KEYWORDS

risk-reducing salpingo-oophorectomy; BRCA1/2; cardiovascular disease; osteoporosis; cognition; health-related quality of life

## Introduction

### Background

Female *BRCA1* germline mutation carriers have a cumulative risk of 44% to develop ovarian cancer before the age of 80 years. For *BRCA2* mutation carriers, this cumulative risk is 17% [1]. In the absence of an effective screening method for ovarian cancer, risk-reducing salpingo-oophorectomy (RRSO) is advised at an age when there is a high risk of developing ovarian cancer (before the age of 35-40 years for *BRCA1* mutation carriers and at the age of 40-45 years for *BRCA2* mutation carriers) provided that the woman no longer has a wish to have children [2,3]. During this procedure, both ovaries and fallopian tubes are removed. Since 2009, the uptake of RRSO in *BRCA1/2* mutation carriers in the Netherlands has increased greatly from 81% to 98% currently [4-6]. While RRSO at the recommended age decreases the risk of ovarian cancer by around 96% [7,8], it also initiates premature surgical menopause owing to a sudden drop in the levels of ovarian hormones. Whether RRSO also reduces the risk of breast cancer is currently debated. Various early studies have reported a risk reduction of 50%, but this is a substantial overestimation owing to bias [8-11].

The relationship between early menopause (either surgically induced or due to premature ovarian insufficiency [POI]) and noncancer health outcomes, including cardiovascular disease

(CVD), osteoporosis, cognition, and health-related quality of life (HRQoL), has been examined previously. However, most of the published studies had a limited follow-up (median <5 years), which is too short to establish an association with long-term health effects [12-15]. Additionally, hormone replacement therapy (HRT) use, cancer treatment, and lifestyle may alter the potential association of RRSO with noncancer health outcomes. *BRCA1/2* mutation carriers may have been treated for breast cancer, which can be cardiotoxic and potentially have a negative impact on the brain [16-19]. Lastly, women with a high familial risk of breast/ovarian cancer may have a healthier lifestyle than age-matched women without a family history of breast cancer, rendering translation of results of previous research on early menopause to this specific population difficult [20].

### Early Menopause and Cardiovascular Risk

Before the age of 50 years, female sex hormones, such as estrogen and progesterone, are likely to protect women against CVD as they have atheroprotective properties [21,22]. Previous studies have shown that women with POI are at higher risk of developing CVD and that earlier age at menopause is associated with a higher cardiovascular mortality rate [23-26]. Additionally, a higher risk of CVD has been observed after surgical menopause compared with natural menopause [27]. However, age at surgical menopause was often not specified or surgery



was performed at later ages than the recommended young ages for RRSO in *BRCA1/2* mutation carriers. Thus, information about the cardiovascular risk of *early* surgical menopause is still limited [27-29]. Furthermore, it is possible that early loss of ovarian hormones is not the *cause* of the higher cardiovascular disease risk in women with POI. The reverse causality hypothesis postulates that POI is the result of accelerated vascular aging, which would also explain a statistical (noncausal) association between earlier natural menopause and increased CVD risk [30]. If this is true, no elevated CVD risk would be expected in women with early surgical menopause due to RRSO.

### Early Menopause and Bone Health

Reproductive hormones play a role in maintaining bone health. Estrogen suppresses bone resorption and stimulates bone formation [31]. Postmenopausal women aged 50 to 55 years have a higher incidence of hip fractures than age-matched premenopausal women, and among postmenopausal women, the incidence of hip fractures rises with age [32]. However, data on the long-term effect of early (surgical or natural) menopause on bone health are limited owing to short follow-up periods.

### Early Menopause and Cognition

The neuroprotective effects of estrogens, progestogens, and androgens have been described in several studies [33]. Rocca et al observed that women who underwent premenopausal oophorectomy (before 56 years of age) for benign reasons had a higher risk of cognitive impairment than age-matched women without oophorectomy [34]. There was a trend for more severe cognitive impairment with younger age at oophorectomy for both unilateral and bilateral oophorectomies. However,

information on *BRCA1/2* mutation carriership was not provided [34]. Additionally, Bove et al observed a faster decline in global cognition in women with an earlier age at surgical menopause [14]. Thus, while there are some data on the effect of surgical menopause on cognition, research on *BRCA1/2* mutation carriers is limited.

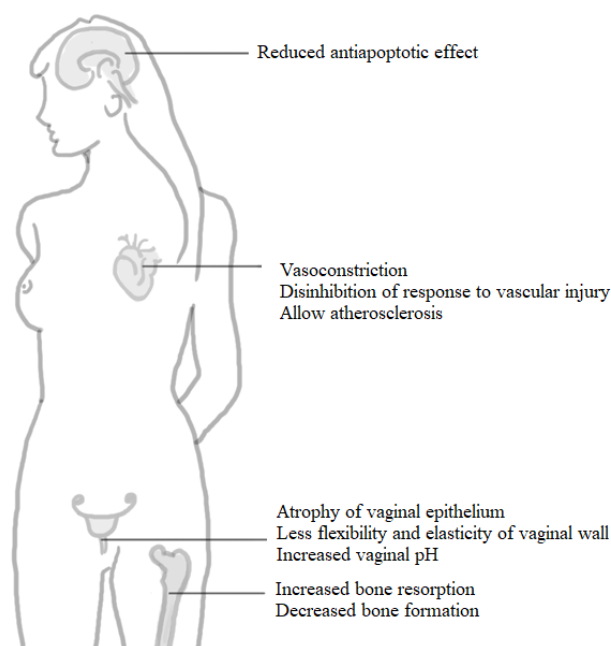
### Early Menopause and HRQoL

RRSO may have an important impact on HRQoL, including generic issues, such as physical, role, and emotional functioning, as well as cancer-related anxiety, sexual functioning, and menopause-specific symptoms [12,35,36]. However, it is not known whether these effects persist over time. A recent study with a mean follow-up of 7.9 years after RRSO found that moderate to severe menopausal complaints were still present in almost 70% of women who underwent premenopausal RRSO, without any improvement over time [37]. The magnitude of the effect of RRSO on sexual functioning and endocrine symptoms is modulated by HRT use [38,39]. However, HRT use is contraindicated for *BRCA1/2* mutation carriers with a history of breast cancer.

The number of postmenopausal years is associated with an increased prevalence of vulvovaginal atrophy [40]. Atrophy of the urethral epithelium may lead to urinary incontinence. To our knowledge, no research has been conducted on the association between early surgical menopause and urinary incontinence, although this generally has a severe impact on sexual functioning and quality of life [41,42].

Figure 1 provides a schematic overview of the effects of a decrease in estrogen levels due to menopause on various organ systems.

**Figure 1.** Overview of the effects of reduced estrogen levels on various organ systems.



A recent Cochrane systematic review on the benefits and harms of RRSO in women with a *BRCA1/2* mutation stated that no conclusions can be drawn regarding bone fracture incidence and HRQoL, and that further research is needed. CVD and

cognition were not included as outcomes in this review, probably because of the paucity of studies [43]. Therefore, the aim of the HARMOny study (Health After eaRly Menopause due to Oophorectomy) is to investigate the long-term health effects of

RRSO. We will conduct a cross-sectional study with prospective follow-up nested in a large Dutch cohort. We hypothesize that women with surgically induced premature menopause are at higher risk of subclinical CVD, compromised bone health and osteoporosis, reduced HRQoL, and impaired cognitive functioning, compared to age-matched women with natural menopause after the age of 50 years. Depending on the results, this may lead to active surveillance of the above health problems to improve long-term health and HRQoL in women who have undergone early RRSO.

## Methods

### Study Aim

The primary aim of our study is to assess the long-term health effects of RRSO on subclinical CVD, bone mineral density (BMD), and cognitive functioning in women at increased familial risk of breast or ovarian cancer mainly due to a *BRCA1/2* mutation. Our secondary study aims are to assess overall HRQoL, endocrine symptoms, such as hot flashes and night sweats, sexual functioning, urogenital problems, and the prevalence of cardiovascular risk factors.

### Recruitment

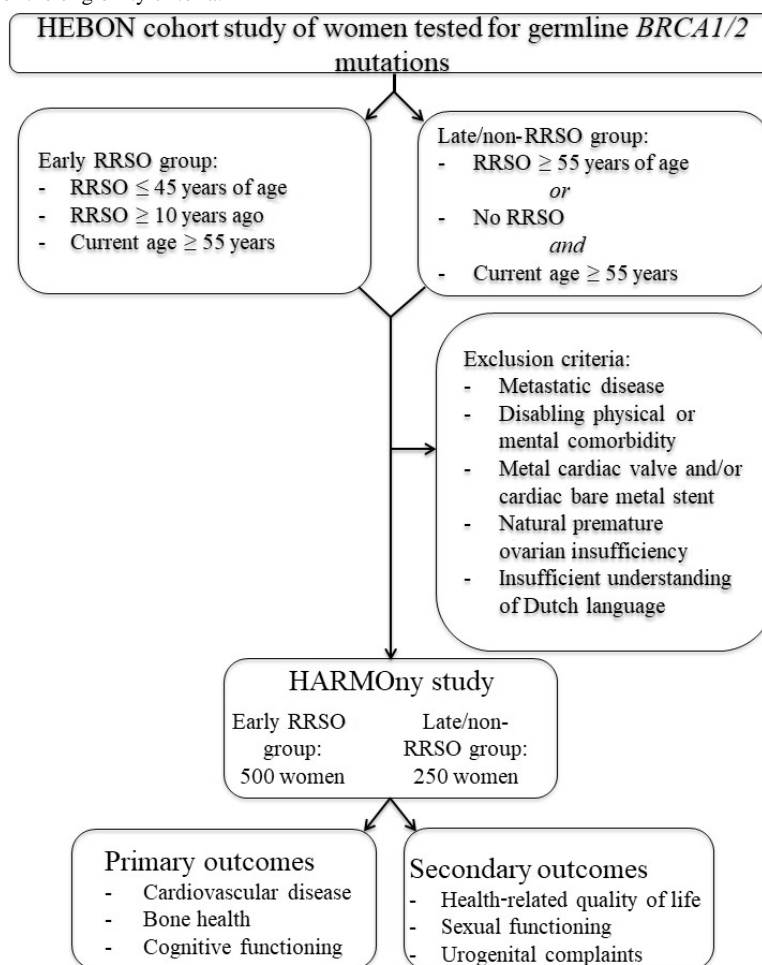
We will include 500 women who have undergone RRSO before the age of 45 years, with a follow-up period of at least 10 years (the early RRSO group). We will compare them with 250 women from the same cohort (frequency matched on current age) who have not undergone preventive RRSO or have undergone RRSO at the age of 55 years or above (the late/non-RRSO group). The exclusion criteria are a metastatic

disease; a serious physical comorbidity or psychiatric disorder; a language barrier; a metal cardiac valve; a bare metal coronary stent, since the reflection of the stent would interfere with the computed tomography scan; and natural POI before the age of 40 years. A history of nonovarian cancer, including breast cancer, is not a reason to be excluded.

Eligible women who are alive will be invited for a clinic visit and questionnaire survey that will assess CVD status, BMD, cognitive functioning, and HRQoL. For eligible women who have died, we will collect information on the causes of death to examine selection bias.

Participants will be selected from the dynamic nationwide HEBON study cohort, a national collaboration on HEreditary Breast and Ovarian cancer in the Netherlands, with women tested for *BRCA1/2* germline mutations included since 1997 by all eight Dutch University Medical Centers (UMCs) and the Netherlands Cancer Institute (NKI). The cohort currently consists of over 3600 proven female *BRCA1/2* germline mutation carriers. Participants have given informed consent for linkage with the Netherlands Cancer Registry and the Dutch Nationwide Pathology Database (PALGA), which can provide information on all prophylactic mastectomies and salpingo-oophorectomies performed in the Netherlands since 1991. This provides us with nearly complete information on the occurrence of RRSO. Data on lifestyle, family history, reproductive factors, and hormone use have been collected from HEBON participants through questionnaires [44].

Figure 2 provides a schematic overview of the patient selection and eligibility criteria of our study population.

**Figure 2.** Schematic overview of the eligibility criteria.

Participants will be asked to complete an online questionnaire and an online cognitive assessment, and they will be asked to visit the outpatient clinic for a cardiovascular and bone health assessment. We will assess several surrogate endpoints of cardiovascular health, that is, coronary artery calcium (CAC) score (CAC scoring), pulse wave velocity (PWV), advanced glycation end products (AGEs), anthropometric measurements, and blood sampling. We will determine nonfasting blood levels of lipids, glucose, HbA<sub>1c</sub>, high-sensitivity cardiac troponin, and high-sensitivity C-reactive protein. BMD is assessed by a dual-energy X-ray absorptiometry (DXA) scan and laboratory blood sampling, and cognitive functioning is assessed by the Amsterdam cognition scan (ACS).

The online questionnaire is divided into the following several topics: general cardiovascular history, family history of CVD, traditional CVD risk factors (ie, diabetes, hypertension, and cholesterol), lifestyle (ie, smoking, alcohol use, and physical activity), female-specific risk factors (hypertensive pregnancy complications, gestational diabetes, contraceptives use, and HRT use, ie, type, duration, and timing), history of fractures, calcium intake, vitamin D supplement use, glucocorticoid use, family history of osteoporosis/fractures, history of inflammatory diseases (rheumatoid disease and thyroid disorders), and perceived cognitive problems. We will assess generic HRQoL with the SF-36 health survey [45,46] and the body image items of the European Organization for Research and Treatment of

Cancer (EORTC) QLQ-BR23 [47,48]. Cancer worries will be measured with the eight items adapted from Lerman et al [49-51]. To assess menopausal symptoms, we will employ the 18-item Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES) and the Hot Flush Rating Scale (HFRS) [52,53]. To assess urogenital problems, the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) [54] will be used. The Sexual Activity Questionnaire (SAQ) [55] will be used to assess sexual functioning. For patients with a breast cancer history, either before or after RRSO, we will collect information on radiotherapy (yes/no and radiation fields), chemotherapy and immunotherapy regimens, and endocrine treatment from medical records.

Measurements of the CAC score as calculated by coronary calcium scoring will be performed according to standardized local protocols at the various UMCs using the Agatston score (AS) and the Multi-Ethnic Study of Atherosclerosis (MESA) coronary heart disease risk score calculator [56,57]. A disadvantage of CAC scoring might be the use of ionizing radiation. However, the radiation dose in the CAC protocol is as low as 1 mSv, which is not expected to be harmful [58]. All patients in our study are aged 55 years or above; thus, the radiation-induced risk of breast cancer from CAC scoring will be negligible with the current protocol [59,60].

The PWV will be assessed with an ambulatory arteriograph (TensioMed Kft) by the research physician. The arteriograph

uses an oscillometric occlusive method, with an upper arm cuff to measure the time interval between the peak of the first systolic wave and the peak of the reflected systolic wave (return time). The device has been validated in numerous studies [61-65].

With aging, the end products of nonenzymatic modification of proteins, lipids, and nucleic acids (AGEs) accumulate endogenously in the serum and tissues. Levels of AGEs in the skin are measured noninvasively by standardized autofluorescence and can predict future cardiovascular events [66,67]. Skin autofluorescence is a quick and noninvasive surrogate marker of tissue accumulation of AGEs [68-70]. AGEs will be measured using the AGE Reader (DiagnOptics Technologies BV; software V 2.3.0.7) on the forearm.

Bone health will be assessed by a DXA scan, a vertebral fracture assessment, and blood levels of bone turnover markers (BTMs) for osteoclast and osteoblast activity (beta-carboxy-terminal collagen crosslinks [ $\beta$ -CTX] and N-terminal procollagen type 1 [PINP]). For logistic reasons, it is not possible to get fasting blood samples for every woman. Since  $\beta$ -CTX values are only valid in fasting blood samples, we will assess this BTM only in those women for whom we have fasting blood samples. PINP will be measured in all samples.

Lastly, women will receive an invitation to fill out the online ACS, which has recently been developed and validated [71]. The ACS is an easy to use tool to obtain online measures of various cognitive abilities [72]. The online test battery is based on seven traditional neuropsychological tests and covers the

following domains: verbal memory, attention, executive functioning, information processing speed, and motor functioning.

Table 1 provides an overview of the tests that will be performed [58,61-63,66,67,69,71-77]. Table 2 provides an overview of the questionnaires used [45-50,52-55].

We will examine the effect of age at RRSO on the risk of breast cancer, contralateral breast cancer, and ovarian cancer, as well as associations between RRSO and the prognosis of subsequent breast cancer and ovarian cancer. Additionally, after completion of the cross-sectional study, we will perform longitudinal follow-up every 4 to 5 years to evaluate incidence rates of outcomes of major interest, such as ischemic heart disease, and evaluate changes in outcomes (CAC, PWV, BMD, and cognitive functioning as assessed by the ACS) over time between the early RRSO group and the late/non-RRSO group. Moreover, with the anticipated prospective follow-up of our study population, we will look at mortality of cardiovascular disease.

All data, including blood and DNA samples, will be stored for 30 years to enable prospective longitudinal follow-up of the study population on the long-term health effects of RRSO. The stored blood samples will allow for future international studies, for example, those on the modifying effects of genetic factors, such as single nucleotide polymorphisms, on the outcomes of interest, and the novel cardiovascular markers or BTMs for these outcomes. All blood samples will be frozen and stored at  $-80^{\circ}\text{C}$  at the NKI.



**Table 1.** Overview of the tests that will be performed.

Aim of the test	Data collection method and references	Outcome variables	Justification
Cardiovascular health	Coronary artery calcium (CAC) scoring [58,73]	Score according to Agatston	Measurements of the CAC score as calculated by coronary calcium scoring will be performed according to standardized local protocols at the various University Medical Centers using the Agatston score (AS) and the MESA <sup>a</sup> coronary heart disease risk score calculator.
Cardiovascular health	Pulse wave velocity (PWV) [61-63]	In meters/second	The PWV will be assessed with an ambulatory arteriograph (TensioMed Kft) by the research physician. The arteriograph uses an oscillometric occlusive method, with an upper arm cuff to measure the time interval between the peak of the first systolic wave and the peak of the reflected systolic wave (return time).
Cardiovascular health	Advanced glycation end products (AGEs) [66,67,69]	In arbitrary units (AU)	With aging, the end products of nonenzymatic modification of proteins, lipids, and nucleic acids (AGEs) accumulate endogenously in the serum and tissues. Levels of AGEs in the skin are measured noninvasively by standardized autofluorescence and can predict future cardiovascular events. AGEs will be measured using the AGE Reader (DiagnOptics Technologies BV; software V 2.3.0.7).
Cardiovascular health	Anthropometric measurements	<ul style="list-style-type: none"> <li>• Blood pressure in mmHg</li> <li>• Pulse frequency per minute</li> <li>• Waist (in cm)/hip (in cm) ratio</li> <li>• BMI in kg/m<sup>2</sup></li> </ul>	Predictors of future cardiovascular events.
Cardiovascular health	Laboratory blood sampling	Nonfasting blood levels for lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), glucose, HbA <sub>1c</sub> , high-sensitivity cardiac troponin, high - sensitivity C - reactive protein	Predictors of future cardiovascular events.
Bone health	Dual-energy X-ray absorptiometry (DXA) scan of the lumbar spine and hip	<ul style="list-style-type: none"> <li>• BMD<sup>b</sup> values in g/cm<sup>2</sup></li> <li>• T and Z scores</li> <li>• Presence of osteopenia (defined as T-scores of -1 to -2.5)</li> <li>• Presence of osteoporosis (defined as T-scores of <math>\geq</math>-2.5)</li> </ul>	The DXA scan is most widely used in clinical practice to screen for osteoporosis and is regarded as the “gold standard.”
Bone health	Vertebral fracture assessment (VFA)	<ul style="list-style-type: none"> <li>• Vertebral height reduction in percentage</li> <li>• Presence of clinical and nonclinical vertebral fractures</li> </ul>	There is a strong additive value of VFA compared with DXA alone [74-76].
Bone health	Laboratory blood sampling [77]	<ul style="list-style-type: none"> <li>• Bone formation by P1NP<sup>c</sup>, mean value in ng/mL</li> <li>• Bone resorption by <math>\beta</math>-CTX<sup>d</sup>, mean value in pg/mL</li> <li>• Level of 25-hydroxyvitamin D in the serum in nmol/L</li> </ul>	Bone turnover markers (BTMs) for osteoclast and osteoblast activity ( $\beta$ -CTX and P1NP). For logistic reasons, it is not possible to get fasting blood samples for every woman. Since $\beta$ -CTX values are only valid in fasting blood samples, we will assess this BTM only in those women for whom we have fasting blood samples. P1NP will be measured in all samples.
Cognitive functioning	Amsterdam cognition scanning (ACS) [71]	<ul style="list-style-type: none"> <li>• Verbal memory</li> <li>• Attention</li> <li>• Executive functioning</li> <li>• Information processing speed</li> <li>• Motor functioning</li> </ul>	The ACS is an easy-to-use tool to obtain online measures of various cognitive abilities [72]. The online test battery is based on seven traditional neuropsychological tests.

<sup>a</sup>MESA: Multi-Ethnic Study of Atherosclerosis.<sup>b</sup>BMD: bone mineral density.<sup>c</sup>P1NP: N-terminal procollagen type 1.<sup>d</sup> $\beta$ -CTX: beta-carboxy-terminal collagen crosslinks.

**Table 2.** Overview of the questionnaires.

Aim of the questionnaire	Topics
Cardiovascular health	General cardiovascular history Cardiovascular disease risk factors (ie, obesity, diabetes, hypertension, and dyslipidemia) Lifestyle (ie, smoking, alcohol use, and physical activity) Female-specific risk factors (ie, hypertensive pregnancy complications, gestational diabetes, contraceptive use, and hormone replacement therapy use) Nontraditional risk factors (history of inflammatory diseases, ie, rheumatoid disease)
Bone health	History of fractures Calcium intake Vitamin D supplements Glucocorticoid use Family history of osteoporosis/fractures History of inflammatory diseases (ie, rheumatoid disease and thyroid disorders)
Cognitive health	Perceived cognitive problems
Health-related quality of life [45-50,52-55]	SF-36 health survey Body image items of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-BR23 Cancer worries; eight items adapted from Lerman et al The 18-item Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES) measure of endocrine symptoms Hot Flush Rating Scale (HFRS) Urogenital Distress Inventory (UDI-6) Incontinence Impact Questionnaire (IIQ-7) Sexual Activity Questionnaire (SAQ)

## Statistical Analysis

We will analyze differences in the cardiovascular risk profile, BMD, and neurocognitive functioning between the early RRSO group and the late/non-RRSO group using multivariable linear regression analyses and logistic regression analyses with clinically relevant cutoff points for the outcomes of interest. The analyses will be adjusted for confounders, including lifestyle, reproductive factors, and medication use, where applicable. For the analysis of patient-reported outcomes, such as HRQoL, sexual functioning, and menopausal symptoms, we will use mixed effect models.

We expect approximately 40% of the women to have a breast cancer history and will perform the analyses separately in women with and those without a breast cancer history, as breast cancer treatment may affect outcomes. Additional subgroup analyses will be performed according to HRT use (yes/no), *BRCA1/2* mutation status, age at RRSO (<40 years/≥40 years), and time since RRSO (10-15 years/>15 years).

## Sample Size Calculation

We based our sample size calculations for cardiovascular status on subclinical atherosclerosis by assessing the differences in the CAC score between women in the early RRSO group and women in the late/non-RRSO group. We chose a clinically relevant cutoff for the CAC score of 100 Agatston units (AU). According to the MESA trial, 10% of subjects between 55 and 65 years of age exceed this value [78]. For sample size estimation, we hypothesized that 20% of the early RRSO group exceeds this value of 100 AU. In logistic regression with an elevated CAC score (>100) as the outcome and with 250 women

in the late/non-RRSO group and 500 women in the early RRSO group, we have 80% power to detect an odds ratio of 1.9 at an  $\alpha$  value of 5%.

With 750 women in our study, we will be able to detect a difference of 0.07 g/cm<sup>2</sup> in BMD between the early RRSO and late/non-RRSO groups, as observed between women with premature and normal menopause and assuming an SD of 0.15 [79]. Statistical power for analysis of cognitive functioning is based on a previous neuropsychological study on the effects of oophorectomy on cognitive impairment and dementia [34]. This study reports relevant differences in 427 women with bilateral oophorectomy before the age of 49 years, compared to age-matched women without oophorectomy, with a median follow-up of 25 years. As our neurocognitive tests are more sensitive than the tests screening for dementia, we expect to be able to detect smaller differences in cognitive functioning and distinguish between different cognitive domains, and with 750 participants, we have 90% power to detect an effect size of 0.25 with a *P* value set at .05 (two tailed). To detect a relevant difference between groups for the various HRQoL measures, we will use a half SD (an effect size of 0.5) to define clinically relevant group differences (over time). This requires about 67 patients per group. The available sample will be more than adequate to conduct subgroup analyses as well.

## Results

This study was funded by the Dutch Cancer Society in 2016. The Institutional Review Board of the Netherlands Cancer Institute approved this nationwide multicenter study in July

2018, and local approval from the participating sites followed in the months thereafter.

This study will be conducted according to the standards of Good Clinical Practice, in agreement with the principles of the Declaration of Helsinki and with the Dutch law as stated in the Medical Research Involving Human Subjects Act (WMO). The study has been approved in writing by the Medical Ethics Committee of the Antoni van Leeuwenhoek/Netherlands Cancer Institute (AVL/NKI) to be conducted in all nine University Medical Centers and the Antoni van Leeuwenhoek and has been registered at “CCMO Toetsingonline” from the Dutch Central Committee on Research involving Human Subjects (file number NL63554.031.17) and on ClinicalTrials.gov (NCT03835793). Written informed consent will be collected from the participants.

In February 2019, we included our first participant, and as of November 2020, we had enrolled 364 participants in our study. Of these 364 participants, 228 are in the early RRSO group and 136 are in the late/non-RRSO group. Recruitment of participants is currently ongoing. Results will be disseminated through peer-reviewed publications and will be incorporated in follow-up guidelines.

## Discussion

To our knowledge, this study is the first to assess the long-term noncancer health outcomes of early surgical menopause in women with a high familial risk of ovarian cancer, focusing on CVD, bone health, cognition, and HRQoL. The issue is important as RRSO at the age of 35–45 years is an increasingly common procedure in *BRCA1/2* mutation carriers, with an estimated uptake in the Netherlands of 81% to 99% [4,5]. We have designed a nationwide, multicenter, multidisciplinary, cross-sectional study with prospective follow-up, comparing 500 women who have undergone RRSO before 45 years of age (more than 10 years of follow-up) with 250 women who have undergone RRSO after 55 years of age or who have not undergone RRSO. The unique features of our study are near complete information on the occurrence of RRSO in the cohort and long-term follow-up of all cohort members, allowing the selection of the eligible population for this study at least 10 years after RRSO. Our study is nested in a cohort of women with a high familial risk of breast and ovarian cancer, which will allow us to evaluate potential differences in disease risks between our study population and the entire cohort in order to quantify any survivorship and selection bias and to adequately interpret the magnitude of our effect sizes.

At present, it is still unclear whether early surgical menopause can be considered as a clinically relevant risk factor for CVD. During normal menopausal transition, CVD risk increases [23,26,78,80]. Women with an early natural menopause (<40 years) are at higher risk of developing CVD, and they have a higher CVD mortality than age-matched peers [23–26]. However, it has been debated whether this association is causal, and it has been speculated that this might also be explained by early vascular aging predisposing to both POI and cardiovascular disease [30,81]. If this is true, an artificial early menopause might not be associated with increased CVD risk. In support of this, a recent study by Krul et al showed that cancer

treatment-induced POI did not affect CVD risk [82]. This renders it even more interesting to investigate CVD risk in women with surgically induced early menopause. To date, this has been addressed in only a few studies, with inconsistent results and with a median follow-up of at the most 5 years, which is too short considering potential delayed effects of estrogen deprivation and the long life expectancy of these women. Furthermore, previous studies vary with respect to HRT use and age at surgery [27–29].

The association between early surgical menopause and long-term bone health has also been rarely examined. Studies were inconclusive regarding decreased BMD and increased fracture risk, and whether these risks remain increased over time [83,84]. In addition, the effect of early RRSO on cognition has not yet been examined. However, both unilateral and bilateral oophorectomies at later ages have been associated with cognitive impairment and dementia, suggesting neuroprotective effects of estrogen on the brain. These effects appear to be age dependent [34,85].

After menopause, women more often report sexual and urogenital problems, such as urinary incontinence, recurrent urinary tract infections, impaired libido, and dyspareunia, which interfere with HRQoL. Women with POI experience these problems even more [86,87]. We do not know if these results can be generalized to surgical early menopause. Studies on long-term HRQoL after RRSO are limited and highly biased by HRT use.

One of the major strengths of our study is that it will be the first to examine the health effects of premenopausal RRSO at less than 45 years with a follow-up of over 10 years compared to controls with natural menopause. Additionally, owing to the large number of participants, we will have sufficient power for subgroup analyses. A limitation of our study could be survivor bias. Owing to the inclusion criterion of at least 10 years of follow-up, patients may already have died of relevant study outcomes before study inclusion. However, as we conduct the cross-sectional study within a well-characterized cohort, we can assess the extent of such bias by collecting cause of death information for potentially eligible but already deceased women.

This initial cross-sectional study will provide prevalence rates of noncancer outcomes. Therefore, we will follow the study cohort prospectively to obtain incidence rates of outcomes of interest and evaluate changes in outcomes over time.

To summarize, the current literature lacks information on long-term noncancer outcomes in women at increased risk of breast/ovarian cancer who have undergone early oophorectomy. With this study, we will be able to provide insights into the prevalence and severity of CVD, osteoporosis, cognitive impairment, and HRQoL effects after RRSO. This knowledge will yield evidence-based information for women and for health care providers about the long-term effects of early RRSO. The results can be incorporated in decision-support tools about risk-reducing surgeries in *BRCA1/2* mutation carriers considering RRSO and can be used to offer individualized counseling about additional screening and interventions for noncancer diseases or complaints after RRSO.

## Acknowledgments

The Dutch Cancer Society (Koningin Wilhelmina Fonds [KWF]) has granted us the funding for this project (registered under grant 10164). The funding body had no role in the design of the study; collection, analysis, and interpretation of data; or writing of the manuscript. We would like to thank Y Rietdijk for designing the study logo and [Figure 1](#).

## Authors' Contributions

FEvL, AHEMM, MJH, BAMHG, EMB, SBS, MAR, MH, and NKA were involved in the conception and design of the study. LT, FEvL, AHEMM, MJH, and BAMHG drafted the manuscript. MvB, JERvL, HCvD, JAdH, CM, EBLvD, MJEM, BFMS, KNG, MCZ, TL, LvDK, MC, MW, MGEMA, KvE, LPVB, CJvA, EBG, IvdB, MAR, MH, EMB, SBS, and NKA were involved in the final version of the manuscript. All authors have read and approved the manuscript.

## Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report by KWF.

[\[PDF File \(Adobe PDF File\), 110 KB - resprot\\_v10i1e24414\\_fig0.pdf\]](#)

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## Abbreviations

- ACS:** Amsterdam cognition scan
- AGEs:** advanced glycation end products
- AS:** Agatston score
- AU:** Agatston units
- BMD:** bone mineral density
- BRCA:** breast cancer gene
- BTM:** bone turnover marker
- CAC:** coronary artery calcification
- CVD:** cardiovascular disease
- DXA:** dual-energy X-ray absorptiometry
- HEBON:** HEreeditary Breast and Ovarian cancer in the Netherlands
- HRQoL:** health-related quality of life
- HRT:** hormone replacement therapy
- NKI:** Netherlands Cancer Institute
- POI:** premature ovarian insufficiency
- PWV:** pulse wave velocity
- RRSO:** risk-reducing salpingo-oophorectomy
- UMC:** University Medical Center



*Edited by G Eysenbach; submitted 18.09.20; peer-reviewed by K Schenck-Gustafsson, S Li; comments to author 02.11.20; revised version received 13.11.20; accepted 17.11.20; published 22.01.21.*

*Please cite as:*

*Terra L, Hooning MJ, Heemskerk-Gerritsen BAM, van Beurden M, Roeters van Lennep JE, van Doorn HC, de Hullu JA, Mom C, van Dorst EBL, Mourits MJE, Slangen BFM, Gaarenstroom KN, Zillikens MC, Leiner T, van der Kolk L, Collee M, Wevers M, Ausems MGEM, van Engelen K, Berger LPV, van Asperen CJ, Gomez-Garcia EB, van de Beek I, Rookus MA, Hauptmann M, Bleiker EM, Schagen SB, Aaronson NK, Maas AHEM, van Leeuwen FE*

*Long-Term Morbidity and Health After Early Menopause Due to Oophorectomy in Women at Increased Risk of Ovarian Cancer: Protocol for a Nationwide Cross-Sectional Study With Prospective Follow-Up (HARMOny Study)*

*JMIR Res Protoc 2021;10(1):e24414*

URL: <http://www.researchprotocols.org/2021/1/e24414/>

doi: [10.2196/24414](https://doi.org/10.2196/24414)

PMID: [33480862](https://pubmed.ncbi.nlm.nih.gov/33480862/)

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Protocol

# Using Big Data to Estimate Dementia Prevalence in New Zealand: Protocol for an Observational Study

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## Abstract

**Background:** Dementia describes a cluster of symptoms that includes memory loss; difficulties with thinking, problem solving, or language; and functional impairment. Dementia can be caused by a number of neurodegenerative diseases, such as Alzheimer disease and cerebrovascular disease. Currently in New Zealand, most of the systematically collected and detailed information on dementia is obtained through a suite of International Residential Assessment Instrument (interRAI) assessments, including the home care, contact assessment, and long-term care facility versions. These versions of interRAI are standardized comprehensive geriatric assessments. Patients are referred to have an interRAI assessment by the Needs Assessment and Service Coordination (NASC) services after a series of screening processes. Previous estimates of the prevalence and costs of dementia in New Zealand have been based on international studies with different populations and health and social care systems. This new local knowledge will have implications for estimating the demographic distribution and socioeconomic impact of dementia in New Zealand.

**Objective:** This study investigates the prevalence of dementia, risk factors for dementia, and drivers of the informal cost of dementia among people registered in the NASC database in New Zealand.

**Methods:** This study aims to analyze secondary data routinely collected by the NASC and interRAI (home care and contact assessment versions) databases between July 1, 2014, and July 1, 2019, in New Zealand. The databases will be linked to produce an integrated data set, which will be used to (1) investigate the sociodemographic and clinical risk factors associated with dementia and other neurological conditions, (2) estimate the prevalence of dementia using weighting methods for complex samples, and (3) identify the cost of informal care per client (in number of hours of care provided by unpaid carers) and the drivers of such costs. We will use design-based survey methods for the estimation of prevalence and generalized estimating equations for regression models and correlated and longitudinal data.

**Results:** The results will provide much needed statistics regarding dementia prevalence and risk factors and the cost of informal care for people living with dementia in New Zealand. Potential health inequities for different ethnic groups will be highlighted, which can then be used by decision makers to inform the development of policy and practice.

**Conclusions:** As of November 2020, there were no dementia prevalence studies or studies on informal care costs of dementia using national data from New Zealand. All existing studies have used data from other populations with substantially different demographic distributions. This study will give insight into the actual prevalence, risk factors, and informal care costs of dementia for the population with support needs in New Zealand. It will provide valuable information to improve health outcomes and better inform policy and planning.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/20225

(*JMIR Res Protoc* 2021;10(1):e20225) doi:[10.2196/20225](https://doi.org/10.2196/20225)

**KEYWORDS**

routinely collected data; repeated measures; dementia; Alzheimer disease; modeling; complex sampling

**Introduction**

Dementia is a global public health priority [1]. There are currently 50 million people living with dementia worldwide, and this number is projected to increase to 82 million in 2030 and 152 million in 2050 [2]. The current global cost of dementia care is over US \$1 trillion per year, and 40% of the cost is due to informal care provided by unpaid carers, who are usually family members [2]. Dementia is a neurodegenerative disease that affects a person's memory, thinking, behavior, and day-to-day functioning. Dementia is recognized as a significant health care challenge in New Zealand that will have major social and economic impacts in the coming years [3]. Since age is a main risk factor for dementia, dementia prevalence will increase as the baby boomer populations in New Zealand and other Western countries enter the older age cohort. However, there is no previous large-scale epidemiological study examining the extent or impact of dementia in New Zealand. There is an urgent need to study dementia prevalence and outcomes to inform public policy and health services planning. Two particular motivations for our research are the potential to estimate dementia prevalence using health administrative data and the use of a novel statistical model to evaluate the informal cost of dementia care for people with support needs in New Zealand [4].

The New Zealand Ministry of Health routinely collects information on people with support needs in the Needs Assessment and Service Coordination (NASC) database. This database contains data that are collected by publicly funded NASC agencies, including basic demographic and health information. However, the information in the NASC database alone is not sufficiently detailed to study the specific needs of people with dementia. We therefore propose linking the NASC data with another Ministry of Health data set, the International Residential Assessment Instrument (interRAI).

There is a suite of interRAI assessments that are currently in use in New Zealand. This study will focus solely on interRAI Home Care (interRAI-HC) and interRAI Contact Assessment (interRAI-CA). The interRAI-HC is a comprehensive geriatric assessment developed by a network of health researchers in over 30 countries. It aims to provide a clinical assessment of medical, rehabilitation, and support needs and abilities. It contains information on about 250 demographic, clinical (including the diagnosis of Alzheimer disease and dementia), and psychosocial factors, which can be used to support care planning, resource allocation, quality measurement, and outcome evaluation. New Zealand has implemented a mandated interRAI-HC assessment for all older adults who are being assessed for publicly funded home support services since 2012 and long-term aged residential care since 2016 [5]. Data on informal costs are collected as informal hours of unpaid care. Additionally, the interRAI-HC captures 8 of the 12 known risk factors for dementia [6]: diabetes, smoking, obesity, physical inactivity, depression, alcohol, hearing impairment, and lack of social contact. Dementia risk factors that are not captured by

interRAI-HC are hypertension, head injury, air pollution, and education. Dementia diagnosis data collected in interRAI assessments show a high degree of accuracy when compared with clinical records [7]. The interRAI-CA is a shorter geriatric assessment used to assess clients urgently, reliably, and efficiently and identify the complexity of the older adult's condition. It is a basic screening assessment that provides clinical information to support decision making about the need and urgency for a comprehensive assessment, support, and specialized rehabilitation services.

Initially, older adults referred to NASC agencies are classified as urgent or nonurgent, and urgent cases are immediately assessed using interRAI-HC [8,9]. Nonurgent cases are only assessed using interRAI-CA but could be reclassified as urgent at a later time, for example, when they are reassessed annually. Therefore, several observations are available for each client as long as they remain in receipt of support services. The assessments can be used to inform care planning, resource allocation decisions, and economic evaluations [7,10]. The interRAI-HC has good convergent validity as compared with the Resource Utilization in Dementia Lite instrument to estimate the societal cost of resource utilization in community-dwelling older adults [10].

**Methods****Study Aims and Objectives**

This study will investigate the prevalence, risks factors, and informal cost of dementia in New Zealand.

Objective 1 is to produce an integrated data set by linking the NASC and interRAI data sets between July 1, 2014, and June 30, 2019. Objective 2 is to produce a descriptive analysis of the routinely collected data for people registered in NASC and interRAI in New Zealand. Objective 3 is to evaluate the risk factors for dementia and the drivers of informal cost. Objective 4 is to calculate an estimate of the prevalence and average informal cost of dementia.

**Study Design**

The study is an observational study comprising 5 years of longitudinal data.

**Study Population**

The study population is people who were registered in the NASC database between July 1, 2014, and June 30, 2019. Patients are referred to NASCs by medical practitioners when they are considered to have needs and requirements for services such as home care or long-term care. The NASC data set contains demographic information, such as age, gender, and ethnicity, along with information on whether the patient was classified as urgent or nonurgent at their first evaluation by NASC.

**Study Sample**

The study sample is people who are registered in the NASC database and were assessed with at least one interRAI-HC or

interRAI-CA between July 1, 2014, and June 30, 2019. This sample contains all urgent cases and a sample of nonurgent cases from the NASC database.

### Eligibility Criteria

Repeated assessments or observations on the same patient will be included in the analysis. Patients included in the sample for analysis will only be those in the NASC database with at least one interRAI assessment between July 1, 2014, and June 30, 2019.

### Ethical Considerations

This study has been approved by the New Zealand Health and Disability Ethics Committee (reference 19/STH/206). The research team will ensure the research meets or exceeds established ethical standards determined by the committee.

### Data Management

#### Data Sources

The primary data source is the Integrated Data Infrastructure (IDI) [11]. The IDI is a large research database. It holds microdata about people and households in New Zealand. The data are about life events, such as education, income, benefits, migration, justice, and health, and come from government agencies, Statistics New Zealand surveys, and nongovernment organizations. Data on an individual person are linked together, or integrated, to form the IDI. Researchers gain access to the IDI data labs by formally applying for a research project. Data in the IDI are deidentified. Numbers that can be used to identify people are encrypted.

Information from interRAI and NASC is available in the IDI. We have been granted approval to access these data (project No. MAA2020-02).

The interRAI and NASC data have encrypted identifiers that are consistent in both data sets. The linkage will be conducted in the Statistics New Zealand Data Lab at the University of Auckland. An integrated data set will be generated. This will result in 3 data sets: (1) the interRAI data set, (2) the NASC data set, and (3) the integrated data set.

#### Time and Data Storage

The 3 resulting data sets (interRAI, NASC, and integrated) will be stored in the Statistics New Zealand Data Lab at the University of Auckland, which is part of the IDI in New Zealand.

### Data Analysis

Statistical analysis will address two different elements: (1) data cleaning and integration and (2) the theory and models.

#### Data Cleaning and Integration

The data cleaning and integration step will focus on data linkage and data cleaning. For objective 1, the information to be linked is the information from NASC (which contains demographics) and the information from interRAI (which contains data on dementia diagnoses, physical and psychosocial health, and informal care). Informal care includes the care provided by unpaid (informal) carers, usually family members. The informal

cost is measured by the interRAI in hours, to which standard unit costs for informal care are applied.

### Theory and Models

For objective 2, we will use basic descriptive statistics and hypothesis tests, such as 2-tailed  $t$  tests and  $F$  tests. For objective 3, we will use marginal regression models obtained from generalized estimating equations (GEEs) for 2 outcomes: dementia presence and number of hours of informal care. We will evaluate risk factors and drivers of the cost, such as ethnicity, gender, severity of the diseases, age, marital status, and comorbidities. GEE models are used for data structures that have repeated observations. In order to correct for nonresponses and missing data, we will use the calibrated sampling weights method [12-14], where each observation is given a weight  $w$  that compensates for differential nonresponses and missing data. For this project, the weights will be estimated using demographic information, such as age, gender, ethnicity, and urgency of the case in the sample of people with dementia and in the whole NASC population. These weights will be incorporated into GEE models using a loss function that yields the minimum loss. The choice of a loss function is usually a balance between the goal of the analysis and the efficiency and complexity of the function. GEE is a well-known method for regression in the presence of correlated data or repeated measures [15,16]. The efficiency of GEE depends on the assumptions made about the variability of the data. For example, a straightforward choice would be independence. Such assumptions are crucial for the second part of the theoretical development or inference. This is the vital step in which we draw valid conclusions from the data.

For objective 4, dementia prevalence will be calculated as a weighted total using the calibrated sampling weights mentioned above. The resulting quantity will then be divided by the number of person-years calculated using the longitudinal data.

Informal cost estimates will be calculated as weighted averages using calibrated sampling weights. The resulting quantity will then be divided by the number of person-years calculated using the longitudinal data. All codes will be programmed in R (The R Foundation).

## Results

As of November 2020, there have been no dementia prevalence studies or studies on informal care costs of dementia using national data from New Zealand. All existing studies have used data from other populations, for which the demographic distribution is significantly different. This study will identify the risk factors and informal costs of dementia (unpaid care) in people 65 years or older who have been assessed for care needs in New Zealand. We will also explore the potential of using routinely collected health data to provide a proxy measure of dementia.

We have obtained ethics approval from the New Zealand Health and Disability Ethics Committee (reference 19/STH/206). The complex sampling design method will be employed in this study to extrapolate the results to the population with disabilities in New Zealand. The population data frame will be the New



Zealand NASC database, and the complex sample will be the interRAI data set (a subset of the NASC data set). This offers the potential to extrapolate results from the interRAI to NASC by using the screening processes to calculate sampling weights. We hope that this approach will provide much needed statistics regarding potential health inequities, which can then be used by decision makers to change policy and practice. We also hope that this opens doors to future research in which larger populations or surveys are linked to interRAI data.

## Discussion

The aim of this study is to investigate the prevalence, risks factors, and informal cost of dementia in New Zealand. The number of people living with dementia in the world has been estimated to be 50 million and is expected to almost double every 20 years [2]. There has never been a study examining the prevalence, risk factors, or cost of dementia in New Zealand. A Deloitte report [3] estimated the prevalence of dementia and identified the main risk factors of dementia by extrapolating epidemiological data from other countries. Our proposed study will advance current research on dementia in New Zealand by using routinely collected local data to estimate the prevalence of dementia. This study will provide insight into the prevalence of dementia in the main ethnic groups in New Zealand, especially those considered to have a higher risk of dementia, such as Māori and Pacific Islander people.

It is mandatory in New Zealand to have Māori consultation for studies that involve data pertaining to Māori people. For the Māori community, there are concerns that policies can occur without a robust Māori data governance partnership that is representative and inclusive and provides accountability back to Māori communities. It has been previously demonstrated that

Māori individuals present at a younger age than non-Māori individuals to a tertiary memory service [17]. This might be expected, as Māori are at greater risk of dementia due to increased prevalence of risk factors such as diabetes and cardiovascular disease. The only epidemiological study that has examined differences in dementia between Māori and non-Māori individuals is the Life and Living in Advanced Age, a Cohort Study in New Zealand (LiLACS NZ) study, a longitudinal study on the health and well-being of octogenarians [18]. LiLACS NZ examined around 500 Māori and 500 non-Māori octogenarians. They found that more Māori people scored below the cutoff in a well-known cognitive screening tool (the Mini-Mental State Examination [MMSE] [19]), but that the prevalence of dementia using a specialist diagnostic assessment was no different between the two groups. This indicates that the MMSE is culturally biased against Māori individuals and overestimates the prevalence of dementia in Māori populations [18]. We agree and have been careful to seek consultation regarding not only the collection and analysis of routinely collected data but also the responsible dissemination of findings as they might pertain to Māori individuals. We have consulted with a senior cultural Māori advisor at a district health board regarding the use of both local and national health data and the dissemination of findings. This advisor supports this study and our endeavor to use routinely collected health data to highlight and address health inequities and suggests that we collaborate with local marae and Māori health centers to discuss how best to present the findings of the study to decision makers, academics, and the public. We have also consulted with a Māori statistician and researcher, who also supports this study and has agreed to be an advisor on this study in order to ensure the safeguarding and sovereignty of data and the responsible dissemination of the study findings pertaining to Māori populations.

## Acknowledgments

We thank Mr Andrew Sporle for his advice on Māori consultation. This team has received funding from the University of Auckland Science/Faculty Research Development Fund New Staff Grant (3716994).

## Conflicts of Interest

None declared.

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## Abbreviations

**GEE:** generalized estimating equation

**IDI:** Integrated Data Infrastructure

**interRAI:** International Residential Assessment Instrument

**interRAI-CA:** International Residential Assessment Instrument Contact Assessment

**interRAI-HC:** International Residential Assessment Instrument Home Care

**LiLACS NZ:** Life and Living in Advanced Age, a Cohort Study in New Zealand

**MMSE:** Mini-Mental State Examination

**NASC:** Needs Assessment and Service Coordination

*Edited by G Eysenbach; submitted 13.05.20; peer-reviewed by N Mohammad Gholi Mezerji, C Sinclair; comments to author 21.08.20; revised version received 06.09.20; accepted 24.11.20; published 06.01.21.*

*Please cite as:*

Rivera-Rodriguez C, Cheung G, Cullum S

Using Big Data to Estimate Dementia Prevalence in New Zealand: Protocol for an Observational Study

*JMIR Res Protoc* 2021;10(1):e20225

URL: <https://www.researchprotocols.org/2021/1/e20225>

doi: [10.2196/20225](https://doi.org/10.2196/20225)

PMID: [33404510](https://pubmed.ncbi.nlm.nih.gov/33404510/)

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Protocol

# Natural Language Processing–Based Virtual Cofacilitator for Online Cancer Support Groups: Protocol for an Algorithm Development and Validation Study

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## Abstract

**Background:** Cancer and its treatment can significantly impact the short- and long-term psychological well-being of patients and families. Emotional distress and depressive symptomatology are often associated with poor treatment adherence, reduced quality of life, and higher mortality. Cancer support groups, especially those led by health care professionals, provide a safe place for participants to discuss fear, normalize stress reactions, share solidarity, and learn about effective strategies to build resilience and enhance coping. However, in-person support groups may not always be accessible to individuals; geographic distance is one of the barriers for access, and compromised physical condition (eg, fatigue, pain) is another. Emerging evidence supports the effectiveness of online support groups in reducing access barriers. Text-based and professional-led online support groups have been offered by Cancer Chat Canada. Participants join the group discussion using text in real time. However, therapist leaders report some challenges leading text-based online support groups in the absence of visual cues, particularly in tracking participant distress. With multiple participants typing at the same time, the nuances of the text messages or red flags for distress can sometimes be missed. Recent advances in artificial intelligence such as deep learning–based natural language processing offer potential solutions. This technology can be used to analyze online support group text data to track participants' expressed emotional distress, including fear, sadness, and hopelessness. Artificial intelligence allows session activities to be monitored in real time and alerts the therapist to participant disengagement.

**Objective:** We aim to develop and evaluate an artificial intelligence–based cofacilitator prototype to track and monitor online support group participants' distress through real-time analysis of text-based messages posted during synchronous sessions.

**Methods:** An artificial intelligence–based cofacilitator will be developed to identify participants who are at-risk for increased emotional distress and track participant engagement and in-session group cohesion levels, providing real-time alerts for therapist to follow-up; generate postsession participant profiles that contain discussion content keywords and emotion profiles for each session; and automatically suggest tailored resources to participants according to their needs. The study is designed to be conducted in 4 phases consisting of (1) development based on a subset of data and an existing natural language processing framework, (2) performance evaluation using human scoring, (3) beta testing, and (4) user experience evaluation.



**Results:** This study received ethics approval in August 2019. Phase 1, development of an artificial intelligence–based cofacilitator, was completed in January 2020. As of December 2020, phase 2 is underway. The study is expected to be completed by September 2021.

**Conclusions:** An artificial intelligence–based cofacilitator offers a promising new mode of delivery of person-centered online support groups tailored to individual needs.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/21453

(*JMIR Res Protoc* 2021;10(1):e21453) doi:[10.2196/21453](https://doi.org/10.2196/21453)

## KEYWORDS

artificial intelligence; cancer; online support groups; emotional distress; natural language processing; participant engagement

## Introduction

### Background

A cancer diagnosis, and its subsequent treatment, has a significant impact on short- and long-term psychological well-being. Many patients and caregivers experience a range of distressing symptoms including worry, fear, irritability, sleeplessness, and guilt, while others develop more severe symptoms such as loss of interest in life [1-3]. Approximately half of all individuals in cancer treatment report undue and persistent emotional distress [4-7]. Persistent distress is associated with poor treatment adherence [8], reduced health-related quality of life [9], and higher mortality [10].

Online support groups are effective in reducing emotional distress [11-13]. They are a convenient alternative for those who cannot attend in-person support groups because of geographic distance, physical health concerns, and other responsibilities [14]. While there are a variety of delivery methods (eg, video or text), professionally led online support groups are typically synchronous (in real time) where participants engage in therapeutic interactions with a therapist and other participants in the group. Group interactions can be recorded and reviewed by participants during or postsession. Cancer Chat Canada (CCC) offers professionally led text-based support groups to patients with cancer and caregivers across Canada, with transcripts available to therapists and participants for postsession review. The online support group in CCC is manual-based, with session-specific themes, readings, and interactive activities. Therapists lead group discussions based on the manual, address new topics brought up by participants during the session, attend to an individual's emotional concerns, and facilitate mutual support.

The helpful therapeutic aspects of online support groups include facilitation of information sharing, expression of emotions, and provision of support as well as coping strategies [13,15]. Participants quickly become accustomed to text-based interactions and show increased feelings of empowerment, reduced social isolation, better managed stress, and improved coping [13]. Emotional expression is expected and encouraged by the therapists, particularly the emotions that participants may consider negative such as sadness, anger, or fear [3]. However, therapists need to gauge the frequency and intensity of expressed emotions from participants and address them in a timely fashion. In text-based online support groups, therapists do not have visual cues and may miss participants' emotional needs when entries

by multiple participants are posted simultaneously on a fast-scrolling screen [16,17]. Failure to recognize and respond to emotional distress expressed by participants can have clinical consequences, such as reduced perceived support and increased group dropouts. These challenges can also make a well-trained therapist feel frustrated and limit their uptake of this form of support group delivery. Another unique challenge is participant engagement; online support group therapists find it difficult to foster group cohesion. They find it harder to promote belonging and deepen group members' connections with one another without visual cues. Both engagement and group cohesion are imperative for optimal outcomes [18,19].

Currently, little is known concerning the mechanisms related to the process of online delivery that can support therapists in delivering optimal virtual online group support. To date, few studies have focused on examining mechanisms of action in therapist-led online support group, such as active therapeutic ingredients, mediators of change, or participant distress which may be associated with reduced level of engagement and participant dropout rates [18]. With the increased popularity of virtual care, more research is needed to understand what factors enhance (or impede) specific patient outcomes for evidence-based programs.

Artificial intelligence (AI) methods, such as deep-learning based natural language processing (NLP), offer a novel solution to addressing these challenges by capturing participants' emotional expression (including distress), level of engagement, and group cohesion in real time during text-based sessions, without imposing a measurement burden [20,21]. For example, if methods of deep learning–based NLP can systematically identify important emotions, such as fear, anxiety, sadness, and depression, then assistance in signaling and monitoring participants who need additional support can be provided. Tracking and monitoring participants' cognitive-emotional states using AI approaches may reduce attrition, improve therapeutic outcomes, and allow therapists to focus their attention more fully on the therapeutic encounters [22].

We aim to explore whether deep learning–based NLP can optimize online support group delivery through the creation of an artificial intelligence–based cofacilitator (AICF). AICF training, testing, implementation, and evaluation uses textual data from the CCC therapist-led online support group service. The AICF prototype will be adapted from an AI-based framework called Patient-Reported Information Multidimensional Exploration (PRIME) for detection of

emotional states, piloted on data from patients with prostate cancer in Australia [23-25].

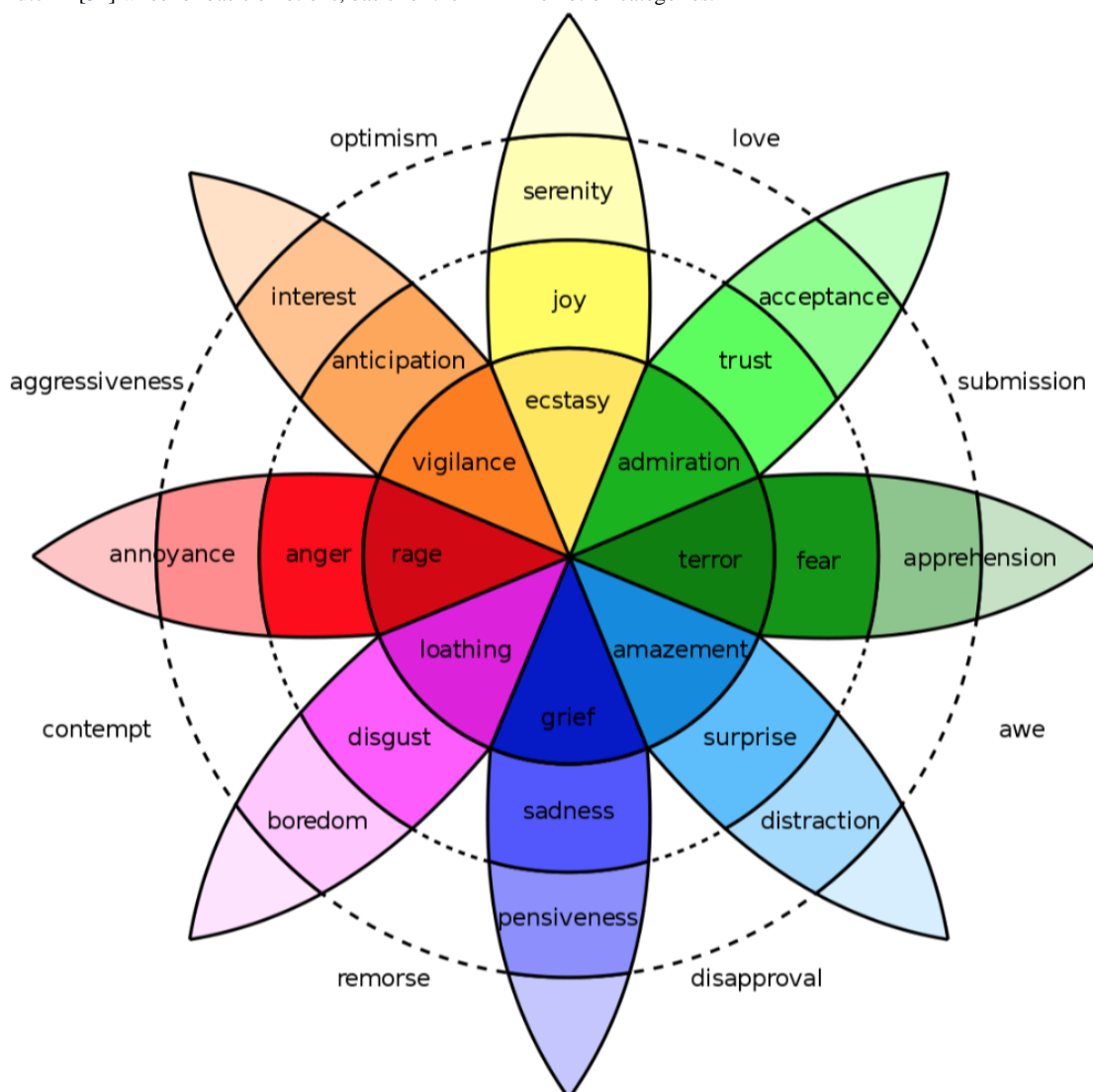
**The PRIME Framework**

This study is built upon the PRIME framework. De Silva et al [24] pioneered AI research for automatic identification of physical and emotional states of patients with prostate cancer for active surveillance to identify their psychosocial needs. The PRIME framework, an automated ensemble of deep-learning based NLP techniques, was developed to analyze text from online patient forums. PRIME has been used to analyze 10 high-volume online patient forums consisting of 22,233 patients with prostate cancer, which generated a text data set of 609,960 conversations. PRIME demonstrated its capabilities in identifying diverse physical symptoms, and functional and emotional outcomes (eg, sadness, anger, confusion) embedded in forum discussions. It generates visualizations of aggregated

expressions of emotion trajectories by patient-reported demographics, decisions, treatment, and side effects [23-25].

PRIME extracts emotions comprehensively by parsing a body of text to different levels of granularity: word, phrase, sentence, post, and all posts of each user, using multiple techniques (vector space modeling, topic modeling, word2vec [26,27], SentiWordNet [28], and named entity recognition) and SNOMED terms [29]. These techniques are used to identify a group of key words associated with a topic as a context variable based on an aggregated measure of features derived at each level, and in turn, determine eight basic emotion categories [30,31], their strengths, and overlaps (eg, anxiety is an overlap between fear and sadness) [24]. The basic emotion categories are based on the Plutchik [31] wheel of basic emotions, illustrated in Figure 1. Each level of extraction will serve as an input for calibration of the subsequent extraction to increase accuracy [23-25]. PRIME will serve as a foundation for the current AICF project algorithm, as outlined below.

**Figure 1.** Plutchik [31] wheel of basic emotions, basis for the PRIME emotion categories.



An AICF will track and monitor online support group participants’ emotional distress through real-time analysis of text-based messages posted during sessions. Specifically, the AICF aims to (1) identify participants who are disengaged or

at-risk for increased emotional distress and track in-session engagement and group cohesion levels, providing real-time alerts for therapist follow-up; (2) generate postsession participant profiles that contain discussion content keywords and emotion

profiles for each session; and (3) automatically suggest tailored resources to participants according to their needs.

## Methods

### Overview

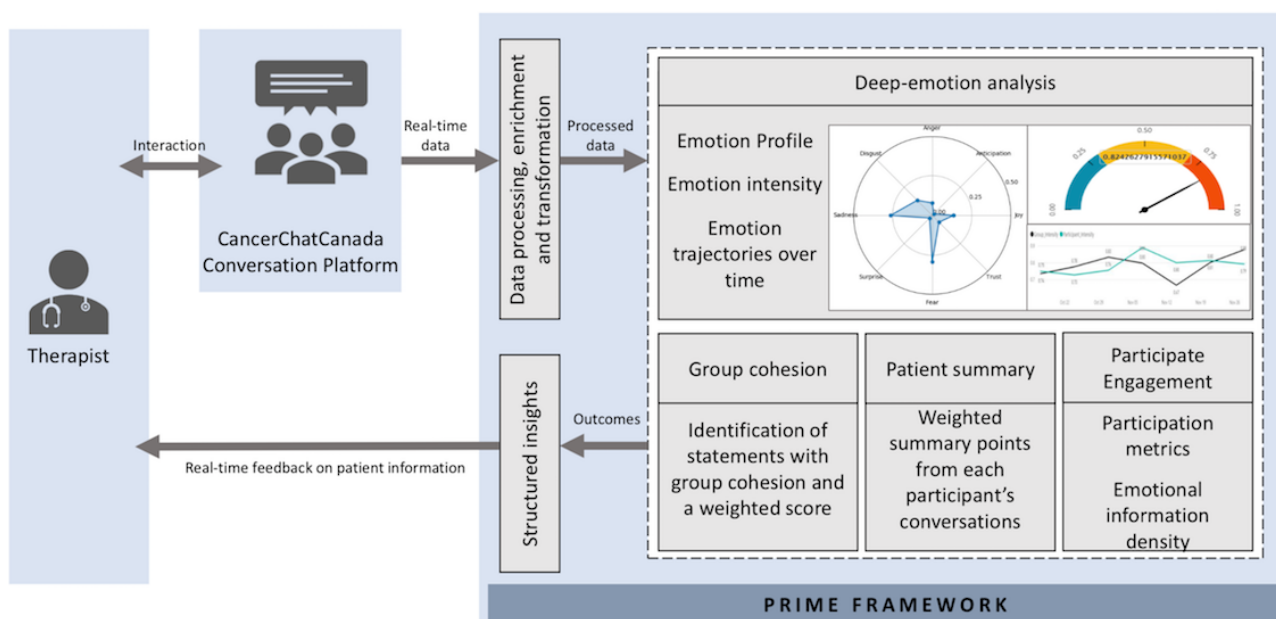
This project has 4 phases: (1) developing an AICF using a subset of existing CCC data based on PRIME, (2) evaluating its performance using human scoring, (3) beta testing the AICF within CCC, and (4) evaluating user experiences. This study will be conducted in compliance with the principles of the Declaration of Helsinki.

### Phase 1: Developing an AICF

#### Summary

In addition to the 8 basic emotions detected by PRIME, the AICF will include additional functionality to support (1) real-time monitoring and alerting of emotional distress, participant engagement, and group cohesion, (2) participant emotional profiling, and (3) tailored resource recommendations. Figure 2 describes the functionalities and process of transforming PRIME to an AICF.

**Figure 2.** Functionalities of AICF. PRIME: Patient-Reported Information Multidimensional Exploration.



To inform development of the AICF, CCC data from 430 unique participants (approximately 80,000 conversations) across multiple sessions in 2 years will be used. The majority of participants were females, aged between 45 and 64 years, living in suburban or rural areas of British Columbia or Ontario. Many had breast cancer and were in the posttreatment period. See participant characteristics in Table 1.

The text data were deidentified to ensure confidentiality, using a risk-based approach in 2 steps. The first step used an open-source clinical text deidentification library (philter-ucsf [32]) to replace identifiers such as name, address, sex, age or year mention, and health care organization (hospital) names with asterisks, preserving word length. The second step involved human review and deidentification of any identifiers that the library missed. The AICF was trained using the deidentified data.

**Table 1.** CCC participant characteristics.

Characteristics	Value (n=430), n (%)
<b>Gender</b>	
Female	383 (89.0)
Male	47 (11.0)
<b>Age group (years)</b>	
18-24	6 (1.5)
25-34	27 (6.2)
35-44	66 (15.3)
45-54	130 (30.2)
55-64	147 (34.2)
65+	54 (12.6)
<b>Location</b>	
British Columbia	146 (34.0)
Ontario	142 (33.0)
Alberta	52 (12.0)
Other province	90 (21.0)
<b>Geography</b>	
Urban	168 (39.0)
Suburban/rural area	262 (61.0)
<b>Type of cancer</b>	
Breast	133 (31.0)
Gynecological	90 (21.0)
Colorectal	43 (10.0)
Head and neck	13 (3.0)
Other cancers	151 (35.0)
<b>Treatment status</b>	
Active treatment	116 (27.0)
Posttreatment	176 (41.0)
Unknown	138 (32.0)

### **Functionality 1: Real-Time Monitoring and Alert**

The AICF is designed to track emotional distress, participant engagement, and group cohesion. First, conversational extracts and user behaviors (eg, emotional intensity, participant engagement) will be used to train an ensemble of machine learning algorithms [33] that predict the likelihood of significant emotional distress. This ensemble method generates a weighted score that offsets potential bias in the 2 approaches as well as takes both emotion and engagement into account. Manually annotated texts of instances of distress were used to train the AICF. For the purpose of assessing the intensity of distress, 10 sessions of chat data were annotated and classified according to levels of distress (none, low, medium, or high) in the participants' statements. Based on the focus group feedback, the therapists highlighted that, apart from the 8 basic emotions, it is important to specifically detect participants' comments indicating hopelessness, distress, and loneliness, which are more

complex emotional experiences specific to a cancer population [34,35]. Identifying these emotions are key in cancer online support groups as they are linked to depression (hopelessness, loneliness) [4] and poor outcomes (distress) [8]. Therefore, emotion intensities for all 11 emotions have been aggregated into group- and participant-specific emotion intensities. The AICF will produce risk scores of significant distress and that will be displayed and updated at each 30-minute interval on a 90-minute session timeline. If a participant's risk score has increased significantly compared to the previous intervals, then the therapist will be alerted. The alert threshold will be finalized in the user testing phase.

Participant engagement is defined by the information density of their text posts, which consists of the emotional content detected by the AICF, number of words per post, and frequency of posting. The AICF will update every 5 minutes to show if participants are participating at high, medium, or low levels or



if they have not posted in some time. Real-time monitoring of participant engagement, relative to the group will also be displayed on the real-time dashboard.

Group cohesion is defined as a sense of belonging to and feeling supported by the group [36]. This is indicated by referring to other participants as “us,” “we,” and “our group”; expressing gratitude for sharing or help from others; commenting that they are looking forward to the next group; or chatting together outside of group time. The AICF will capture the group cohesive statements and present an aggregated score that denotes the level of group cohesiveness among all members. Group cohesive statements (100 examples) were annotated by the therapists from the CCC data, and keywords and phrases derived from these examples were used as seed terms in a word embedding model.

### Functionality 2: Participant Emotional Profiling

The AICF will use features from PRIME to generate a collection of key phrases and topics and an emotional profile for each participant over a 90-minute session. The summary will consist of participant clinical and sociodemographic characteristics and will display key phrases that indicate emotional distress and the intensity [23] of emotion associated with each concern on a 90-minute timeline. The display time window can be expanded as sessions continue.

### Functionality 3: Tailored Resource Recommendations

The AICF will use outcomes from the first 2 functionalities to train an unsupervised incremental learning algorithm that merges similar participant profiles and differentiates dissimilar ones. The incremental learning feature will maintain these learned groupings (eg, presurgery vs postsurgery) over time, uncovering

shared group behaviors and patterns. These will then be combined with known participant characteristics (eg, location, age), use of psychosocial resources (eg, sexual health clinic), and timing for a specific issue (eg, sexual health) from CCC data as inputs to a recommender system. Using association rule mining algorithms, a list of resources with predicted scores will be generated; resources with the highest predicted scores will be recommended to a participant [37]. Test data will be used to evaluate relevance and reliability of each recommendation. This functionality will increase tangible support and service quality without incurring increased workload on the therapists.

### Phase 2: Human Scoring

To develop the AICF, the emotion labeling outputs will be scored by a team of psychology undergraduate and graduate students, including 2 doctoral-level clinical psychology therapists. The team will score 20% of the output as feedback to retrain the AICF. This updated version will be run on the remaining 80% of the data. Each AICF version will be saved before it is trained on new data. To evaluate the AICF, 2 online support group groups' messages will be withheld for the final testing phase of the AICF.

The team will score the output using guides based on definitions from the literature and examples from well-established psychometric measures (Table 2). For example, sadness and fear were selected for the first round of human scoring due to their relevance as symptoms of anxiety and depression, and they were the emotions in the high distress post category most commonly identified by annotators. The output will be scored at the sentence level, such that the target output must be clearly present in the sentence, without additional textual context.

**Table 2.** Target measures for human scoring.

Output	Category	Description
Sadness	Emotion	Expressing loss, grief, unhappiness, hopelessness; feeling low, down, or blue; behaviors such as crying, withdrawing. Possible indicator of depression (persistent, high distress [31])
Fear	Emotion	Feeling scared, panicked, alarmed, apprehensive; less intensely worried, anxious, stressed, irritable, tense; being unable to focus, relax. Possible indicator of anxiety (persistent, high distress [31])
Group cohesion	Group process	A culmination of participation, engagement, expressed mutual support, gratitude for other members, looking forward to future chat sessions and referring to the group as “we” and “us” to indicate a sense of belonging [38].
Emotional profiling	Postgroup feature	A text summary of key phrases with high emotional content for each participant, scored for accuracy.
Tailored resource recommendation	Postgroup feature	A list of relevant psychosocial resources will be generated for each participant based on the conversations during the session.

Using the literature, the scorers will note the instances in which the AICF has (1) correctly identified each output instance (true positive); (2) incorrectly identified an output instance (false positive); (3) correctly identified the lack of an output (true negative); or (4) missed an output in a sentence (false negative). For example, from the sentence “Yesterday I had a melt down, just felt so sad and cried, it came out of nowhere,” the AICF correctly identified the comment's sentiment as sadness and so did the human scorer (true positive). From the sentence “I can

still laugh at some pretty bad jokes,” the AICF incorrectly identified the comment's sentiment as sadness, whereas the human scorer rated the comment's sentiments as no sadness (false positive). To judge the emotional intensities generated by the AICF, the scorers defined 4 levels of distress: low, moderate, moderate-high, and high.

Upon completion of the scoring, AICF performance will be evaluated for sadness, fear, and group cohesion measures using recall, precision, and F1 score. Precision is defined as a measure

of result relevancy while recall is defined as a measure of how many truly relevant results are captured. The F1 score [39], which is the weighted average of precision and recall, takes both false positives and false negatives into account. For F1 scores below 80%, scorer feedback will be used to improve the AICF until it achieves 80%. The scoring results will be used to generate the list of keywords of queried expressions in the word embedding model, while linguistic rules will be added to handle exceptions such as negations, idioms, irony, or expressed sarcasms that are unique to participants with cancer. This feedback loop will improve the performance of each functionality using domain expertise [40] to produce an acceptable evaluation F1 score.

### Phase 3: Beta Testing

#### Summary

The AICF will be deployed and tested in the CCC platform background (out of the therapists' view) in 3 groups. It will then be run for therapist use and feedback for beta testing on 10-12 groups to analyze the performance of the AICF system output, such as all emotions expressed (including distress), intensity, group cohesion, engagement, and emotional profiling features (see Table 2). We hypothesize that the AICF output will be highly correlated with standard clinical measures of psychological outcomes and have high sensitivity and predictive values for distress. These quantitative evaluations will provide evidence to support the AICF's validity and reliability.

#### Design

A single-arm trial to evaluate the AICF's validity and reliability among CCC therapists and participants.

#### Participants

Ten therapists and 100 support group participants (ie, patients and caregivers) (10-12 groups) will be recruited through a multipronged approach, including in-person (University Health Network clinics), print (flyers and posters posted at University Health Network locations), and digital media (eg, Twitter, Google, and Facebook [41], CCC platform, and webpages of CCC provincial partners across Canada). In-person recruitment will take place at University Health Network clinics using protocols approved by the University Health Network research ethics board. A study coordinator will explain the study prior to informed consent. For online and print recruitment, respondents will be provided with the study webpage and phone number of the research team for study inquiry. Interested patients will be followed-up by a call from the study coordinator for study details. Study log will be maintained and reasons for nonparticipation collected. The existing CCC therapist roster will be used to recruit therapist-participants directly. Therapists will receive training on the AICF. An estimated 120,000 posts (200 posts/user/session  $\times$  6 sessions  $\times$  100 users) will be generated, sufficient for the sensitivity and specificity analysis [42]. This study has been approved by the University Health Network research ethics board.

#### Measures

Participant distress will be assessed by standardized measures pre and postprogram by several scales. The Impact of Event

Scale-Revised [43] is composed of 22 items rated on a 5-point Likert scale, yielding a total score ranging from 0 to 88—8 items on intrusion (Cronbach  $\alpha$ =.87-.94), 8 items on avoidance (Cronbach  $\alpha$ =.84-.87), and 6 items on hyperarousal (Cronbach  $\alpha$ =.79-.91). The 7-item Hospital Anxiety and Depression Scale (HADS) [44], with items rated on a scale of 0 to 3, yielding a total score ranging from 0 to 21 has 2 subscales: anxiety and depression (Cronbach  $\alpha$ =.88 and .92, respectively) [44]. The 18-item Brief Symptom Inventory [45] is rated on a 5-point Likert scale, and the sum is transformed into a T-score. The Brief Symptom Inventory is composed of 3 dimensions: somatization, depression, and anxiety (Cronbach  $\alpha$ =.71-.85) [45]. A participant will be defined as having significant distress if they score above the cut-offs for any of the scales: cancer-related distress (Impact of Event Scale-Revised score  $>24$ ), symptoms of depression (HADS score  $>10$ ), or anxiety (Brief Symptom Inventory T-score  $>60$ ).

Participant postsession emotionality will be assessed using the Positive and Negative Affect Schedule [46], a 20-item self-report measure of positive and negative affect (Cronbach  $\alpha$ =.89 and .85, respectively). Postprogram group cohesion will be measured using the 19-item Therapeutic Factor Inventory [47]—Instillation of Hope (4 items), Secure Emotional Expression (7 items), Awareness of Interpersonal Impact (5 items), and Social Learning (3 items). The items are rated on a scale from 1 to 7 and a mean score is based on a sum of the item ratings multiplied by factor score weightings (Cronbach  $\alpha$ =.71-.91) [47]. Therapists will assess the AICF's usability postsession using the 10-item System Usability Scale using a 5-point Likert scale of agreement with scores ranging from 0 to 100 (Cronbach  $\alpha$ =.95)[48]. Finally, the online support group experience will be measured using the 24-item Counsellor Activity Self-Efficacy Scale [49], with items rated on a 10-point Likert scale (Cronbach  $\alpha$ =.96) [49].

#### Emoji Scale

Emoji scales validated as representations of physical and emotional quality of life in cancer populations [50] will be used to track emotions of the participants during each session. For AICF validation, we will employ an automatic check-in that will occur at three 30-minute intervals using 9 different emoticons (eg, worried, sad, supported) from which participants can choose to represent their emotional states in the moment. Each participant will provide up to 300 emoji ratings (3 $\times$ 10 sessions).

#### Statistical Analysis

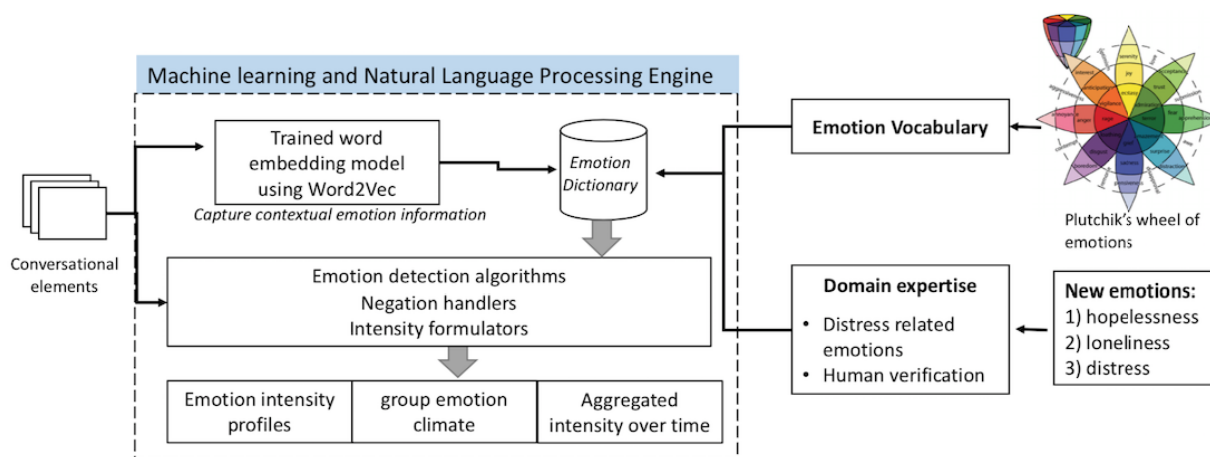
The ability of the AICF to correctly identify distress will be assessed. First, a chi-square test will be used to assess the sensitivity and specificity of the AICF against the self-reported emoji at the 30-minute interval. Second, linguistics inquiry word count [51] will be performed on each post. Linguistics inquiry word count scans each post for the linguistic markers of distress (eg, first-person singular pronouns, and words that Linguistics inquiry word count classifies as sad, anxiety or fillers) and provides a correlation coefficient. We hypothesize that correlations between linguistics inquiry word count and AICF output would be strong ( $\geq 0.7$ ). Third, a precision-recall curve (positive predictive value vs sensitivity) will be used to map

AICF classifications against established cut-offs of a standardized measure. An area under the curve >80% would be considered high performance [52]. The precision-recall curve can be used to inform the statistical threshold for distress that warrants a therapist alert. Fourth, construct (convergent) validity of AICF sentiment analysis will be compared against self-reported standardized measures. We hypothesize that all positive and negative emotions extracted will be strongly correlated (Pearson correlation coefficient  $\geq 0.7$ ) with Positive and Negative Affect Schedule subscales scores. For example, the extracted negative emotions will be positively correlated with HADS. Finally, internal consistency will be measured among extracted negative and positive emotions using Cronbach  $\alpha$ .

### Phase 4: Evaluation of User Experiences

Participants will rate their satisfaction with their online support group experience (eg, group cohesion) using the Therapeutic Factor Inventory. Therapists will provide ratings of system usability (with the System Usability Scale) and perceived self-efficacy measure (with the Counsellor Activity Self-Efficacy Scale) in leading the groups. All of these ratings are expected to be high (>80th percentile). Quality indicators, such as study attendance and dropout rate (defined as participants missing more than 2/10 sessions) will be compared using chi-square tests to those in a special topic group (eg, sexual health group). We expect that the dropout rate will be 50% less than those of existing groups.

Figure 3. From PRIME to AICF prototype—3-stage transformation process.



The intensity of each emotion for a given conversational extract is based on the output of the emotion classifier and the intensifier classifier. The emotion classifier detects each of the 11 emotions (8 basic emotions plus hopelessness, loneliness, and distress) while the intensifier classifier serves to augment or diminish the strength of each emotion. Table 3 presents several results from the initial experiment. The aggregate intensity for each emotion during the conversation is calculated using

## Results

Phase 1 was initiated in August 2019 and completed in December 2019. Phase 2 was initiated in January 2020, and as of December 2020, is ongoing. The study is expected to be completed by September 2021.

Preliminary results regarding real-time monitoring of emotional distress are available and will serve as a baseline for comparison of future versions of the AICF.

The PRIME framework has been configured to suit the above requirements and retrained using the CCC data and the human annotation of distress.

Using this data set and relevant literature, 2 clinical psychology doctoral students developed an annotation guideline (Multimedia Appendix 1). This guideline was used to categorize text-based data from one CCC online support group, comprising 8 participants over 10 sessions, by distress severity: low, moderate, moderate-high, or high level of distress, or “unable to identify” (Multimedia Appendix 2).

The PRIME framework emotion detection algorithms were transformed for distress severity detection in the AICF in 3 stages (Figure 3). The outputs were used to visualize each participant and group emotion profiles, and monitoring emotion intensity fluctuations over time.



where  $h$  is the emotion classifier,  $f$  is the intensifier classifier,  $t$  is a word in set  $C$ ,  $t_i$  is the corresponding intensifier term,  $|C|$  is the count of words in  $C$ , and  $E$  is a vector of  $x$  emotions. This intensity score is designed to allow the AICF to track individual changes over time.

**Table 3.** Demonstration of emotion intensity calculation.

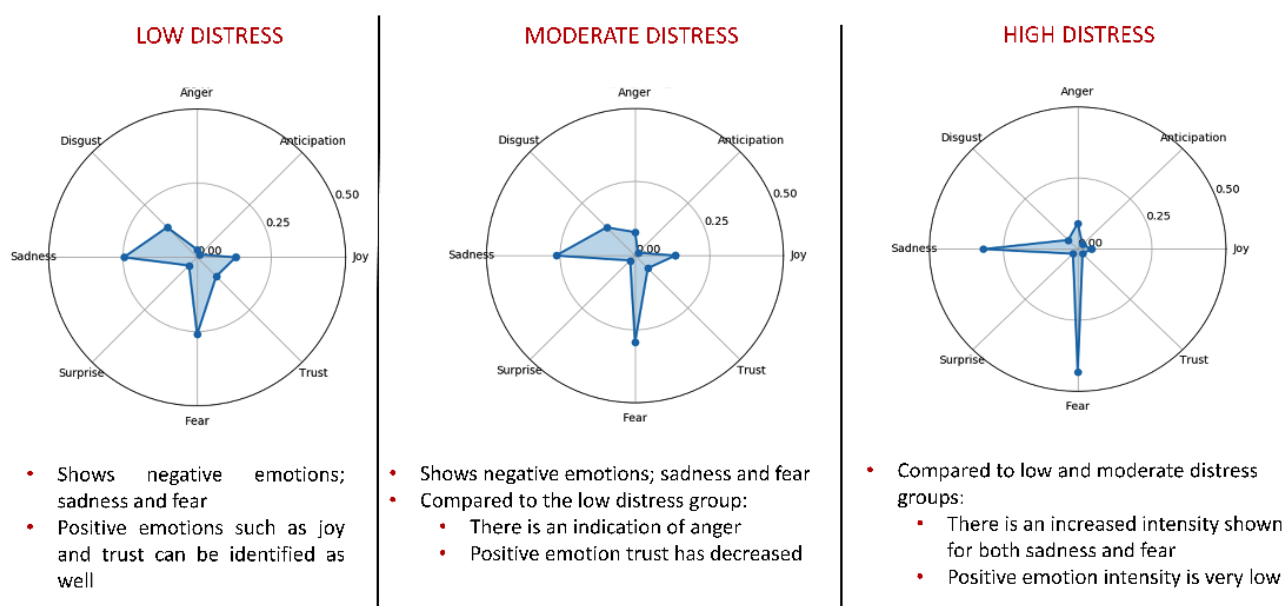
Extract	Emotion		Intensifier	
	Term	Classifier	Term	Classifier
“All the medicine I took make me too sleepy or sedated.”	_a	None	—	0.5
“yes <i>very</i> exhausting”	exhausting	sad	very	0.8
“This life is <i>very</i> fragile”	fragile	sad	very	0.8
“well I feel <i>totally</i> useless since I had this cancer”	useless	sad	totally	0.9
“I sense we are <i>losing</i> energy.”	losing energy	sad	—	0.5
“I feel <i>so</i> depressed regarding all this, but I went to see my family today”	depressed	hopelessness	so	0.7
“Relaxing days ahead no more treatments”	Relaxing	joy	—	0.5
“I love talking with this group!”	love	joy	—	0.5

<sup>a</sup>No term.

Figure 4 shows radial graphs displaying the AICF classification of emotions expressed by individuals with different levels of distress. Distress was calculated as the aggregation of 4 negative basic emotions (anger, sadness, fear, disgust). According to the AICF, people with high distress experienced intense levels of

sadness and fear, while those with moderate and low distress expressed similar profiles except that moderate distress individuals express more anger than their low distress counterparts.

**Figure 4.** AICF classifications of emotions across levels of participant distress. Note: Given the small sample of data available, the emotion intensity scale was adjusted to 0.5.



When compared with the human annotation of distress levels, the AICF was able to correctly identify specific types and intensity of emotion from the 8 participants in 10 sessions for 78% of instances for low distress, 63% for moderate distress, and 85% for high distress. The baseline performance for distress classification was 72% agreement with the annotators with advanced training in clinical psychology.

## Discussion

### General

The AICF, an extension of the PRIME framework, represents a novel approach to help cancer online support group therapists track and monitor individual participant emotional text-based

expressions that may indicate important mental health changes and outcomes, such as high distress, indicative of anxiety and depression. It also has the potential to track important online support group outcomes such as increased distress, participant engagement, and group cohesion.

Preliminary findings show that the AICF demonstrated acceptable performance in identifying emotional distress and target emotions. CCC patients experienced some distress when they signed up for online support groups which offered a rich emotional content of real-world data for distress detection algorithm training. Our results support the findings of Funk et al [53] who used a combination of techniques developed for basic emotion detections to predict clinically meaningful outcomes and symptoms of eating disorders, with a reported



area under the receiver operating characteristic curve of 73%. However, the AICF has shown a lower accuracy (63%) in identifying moderate distress compared to the high (85%) and low distress (78%). One possible explanation is that moderate distress is a relatively ambiguous concept that even human experts may find it difficult to distinguish. The number of identified instances of moderate distress was lower than those of high and low distress as the human annotators were more likely to classify a distress statement as either high or low and these categories yielded the highest agreement between human annotators. Therefore, this contributed to the AICF having a hard time distinguishing the moderate level from the other levels of distress. The final evaluation will provide a more complete picture of distress identification.

The AICF has been designed to extract clinically important emotional outcomes based on a combination of basic emotions. While the literature predominantly focuses on sentiment or basic emotion detection on Twitter for commercial and political use [54-56], the AICF is better for clinical settings in several ways compared to previous automated deep emotion and intensity detection tools: The AICF was trained and applied on distress data from patients with cancer in clinical settings, instead of tweets that are free-flowing statements posted by the general public and that do not usually contain dialectic exchanges or symptoms or outcomes. Our data allow the AICF to identify more granular emotions and changes over time. The AICF has incorporated clinically trained therapists to identify distress and clinical outcomes from the data while most studies relied on hashtags to classify topics and emotions or on laymen annotators [55]. In one of the few studies [57] that attempted to identify emotions in a cancer population [57] using recurrent neural network models to extract common basic emotions such as fear and hope from tweets by patients with cancer, the authors identified joy as the most commonly shared emotion, followed by sadness and fear; these findings are similar to ours. However, the AICF will contribute to the uncharted areas of clinical psychology and psychiatry in which automatic emotion detection and classification systems have not yet been fully explored. This unique project attempts to identify complex emotions such as hopelessness and loneliness and that will open an avenue of research with clinical utilities.

The development phase was to evaluate the AICF performance on a training data set, to ensure that it is correctly classifying the key target outputs (detection of sadness and fear, engagement, group cohesion, emotional profiling in radar graphs). These features will be built into real-time and postgroup dashboard features for the online therapist leaders. The next

phase involves human scoring for the emotion classification (eg, anger, joy) to ensure that the AICF is accurately labeling the emotion and its intensity. Once evaluated, this emotion data will be deployed in real-time engagement tracking and in the individual participant postsession summary, with end-user input on usability and effectiveness from the therapist leaders.

One limitation is that the AICF relies on human annotated training data and human scoring for performance evaluation. Human input can yield variable results as it requires judgement when classifying ambiguous posts. To reduce this variability, detailed literature-based guides were created for each emotion. Two doctoral-level clinical psychology-trained therapists created the guides and annotated the data independently, after which the results were reviewed. Another limitation is that the AICF prototype is based on PRIME, which was developed on data from patients with prostate cancer (all male participants, mostly aged 50 and older) whereas the CCC data represent a wider range of participant demographics and cancer types. A difference in distress and emotion expression is expected from the CCC participants in therapist-led synchronous groups. The AICF's detection of more complex outcomes (eg, group cohesion) requires additional annotations, algorithm training, and performance evaluation, as this is a new broadly defined outcome, outside the basic emotions. Applications of any prototype such as the AICF require adaptations for the specific platform and desired outcomes. Lastly, due to protection of personal health information, the data deidentification process removed some of the information as the software has masked keywords that were also used in names.

## Implications

Online support groups are accessible and effective at reducing cancer-related emotional distress. However, therapists find it challenging to monitor individual participant distress and engagement in the absence of visual cues while responding to multiple participants' messages simultaneously. Optimal online support group delivery and participant mental health outcomes require the therapist to effectively address and track markers of high distress. These markers include participants posting messages indicating intense sadness or fear, or participants withdrawing due to emotional dysregulation. An AICF can assist by detecting and flagging issues (eg, a spike of distress) that are amenable to treatment in real time, thus allowing therapists to provide higher levels of individual support. An AICF presents a unique opportunity to strengthen person-centered care in the online support group settings by attending to individual needs while expanding access to high-quality virtual health care.

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## Acknowledgments

Special thanks to Jessica Ramlakhan for formatting the manuscript, and to Jinny Hong for annotating the training data. This research is funded by the Ontario Institute for Cancer Research Cancer Care Ontario Health Services Research Network.

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## Conflicts of Interest

None declared.

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## Multimedia Appendix 1

Distress human annotation guidelines.

[\[DOCX File , 69 KB - resprot\\_v10i1e21453\\_app1.docx \]](#)

## Multimedia Appendix 2

Distress annotation method.

[\[DOCX File , 139 KB - resprot\\_v10i1e21453\\_app2.docx \]](#)

## Multimedia Appendix 3

OICR-CCO Health Services Research Grant peer review reports.

[\[PDF File \(Adobe PDF File\), 72 KB - resprot\\_v10i1e21453\\_app3.pdf \]](#)**References**

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## Abbreviations

**AI:** artificial intelligence

**AICF:** artificial intelligence–based cofacilitator

**CCC:** Cancer Chat Canada

**HADS:** Hospital Anxiety and Depression Scale

**NLP:** natural language processing

**PRIME:** Patient-Reported Information Multidimensional Exploration

*Edited by G Eysenbach; submitted 16.06.20; peer-reviewed by M Antoniou, D Saleh; comments to author 18.08.20; revised version received 04.09.20; accepted 24.11.20; published 07.01.21.*

### *Please cite as:*

Leung YW, Wouterloot E, Adikari A, Hirst G, de Silva D, Wong J, Bender JL, Gancarz M, Gratzner D, Alahakoon D, Esplen MJ. *Natural Language Processing–Based Virtual Cofacilitator for Online Cancer Support Groups: Protocol for an Algorithm Development and Validation Study*

*JMIR Res Protoc* 2021;10(1):e21453

URL: <https://www.researchprotocols.org/2021/1/e21453>

doi: [10.2196/21453](https://doi.org/10.2196/21453)

PMID: [33410754](https://pubmed.ncbi.nlm.nih.gov/33410754/)



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Protocol

# Creating Respectful Workplaces for Nurses in Regional Acute Care Settings: Protocol for a Sequential Explanatory Mixed Methods Study

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## Abstract

**Background:** Negative workplace behaviour among nurses is an internationally recognised problem, despite the plethora of literature spanning several decades. The various forms of mistreatments and uncaring attitudes experienced by nurses include workplace aggression, incivility, bullying, harassment and horizontal violence. Negative behaviour has detrimental effects on the individual nurse, the organisation, the nursing profession and patients. Multi-level organisational interventions are warranted to influence the “civility norms” of the nursing profession.

**Objective:** The aim of this study is to investigate the self-reported exposure to and experiences of negative workplace behaviours of nursing staff and their ways of coping in regional acute care hospitals in one Local Health District (LHD) in NSW before and after Respectful Workplace Workshops have been implemented within the organisation.

**Methods:** This study employs a mixed methods sequential explanatory design with an embedded experimental component, underpinned by Social World’s Theory. This study will be carried out in four acute care regional hospitals from a Local Health District (LHD) in New South Wales (NSW), Australia. The nurse unit managers, registered nurses and new graduate nurses from the medical and surgical wards of all four hospitals will be invited to complete a pre-survey examining their experiences, perceptions and responses to negative workplace behaviour, and their ways of coping when exposed. Face-to-face educational workshops will then be implemented by the organisation at two of the four hospitals. The workshops are designed to increase awareness of negative workplace behaviour, the pathways to seek assistance and aims to create respectful workplaces. Commencing 3 months after completion of the workshop implementation, follow up surveys and interviews will then be undertaken at all four hospitals.

**Results:** The findings from this research will enhance understanding of negative workplace behaviour occurring within the nursing social world and assess the effectiveness of the LHD’s Respectful Workplace Workshops upon the levels of negative workplace behaviour occurring. By integrating qualitative and quantitative findings it will allow for a dual perspective of the social world of nurses where negative and/or respectful workplace behaviours occur, and provide data grounded in individuals lived experiences, positioned in a macro context

**Conclusions:** It is expected that evidence from this study will inform nursing practice, and future policy development aimed at creating respectful workplaces.

**Trial Registration:** Australian New Zealand Clinical Trials Registry (Registration No. ACTRN12618002007213; 14 December 2018).

**International Registered Report Identifier (IRRID):** PRR1-10.2196/18643

**KEYWORDS**

bullying; culture; negative behavior; nurses; methods; workforce

## Introduction

### Background

Various forms of negative workplace behavior have been reported across the health care professions, including in nursing [1,2], allied health professions [3], and medicine [4]. In addition to making working life unpleasant and stressful, the existence of a negative workplace culture risks patient safety [4]. The term negative workplace behavior is a euphemism that encompasses a wide range of undesirable behaviors, such as bullying (either physical or otherwise), harassment, horizontal violence, and incivility. The commonality is that the behaviors occur in the workplace; however, there are differences in definitions [2], as does the identity of the perpetrators. Bullying is characterized by repetitive acts that are directed at a person or group by one or more perpetrators in a position of power [5], whereas horizontal violence occurs between peers in equal positions [6]. In addition to these reported high-intensity behaviors, it has been suggested that incivility, as defined by Pearson et al [7] as “low-intensity deviant behavior with ambiguous intent to harm the target, in violation of workplace norms,” occurs daily and is accepted as a normal part of the nursing *socialization process*. Owing to the varying terms used in the literature, the term *negative workplace behavior* will be used throughout this paper to be inclusive of bullying, harassment, horizontal violence, and incivility.

Negative workplace behavior in nursing has been extensively explored, and there is a great variation in the reported incidences [1,2]. Regardless of this variation, it is widely accepted that negative workplace behavior continues to be a significant issue impacting nurses both personally and professionally [8,9] not only in Australia but internationally [2]. However, caution is necessary while comparing the reported prevalence rates of negative workplace behavior between countries due to differences in terminology, the lack of definitional consensus, and the multiplicity of assessment measures used in different studies. Reporting is also influenced by pre-existing intercultural differences in the tolerance and perceptions of bullying or similar behaviors [2,10].

Although negative workplace behavior entails the actions of an individual or a group, organizational culture, workloads, and leadership styles have all been shown to affect its occurrence [10]. It has been suggested that organizations seeking to mitigate negative workplace behaviors should aim to improve organizational processes that inform the management of bullying, implement skills-based training in communication and conflict management, and aim to promote accountability, transparency, and respectful peer alliances [11,12]. In the literature, there is little evidence of effective strategies that have been implemented in acute care settings to address negative workplace behavior experienced by nurses [2,13]. Of 18 previous quantitative studies that were recently reviewed critically, as reported elsewhere [2], all were descriptive and

exploratory, as opposed to interventional studies. The available literature sanctions intervention at multiple levels to influence the *civility norms* of the nursing profession, clearly emphasizing on the modification of culture and practice [13]. It is evident in nursing as well as other disciplines that interventions with integrated, organization-wide approaches improve *civility* [13-16], whereas interventions focused on individuals have less impact [17,18]. Therefore, rather than focusing on individual interventions, such as targeting new graduate nurses (NGNs) to improve resilience [19], the research methodology described in this paper takes a multi-level approach. The protocol targets NGNs, registered nurses (RNs), and senior RNs in managerial positions. The study will investigate participants' experiences of negative workplace behavior and their ways of coping when exposed in an environment where an intervention was being implemented at an organizational level concurrently, at the time the research was being undertaken.

### Theoretical Framework

The theoretical framework that underpins this research protocol is the Social Worlds Theory [20]. Social Worlds Theorists explain society as shaped and upheld via repeated interactions between individuals [21] and that society as a whole can be conceptualized as consisting of a mosaic of social worlds that both touch and intersect [22]. These social worlds refer to groups where there is *a set of common or joint activities or concerns, bound together by a network of communication* [23]. Social worlds develop around one primary activity (eg, delivery of patient care). There are also sites where these activities occur (eg, within the hospital setting) and technology relating to performing the activities is always involved (eg, clinical and technical skills). Each individual within the social world is engaged in a relevant activity; however, some individuals are, or believe themselves to be, more *authentically* belonging and more suited to that world [24]. Claims of authenticity can lead to conflict and power struggles and consequently to the creation of excommunicated individuals of social subworlds [24]. The ongoing conflict and the creation of subworlds within the primary social world of nursing is evident, and tension and conflict manifest in the form of negative workplace behavior.

## Methods

This study is ongoing and has been registered with the Australian New Zealand Clinical Trials Registry (Registration No. ACTRN12618002007213; December 14, 2018).

### Study Aims

The aim of this study is to investigate the self-reported exposure to and experiences of negative workplace behaviors of nursing staff and their ways of coping in regional acute care hospitals in one local health district (LHD) in New South Wales before and after Respectful Workplace Workshops have been implemented within the organization.

### The Study Design

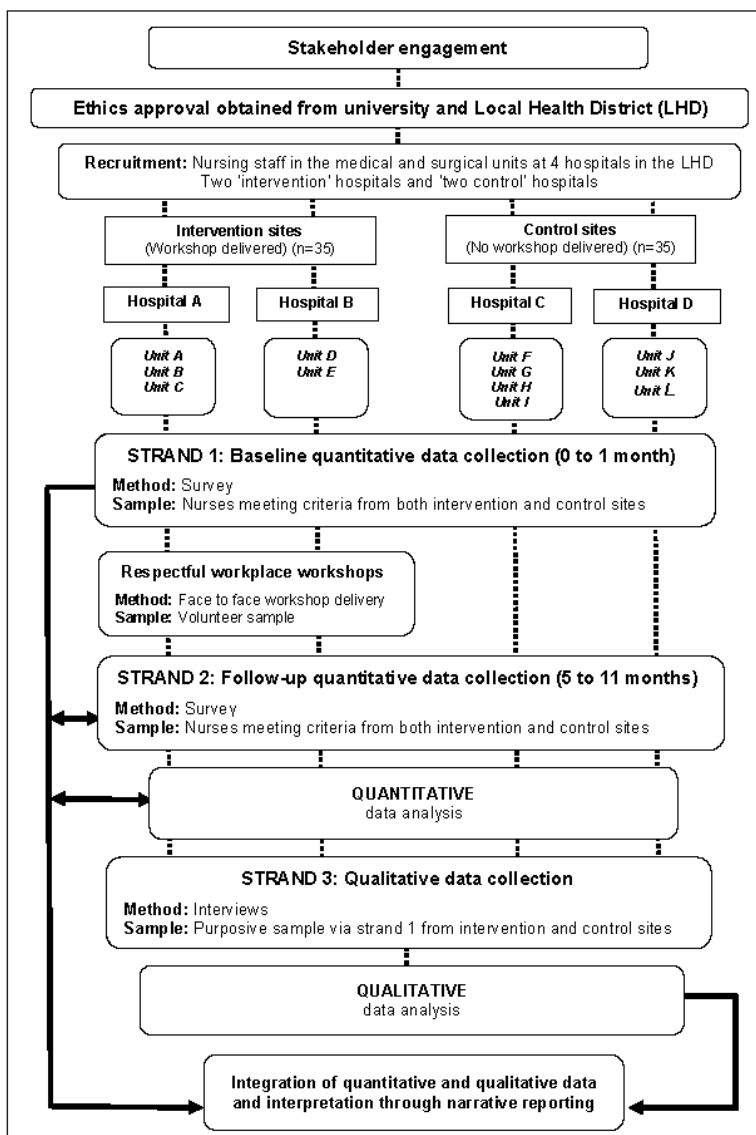
This study uses a mixed methods, sequential explanatory design [25] with an embedded experimental component [25,26]. Data collection will occur in 3 distinct strands:

- Strand 1: an initial survey before the delivery of the Respectful Workplace Workshops by the organization (quantitative).
- Strand 2: follow-up surveys after conducting the workshops at 2 of the 4 hospitals involved in the study (quantitative).

- Strand 3: interviews with nursing staff from across all the hospitals involved in the study (qualitative).

The sequence of the strands is presented in Figure 1. The mixed methods approach recognizes that neither quantitative nor qualitative study designs alone are able to capture the nuances of particular phenomena, whereas the combination of both takes advantage of their respective strengths [25]. Integrating qualitative and quantitative findings will allow triangulation and a broader perspective of the participants’ social worlds, with data grounded in individuals’ lived experiences, positioned in a macro-organizational context [27].

Figure 1. Flowchart showing the entire research process for the mixed methods study.



### Stakeholder Engagement

The research team collaborated early in the study design process with stakeholders from within the organization. Consultation took place with the LHD Respectful Workplace Workshop delivery team, the research committee, the executive director of nursing, and the directors of nursing, nurse unit managers (NUMS), and clinical nurse educators (CNEs) at each proposed hospital site. Stakeholder engagement in health care research

is advocated to increase collaboration between researchers and users, thereby increasing research impact and knowledge translation [28]. This collaborative design process allowed for the negotiation of included hospitals to meet both researcher and organizational needs by assisting and aligning with the organization’s plan to deliver Respectful Workplace Workshops at the proposed sites. The consultation also allowed the identification of potential barriers in undertaking the study, including teaching workloads for the workshop delivery team



and clinical workload and time required away from the wards for staff to attend the workshops.

### The Respectful Workplace Workshops

The Respectful Workplace Workshops will occur in the intervening period of data collection between strand 1 and strand 2. The workshops comprise 3 copyrighted face-to-face training modules developed for LHD delivery. The aim of the modules is to promote respectful workplace behavior by improving communication between staff members with the aim to recognize, manage, and mitigate negative workplace behavior [29]. These workshops have previously been delivered at other metropolitan hospitals within the LHD but not at those selected for this study.

The Respectful Workplace Team, an education division within the LHD, delivers the workshops, with all workshop facilitators having completed relevant prior training. The workshops require staff to attend face-to-face teaching sessions. Modules 1 and 2 require 2 hours of contact time and, to assist with rostering, the team has combined modules 1 and 2 into a single 4-hour workshop. Module 3 is only for nurse unit managers and requires attendance for a further 4 hours of face-to-face contact. The workshops will be made available to staff on various days over a 3-month period to increase attendance and minimize disruption.

The modules use a combination of training methods, including role-play, brainstorming, didactic teaching with PowerPoint presentations, and workbooks. The first two modules aim to challenge participants and encourage reflection on responsibilities and contributions to support a respectful workplace. These modules provide participants with a structured conversation template to assist with clear, direct, and respectful communication, allowing for role-playing of these conversations to assist the translation of theory into practice. The third module explores the manager's role in supporting a respectful workplace and aims to improve managerial skills by using resolution pathways and coaching of other staff. Although workshop attendance is not compulsory, the directors or nursing have agreed to support and encourage attendance and roster staff accordingly.

### Setting, Sampling, and Participants

Study setting, sampling, and participant recruitment will be based on the inclusion criteria pertinent to the research aims [30]. To minimize selection and participant bias, comprehensive and rigorous criteria have been developed. Potential hospitals and units for inclusion were selected in consultation with the Respectful Workplace Team, the members of which are employed in the LHD to deliver Respectful Workplace Workshops in the hospitals. The selection of hospitals and units was based on the presence of minimal or no previous attendance by nurses at the Respectful Workplace Workshops. A total of 9 employees across the 4 hospitals were identified as having potentially attended the workshops previously at other hospitals within the health district. The hospitals chosen are of similar size, with similar service availability and case mix. Regional hospitals were selected because the phenomenon under investigation is of significant concern in nonmetropolitan

locations, where ongoing staffing and recruitment issues exist [31]. Being in the same LHD, all 4 hospitals have the same centralized executive leadership, are subject to the same bullying and negative workplace behavior policies, and are subject to the same human research ethics committee governance processes. In total, 2 of the 4 hospitals were assigned to have the Respectful Workplace Workshops delivered within the 6-month study period; these hospitals (A and B) are referred to as the *intervention sites* in Figure 1. The other 2 hospitals did not have the workshop delivered until after data collection of strands 2 and 3 was completed. Those hospitals (C and D) are referred to as the *control sites* in Figure 1.

This study included 12 wards or units across 4 nonmetropolitan, regional acute care hospitals within the same New South Wales LHD. The units were selected on the basis that they were general medical or surgical wards, where most NGNs were employed.

Targeted study participants may be categorized as follows:

- NGNs in their first 12 months of practice following the completion of a Bachelor of Nursing degree.
- RNs who had been employed for more than 1 year at a minimum of 0.6 full-time equivalent.
- Senior RNs are employed in permanent leadership roles, who have managerial responsibilities for other staff members and patients, including NUMs, CNEs, and clinical nurse specialists.

Nursing staff known to have attended the workshops previously will be excluded from selection and others who indicate in the initial survey screening questions that they had previously attended the workshop will also be excluded from the data analysis. Owing to the relatively low number of previously exposed participants spread across 12 wards or units, the risk of contamination bias at a site level was considered minimal.

The participants will be allocated into clusters according to hospitals at which they are working; thus, they will be employed at hospitals where the workshops were either delivered or not delivered. Nested sampling will be undertaken for the qualitative and quantitative components of the study. The sample of the qualitative component is a subset of those who participated in the quantitative components. Survey participants will be a volunteer sample of nursing staff working in the medical and surgical wards in all 4 participating hospitals. The sample for the qualitative component of the study will be purposively chosen from survey respondents who will volunteer to be interviewed to represent the roles of the nurses and sites where they are working.

The total target population is 230 at the time of writing this paper, which includes 64 NGNs, 154 other RNs, and 12 senior RNs with managerial roles. Assuming a 30% response rate ( $n=69$ ), 5% type 1 error, and 80% power to detect an effect size equivalent to 0.7 of the SD, it is anticipated that it will be necessary to recruit 35 participants from the hospitals where the Respectful Workplace Workshops will be delivered and 35 from those where no workshops are conducted.

## Strand 1 and 2: Surveys (Quantitative)

Surveys will be administered on 2 occasions, separated by several months. First, a baseline survey will be conducted across all 4 participating hospitals within the first month after initiation of the study, with the second follow-up survey conducted between 5 and 11 months after initiation. In the intervening period, the Respectful Workplace Workshops will be conducted at 2 of the 4 hospitals.

This component of the study is designed to investigate NGNs', RNs', and senior RNs' experiences and perceptions of negative workplace behaviors occurring in medical and surgical wards as well as whether there are any observable differences over the period of the study between the two sites where the workshops will be conducted as compared with the other two sites. The survey will also examine the ways of coping by respondents after being exposed to negative workplace behaviors. The initial survey will capture data from the NGNs within their first 3 months of employment, when they are reportedly most vulnerable and require most support [32]. Participants do not need to complete the strand 1 survey or attend the workshops to participate in the strand 2 survey.

With careful consideration of the content and layout, the questionnaire was informed by a literature search to identify the validated instruments. The recruitment package consists of multiple parts, as follows:

- A participant information statement detailing the nature of the study according to the ethics requirements
- Demographic and background questions
- Negative Acts Questionnaire—Revised (NAQ-R) [33]
- Purpose-designed self-assessment of exposure to bullying and incivility questions
- Purpose-designed questions informed by the learning outcomes of the workshops
- Management of bullying and incivility questions (NUMs only)
- Ways of Coping Questionnaire (WCQ) [34]
- A separate consent form to return for volunteering to participate in a subsequent interview

Permission was granted for the use of the NAQ-R [33], which was originally designed to measure exposure to bullying in the workplace. This instrument consists of 22 items measuring exposure to negative workplace behaviors, with response alternatives on a 5-point Likert-type scale, where the higher the score, the greater the frequency of exposure to negative acts. The Cronbach  $\alpha$  for the NAQ-R is .95 for the total scale, meaning that it has a high level of consistency between the questionnaire items. The NAQ-R has 3 subscales: person-related bullying, work-related bullying, and physically intimidating bullying [33]. Two additional items will be added to the NAQ-R to assess the perceived degree to which patient care is compromised or obstructed and whether respondents felt that they have been isolated from supportive peers. The addition of these items was justified by evidence from a recent integrative review of relevant literature [2].

The purpose-designed self-assessment of exposure to bullying questions also uses a 5-point Likert-type scale response, where

higher scores indicate increased exposure. Before answering this section, respondents are asked to consider the definition of *workplace bullying* from the New South Wales Ministry of Health [35]. Participants were also asked whether they had been exposed to incivility at work over the previous month, with response alternatives as follows: 1=no; 2=yes, but only rarely; 3=yes, now and then; 4=yes, several times per week; and 5=yes, almost daily. For this question, the definition of *workplace incivility* is "lower level, subtle forms of workplace mistreatment." Examples include: *having your ideas or opinions dismissed; having derogatory or demeaning remarks made about your work; eye rolling; feeling belittled or humiliated; and being stared at, watched, or being excluded from social activities.*

Participants are asked to identify the designation of the *perpetrator* of the negative workplace behavior to which they had been exposed. Response options are as follows: manager, colleagues (other RNs), endorsed enrolled nurses, assistants in nursing, patients, doctors, students, and others. The turnover intentions of participants will be measured on a Likert scale (strongly disagree, disagree, unsure, agree, and strongly agree) in response to the statement that "the impacts of bullying and incivility in my workplace make me think about leaving my current position." Likert scale responses are also used as a self-assessment measure of participants' capabilities to respond to and manage bullying and incivility. Participants are asked about policy awareness and their perceived capacity to use resolution pathways, challenge disrespectful behavior, and know when to escalate and ask for assistance.

The WCQ is a 66-item instrument that is designed to examine coping processes in stressful encounters [34]. Revised in 1985, it is in the public domain and no special permission was required for its use [34]. Respondents are asked to indicate to what extent they use particular strategies to cope when exposed to negative workplace behavior using the following responses: 0=not used, 1=used somewhat, 2=used quite a bit, and 3=used a great deal. The WCQ consists of 8 subdomains, including 1 problem-focused scale, 6 emotion-focused scales, and an eighth scale containing both problem-focused and emotion-focused items [34]. The Cronbach  $\alpha$  for each scale ranged from .61 to .79 [34].

The NGNs, RNs, and senior RNs will be invited to complete the surveys on either hardcopy or on the internet via *REDCap* (Hunter Medical Research Institute, 2020), which is a secure web-based application for building and managing web-based surveys and databases. Details of how to access the web-based survey will be displayed on information posters in the wards or units, with responses uploaded automatically to the database. The web-based option allows nurses to participate without the risk of being seen taking a hardcopy from the ward or unit, whereas the alternative hardcopy option considers limitations in access to the internet. Hardcopies can be returned anonymously by either depositing them into brightly colored, sealed boxes in the staff rooms or sending them directly to the research team in the self-addressed, reply paid envelopes. To increase the response rates, all potential respondents will receive an email reminder from the new graduate coordinator at their

particular hospital at 2 and 4 weeks after the initial survey distribution.

### Strand 3: Interviews (Qualitative)

The qualitative research component adheres to the COREQ (Consolidated Criteria for Reporting Qualitative Studies) [36]. A completed COREQ checklist has been appended as [Multimedia Appendix 1](#) to this study.

The qualitative strand occurring after preliminary quantitative data analysis aims to broaden and deepen the understanding of nurses' experiences and perceptions of workplace behavior by allowing exploration through dialog in semistructured, one-on-one interviews [27]. To participate, informants will be purposively selected to be representative of nursing roles and hospital sites from the consenting participants in strand 1 ([Figure 1](#)). The informants need not attend the workshops to participate in an interview but must work on one of the wards included in the sampling frame. The interviews are expected to last up to 1 hour and will be audio-recorded, then transcribed verbatim by a transcription service with which the university has a confidentiality agreement for subsequent content analysis. The sample size in the qualitative strand cannot be postulated, as it will be determined by developing theoretical categories [37]. Data collection and analysis will occur concurrently, and it is anticipated that interviews will continue until such time that *no new theoretical insights nor new properties of core theoretical categories emerge* [37].

### Quantitative Data Analysis

The quantitative data will be analyzed using Stata 14 (TM; StataCorp LP), a statistical software that enables users to analyze, manage, and produce graphical presentations of data [38]. Participant characteristics will be summarized separately for intervention and control sites. Differences between groups for categorical variables will be assessed using chi-squared tests (or Fisher exact, the nonparametric equivalent) and Student's *t* tests for continuous variables. Differences between intervention and control sites in exposure to bullying (as assessed by the NAQ-R) and ways of coping (as assessed by the WCQ) will be assessed for all nurses at strand 2. Statistician support will be pursued to assist with analysis.

### Qualitative Data Analysis

The qualitative data will be organized using NVivo software (version 11; QSR International) [39]. The data analysis process will be guided by the Straussian Grounded Theory (SGT) [40,41], the method of choice for researchers framing their research within the Social Worlds Theory [42]. The aim of SGT is to generate an *explanatory theory that closely approximates the reality it represents* [43] and explore not only the phenomenon but also how the actors involved respond to this phenomenon and the consequences of their actions [40]. The SGT method includes a 3-stage approach: open coding, axial coding, and selective coding [40,44]. In the initial stage of open coding, the researcher is immersed in the transcribed interview data line-by-line using constant comparison to identify the categories of data [40,44]. Constant comparison involves reading and rereading transcripts, constantly comparing similarities and differences and sorting data into categories [45]. The axial

coding stage involves the identification of relationships between data categories [40,44]. One of the key features of SGT is using a coding paradigm to assist with analyzing, refining, and aligning categories [40]. In the final, selective coding stage, categories are refined and integrated, ultimately leading to a small number of core categories that will link directly to the data [40,44]. The researchers will ensure the trustworthiness of the study by considering the validity standards that ensure rigor, confirmability, credibility, dependability, and transferability [46].

### Data Integration

Owing to the separative approach to data analysis, where quantitative and qualitative data are collected and analyzed separately [47,48], the integration of data will occur in the interpretation phase to assimilate the 2 analyses of the phenomena [47-50]. This approach is known as meta-inference and is achieved through a narrative reporting process, writing both qualitative and quantitative findings together on a theme-by-theme or concept-by-concept basis [51]. There are inherent challenges in undertaking data integration in mixed methods studies, and there are few examples of mixed methods research integration [52]. Challenges include researchers' experience and methodological preferences; the nature of the data and avoidance of placing greater emphasis to one set of findings over the other; the design and timing of the phases of the study; and publication requirements and the target audience [52].

### Ethical Considerations

The research project adheres to the National Statement on Ethical Conduct in Human Research Council [53] and is approved by both the LHD and university ethics committees. Potential participants will be informed of the aim and requirements for participation via a participant information statement to ensure informed consent. Participants will be informed of their rights, privacy and confidentiality, the usage and storage of information, contact for complaints, and dissemination of results in the participant information statement. Completion of the survey will indicate respondent consent for the quantitative components of the study. A written consent form for an individual interview will be obtained before the interview. Given that the nature of the research topic may elicit an emotional response, participants can bring a support person with them to the interview, if they wish. The contact details of the free Employee Assistance Program counseling service will be made available as well as contact details for Beyond Blue [54], a national not-for-profit organization providing online and telephone support for individuals experiencing distress. Participants' autonomy will be respected and they may withdraw from the study at any time without any adverse consequences. Data will be stored confidentially and will be deidentified.

## Results

This study is currently ongoing and the results, using the recruitment, data collection, and data analysis methodology described above, are expected to be available no later than the end of 2022.



## Discussion

### Principal Findings

This paper has presented the protocol of an ongoing study that aims to investigate the nurses' experiences of negative workplace behavior and their ways of coping in an environment where an intervention is being implemented by the health service in which they are employed. The Respectful Workplace Workshops aim to empower nurses to recognize negative workplace behavior as well as promote and reinforce *civility* and *workplace courtesy* to create a respectful and supportive workplace, where nurses feel safe to practice. In addition to the before-and-after approach, the study design has included both *intervention* and *control* sites, making it possible to compare the results between the sites where the workshops are delivered and sites where the education has been temporarily withheld until after the research has been completed. It is anticipated that at the sites where the workshops occur, there will be an overall reduction in the levels of perceived negative workplace behaviors, as identified by the NAQ-R. Given that there have been limited strategies implemented in the health care setting to address negative workplace behaviors, this study may help understand to what extent, if at all, an intervention designed to intervene at professional and organizational levels is effective for the workplace culture and climate. Hence, the research relates more to organizational, macro-level *environmental* consequences of negative workplace behavior than on individuals, although the latter is also of considerable interest.

One of the benefits of undertaking this research in relatively small regions, as opposed to major metropolitan hospitals, is that the target population is more confined and therefore less subject to external influences that may create bias or confound results. Regional hospitals have a smaller number of staff members, with a more limited rotation of rosters, making the recruitment of study participants more targeted. Such hospitals and wards also tend to be more closely knit, with staff members who often know each other well and have worked together for long periods. Although a core group of long-term staff members may exist, it is also a reality that staff turnover is problematic in nonmetropolitan locations, where staff cannot be readily replaced should they decide to leave. It may be that the long-term staff members' attitudes, opinions, and values affect the general tenor of the social world they inhabit, and it may be perceived that new staff do not belong. This can be exacerbated if the new recruits are younger and less experienced. It is expected that this study will explore such factors, especially in the qualitative component.

The study design and methodology have several strengths. First, by undertaking mixed methods research, it will provide different perspectives about the same phenomenon. This study will also use the inclusive term *negative workplace behaviors* to capture the conceptual differences and variety of behaviors. Unclear, definitional consensus and clarity of the concept of bullying,

harassment, horizontal violence, and incivility within the nursing profession suggests that the previous research had lacked focus, direction, and depth [2,55]. A synthesis of terms and greater conceptual clarity may improve identification, support, and intervention at personal, professional, and organizational levels. This inclusivity has the potential to provide insights into the current level of various forms of negative workplace behaviors to which NGNs as well as more experienced RNs are exposed. To the best of our knowledge, this is the first such inclusive approach to investigate this issue within the social world of nursing practice.

### Potential Limitations

Though inclusive of 4 regional hospitals and 12 wards, the findings from this study will be limited to a single LHD with one overarching management team, which affects generalizability. In addition, there are a number of threats to internal and external validity [56]. Care is necessary in the selection of the *control* and *intervention* groups to ensure they are of equal size and comparable, so as to minimize confounding variables [55]. Maturation also needs to be considered [56], including the reflection of natural changes within the participants over the duration of the study. For example, a new graduate's skills may improve, so that they are increasingly *fitting in* and *getting the job done* and perhaps less subject to negative behaviors. The research team also needs to consider that an unplanned event may occur during the study, which may impact the results unintentionally, such as staff changes or change of manager [56]. Low survey response rates and difficulty recruiting for interviews may also be a potential limitation. Owing to the sensitive nature of the research topic, staff members may be reluctant to participate. Attendance at the Respectful Workplace Workshops is also reliant upon managerial engagement to maximize attendance from each ward.

### Conclusions

The findings from this research will add to the volume of literature on negative workplace behavior in the health care professions; however, it will add new perspectives through using multiple, previously validated survey instruments in combination with qualitative, in-depth interviews. The integration of quantitative and qualitative methods will allow for a dual perspective contextualized with the theoretical lens of the Social Worlds Theory to provide data grounded in individuals' lived experiences and positioned in a macro-organizational reality. A further perspective is provided by the opportunity to perform the research in conjunction with the delivery of the LHD's Respectful Workplace Workshops. By collecting pre- and postworkshop data and from sites both exposed and not exposed to the workshops, it is expected to add insights into the efficacy of such interventions. It is anticipated that evidence from this study will inform future nursing practice and policy development aimed at creating respectful workplaces.



## Acknowledgments

The authors would like to acknowledge the LHD, the directors of nursing of the participating hospitals, the NUMs, and participating nurses. The primary author (NH) was successful in securing a small grant under a blinded review for the statistical analysis of this project. The funding body had no role in the design of this study or in the collection, analysis, and interpretation of data. The data sets generated and analyzed during this study are not publicly available due to their confidentiality and ethical terms but can be requested from the corresponding author when necessary.

## Authors' Contributions

All authors have read and approved the manuscript. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. They were involved in drafting the manuscript or revising it critically for important intellectual content and gave final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. The authors agreed to be accountable for all aspects of the work in 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

Consolidated criteria for reporting qualitative (COREQ) checklist.

[\[DOCX File, 24 KB - resprot\\_v10i1e18643\\_app1.docx\]](#)

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## Abbreviations

- CNE:** clinical nurse educator  
**COREQ:** consolidated criteria for reporting qualitative  
**LHD:** local health district  
**NAQ-R:** Negative Acts Questionnaire–Revised  
**NUM:** nurse unit manager  
**RN:** registered nurse  
**SGT:** Straussian Grounded Theory  
**WCQ:** ways of coping questionnaire

*Edited by G Eysenbach; submitted 09.03.20; peer-reviewed by S Brownie, S Musy, C Surr, K Piil; comments to author 09.08.20; revised version received 26.11.20; accepted 07.12.20; published 11.01.21.*

*Please cite as:*

Hawkins N, Jeong S, Smith T

*Creating Respectful Workplaces for Nurses in Regional Acute Care Settings: Protocol for a Sequential Explanatory Mixed Methods Study*

*JMIR Res Protoc* 2021;10(1):e18643

URL: <http://www.researchprotocols.org/2021/1/e18643/>

doi: [10.2196/18643](https://doi.org/10.2196/18643)

PMID: [33427678](https://pubmed.ncbi.nlm.nih.gov/33427678/)

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Proposal

# Online Self-Determination Toolkit for Youth With Disabilities: Protocol for a Mixed Methods Evaluation Study

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## Abstract

**Background:** Youth with disabilities encounter many challenges during their transition to adulthood including finding employment. Jobs are often inaccessible, and youth often face a lack of support, discriminatory attitudes, and sometimes low self-confidence. Therefore, it is critical to help youth enhance their self-determination skills to advocate for their needs in the workplace.

**Objective:** The aim of this paper is to describe how an online toolkit aimed to improve self-determination in advocating for needs, including disability disclosure and accommodation requests to employers, was co-created with youth with disabilities.

**Methods:** We will use a mixed method design in which qualitative data (ie, focus groups and mentored discussion forum) are collected to understand the contextual factors during the intervention that could affect outcomes or explain results through the pre-post questionnaires. Fifty youths with disabilities aged 15 to 24 years will be recruited.

**Results:** Data collection is in progress. Planned analyses include focus groups and pre-post surveys to determine the impact of the intervention on self-determination. A qualitative content analysis of the focus groups and all open-ended survey questions will be conducted to understand the impact of the toolkit.

**Conclusions:** Our online toolkit includes evidence-informed content that was co-created with youth who have a disability. It has potential for educational and vocational programming for youth with disabilities.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/20463

(*JMIR Res Protoc* 2021;10(1):e20463) doi:[10.2196/20463](https://doi.org/10.2196/20463)

## KEYWORDS

disability; involvement; occupational therapy; rehabilitation; youth

## Introduction

### Background

Although there is substantial evidence that people with disabilities are a strong asset to our workforce, their employment rates are persistently lower than people without disabilities [1].

This trend is especially true for youth with disabilities, who have significantly lower employment rates compared with youth without disabilities. For example, the employment rate for youth in Canada aged 20 to 24 years with a severe disability is 35% and youth with a mild or moderate disability is 57% compared with 87% of youth without a disability [2]. For youth aged 15 to 19 years with disabilities, their employment rates are 40%



compared with 51% of youth without disabilities [2]. Some research shows that significantly more youth with disabilities leave high school and remain unemployed compared with youth without disabilities [3,4]. Therefore, it is critical to provide them with support and tools to enhance their employment outcomes.

### Employment and Youth With Disabilities

There are approximately 540,000 Canadians aged 15 to 24 years who have disabilities [5]. Such youth represent a unique population facing a challenging transition to adulthood and are at an increased risk for poor health outcomes and psychological distress [6-8]. Many youths, especially those with disabilities, often find the transition to adulthood and securing work to be difficult [9-12]. Although there are often many stereotypes about people with disabilities, many of them, including youth, are willing and able to work, yet they remain one of the most marginalized groups in the labor force [10,11]. Research consistently shows that having a disability can be an obstacle to finding work, where people encounter difficulties at both the societal (ie, stigma and discrimination, inaccessible jobs) and individual (ie, low self-confidence) level [4,9,13-16]. As a result of such barriers, youth with disabilities commonly have higher unemployment rates compared with youth without disabilities [17]. Focusing on youth and young adults with disabilities is particularly worthwhile because they often have difficulties with developmental tasks, social development, and role functioning [6,18]. Additionally, this period of emerging adulthood (ie, 18 to 25 years) is characterized by identity exploration, instability, and development of executive functioning, all factors that are critical for achieving independence and securing employment [6]. This developmental period is an optimal time to enhance positive behaviors while developing work-based identities [6,8,10].

### Workplace Disability Disclosure and Accommodation

In many countries, workplace accommodations (eg, modified environment, flexible hours, adaptive technology) are supported by human rights and accessibility legislation that places a duty on employers to provide reasonable accommodations to employees with disabilities [19,20]. Disclosure of a disability or health condition is a prerequisite to receiving workplace accommodations [21-23], which have potential to improve work participation and well-being [24,25]. However, research shows that many people with disabilities are reluctant to tell an employer about their condition because they are concerned about potential discrimination or job loss [9,11,25,26]. For example, some 55% of Canadians with disabilities believe that hiding their disability increases their chances of getting hired and promoted [17]. Such high rates of nondisclosure are concerning because working without accommodations can hinder health, quality of life, and work productivity [27-29]. Youth may be particularly reluctant to disclose their disability to an employer given their inexperience and/or engagement in precarious work (ie, part-time, casual, or contract work) [4]. Although many people with disabilities could benefit from having workplace accommodations, only a small proportion of employees are disclosing their needs [30-33]. This trend is concerning, especially for youth with disabilities who often have unique developmental needs; workplace policies that are

typically implemented for adults may be inappropriate for youth [30,33]. Therefore, providing them with additional support on how they could advocate for their needs may be worthwhile.

### Self-Determination and Youth With Disabilities

Youth with disabilities often have lower levels of self-confidence and self-determination (ie, attitudes and abilities required to act as the primary agent in one's life to make choices free from external influence [34]) compared with youth without disabilities [35], which are important factors that can affect employment outcomes. This trend often results from having fewer opportunities to develop self-advocacy and independence skills than youth without disabilities. For individuals to develop self-determination they need to establish coping behaviors when facing adverse situations (eg, rejection from employers, unemployment) through having a consistent effort and exposure to social learning experiences. Some studies have shown that having high self-efficacy can lead to positive outcomes compared with having lower self-efficacy [36]. For example, Bandura [37] explains that self-efficacy can be improved through mastery of experience, social modeling, verbal persuasion, and improving physical and emotional states. Other research has shown that students with disabilities who have high self-determination have favorable employment outcomes, access to job benefits, and financial independence 1 to 3 years after postsecondary graduation [38]. Indeed, self-determination is often a predictor of students' transition outcomes 2 years after graduation [16]. Given the importance of self-determination in enhancing employment outcomes, the aim of our study is to develop an online toolkit to optimize self-determination of youth with disabilities, specifically helping them to advocate for their needs and consider the pros and cons of disclosing their condition and requesting workplace accommodations.

### Online Toolkit to Enhance Self-Determination

One potential way to address vocational possibilities for youth with disabilities is through an online toolkit to enhance self-determination. Toolkits offer a way to package multiple knowledge translation (KT) strategies that educate and facilitate behavior change [39] and outcomes [40]. KT toolkits provide a simple, more flexible method for promoting and using best practices [40]. To be effective, toolkits should provide high-quality evidence to guide their use or implementation and have a planned approach and active engagement [39,40]. Combining online resources with interactive KT strategies may increase the likelihood of successful outcomes in evidence-based practice knowledge, skills, and behavior [41,42]. Our toolkit is an online interactive PDF that includes a PowToon video (PowToon Ltd), Articulate 360 (Articulate Global Inc) e-learning, and simulations.

### Theoretical Framework: Social Cognitive Career Theory

Learning and behavior change are greatly influenced by how well a message is heard, understood, and trusted and how much support individuals receive in translating new knowledge into changing practices [43,44]. We draw on social cognitive career theory to inform our understanding of youths' development of self-determination after using our toolkit to enhance disability

disclosure. This theory is an expansion of Bandura's [37] psychological theory of social cognition that focuses on cognitive and motivational processes. In the context of vocational psychology, this theory was expanded to include career development [45]. This theory focuses on how people make work decisions, develop interests, and cope with work-related barriers and involves three main constructs: self-efficacy (ie, a person's belief about their capability to organize and execute courses of action that are required to attain a type of performance), outcome expectations (ie, personal beliefs about the consequences of performing particular behaviors), and personal goals (ie, determination to participate in an activity or affect a future outcome) [37,46]. Each of these constructs is foundational toward achieving independence and work-related goals. Having goals allows individuals to exercise personal agency while contributing to enhanced self-efficacy in work-related roles [47].

Social cognitive career theory considers the ways in which individuals acquire and maintain behavior while also incorporating the social environment in which individuals perform behaviors [37]. The theory also considers a person's past experiences that influence whether behavioral action will occur. Such past experiences can influence reinforcements and expectations that affect whether a person will engage in specific behaviors and the reasons for their engagement [37].

Within the context of our intervention, we hypothesize that the online toolkit will help increase self-determination. Specifically, when an individual has strong self-determination skills (ie, capability of executing behaviors) and expects a positive or successful outcome they will be more inclined to form goals for sustaining or increasing their participation in an activity [47]. Using a theory-framed approach [48], specifically drawing on the social cognitive career theory, will help to provide context for us to consider how our online toolkit might influence self-determination for youth with disabilities.

## Methods

### Objectives

The primary objective of this project is to describe how an online toolkit was co-created with youth with disabilities to improve their self-determination and describe the evaluation plan.

### Design

We will use a mixed method design in which qualitative data (ie, focus groups with a pre-post survey and mentored discussion forum) are collected to understand the contextual factors during the intervention that could affect outcomes or explain results (through pre-post questionnaires) [49,50]. The rationale, design, and content of our intervention are based on several systematic reviews that focused on the benefits of hiring people with disabilities [1], workplace disclosure and accommodation requests for youth with disabilities [51,52], the role of gender in finding and maintaining employment among youth with disabilities [53], vocational interventions for youth with disabilities [54], mentorship programs to facilitate transition to employment for youth with disabilities [55], and a review of electronic mentoring programs and interventions for youth with

disabilities [56]. Needs assessments of youth with disabilities, employers (eg, disability awareness/confidence), and clinicians regarding disclosure and accommodations were also conducted in an earlier phase of this study [57-60]. There are currently no online toolkits that address work-related self-determination for this population.

Institutional ethical approval and informed written consent will be obtained from all participants prior to starting. We will follow the best practices in developing, implementing, and evaluating user-centered content as a KT strategy [39-42,61,62] including the consolidated framework for implementation research [63].

### Procedures for Development of Youth Toolkit Intervention

The purpose of the intervention is to improve the self-determination of youth with disabilities through an online toolkit about disability disclosure and workplace accommodations. The intervention, which was co-created with two youths who have disabilities (one with a visible physical disability and one with an acquired brain injury) along with a knowledge user advisory group and evidence-informed content from our team. The youths were recruited as paid project staff (ie, youth facilitators) and received appropriate training in research and project-specific training. We wrote the toolkit in youth-friendly, lay language. Several sections and tools within the toolkit were written and co-designed by youths. We then had an additional three youths with disabilities review our toolkit for usefulness and comprehensiveness. The youths also provided suggestions for layout and graphic design. After incorporating their suggestions, we had it reviewed by our hospital's health literacy committee. Finally, our team reviewed the content, layout, and graphics at all stages with youths.

### Interactive and Immersive Learning Tools

We codeveloped interactive and immersive learning tools with youth with disabilities that included information about what a disability disclosure is and why it is important, things to consider before disclosing, how and when to ask for workplace accommodations, learning to self-advocate, knowing your rights (including a PowToon video co-designed with youth), and a words of advice section (including youth and employer case studies). We also included two simulations.

### PowToon Animated Video

Our previous systematic reviews and needs assessments revealed that youth with disabilities wanted more information about workplace rights [51,57]. Therefore, we developed an interactive tool that specifically addressed this (Multimedia Appendix 1). We had a youth with a disability (ie, a paid member of our team) design a PowToon, a user friendly web-based animated video tool. The youth first researched relevant content with input from the research team. They then developed a script, which was audio recorded and used voiceover with the video. Next, graphics were added to the sound and slides were created with visuals from PowToon. Finally, the timing and appearance of all the elements were adjusted accordingly. The final version of the video will be embedded within the appropriate section of the toolkit.

### **Articulate Storyline**

Another tool within the online toolkit involved Articulate 360, which is a multimedia platform and e-learning authoring tool. A youth with a disability wrote the story based on their lived experience with looking for a job and returning to work after an acquired brain injury ([Multimedia Appendix 2](#)). They sought feedback from the research team and scripted the story using the branching feature, which allows participants to follow different routes depending on their actions. We worked through the whole storyline as a team and assisted with the graphic design. Next, animated buttons were inserted so the previous and next slides could be triggered. Additionally, given that this is an interactive tool, layers for each slide were created so that when a participant clicks on a specific aspect of the slide, it would trigger a different response along with appropriate feedback. Finally, the text-to-speech tool was used to add audio.

### **Simulations**

We integrated two simulations (ie, life-like environments and contrived social situations that mimic problems or conditions that arise in professional encounters) [64] into the toolkit. One focused on a youth with a disability in a job interview and the other one involved a recently hired youth with a disability who was asking their employer for workplace accommodations. By involving youth with disabilities in building the scenarios for these simulations, it helped to enhance their relevance and authenticity [64-66].

The simulation development sessions each lasted 2 hours and were facilitated by a researcher who is certified in SIM-One simulations (ie, briefing, debriefing, and facilitation). The first session focused on building the simulation scenario content (with three youths who have disabilities), and the second session was centered on piloting the scenario with live actors (ie, simulated participants) who trained for their character roles prior to participating in this session.

We asked the youth for feedback on the simulation content, its relevance for youth with disabilities, and any recommendations they had for further development. We then worked with a simulation educator and simulated participants to finalize a scenario script. We piloted the disability disclosure scenario with feedback from youth and the research team. We incorporated all feedback into the final version of the simulation, which was filmed and embedded within the toolkit.

### **Mentored Discussion Forum**

The purpose of this intervention is to combine the youth toolkit with mentor-based learning, provided through a secure, online platform (myability.ca). This consists of case-based mentored discussions (ie, 50 participants total; 10 participants per group, plus mentor, across 5 groups). Each topic will cover the toolkits and simulations and other interactive materials. Trained mentors will lead discussions while encouraging interaction and support between participants. Mentors will be hired as project staff and will undergo appropriate training.

The mentored discussion forum consists of asynchronous discussions (ie, separate discussion for each main topic in the toolkit) aligned with the topics in the youth toolkit. Participants

can view the discussions and the toolkit at their own pace, ask questions, and chat with the mentor and other participants. The discussion is open to the other participants in the group and available only to the participants in that particular group (ie, they cannot see participant discussions who are in another group). Participants can decide when they want to log in and contribute at a time that is convenient for them. Mentors will post their availability when they will be logged in so that participants have an opportunity to discuss things in real time.

Trained mentors will include near-peers (ie, young adults with a disability who have job experience) who have completed a youth mentor or equivalent training. Mentors will introduce the topics in the same order and will be trained to respond to participant comments in a similar manner—providing informational, appraisal, and emotional support. Prior to working with participants, mentors will practice their skills with fellow mentors and other research team members whose recent experiences will be similar to those of mentored participants (eg, training on active listening, perspective taking, confidentiality, maintaining boundaries, positive modeling, trust building through interactive training, and mentoring).

Mentors will lead discussions based on the youth toolkit over 2-week periods during the course of 6 months (each participant would only take part once). We would offer them at different times throughout the year to capture different youth (eg, summer break, March break). Mentors will have an opportunity to meet (virtually) before joining our project website.

### **Sample and Recruitment**

All participants will be recruited through invitation letters, referrals, or advertisements via our project partners. We will collaborate with our partners ([Multimedia Appendix 3](#)) and other relevant community agencies that help young people with disabilities find employment to identify eligible participants. Using such an approach to obtain a purposive sample has been effective in previous studies. We will recruit 50 youths (aiming for an equitable representation of genders) to take part in one of several focus groups (10 participants in each). Youth participants aged 15 to 24 years (based on the United Nations definition of youth) [67] will be included based on the following criteria: able to read/write in English; have a disability (ie, defined as impairments in body function or structure, activity limitations, and participation restrictions) and currently employed, enrolled in training, or seeking employment; and willingness to be audio recorded.

### **Focus Groups**

After developing the content, we will host focus groups (2 hours each) with participants to gather feedback on the content, usability, and layout of the toolkits. During the focus groups, a researcher will give participants an opportunity to go through the toolkit and will answer any questions they may have. Participants will receive a link to the toolkit, which is hosted on the Holland Bloorview Kids Rehabilitation website, and/or a copy of the interactive PDF of the toolkit to review in advance of the focus group. We will go through each section with the youths, facilitated by a member of our research team, while asking them about the relevance and usefulness of each section.



We will also ask about what they liked most and least, what they learned (if anything), and any other thoughts that they would like to discuss relevant to the toolkit and topic.

### **Pre-Post Surveys**

After testing at our pilot sites and refining the toolkits based on feedback from the focus groups, we will work with our project partners to embed these educational tools as part of ongoing training (eg, youth employment and life skills programs), a strategy linked with higher likelihood of facilitating change [68]. We will train researchers and knowledge user champions to deliver the intervention offsite through our partners and networks. The toolkits and simulations will be available through our project website and linked to our project partners, where youth can self-refer to access the tool and health care providers can also direct youth to this resource. Participants using the toolkits and simulations will be asked to complete a brief online survey via Research Electronic Data Capture, and we will assess wider scale uptake [63].

### **Feasibility and Sample Size**

To test the primary hypothesis that our intervention will improve self-determination for youth with disabilities [69], a *t* test will be used. With an alpha of .05, power of 80%, and at least a medium effect size (ie, 0.50), a sample size of at least 50 is needed [70,71]. This sample size, which incorporates the possible attrition of participants, is suitable for this study design [72], and there are sufficient eligible participants to draw upon through our partners and collaborators.

### **Data Collection**

The data collection for this study is currently in progress.

### **Measures**

All standardized measures have good internal consistency, construct-related and criterion validity, and test-retest reliability and are widely used for people with disabilities. We will use Arc's self-determination scale, a self-report measure assessing self-determination for disabled adolescents [69] (subscales on autonomy, self-realization, and psychological empowerment), and community participation (subscales related to workplace) [73].

### **Secondary Measures**

Secondary measures for all participants will include demographic measures such as age, gender, type of disability, assistive devices, education level, and type of work. We will have open-ended questions asking what they liked most and least about the intervention. We will draw on the community impacts of research-oriented partnerships, subscales on personal knowledge and development [74], and subscales from the toolkit evaluation questionnaire by Malik et al [75]. To assess the simulations that are embedded within the toolkit, we will draw on some satisfaction questions from Kirkpatrick and Kirkpatrick [76] evaluating training programs. To measure the broader impacts of the interventions, we will use the consolidated framework for implementation research [63,77] and the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework [78]. Secondary qualitative data consists

of open-ended questions in the pre- and postsurvey and transcripts of the focus groups and mentoring discussion forums.

## **Results**

Data collection for this study is in progress. The proposed analysis is outlined in further detail below.

### **Quantitative Data Analyses**

Quantitative data will be analyzed using SPSS Statistics (IBM Corp). Descriptive statistics provide an overview of the sample characteristics using means and standard deviations for continuous factors and frequencies and proportions for categorical factors. Chi-square and *t* test analyses will be conducted to test intervention effects (comparing preintervention survey primary outcomes, time 1) and posttest data (immediately postintervention, time 2). Separate analyses will be run for each outcome while exploring gender. To control for type I error rate, a Holm sequential correction will be applied. Effect sizes for *t* tests and Cohen *d* will be reported [70] with a level of .05 for statistical significance.

### **Qualitative Data Analyses**

All open-ended questions will be entered into NVivo (QSR International). Researchers will independently read all transcripts while noting key codes. Our objectives will guide the analysis, and data will be analyzed separately for focus groups and discussion forum data. An inductive, open-coding content analysis will be used [79] while specifically noting codes around disclosure, accommodations, mentoring, and disability awareness. Two researchers will read all transcripts to familiarize themselves with the data, generating initial codes, and revising and defining the codes and themes [79]. We will then meet to discuss our codes and revise them until consensus is reached among the research team on the final coding scheme (ie, separate ones for discussion forum and focus group data). We will apply all of the codes to the transcripts where they will be categorized into themes and subthemes. After the discussion forum and focus group transcripts are coded once in their entirety, they will be compared and contrasted using a qualitative comparative method [80] to see whether any differences within and between the groups appear. We will develop a thematic comparison table to help analyze what themes may be present in each group, and representative quotes will be extracted.

Strategies to ensure rigor and trustworthiness (ie, transferability, dependability, conformability) of the findings include prolonged engagement, peer debriefing, and descriptive participant accounts [81,82]. We will keep an audit trail of the decisions made during the analysis [79]. We will include excerpts from the transcripts that were reflective of the participant experiences to illustrate the themes [79]. We will also have peer debriefing discussions among the research team, which will include considering how our background training and experience may have influenced with the development of the themes while noting this in our audit trail [79].



## Discussion

### Principal Findings

This study will make several contributions to knowledge. First, most research on accommodations focuses on return to work among adults. Research focusing on workplace accommodations for youth with disabilities is lacking [30,52]. Second, more theoretically informed work is needed to support youth disclosing their condition through the development of evidence-informed interventions. Establishing innovative interventions that are scalable to a wide range of knowledge users could help to enhance disclosure discussions and inclusive

environments, ultimately helping young workers to succeed in maintaining meaningful and productive employment.

### Conclusion

This intervention was co-created with youth with disabilities to help enhance their self-determination and self-advocacy skills in finding and maintaining employment. Helping youth with disabilities to develop such skills is important because they are an underrepresented group in the labor market. Our intervention may help youth to enhance their employment while helping them on their career pathway as they transition to adulthood. Our intervention can also serve as an accessible tool to supplement traditional vocational programming for youth with disabilities.

### Acknowledgments

We would like to thank our project partners and collaborators for their contributions to this toolkit and the staff and trainees in the Transitions and Inclusive Environments lab for their support in this project. This study was funded in part by the Canadian Institutes of Health Research–Social Sciences and Humanities Research Council Partnership Grant (01561-000 and 895-2018-4002) awarded to SL and the Kimel Family Fund through the Holland Bloorview Kids Rehabilitation Hospital.

### Authors' Contributions

SL, MH, NT, JS conceived the study and developed the initial study protocol. SL wrote the protocol for publication and provided ongoing oversight for the data collection during the study. PK contributed to the toolkit development and evaluation plan. All authors read and approved the final protocol for publication.

### Conflicts of Interest

None declared.

#### Multimedia Appendix 1

PowToon animation.

[PDF File (Adobe PDF File), 290 KB - [resprot\\_v10i1e20463\\_app1.pdf](#) ]

#### Multimedia Appendix 2

Articulate storyline.

[PDF File (Adobe PDF File), 2438 KB - [resprot\\_v10i1e20463\\_app2.pdf](#) ]

#### Multimedia Appendix 3

Project partners.

[PDF File (Adobe PDF File), 23 KB - [resprot\\_v10i1e20463\\_app3.pdf](#) ]

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**Abbreviations****KT:** knowledge translation**RE-AIM:** reach, effectiveness, adoption, implementation, maintenance

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*Edited by G Eysenbach; submitted 19.05.20; peer-reviewed by R Lee, S Lin; comments to author 28.06.20; revised version received 15.07.20; accepted 28.07.20; published 11.01.21.*

*Please cite as:**Lindsay S, Kosareva P, Sukhai M, Thomson N, Stinson J**Online Self-Determination Toolkit for Youth With Disabilities: Protocol for a Mixed Methods Evaluation Study**JMIR Res Protoc 2021;10(1):e20463**URL: <http://www.researchprotocols.org/2021/1/e20463/>**doi: [10.2196/20463](https://doi.org/10.2196/20463)**PMID: [33427688](https://pubmed.ncbi.nlm.nih.gov/33427688/)*

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Protocol

# Evaluation of Self-Care Activities and Quality of Life in Patients With Type 2 Diabetes Mellitus Treated With Metformin Using the 2D Matrix Code of Outer Drug Packages as Patient Identifier: Protocol for the DePRO Proof-of-Concept Observational Study

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## Abstract

**Background:** Diabetes mellitus (DM) is one of the most common noncommunicable diseases. DM has a substantial negative impact on patients' quality of life, which is measured using a variety of diabetes-specific measures covering multiple aspects of patients' psychological state, behavior, and treatment satisfaction. A fully digital data collection system, including patient identification, would represent a substantial advance in how these patient-reported outcome (PRO) data are measured. Within the European Union, one way to identify patients without the involvement of health care professionals is to use the unique 2D matrix codes on the packaging of prescription medication—for example, metformin, the recommended initial treatment for patients with type 2 DM (T2DM).

**Objective:** In the DePRO study we aim to (1) describe the self-care activities of patients with T2DM using metformin-containing medication; (2) describe the self-reported health status (eg, presence of diabetes complications and quality of life) of these patients; (3) describe associations between self-care activities and demographics and disease characteristics; and (4) assess the usability of the my ePRO app.

**Methods:** DePRO is an observational, multicenter, cross-sectional, digital, patient-driven study conducted in Germany. Patients with a prescription for a metformin-containing medication will be given a postcard by their pharmacist, which will include a download link for the my ePRO app. In total, 12 diabetes-focused pharmacies, selected to represent urban and rural areas, will be recruited. Participants will use their own mobile device (bring your own device) to download the my ePRO app and access the DePRO study, for which they can register using the 2D matrix code on their medication. An electronic informed consent form will be displayed to the patients and only after giving consent will patients be able to complete the study questionnaires. The PRO instruments used in the study are the Summary of Diabetes Self-Care Activities Scale, the Diabetes Treatment Satisfaction Questionnaire, and the 5 level, 5-dimension EuroQol Questionnaire. Patients will also be asked to complete a questionnaire with items addressing demographics, patient characteristics, disease history, complications, and concomitant medications. Data will be transferred to the study database by the app upon completion of each questionnaire. Statistical analyses of primary and secondary endpoints will be exploratory and descriptive.

**Results:** Enrollment began in June 2020. The estimated study completion date is December 31, 2020, and the planned sample size is 300 patients.

**Conclusions:** The DePRO study uses completely digital data collection, including authentication of eligible patients and completion of the study questionnaires. Therefore, the design of the DePRO study represents a substantial advance in the evaluation of the digital capturing of PRO data.

**Trial Registration:** ClinicalTrials.gov NCT04383041; <https://clinicaltrials.gov/ct2/show/NCT04383041>

**International Registered Report Identifier (IRRID):** PRR1-10.2196/21727

(*JMIR Res Protoc* 2021;10(1):e21727) doi:[10.2196/21727](https://doi.org/10.2196/21727)

## KEYWORDS

self-care activities; quality of life; type 2 diabetes mellitus; patient-reported outcome measures; digital observational study; bring your own device

## Introduction

### Background

Diabetes mellitus (DM) is one of the most common noncommunicable diseases, with a growing global prevalence which is impacting negatively on the sustainability of health care systems [1]. According to the International Diabetes Federation, DM affected 463 million people globally in 2019, a number forecast to grow to 578 million by 2030 [2]. An estimated 8.5% of the adult population in Europe has DM, with national prevalence rates ranging from 2.4% to almost 15% [3]. DM has a high negative impact on society as a result of the severe comorbidities and complications associated with the disease [4]. Several studies have estimated that 90%-95% of all patients with DM are affected by type 2 DM (T2DM) and that the prevalence of T2DM will continue to increase due to population aging [2,5]. The complications of DM affect patients' quality of life [6,7] and increase the risk of negative events such as emergency department visits, hospitalization, and death, with consequences for health care costs and the sustainability of health care systems [8]. Clinical recommendations refer to diabetes self-care and self-management as key to preventing disease complications and maintaining patients' health and quality of life over time [9,10].

Assessment of psychosocial functioning and health-related quality of life has gained prominence in the care and treatment of patients with diabetes over the past decade. This has resulted in the development of a variety of diabetes-specific measures covering multiple aspects of patients' psychological state, behavior, and treatment satisfaction. These include, for example, the Summary of Diabetes Self-Care Activities Scale (SDSCA) and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [11,12].

It has been estimated that there were 6.9 million patients with T2DM in Germany in 2015 [13]. The recommended initial treatment for patients with T2DM is metformin [14]; in 2018, a total of 606 million daily doses of metformin were prescribed in Germany, corresponding to 160 different medications provided by 25 marketing authorization holders [15].

Within the European Union the Falsified Medicine Directive (Directive 2011/62/EU) defines "the characteristics and technical specifications of the unique identifier of the safety features ...

that enables the authenticity of medicinal products to be verified and individual packs to be identified" [16]. This 2D matrix code on the outer packaging of medication contains a country code, a product code, a serial number, the expiry date, and the charge of the medication. Once a patient has possession of the package, the 2D matrix code is no longer an identifier only of the medication, but also of the patient as the user of this medication.

### Objectives

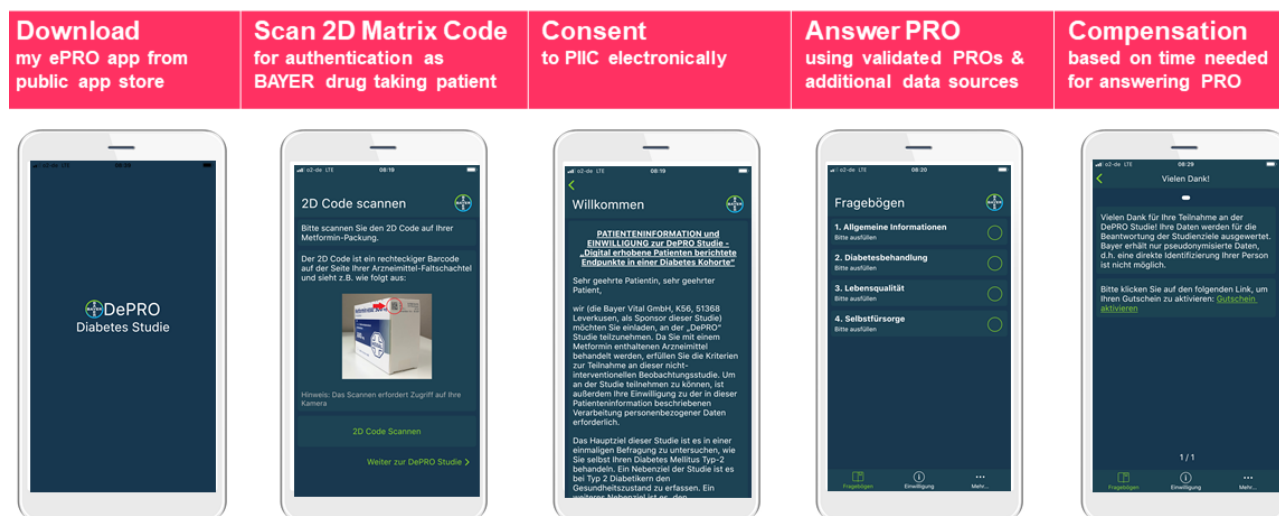
In the DePRO study we aim to (1) describe the self-care activities of patients with T2DM using metformin; (2) describe the self-reported health status (eg, presence of diabetes complications and quality of life) of these patients; (3) describe associations between self-care activities and demographics and disease characteristics; and (4) assess the usability of the my ePRO app.

## Methods

### Study Design

DePRO is an observational, multicenter, cross-sectional, digital, patient-driven study conducted in Germany. Patients with a prescription for a metformin-containing medication will be eligible for participation and will be consecutively invited to participate. Patients receiving metformin-containing medication will be given a postcard by their pharmacist, which will include a download link for the my ePRO app. Patients will conduct the entire study without any support from the pharmacist. Participants will use their own mobile device (smartphone or tablet) to download the my ePRO app and will be directed through the app to the DePRO study. For registration and authentication they will use the unique 2D matrix code on their metformin-containing drug package. An electronic informed consent form will be displayed to the patients and only after giving consent will patients be able to complete the study questionnaires. After completing the questionnaires and uploading a picture of the metformin-containing drug package, patients will receive compensation for their time, in the form of a voucher or a donation to charity (Figure 1 and Multimedia Appendix 1). Data will be transferred to the study database by the app upon completion of each questionnaire. The final data analysis for the study will be performed by a contract research organization, Institut Dr. Schauerte, Munich, Germany (IDS).

**Figure 1.** Recruitment and data capturing process with the my ePRO app. EQ-5D-5L: 5-level, 5-dimension EuroQol Questionnaire; PIIC: patient information and informed consent form; PRO: patient-reported outcome.



## Ethical Considerations

The study protocol has been approved by the Ethics Committee of the Medical Association North Rhine (approval no. 2020084).

## Patients

Adult patients with a valid prescription for a metformin-containing medication will be enrolled in a public pharmacy after the decision for treatment with metformin has been made by their treating physician and informed consent is given by patients. No restrictions on potential eligibility for the DePRO study will be applied.

## Study Device: my ePRO App

The my ePRO app is a data capture tool which can be used for either stand-alone studies or piggy-backed on randomized controlled trials and observational studies to track patients' health status. The app uses standardized, validated patient-reported outcome (PRO) instruments. Furthermore, the app has the capacity to gather additional data (physical activity, face and voice recognition, weather data) based on the research questions in each study. Users are provided with a unique app account, free of charge. By using the quick response (QR) code scanner built into the app patients can scan either a study-specific QR code provided on a patient information leaflet or the medication-specific 2D matrix code on the outer packaging of their medication. The latter option leads to company-specific pages where studies and the respective consent forms are offered. The my ePRO app is available for the most common device types (smartphones and tablets) running the most widespread mobile operating systems (Android and iOS). The my ePRO app was co-developed by IDS and Bayer, and is hosted by IDS.

## Data Transfer and Processing

Generally, the app will be used online. When not connected to the internet (offline mode), the app stores the entered data so

that no data loss occurs. Data are transferred to the database as soon as the device is online again.

## Data Collection and Outcome Measures

The treating physician will have prescribed a metformin-containing medication, but will not contribute to data collection during the study. The patient's data and answers to the questionnaires will be captured directly by the patient in the relevant sections of the my ePRO app using their own mobile devices.

By scanning the 2D matrix code with the my ePRO app, the patient is linked to a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterward, only the authorized contract research organization personnel at IDS are able to link the patient identification code to the medication package used. For collection of data on concomitant medication use, the app can be used to scan the barcodes on the outer packaging of both prescription and nonprescription drugs. The number of invited, participating and nonparticipating patients—as stated to the inviting pharmacist—and the reasons given for nonacceptance of study participation will be collected by the pharmacist in a recruitment log.

The PRO instruments used in the study are the SDSCA, the DTSQ, and the 5-level, 5-dimension EuroQol Questionnaire (EQ-5D-5L). The SDSCA is a questionnaire which assesses levels of self-care in adults with diabetes and was developed by Toobert et al [11]. The DTSQ is used to assess patients' satisfaction with their diabetes treatment [12]. The EQ-5D-5L is a widely used instrument for measuring generic health status using a 5-dimension descriptive system and a visual analog scale [17], both of which are included in the DePRO study.

To complete the clinical picture of each patient the following variables will be collected in a questionnaire (not previously validated) requesting patients' self-reported age; sex; weight; height; geographic region (first 2 digits of postal code);



concomitant medication; education level; family income; time from the diagnosis of T2DM; occurrence of diabetes microvascular complications (diabetic kidney disease, diabetic retinopathy, diabetic neuropathy, and diabetic foot); occurrence

of diabetes macrovascular complications (coronary arterial disease and stroke); and glycated hemoglobin (Hb<sub>A1c</sub>; [Table 1](#) and [Multimedia Appendices 2](#) and [3](#)).

**Table 1.** Data captured within DePRO study by origin.

Data captured	Data source	
	Patient	Pharmacist
<b>Study information</b>		
Date and time of data collection within my ePRO app	X	
Primary reason for discontinuation (if applicable; eg, consent withdrawn by patient)	X	
Reasons for nonacceptance of study participation		X
Picture of the metformin-containing drug package	X	
<b>Patient characteristics</b>		
Demography (eg, age, sex, geographic region, education level, family income)	X	
Patient characteristics (eg, height, weight)	X	
Disease history	X	
Microvascular complications (diabetic kidney disease, diabetic retinopathy, diabetic neuropathy, and diabetic foot)	X	
Macrovascular complications (coronary arterial disease, stroke)	X	
Glycated hemoglobin (Hb <sub>A1c</sub> )	X	
Concomitant medication (QR <sup>a</sup> code scan)	X	
<b>PRO<sup>b</sup> results</b>		
DTSQ <sup>c</sup>	X	
SDSCA <sup>d</sup>	X	
EQ-5D-5L <sup>e</sup>	X	
EQ-5D VAS <sup>f</sup>	X	

<sup>a</sup>QR: quick response.

<sup>b</sup>PRO: patient-reported outcome.

<sup>c</sup>DTSQ: Diabetes Treatment Satisfaction Questionnaire.

<sup>d</sup>SDSCA: Summary of Diabetes Self-Care Activities.

<sup>e</sup>EQ-5D-5L: 5-level, 5-dimension EuroQol Questionnaire.

<sup>f</sup>VAS: visual analog scale.

## Statistical Analyses

### Primary and Secondary Endpoints

Statistical analyses of primary and secondary endpoints will be exploratory and descriptive. The study is not designed to confirm or reject predefined hypotheses.

### Patient Population Size

The DePRO study aims to assess the current self-care activities of patients with T2DM in Germany within a cross-sectional design by testing the feasibility of data collection with the my ePRO app. We will therefore recruit 12 diabetes-focused pharmacies, selected to represent urban and rural areas across Germany, to participate in the DePRO study. Based on a previously conducted feasibility assessment with these pharmacies, the mean number of patients filling a

metformin-containing prescription per quarter is approximately 4500. Assuming a variability of  $\pm 15\%$  per quarter, 5175 postcards providing the download code for the my ePRO app will be provided to the pharmacies, representing the maximum sample size. Therefore, a planned recruitment time of 3 months, which covers the typical treatment situation of patients with T2DM (at least quarterly visits are necessary to receive a metformin prescription), determines the sample size of the DePRO study. For sample size considerations, we assume that 7%-10% of invited patients will complete the study. We further assume that the SD of SDSCA would be 13 points, according to the SD observed in the study by Ausili et al [18]. Given this assumption, a sample size of 300 patients is required to obtain a 95% confidence interval of the mean level of self-care with a precision (ie, width of the interval) equal to 3 points.

## Results

The DePRO study uses completely digital data collection. All data are patient reported and are not verified by any health care professional. The recruitment of patients is not based on the diagnosis of an investigator, but on the consequence of a diagnosis—namely the prescription of an approved drug. By providing software (my ePRO app) to patients and authenticating with available hardware (the outer packaging of the medication, containing the 2D matrix code), it will be possible to collect data directly from patients.

Enrollment began in June 2020. The estimated study completion date is December 31, 2020.

## Discussion

### Rationale for Study Design

The DePRO study will not only evaluate PROs measured using validated instruments, but also describe the feasibility of a fully digital data capture workflow. The study focuses on data which can be easily and reproducibly generated by patients and do not need any further validation by health care professionals. It is not necessary for health care professionals to be part of the data collection workflow for PRO assessment. This has already been achieved in randomized controlled trials and observational studies, by offering ePRO tools which enable patients to complete PROs whenever and wherever they want. The innovation in the approach taken in the DePRO study is to also bypass the need for the involvement of health care professionals in the authentication of eligible patients. By using the 2D matrix code on the outer packaging of medication a valid and uniform authentication is possible across the European Union. This was not possible previously, because linear bar codes (the former standard for pharmaceuticals in the European Union) cannot encode dynamic data such as batch numbers and expiry dates and therefore do not provide a unique identifier for each package [19]. According to the Commission Delegated Regulation (European Union) 2016/161 [20], all prescription drugs (with specific exceptions such as radionuclide generators and precursors) are now required to bear a 2D matrix code on their packaging, allowing remote patient authentication across a range of indications. The methodology can be applied in longitudinal as well as cross-sectional studies (patients can scan multiple new packs of medication over time, according to the defined logic in the back end of the app and the objectives of each study). Furthermore, the sample size of future studies using this methodology would no longer be limited by the number of health care professionals willing to recruit patients, but by the number of prescriptions issued. There are analogies between the scalability of studies using the my ePRO app and the Apple Heart Study [21]. In both studies, a large quantity of hardware (Apple Watches/prescribed drugs) is available in the market and can be used to authenticate patients. The sponsor of a study provides publicly available software (Apple Heart Study app/my ePRO app) to patients. Patients enter data without the help of health care professionals. In the case of the Apple Heart Study, and potentially of the DePRO study, the participation rate is low (in the Apple Heart Study 419,297 patients were recruited

from among more than 30 million device users, and 2161 patients received notifications of an irregular pulse).

General Data Protection Regulation (GDPR) requirements are fulfilled by the electronic informed consent form, which can also be adapted as needed for other potentially applicable data protection standards. Because health care professionals are not involved in PRO data collection, it would be beneficial for the results of the my ePRO app questionnaires to be transferred to the electronic health record of the patients. Current plans are for transfers of this sort to be enabled in Germany in 2021 through the provisions of the Digital Healthcare Act (DVG). Such a closed loop will ensure patient centricity and autonomy in data collection, storage, and sharing.

Some limitations of the DePRO study should be considered. First, the study only includes data from PROs. Second, the technology used to obtain data relies on the 2D matrix code of the outer drug package and not on a validated diagnosis by a health care professional. However, this study explicitly assesses the advantages and disadvantages of this way of capturing data. Third, it is possible that only technophile patients who are using the my ePRO app will decide to participate in the study. This may constitute a selection bias. Because T2DM affects predominantly older people and older people tend to be less inclined to use mobile devices and apps, the bias introduced may be considerable. In addition, it is unavoidable that even in the subgroup of technophile patients there might be relevant differences between those participating and those not participating. Fourth, among patients using the my ePRO app it will not be possible to distinguish for certain between patients using metformin and those not taking metformin, but documenting their health status within the my ePRO app. By using a recent drug package supplied by the pharmacist inviting the patient to the study, the medication intake behavior is an unverifiable variable. However, to prevent inappropriate participation, mitigation activities (checking 2D matrix codes for duplicate entries, blocking of the scanning tool after the start of documentation, and preventing patients from re-entering data after withdrawing consent) have been implemented in the my ePRO app. Fifth, this is a single-arm cohort study without a comparison group. However, the study is not designed to compare self-care behavior between my ePRO app users and other groups. By contrast, the study aims at understanding both the behavior and the outcomes of my ePRO app users, identified by the possession of metformin-containing drug packages, by investigating their my ePRO app data. Sixth, only patients using metformin will be able to participate in the study, precluding generalization of results to patients with other treatments. However, this study specifically aims to investigate self-care activities among patients with metformin-treated T2DM, a major subset of the overall T2DM population. Seventh, although the study aims to include participants from a variety of geographic regions, there may be local limitations that reduce the representativeness of patients recruited, such as patient access to recruiting pharmacists. Furthermore, recruitment through diabetes-focused pharmacies will limit the representativeness of the study population as a subset of the German diabetes population. Nevertheless the provision of the my ePRO app within public app stores may mean that the population sample

is not limited to patients recruited in pharmacies—if the information that there is a study available spreads among patients, participants from a larger variety of geographic regions may be recruited. Finally, analysis results transferred to the sponsor will be anonymized; therefore, in cases of incomplete data there will be no possibility of contacting the patient for

clarification and no possibility of performing source-data verification. Hence, it will be difficult to assess data quality.

## Conclusions

The design of the DePRO study represents a substantial advance in the evaluation of the digital capturing of PRO data.

## Acknowledgments

This study was funded by Bayer Vital GmbH (Leverkusen, Germany) and was conducted in collaboration with the host of the my ePRO app (Institut Dr. Schauerte, München, Germany) and Westdeutsches Diabetes- und Gesundheitszentrum (Düsseldorf, Germany) where the user experience of patients with diabetes using the study app was tested. Statistical support was provided by Frank Kleinjung (Bayer AG). Elisabeth Caroline Blinn (Bayer Vital GmbH) was responsible for site management activities and provided comments on an advanced draft of the manuscript. Editorial support at the final draft stage was provided by Paul Overton, PhD (Beacon Medical Communications Ltd, Brighton, UK) and funded by Bayer Vital GmbH.

## Authors' Contributions

CM was responsible for the study design and drafting of this article, wrote the protocol, and was responsible for the initiation and conduct of the study. SM contributed to the protocol, study design, and drafting of this article. IS contributed to the protocol, study design, and drafting of this article. All authors revised the article critically for important intellectual content, and all authors approved the final version.

## Conflicts of Interest

CM is an employee of Bayer Vital GmbH (Leverkusen, Germany). IS is the COO of Institut Dr. Schauerte. SM has received support from Bayer Vital GmbH.

### Multimedia Appendix 1

My ePRO app screenshots.

[[PNG File, 2923 KB - resprot\\_v10i1e21727\\_app1.png](#)]

### Multimedia Appendix 2

Study questionnaire (German).

[[XLSX File \(Microsoft Excel File\), 16 KB - resprot\\_v10i1e21727\\_app2.xlsx](#)]

### Multimedia Appendix 3

Study questionnaire (English).

[[XLSX File \(Microsoft Excel File\), 15 KB - resprot\\_v10i1e21727\\_app3.xlsx](#)]

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## Abbreviations

- DM:** diabetes mellitus
- DTSQ:** Diabetes Treatment Satisfaction Questionnaire
- EQ-5D-5L:** 5-level, 5-dimension EuroQol Questionnaire
- PRO:** patient-reported outcome
- QR:** quick response
- SDSCA:** Summary of Diabetes Self-Care Activities
- VAS:** visual analog scale



*Edited by G Eysenbach; submitted 23.06.20; peer-reviewed by T Bailey, T Taveira-Gomes; comments to author 26.09.20; revised version received 01.12.20; accepted 15.12.20; published 11.01.21.*

*Please cite as:*

*Mueller C, Schauerte I, Martin S*

*Evaluation of Self-Care Activities and Quality of Life in Patients With Type 2 Diabetes Mellitus Treated With Metformin Using the 2D Matrix Code of Outer Drug Packages as Patient Identifier: Protocol for the DePRO Proof-of-Concept Observational Study*

*JMIR Res Protoc 2021;10(1):e21727*

*URL: <http://www.researchprotocols.org/2021/1/e21727/>*

*doi: [10.2196/21727](https://doi.org/10.2196/21727)*

*PMID: [33427685](https://pubmed.ncbi.nlm.nih.gov/33427685/)*

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Protocol

# Investigating Users' and Other Stakeholders' Needs in the Development of a Personalized Integrated Care Platform (PROCare4Life) for Older People with Dementia or Parkinson Disease: Protocol for a Mixed Methods Study

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## Abstract

**Background:** Dementias—including Alzheimer disease—and Parkinson disease profoundly impact the quality of life of older population members and their families. PROCare4Life (Personalized Integrated Care Promoting Quality of Life for Older Adults) is a European project that recognizes the benefit of technology-based integrated care models in improving the care coordination and the quality of life of these target groups. This project proposes an integrated, scalable, and interactive care platform targeting older people suffering from neurodegenerative diseases, their caregivers, and socio-health professionals. PROCare4Life adopts a user-centered design approach from the early stage and throughout platform development and implementation, during which the platform is designed and adapted to the needs and requirements of all the involved users.

**Objective:** This paper presents the study protocol for investigating users' needs and requirements regarding the design of the proposed PROCare4Life platform.

**Methods:** A mixed qualitative and quantitative study design is utilized, including online surveys, interviews, and workshops. The study aimed to recruit approximately 200 participants, including patients diagnosed with dementia or Parkinson disease, caregivers, socio-health professionals, and other stakeholders, from five different European countries: Germany, Italy, Portugal, Romania, and Spain.

**Results:** The study took place between April and September 2020. Recruitment is now closed, and all the data have been collected and analyzed in order to be used in shaping the large-scale pilot phase of the PROCare4Life project. Results of the study are expected to be published in spring 2021.

**Conclusions:** This paper charts the protocol for a user-centered design approach at the early stage of the PROCare4Life project in order to shape and influence an integrated health platform suitable for its intended target group and purpose.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/22463

(*JMIR Res Protoc* 2021;10(1):e22463) doi:[10.2196/22463](https://doi.org/10.2196/22463)

**KEYWORDS**

dementia; older adults; neurodegenerative diseases; integrated care; health care technologies; user-centered design

## Introduction

### Background

Among the common chronic diseases, dementias—including Alzheimer disease (AD)—and Parkinson disease (PD) are the most disabling, profoundly impacting the quality of life of older population members and their families [1]. As a result, European health care systems are being challenged by the increasing demand and need for long-term care and services as well as increased health costs [2,3]; therefore, finding and implementing alternative health care solutions to face these challenges are needed [4].

Integrated care is defined as “services that are managed and delivered so that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services, coordinated across the different levels and sites of care within and beyond the health sector, and according to their needs throughout the life course” [5]. Integrated care is able to help improve care coordination and decrease the costs of care for populations with complex needs [2]. This shift in the type of care for older people does not intend to neglect good disease management but rather to optimize older people’s physical and mental capacities [6]. On the other hand, assistive technologies can help older people with chronic conditions to live independently for a longer period [7], reduce caregiver burden, and improve the work satisfaction of professional carers [7-11]. Recent studies reveal that patients identify technology as something useful that can be used for leisure and to increase their freedom and independence. Caregivers find that technology incorporated into their lives, and into the lives of the people they care for, provides them with increased peace of mind and can ease the interactions with other stakeholders [12]. Furthermore, health professionals consider that technologies reduce their workload and allow them to devote more attention to patients who require it [13].

### PROCare4Life Project

Personalized Integrated Care Promoting Quality of Life for Older People (PROCare4Life) is a European Commission Horizon 2020 project (grant agreement No. 875221) that recognizes that, today, an integrated care process should be adopted for harmonizing, from a holistic perspective, health models with social services. Therefore, the project intends to develop and test a technology-based, integrated, scalable, and interactive care platform addressed to patients suffering from neurodegenerative diseases, such as PD or dementias; their

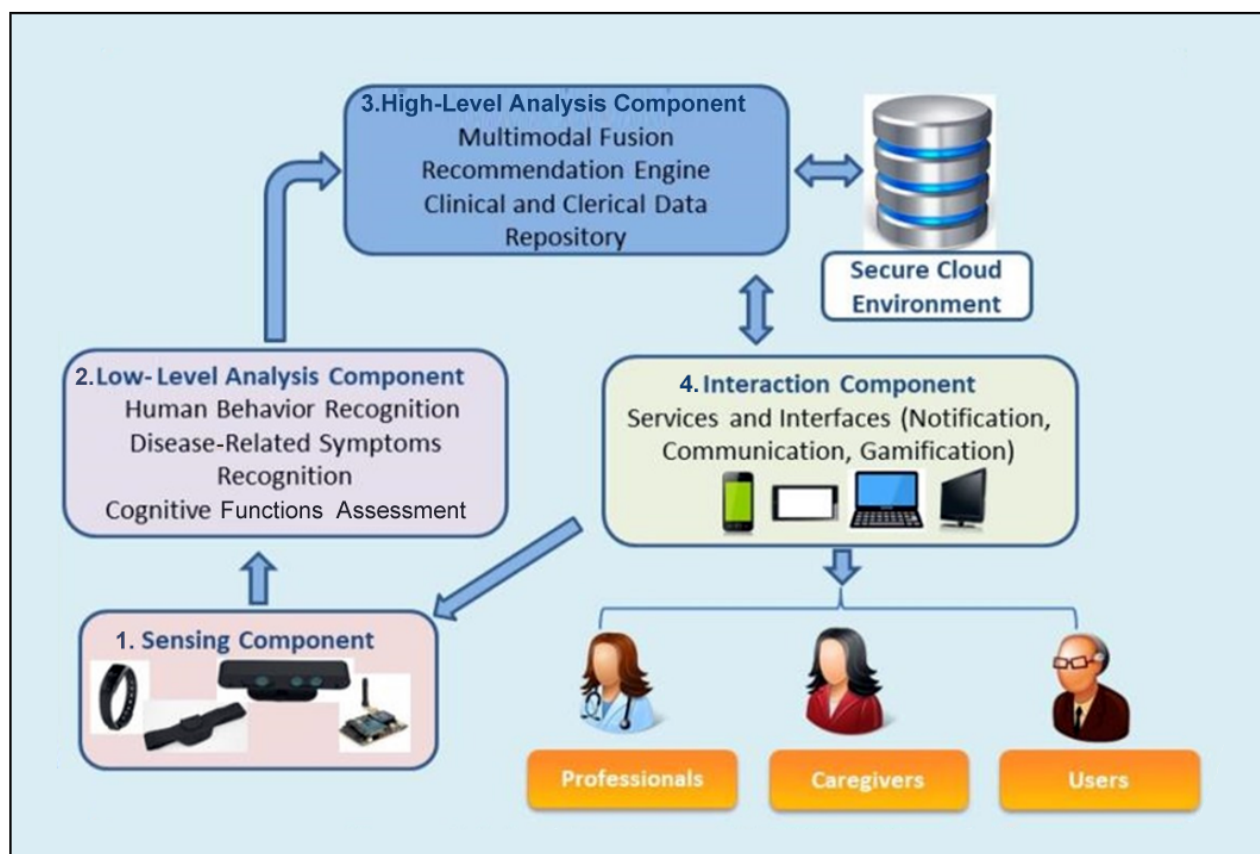
caregivers; and socio-health professionals. The aims of this 36-month project are as follows: (1) to improve the quality of life of patients, (2) to enable active living and better disease management, (3) to support professionals in the decision-making process, (4) to facilitate efficient communication between all stakeholders, and (5) to ensure reliable and protected access to data within Europe. These aims will be achieved through large-scale assessments across Europe (ie, more than 1500 end users from five countries), with a final scope to validate the reliability of the overall system in a real-life context.

The technology of the PROCare4Life platform works through different components as follows:

1. Sensing component, which is responsible for patients’ data acquisition through a set of employed sensors (eg, audio, depth, and presence sensors and wearable devices); these sensory data are first preprocessed and filtered before feeding into the next component.
2. Low-level analysis component, where the data received from the sensing component are further processed and analyzed in order to recognize individual disease-related symptoms, human behavior, and cognitive abilities.
3. High-level analysis component, where the input from the low-level analysis is fused with other personal information (ie, social and medical) in order to build a profile for each patient. This profile will be used to provide personalized recommendations regarding promotion of social networking, nutrition, leisure, and best daily activities for increasing well-being and improving physical and mental conditions. All the data developed within this component will be contained within a secure cloud environment.
4. The interaction component, where, through different services and interfaces, the generated information will be shown to the users via various digital devices (eg, mobile phone, tablet, and PC). This information can serve as notifications in the form of alerts or reminders or as a communication tool, providing a safe information channel for the social and health professional to access the patients’ profiles, read and provide reports, or receive updates about the patients’ conditions or, finally, as gamification, allowing the users to engage in motivating cognitive and functional games.

PROCare4Life takes into consideration that when it comes to the inclusion of technology in health care systems, patients tend to have different priorities compared to caregivers and professionals [14]. Hence, the project adopts a user-centered design (UCD) approach, where all the end users are included rather than only the patients (see [Figure 1](#)).

**Figure 1.** Technology of the PROCare4Life platform (source: PROCare4Life grant agreement, funded by The European Commission). PROCare4Life: Personalized Integrated Care Promoting Quality of Life for Older People.



## User-Centered Design

UCD is an iterative design process that advocates for actively engaging the users and incorporating their feedback to ensure that tools are developed with a full understanding of their needs and requirements [15,16]. The three key principles that underlie the UCD approach are as follows: (1) the design has to be based on the specific understanding of the users' needs and requirements [17], (2) the design is refined and reshaped based on the user feedback throughout the whole development, and (3) the design process includes a multidisciplinary team, skills, and perceptions [18]. A number of studies have reported benefits from using UCD in the development of technology-assisted health measures. Bilodeau et al [19] reported that the UCD process facilitated optimization of comprehensiveness and relevance of content among a relatively small sample of dementia patients and their caregivers in shared decision making. Implementing a UCD process iteratively contributed to the development of an app for cancer screening, reflecting the needs and concerns of patients [20]. Also, the UCD process was recently implemented with success to develop a prototype for a digital cognitive aid in the anesthesiology emergency field, demonstrating high usability and user satisfaction [21].

Regardless of these promising results, health technology developers have been criticized for neglecting to incorporate UCD in the development process or for their failure in reporting the integration of a UCD approach throughout the development of their interventions. Possible reasons for this could be the

limited resources and time to support the research and usability testing [22].

## Research on User Needs and Requirements

Integration of care services for older adults was proposed by the World Health Organization [23]. The Integrated Care for Older People (ICOPE) approach emphasizes the need for integrated health care models to be organized, coordinated, and delivered around older adults' needs, preferences, and goals in the context of their daily lives as a family or community member [6,24]. In fact, in developing a useful and successful technological intervention that meets the needs and requirements of the end users, it is crucial to involve them at an early stage of the design process [25,26].

A review by Vermeer et al [27] indicated that research on the needs of older people living with dementia and their caregivers remained mainly qualitative, with more focus on the needs of caregivers than patients and a clear difference in perspectives. For instance, results from focus groups revealed that dementia patients had some concerns over the use of trackers, while their caregivers had a great interest in their use [28].

A previous information and communication technology (ICT)-based European project named ICT services for Life Improvement for the Elderly (ICT4Life) was funded by Horizon 2020 (grant agreement No. 690090). This project aimed to provide an integrated ICT platform that was able to facilitate integration of health care services and provide better communication between AD and PD patients, their caregivers, and socio-health professionals. ICT4Life had an end-user



approach, where the needs and the expectations of the target population were considered throughout the development of the platform, starting with research on users' requirements. While the use of the ICT4Life platform was accompanied with better and more personalized care for elderly patients with cognitive impairments [29], the research on users' requirements involved limited study sites and a very low number of participants [30].

Adopting a UCD approach, PROCare4Life intends to build upon what has already been learned and to benefit from the knowledge gained from previous projects. Therefore, the project devoted its first phase to study user requirements and to investigate the key personal, social, health, and psychological factors that influence the daily lives of potential end users. The aim of this project phase is to define users' needs and expectations regarding the use of technology within the integrated health care system. Collected data shall be used in the setup of the iterative cycles in the pilot phases, allowing a user-centered cocreation of a platform that supports patients, caregivers, and socio-health professionals in their functions.

Research on users' requirements aims to involve approximately 200 subjects and is planned to take place in five different European countries: Germany, Italy, Portugal, Romania, and Spain. Surveys and interviews shall yield different perspectives. Preliminary results shall flow into workshops utilizing the interaction of potential users with the platform to evaluate and structure its aspects. The overall objectives are as follows:

1. Collection of detailed information on the opinions, thoughts, experiences, and feelings of users (eg, patients, caregivers, and other stakeholders, including socio-health care professionals) regarding their needs and difficulties during the health care process, to identify how a technology system

such as PROCare4life can fit their needs and meet their demands.

2. Identification of those aspects that the PROCare4Life platform should consider in order to achieve success in its acceptance, development, and marketing (eg, strengths and weaknesses, factors that influence the digital health care market, and communication channels through which to adequately diffuse the product).

This paper aims to present the study protocol for investigating users' needs and requirements regarding the design of the proposed PROCare4Life platform.

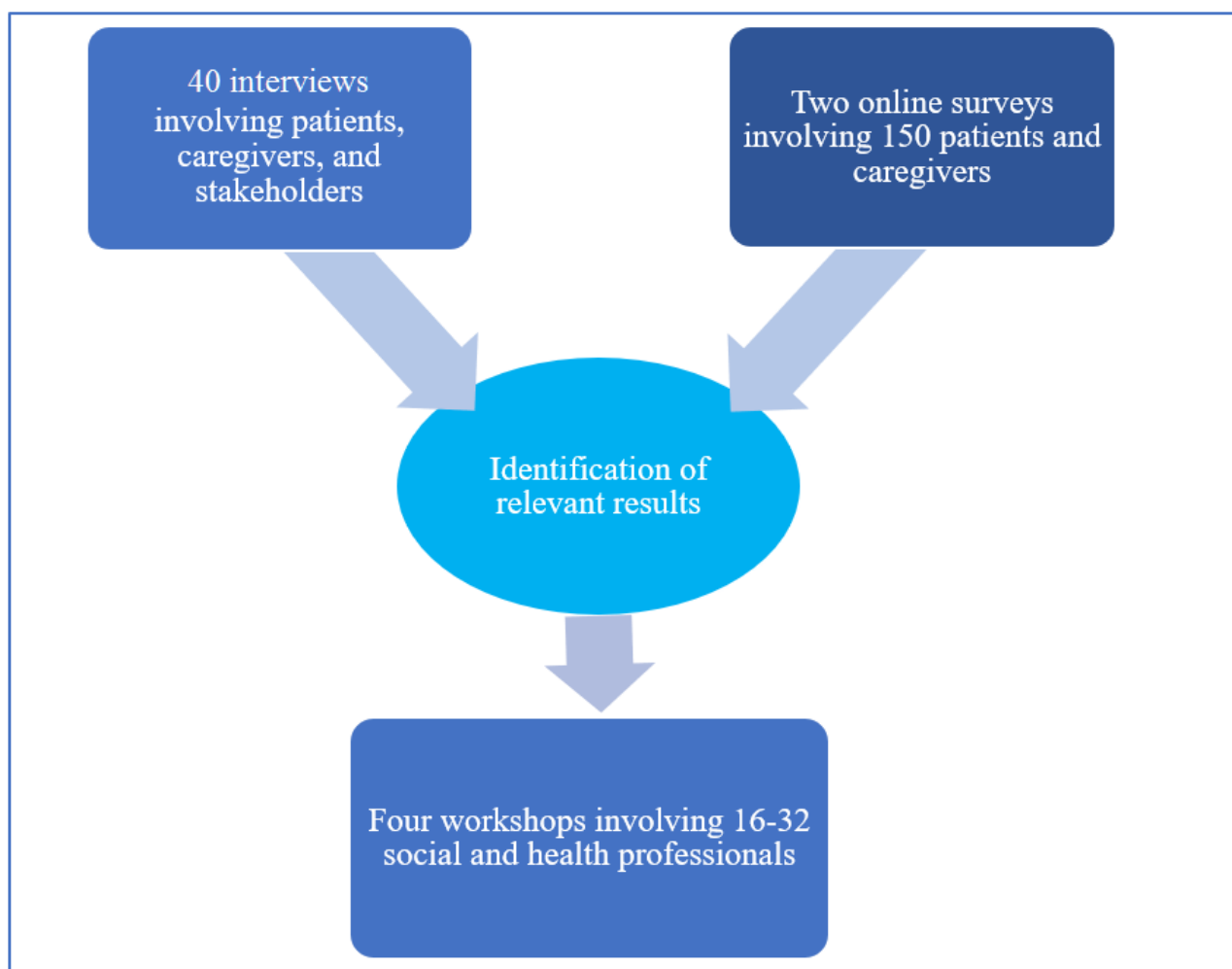
## Methods

### Study Design

The study applied a mixed qualitative and quantitative research design and included different modalities of interaction, such as interviews, workshops, and online surveys. The study started by conducting online surveys and interviews; their relevant results were then discussed and analyzed by a multidisciplinary team in order to be used in reshaping the workshops (see [Figure 2](#)), which corresponds to the key principles of the UCD approach.

While quantitative research methods are used to provide general facts about a certain topic, qualitative research methods are more important for in-depth knowledge about the experiences and ideas of end users regarding health care issues [31]; qualitative methods have also been used as a way to engage patients and stakeholders in health research [32]. Using a mixed methods design allows the study to yield rich and comprehensive data that can better reflect the participants' points of view [33] and thereby ensures the end users' involvement in the project, which is a key principle of the UCD approach.

**Figure 2.** Mixed methods study design. The study started by conducting surveys and interviews; relevant results were identified and discussed in the workshops.



### Study Setting and Eligibility Criteria

The study started in April 2020 and ran until September 2020. It took place in five European countries: Germany, Italy, Portugal, Romania, and Spain. Patients were included if they were 65 years of age or older, clinically diagnosed with PD or dementia, and willing to participate in the study. Online survey participants should have a smartphone and/or computer with web access. Patients with significant cognitive impairment, intellectual disability, or other serious psychiatric conditions that affect their ability to use mobile phones or computers were excluded.

Caregivers were considered eligible if they were 18 years of age or older, caring for patients diagnosed with PD or dementia, formal (ie, paid) or informal (ie, not paid) caregivers, aware of the patients' daily needs, and willing to participate. Online survey participants should have access to a mobile phone and/or a computer with web access.

Socio-health professionals were included if they were qualified and worked in medical or social care for PD or dementia patients (eg, physiotherapists, social workers, and occupational therapists), had a mobile phone or computer with web access, and were willing to participate.

Other stakeholders were included if they were in a responsible position within one of the following four categories:

1. Market actors: defined as those who work as health care providers either in public or private sectors.
2. Academic persons: people who work in research areas related to integrated care systems or assisted technologies for older adults.
3. Media actors: people who work for a relevant media outlet (eg, press, journalists, and bloggers).
4. Decision makers: policy makers and relevant health authorities.

### Recruitment

Each participant organization was assigned to recruit a number of participants for the different aspects of the study; this specific number was discussed and agreed on during the first project meeting, based on the effort expected from each organization related to their skills, experience, number of researchers involved, and access to users. The distribution of numbers was intended to ensure an equal distribution of all the countries involved in the project (see Table 1). Different recruitment strategies and channels were used as follows: (1) databases of the participating organizations, (2) national patient associations, (3) social networks (eg, Twitter, Facebook, and LinkedIn), (4) communication channels (eg, partner magazines), (5)

face-to-face interactions by the nature of the organizations (ie, some hospitals, despite COVID-19, have allowed interaction with patients and caregivers), and (6) PROCare4Life's website [34].

At every organization involved, the purpose of the PROCare4Life project was explained and the subjects who showed interest received information about the project either by phone or email. Subjects who met the inclusion criteria were

asked to participate and were informed about the time frame of the study.

Due to COVID-19 security alerts in most of the European countries, all face-to-face interactions, such as interviews or group interactions (ie, workshops), were undertaken remotely via telephone or in online conference rooms. Virtual interaction ensured protection to all the stakeholders, while still engaging them in the UCD research, and allowed the project to go ahead with the large participant numbers.

**Table 1.** Distribution of participants per organization for each mode of data collection.

Name of organization	Country	Number of participants, n (%) <sup>a</sup>				
		Patient interviews (n=5)	Caregiver interviews (n=5)	Stakeholder interviews (n=30)	Workshops for health and social professionals (n=4 <sup>b</sup> )	Online surveys (n=150)
Asociación Parkinson Madrid	Spain	2 (40)	1 (20)	2 (7)	1 (25)	25 (17)
Kinetikos	Portugal	N/A <sup>c</sup>	N/A	4 (13)	N/A	N/A
Campus Neurológico Sénior	Portugal	1 (20)	1 (20)	6 (20)	1 (25)	25 (17)
Casa di Cura del Policlinico	Italy	1 (20)	1 (20)	5 (17)	1 (25)	25 (17)
Wohlfahrtswerk für Baden-Württemberg	Germany	1 (20)	1 (20)	5 (17)	1 (25)	25 (17)
Münster University	Germany	N/A	N/A	6 (20)	N/A	N/A
Universitatea de Medicina si Farmacie "Carol Davila" din București	Romania	N/A	1 (20)	2 (7)	N/A	25 (17)
Spitalul Universitar de Urgență București	Romania	N/A	N/A	N/A	N/A	25 (17)

<sup>a</sup>Percentages may not add up to 100% due to rounding.

<sup>b</sup>There were four workshops, with 4 to 8 participants each.

<sup>c</sup>N/A: not applicable; the respective participants from this organization did not participate in this mode of data collection.

## Data Collection

### Online Surveys

Two anonymous open surveys were developed using the EUSurvey application; the two online surveys were available on the project's official website [35], where a post was written explaining the purpose of the surveys. Both surveys were launched on May 27, 2020, and ran until July 31, 2020; they were also distributed using mailing lists to some local patients' associations and network organizations, aiming to recruit 150 participants, including patients and caregivers. Each participant had to agree to provide their consent before starting the survey; after that, participants could choose either the patient or caregiver version. The patient version included the 36-item Short Form Health Survey (SF-36), which is a widely used questionnaire to evaluate health-related quality of life [36]. The caregiver version included the 7-item Zarit Burden Interview to measure caregiver burden [37,38]. Both versions included questions related to the key performance indicators to be achieved within the project (eg, feelings of safety; feelings of autonomy; perception of empowerment; improvement of social participation, mental condition, and/or physical condition; anxiety; depression; and fall reduction), as well as other questions about technology acceptance, willingness to pay for such technologies, and the desired features and functionalities to be included in the PROCare4Life platform. Participants were

not obligated to answer all the questions; however, at the end of the survey they had to click *send*, otherwise their participation would not be considered. The surveys were available in different languages, including English, German, Spanish, Italian, Romanian, and Portuguese. If needed, more information about the project or how to fill in the survey was sent to the participants via email, text message, or video call.

### Interviews

A total of 40 semistructured interviews were carried out—5 patients, 5 caregivers, and 30 stakeholders—in the period from June to July 2020. Some of the researchers involved in developing the questions have previously worked on another European ICT project named ICT4Life (see Introduction); as ICT4Life also included assessment of user needs and requirements, the researchers used their past experience in helping to develop the questions for this study. In addition to the sociodemographic questions, the main questions' topics were about participants' experiences with the process of care, technology usage and acceptance, and the desired characteristics and expected outcomes of the proposed platform. Patient and caregiver interviews included some closed-ended questions; in particular, those asking about care services, symptoms, and activities of daily living (ADLs). Using closed-ended questions has been recommended with older people suffering from dementia, as it helps to facilitate communication with this population [39].

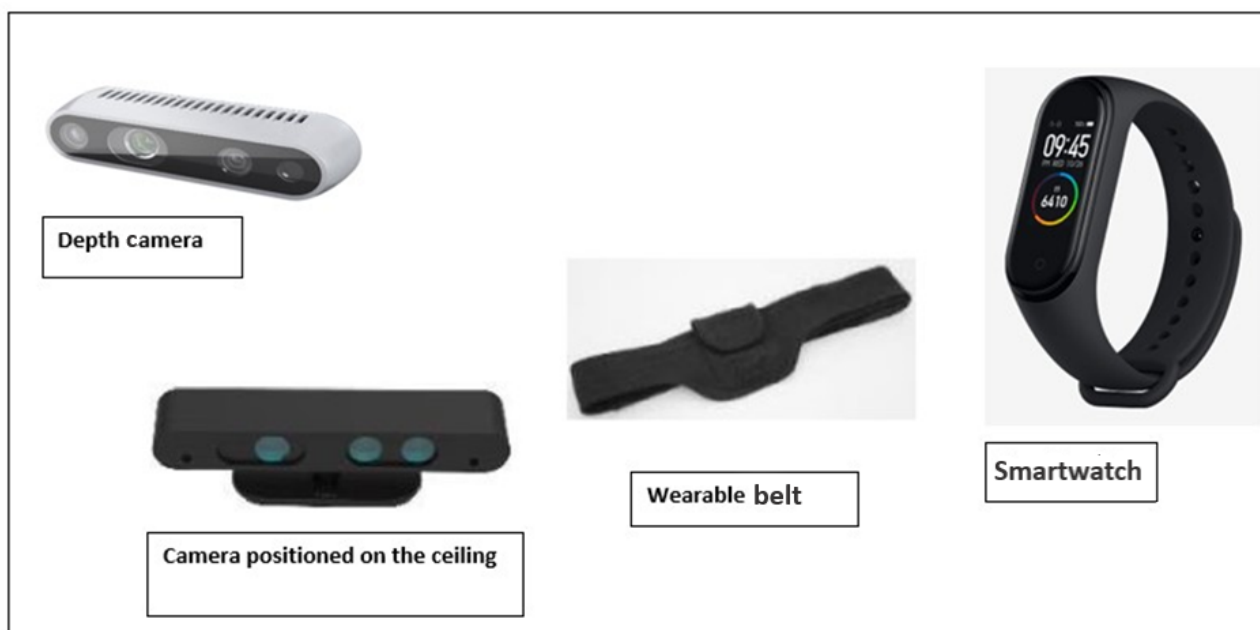
Different versions of questions were developed; for instance, for patients, the main topics included disease-specific questions, patients' problems regarding their symptoms and how these could affect their ADLs, their needs and experiences with the health care process, and their attitudes and opinions toward using technology in the health care process. Caregivers were asked about their working experience and how technology-assisted platforms such as PROCare4Life would influence their roles as caregivers.

For other stakeholders, depending on the category they belonged to, there were supplemental questions. For instance, specific

questions for academic stakeholders were included regarding the current status of research on the topic of technology-assisted, integrated health care platforms. Decision makers were asked about the existing systems of care, their readiness for innovation, and barriers they may encounter in integrating this type of care solution.

Interviews included showing the participants some images of the devices and wearables (see Figure 3) to be used with the proposed platform along with a brief explanation, with questions aiming to identify their opinions regarding the platform features and functionalities.

**Figure 3.** Example images of PROCare4Life tools and sensors viewed in interviews and workshops. PROCare4Life: Personalized Integrated Care Promoting Quality of Life for Older Adults.



### Workshops

Four workshops took place between July and August 2020; each one included 4 to 8 socio-health professionals. The workshops have the advantage over other interview methods of both sharing questions in a group and allowing participants to test predefined parts of platform, such as mock-ups, drawings, and diagrams, allowing them to discuss these during the workshops to give feedback. In these workshops, relevant results obtained from the surveys and interviews were discussed and evaluated (see Figure 2).

### Data Analysis

#### Quantitative Analysis

Quantitative analysis was descriptive. The mean, median, standard deviation, and range of values were calculated. For categorical variables, absolute and relative frequencies were used to describe the data.

#### Qualitative Analysis

Researchers from the centers involved in the study transcribed the collected data from interviews and workshops and then translated them into English. Transcription templates have been provided using Microsoft Excel sheets and were made available

for all involved partners. The analysis process was done by researchers from the Asociación Parkinson Madrid (APM) and Münster University following the thematic analysis approach [40,41], which involves six phases:

1. Familiarization with the data, which will involve reading the data and further organizing them with regard to the target groups and the question categories.
2. Acquiring identification codes.
3. Combining codes to generate different themes.
4. Reviewing themes in order to identify the recurrent themes; this phase also involves recreating, rearranging, or combining different themes together, aiming to make sense out of the data in relation to the research questions.
5. Defining and naming the themes, which will include checking the literature and relating the findings to other studies.
6. Finalizing the results with an explanation of the meaning and significance of the results along with reporting on the whole process of analysis.

The results were validated using a comparison of qualitative and quantitative data and through a discussion of the results with the end-user groups (eg, in the workshops). In addition,



bias was avoided by analyzing qualitative data in two phases by researches from APM and Münster University.

## **Ethical Consideration**

### ***Ethical Approval***

The study protocol received approvals from the local ethical committees in Germany, Italy, Portugal, Romania, and Spain.

### ***Data Handling and Management***

The partners (ie, APM, Casa di Cura del Policlinico, Campus Neurológico Sénior, Wohlfahrtswerk für Baden-Württemberg, Spitalul Universitar de Urgență București, and Universitatea de Medicina si Farmacie "Carol Davila" din București). and the supporting partners (ie, Kinetikos and Münster University) established procedures and responsibilities for data protection management prior to the start of any processing of personal data, according to legal regulations and following good practice in research. In addition, they nominated responsible persons for data management from each study organization and each supporting organization.

### ***Informed Consent***

Once the study had been fully explained to the subject, written or digital informed consent was obtained prior to any study-related procedure, according to Good Clinical Practice and International Conference on Harmonization standards.

### ***Security and Adverse Event Reporting***

There were no direct physical risks for any of the participants in these interviews, workshops, and online surveys. There was a small risk of personal data theft; however, the PROCare4Life consortium received advice from professionals in the field of data management and protection and took all possible precautions to mitigate this risk, including encryption and secure storage.

### ***Withdrawal of Participants***

Participation in this study was entirely voluntary. Participants had the right to withdraw from the study at any time, without

giving reasons or experiencing any disadvantage in terms of the quality of care they would receive if they did not participate. After the withdrawal, their data were not considered for statistical purposes. No replacements were considered.

## ***Results***

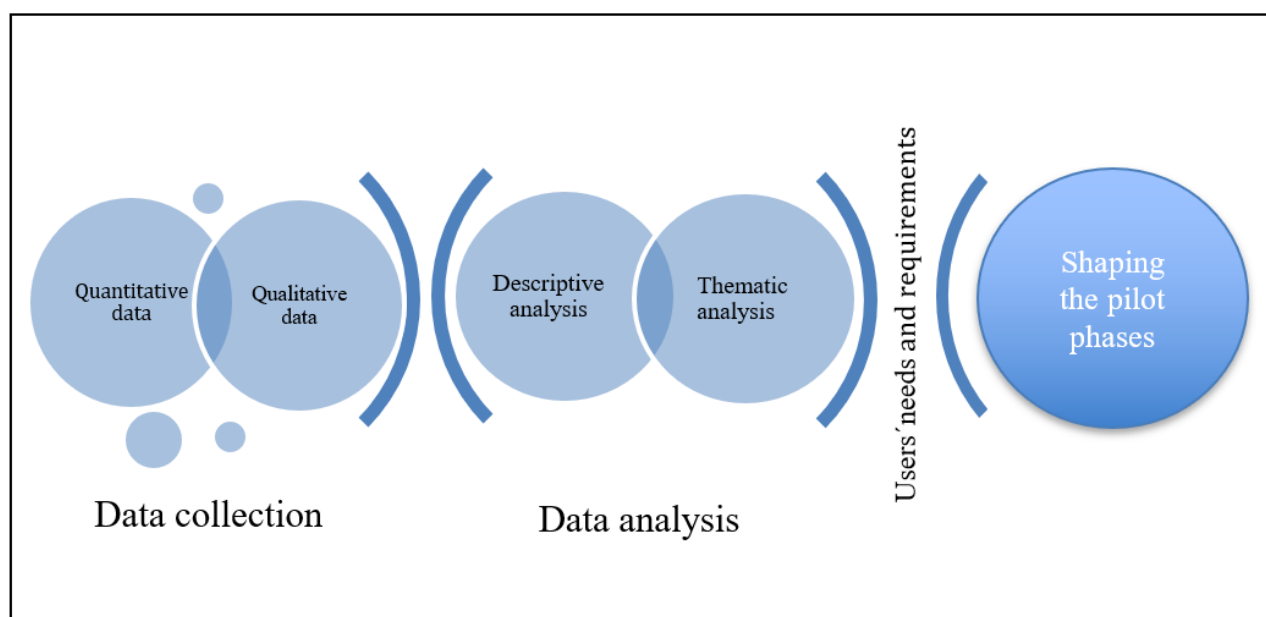
Recruitment is now closed. All the data have been collected and analyzed in order to be used in shaping the large-scale pilot phase of the PROCare4Life project. Results of the study are expected to be published in spring 2021.

## ***Discussion***

Early involvement of end users assures the suitability of a product for its intended target group and purpose [42]. UCD allows users to shape and influence the product design, which can ultimately increase usability [22] and reliability [42]. PROCare4Life aims to apply the UCD approach from the early stage of the project until the last release of the proposed integrated care platform. The data gathered from the user requirements study will help the research team in designing the different modules and services of the platform (ie, deciding which technology should be developed and how it can be used effectively). The experience with the different methods used in the study will be valuable for preparing the iterative cocreation cycles of the pilot phases of the PROCare4Life platform (see Figure 4). Furthermore, we expect the gathered information to form the base of the development strategy for the final PROCare4life platform.

In conclusion, this manuscript reports on the protocol for a mixed methods study of users' needs and requirements using the UCD approach for the European deployment of a personalized integrated care platform targeting older people with neurodegenerative disease, caregivers, and other stakeholders, including socio-health professionals.

**Figure 4.** The process of investigating the users' needs and requirements. Qualitative and quantitative data were collected and analyzed using thematic and descriptive analysis methods. The identified results will be used to shape the pilot phases of the PROCare4Life project. PROCare4Life: Personalized Integrated Care Promoting Quality of Life for Older Adults.



## Acknowledgments

The authors would like to thank the patients, caregivers, and professionals who agreed to participate in this study; the researchers from the study sites; and all the consortium members of the PROCare4Life project. We would also like to thank Iulian Nastasa, data protection officer at the Universitatea de Medicina si Farmacie "Carol Davila" din București, for advice on ethical considerations. PROCare4Life is funded by the European Commission via the Horizon 2020 program (grant agreement No. 875221).

## Authors' Contributions

All authors were involved in developing the details of the study during the project development. MA, MM, RBM, and MB conceptualized the paper. MA completed the first draft. All authors contributed significantly to the manuscript and approved the final version.

## Conflicts of Interest

None declared.

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## Abbreviations

**AD:** Alzheimer disease

**ADLs:** activities of daily living

**APM:** Asociación Parkinson Madrid

**ICOPE:** Integrated Care for Older People

**ICT:** information and communication technology

**ICT4Life:** ICT services for Life Improvement for the Elderly

**PD:** Parkinson disease

**PROCare4Life:** Personalized Integrated Care Promoting Quality of Life for Older Adults

**SF-36:** 36-item Short Form Health Survey

**UCD:** user-centered design

*Edited by G Eysenbach; submitted 13.07.20; peer-reviewed by E Wouters, A Tsolaki; comments to author 21.08.20; revised version received 27.09.20; accepted 10.11.20; published 12.01.21.*

*Please cite as:*

Ahmed M, Marín M, Bouça-Machado R, How D, Judica E, Tropea P, Bentlage E, Brach M

*Investigating Users' and Other Stakeholders' Needs in the Development of a Personalized Integrated Care Platform (PROCare4Life) for Older People with Dementia or Parkinson Disease: Protocol for a Mixed Methods Study*

*JMIR Res Protoc* 2021;10(1):e22463

URL: <https://www.researchprotocols.org/2021/1/e22463>

doi: [10.2196/22463](https://doi.org/10.2196/22463)

PMID: [33433394](https://pubmed.ncbi.nlm.nih.gov/33433394/)



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Protocol

# Step and Distance Measurement From a Low-Cost Consumer-Based Hip and Wrist Activity Monitor: Protocol for a Validity and Reliability Assessment

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## Abstract

**Background:** Self-tracking via wearable and mobile technologies is becoming an essential part of personal health management. At this point, however, little information is available to substantiate the validity and reliability of low-cost consumer-based hip and wrist activity monitors, with regard more specifically to the measurements of step counts and distance traveled while walking.

**Objective:** The aim of our study is to assess the validity and reliability of step and distance measurement from a low-cost consumer-based hip and wrist activity monitor specific in various walking conditions that are commonly encountered in daily life. Specifically, this study is designed to evaluate whether and to what extent validity and reliability could depend on the sensor placement on the human body and the walking task being performed.

**Methods:** Thirty healthy participants will be instructed to wear four PBN 2433 (Nakosite) activity monitors simultaneously, with one placed on each hip and each wrist. Participants will attend two experimental sessions separated by 1 week. During each experimental session, two separate studies will be performed. In study 1, participants will be instructed to complete a 2-minute walk test along a 30-meter indoor corridor under 3 walking speeds: very slow, slow, and usual speed. In study 2, participants will be required to complete the following 3 conditions performed at usual walking speed: walking on flat ground, upstairs, and downstairs. Activity monitor measured step count and distance values will be computed along with the actual step count (determined from video recordings) and distance (measured using a measuring tape) to determine validity and reliability for each activity monitor placement and each walking condition.

**Results:** Participant recruitment and data collection began in January 2020. As of June 2020, we enrolled 8 participants. Dissemination of study results in peer-reviewed journals is expected in spring 2021.

**Conclusions:** To the best of our knowledge, this is the first study that examines the validity and reliability of step and distance measurement during walking using the PBN 2433 (Nakosite) activity monitor. Results of this study will provide beneficial information on the effects of activity monitor placement, walking speed, and walking tasks on the validity and reliability of step and distance measurement. We believe such information is of utmost importance to general consumers, clinicians, and researchers.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/21262

(*JMIR Res Protoc* 2021;10(1):e21262) doi:[10.2196/21262](https://doi.org/10.2196/21262)

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**KEYWORDS**

activity monitor; pedometer; measurement; validity; reliability; walking; step count; distance

## Introduction

Self-tracking via wearable and mobile technologies is becoming an essential part of personal health management [1,2]. In recent years, wearable devices such as those made by Fitbit (eg, One, Flex, Ultra) and ActiGraph (GT9X, GT3X) have been widely introduced into the consumer market as physical activity monitors. The relatively low cost, interface capabilities, ease of use, and wide commercial availability of these devices may ultimately change the way researchers and clinicians alike monitor their patients' physical activity [3,4] by providing remote access to patient-generated data [5]. In particular, Fitbit [6-14] and ActiGraph [15-25] trackers have received considerable attention.

Depending on the type of activity monitor, companies recommend wearing them at the waist, wrist, pocket, hip, or bra. These wearables devices contain different tools for measurement such as piezoelectric pedometers, single triaxial accelerometers, or inertial measurement unit that combine accelerometers, gyroscopes, and sometimes magnetometers. Using proprietary algorithms, data from measures collected along with information input by the user can estimate steps, distance, physical activity, kilocalories, and sleep [4,5,25,26]. Among these outputs, step and distance measurements while walking remain the most popular and translatable outputs in use today [4,25,27-29].

At this point, it is important to recall that valid and reliable step count and distance estimates are vital output metrics and constitute crucial selection criteria for use in clinical practice [28]. However, little information is available to substantiate the validity and reliability of step and distance measurement from consumer-based hip and wrist activity monitors [26,30,31]. More specifically, despite the increasing number of published works on the evaluation of the most well-known activity monitors [17,25,27,32,33], only a few addressed low-cost activity monitors. For instance, the GT3X (ActiGraph LLC), one of the most well-known and studied accelerometer in research and clinical setting [6-14], costs around €25 (US \$250) for one device [34] plus the price of the software and accessories. Fitbit activity trackers also have been the subject of many studies [15-25]; for example, the Charge (Fitbit Inc) costs around €150 (US \$170) [35]. This observation is all the more relevant as the selling price is a main barrier to purchase [36]. Indeed, numerous activity monitors available on the market are rather expensive and beyond the financial means of a significant segment of society.

Within this context, the aim of our study is to assess the validity and reliability of step and distance measurement from a low-cost consumer-based hip and wrist activity monitor specific to various walking conditions commonly encountered in daily life. This study is designed to evaluate whether and to what extent validity and reliability of step and distance measurement from a consumer-based hip and wrist activity monitor could depend on the sensor placement on the human body and the walking task being performed. Human locomotion in daily life involves walking at non-self-selected speeds, walking upstairs, walking downstairs, turning... in other words, not just straight line

walking on flat ground at a comfortable speed. While reliability and validity of activity monitors for walking on flat ground is quite well documented in the growing literature on the subject [20,23,26,37-54], ascending and descending stairs has received less attention [20,23,44-48,50,51,53,55].

## Methods

### Participants

Young healthy adults aged 18 to 40 years will voluntarily participate to this work. Participants will be recruited in the Grenoble area (France) through open recruitment and direct invitation. From previous similar studies, we have identified that a minimum of 30 participants will be necessary to demonstrate significant differences between the experimental settings [38,47,56,57]. Participants cannot have any history of injury, surgery, or pathology to lower extremities that affects their gait.

The following participant demographic and anthropometric data will be collected: gender, age, body height, body weight, foot length, dominant leg, dominant arm, leg length, arm length, and physical activity level.

Each participant will sign a written informed consent prior to their participation in compliance with the Declaration of Helsinki. This study was approved by the local ethics committee (CER Grenoble Alpes, Avis 2019-04-09-4).

### Materials

#### Activity Monitors

The PBN 2433 (Nakosite USA Ltd) activity monitor has been selected according to previous recommendations that an activity monitor should cost less than €150 (US \$185), require no monthly costs for a subscription, provide real-time feedback to the user, and have no chest strap for heart rate measurements [58,59].

The PBN 2433 is a small, inexpensive activity monitor (dimensions: 12 mm × 8 mm × 4 mm; weight: 31.2 g; €15 [US \$20]) worn on a wrist band or clipped on the hip. The PBN 2433 tracks step count (total steps per day), calories burned (kcal/day), distance traveled (km/day), and exercise time (h/day). A multiple LCD screen displays direct feedback on outputs. No Bluetooth connection, supplementary app, or mobile or smartphone are needed. It sets up with weight (kg) and stride length (cm). Weight will be obtained by asking participant about their approximative weight. For stride length measurement, participant will be asked to walk 10 steps and the distance traveled will be divided by 10 to obtain an average stride length as is recommended by the manufacturer.

During all experiments, participants will be asked to wear four PBN 2433 activity monitors simultaneously in these locations on their body:

- Fitted on the right hip, positioned over the right anterior iliac spine via the manufacturer-provided silicone clip
- Fitted on the left hip, positioned over the left anterior iliac spine via the manufacturer-provided silicone clip

- Fitted to the right wrist using the manufacturer-provided wristband and positioned on the dorsal aspect of the wrist just proximal to the radial and ulnar processes
- Fitted to the left wrist using the manufacturer-provided wristband and positioned on the dorsal aspect of the wrist just proximal to the radial and ulnar processes

### Video Processing

Participants will also be videorecorded with an embedded camera (HERO4, GoPro Inc) fixed on the chest thanks to the dedicated harness. The camera lens will be oriented toward the ground in order to capture all steps taken by the participant. In other words, as previously done by others [19,22,23,30,38,43,45,56,58,60-64], we will use the video-based step count as the gold standard for actual step count. Video-based step counting will be independently conducted by two observers, with a third observer repeating the count in case of discrepancy between obtained step counts [27,28,65,66].

### Experimental Procedure

Participants will attend two similar experimental sessions in an indoor environment separated by 1 week. During each experimental session, two different experiments will be conducted.

In experiment 1, as was previously proposed in published studies designed to evaluate the validity of activity monitors for measuring step counts and distance traveled while walking [18,20,24,54], participants will be required to complete a standard 2-minute walk test during which they will be videotaped. This walking task will be performed in an enclosed, wide, long, flat, 30-m corridor with the instruction to walk back and forth on the course all throughout the 2-minute period. This walking task will be performed under 3 walking speed [67]: (1) very slow walking speed, with the instruction “Walk very slowly”; (2) slow walking speed, with the instruction “Walk a little faster, but slower than normal”; and (3) usual walking speed, with the instruction “Walk at your normal, preferred speed.”

In experiment 2, participants will be videotaped during the walking task performed at usual walking speed under 3 conditions [68,69]: walking on flat ground, walking upstairs, and walking downstairs.

During the walking on flat ground condition, participants will complete a standard 2-minute walk test as proposed in experiment 1. During the walking upstairs condition, participants will be asked to ascend flights of stairs located inside a building stairwell for 2 minutes. During the walking downstairs condition, participants will be asked to descend flights of stairs located inside a building stairwell for 2 minutes. At this point, it is important to mention that handrails do represent important safety features to assist users to maintain their balance and prevent falls on stairs. However, for methodological reasons, participants will not be permitted to use handrails on stairs in the walking upstairs and walking downstairs experimental conditions.

During each experimental session and for each experiment, the order of the 3 experimental conditions will be randomized over

participants to reduce potential carryover effects. Only one 2-minute walking trial per condition will be performed. Before to the formal walking trial, participants will complete a practice trial to familiarize themselves with the walking task. A 2-minute rest period will be given between each walking trial in order to record the step and distance counts from each activity monitor. During this period, participants will be instructed to stand still. The number of steps and walking distance measured by each activity monitor will be noted from the tracker display before and immediately after the completion of each trial.

### Statistical Analysis

Descriptive statistics and their corresponding 95% confidence intervals will be determined for all dependent variables. Step count and walking distance errors from each activity monitor will further be calculated as follows:

- $Step\ count\ error = [(steps\ measured - actual\ steps) / actual\ steps] \times 100\%$
- $Distance\ error = [(distance\ measured - actual\ distance) / actual\ distance] \times 100\%$

where:

- Steps counted and distance measured are the value of steps and distance provided by the activity monitor
- Actual steps is the number of steps manually counted from video
- Actual distance is the distance measured using a measuring tape

An error score of zero indicates no difference; a positive error score represents an overestimation of the step and distance counts; a negative error score represents an underestimation.

Validity will be determined by comparing the activity monitor outputs (step and walking distance) with the criterion measures (ie, step count determined from video recordings and distance measured using a measuring tape), using mean differences, mean absolute percentage errors (MAPE), and intraclass correlation coefficients (ICC). According to Feito et al [70,71], a MAPE exceeding 5% can be considered as a practically relevant difference. Repeated-measures analysis of variance (ANOVA) will be used to determine whether a significant difference exists between validity of activity monitor placements and walking conditions. In cases when ANOVA shows a significant difference, post hoc analysis will be performed via Bonferroni tests or, when variances is not assumed to be equal, via Games-Howell tests.

The correlation and level of agreement of the steps and distances estimated by the activity monitor to the criterion measures will be further assessed by calculating a Spearman correlation coefficient or Pearson correlation coefficient ( $r$ ) and ICC, respectively. The parametrical or nonparametrical correlation formula is selected based on the linearity of the relationship between the two measured variables. A correlation coefficient value from .00 to .20 is considered poor, .20 to .40 fair, .40 to .60 moderate, .60 to .80 substantial, and .80 to 1.00 almost perfect [72]. An ICC value from .00 to .40 is considered poor, .40 to .59 fair, .60 to .74 good, and .75 to 1.00 excellent [73]. Bland-Altman plots will further be constructed to visually assess



agreement of activity monitor estimates with the criterion measures [74].

Between-day reliability will be determined by calculating ICC between results obtained during session 1 and session 2. We will also compute the mean differences, standard error of measurements, and the MAPE between both experimental sessions. Significant differences between session 1 and session 2 will be determined by paired-sample *t* test or its nonparametric equivalent, the Wilcoxon signed-rank test. A Bland-Altman plot will be constructed to analyze the agreement between the two assessments.

Statistical significance will be set a priori at  $P < .05$ . All statistical calculations will be completed using the R software environment version 3.1.0 (R Foundation for Statistical Computing).

## Results

Participant recruitment and data collection began in January 2020. As of June 2020, we enrolled 8 participants. Dissemination of study results in peer-reviewed journals is expected in spring 2021.

## Discussion

Physical activity is now widely recognized as crucial for health status maintenance [75-78], whereas physical inactivity has been identified as one of the most important factors in the rise of noncommunicable diseases [78,79]. For these reasons, regular daily physical activity is fully recommended [41,80,81]. It is known that real-time monitoring of physical activity can lead

to a perceptible improvement of the physical activity level [2,82-84]. Various activity monitors are available on the market for this purpose. Most of them are designed to measure steps and distance traveled while walking [4,5,26,27]. Although their beneficial effect on health is now well documented [2,82-84], little information is available to substantiate the validity and reliability of step and distance measurement, especially from low-cost consumer-based hip and wrist activity monitors.

To the best of our knowledge, this is the first study that examines the validity and reliability of step and distance measurement during walking conditions using the PBN 2433 activity monitor. To achieve this goal, young healthy participants will be asked to wear four PBN 2433 activity monitors simultaneously, placed on each hip and each wrist. Participants will be also instructed to perform various walking conditions that are commonly encountered in daily life during two experimental sessions.

On the whole, considering the existing literature on the topic, we hypothesize that the validity and reliability of step count and distance output from the PBN 2433 activity monitors will depend on the following factors:

- Sensor placement locations on the user's body [21,38,46,51,85,86]
- Walking speed [38,55,87-91]
- Walking tasks being performed [23,46,50,55]

Taken together, these will provide beneficial information on the effects of activity monitor placement, walking speed, and walking tasks on validity and reliability of step and distance measurement. We believe that such information is of utmost importance to general consumers, clinicians, and researchers.

## Acknowledgments

This work was supported by the French National Research Agency in the framework of the *Investissements d'avenir* program (ANR-10-AIRT-05 and ANR-15-IDEX-02). The sponsors had no involvement in the study or approval of the manuscript for publication. This work forms part of a broader translational and interdisciplinary project, GaitAlps (NV).

## Conflicts of Interest

None declared.

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## Abbreviations

**ANOVA:** analysis of variance

**ICC:** intraclass correlation coefficient

**MAPE:** mean absolute percentage error

*Edited by G Eysenbach; submitted 09.06.20; peer-reviewed by Z Svoboda, S Lim; comments to author 25.06.20; revised version received 02.07.20; accepted 14.07.20; published 13.01.21.*

*Please cite as:*

*Carlin T, Vuillerme N*

*Step and Distance Measurement From a Low-Cost Consumer-Based Hip and Wrist Activity Monitor: Protocol for a Validity and Reliability Assessment*

*JMIR Res Protoc* 2021;10(1):e21262

URL: <http://www.researchprotocols.org/2021/1/e21262/>

doi: [10.2196/21262](https://doi.org/10.2196/21262)

PMID: [33439138](https://pubmed.ncbi.nlm.nih.gov/33439138/)

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Protocol

# Technology Enabled Clinical Care (TECC): Protocol for a Prospective Longitudinal Cohort Study of Smartphone-Augmented Mental Health Treatment

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## Abstract

**Background:** Even before COVID-19, there has been an urgent need to expand access to and quality of mental health care. This paper introduces an 8-week treatment protocol to realize that vision—Technology Enabled Clinical Care (TECC). TECC offers innovation in clinical assessment, monitoring, and interventions for mental health. TECC uses the mindLAMP app to enable digital phenotyping, clinical communication, and smartphone-based exercises that will augment in-person or telehealth virtual visits. TECC exposes participants to an array of evidence-based treatments (cognitive behavioral therapy, dialectical behavior therapy, acceptance and commitment therapy) introduced through clinical sessions and then practiced through interactive activities provided through a smartphone app called mindLAMP.

**Objective:** TECC will test the feasibility of providing technology-enabled mental health care within an outpatient clinic; explore the practicality for providing this care to individuals with limited English proficiency; and track anxiety, depression, and mood symptoms for participants to measure the effectiveness of the TECC design.

**Methods:** The TECC study will assess the acceptability and efficacy of this care model in 50 participants as compared to an age- and gender-matched cohort of patients presenting with similar clinical severity of depression, anxiety, or psychotic symptoms. Participants will be recruited from clinics in the Metro Boston area. Aspects of TECC will be conducted in both Spanish and English to ensure wide access to care for multiple populations.

**Results:** The results of the TECC study will be used to support or adapt this model of care and create training resources to ensure its dissemination. The study results will be posted on ClinicalTrials.gov, with primary outcomes related to changes in mood, anxiety, and stress, and secondary outcomes related to engagement, alliance, and satisfaction.

**Conclusions:** TECC combines new digital mental health technology with updated clinical protocols and workflows designed to ensure patients can benefit from innovation in digital mental health. Supporting multiple languages, TECC is designed to ensure digital health equity and highlights how mobile health can bridge, not expand, gaps in care for underserved populations.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/23771

(*JMIR Res Protoc* 2021;10(1):e23771) doi:[10.2196/23771](https://doi.org/10.2196/23771)

**KEYWORDS**

mental health care; access; multi-language; smartphone; app; quality improvement; protocol; mental health; treatment; acceptability; efficacy; COVID-19

## Introduction

Both the short- and long-term effects of the COVID-19 pandemic are already leading to a paradigm shift across the health care industry [1-3]. The pandemic has underscored systemic health disparities, clinician shortages, and financial strain that highlight the need for new innovation [4-6]. As the field looks toward technology to offer accessible and cost-effective solutions, now is the time to consider how digitally informed care can provide improved outcomes while reducing access inequities for marginalized communities [7-10].

It is clear that the rapid adoption of technology in health care, especially telehealth, has been catalyzed by COVID-19. The mental health field has also adopted telehealth quickly with one clinic converting to 100% digital visits within 72 hours [11]. Data suggests the mental health field is now the largest user of telehealth [8], with prior barriers toward adoption now largely overcome [12-14]. Although concerns around telehealth visits remain, especially around the impact on the therapeutic alliance, research suggests a positive response from both patients and clinicians with no clear harm to alliance documented [15].

Yet, the increased uptake of telehealth can only address access to a limited extent, and the unmet need for mental health care continues to expand during the pandemic. Marginalized communities remain at a higher risk for exposure and with lower access to care. The Centers for Disease Control and Prevention recently reported that, regardless of age, Latinos are four times more likely to contract COVID-19 than their non-Latino White counterparts [16], and rates of psychosocial distress have increased most in the Latino community compared to any other group [17]. Although telehealth can increase access to care for some, meeting the rapidly rising needs of underserved populations—linguistic barriers, financial strains, culturally competent providers—will require more than just virtual face-to-face health care visits.

To increase access to care, the Technology Enabled Clinical Care (TECC) protocol will offer all aspects of treatment in Spanish and English. Research has shown that individuals with limited English proficiency are less likely to seek out specialty treatment like mental health care and, when diagnosed, have more severe long-term mental health complications [18]. With an estimated 25.4 million Americans who speak English less than “very well” [19], it is imperative that the mental health care field take a more active stance in tackling this unmet need. Although the app will be available in both Spanish and English languages, the Spanish version of the app will first be tested and reviewed for linguistic and cultural appropriateness before being used in clinical practice. This will be done by asking bilingual individuals for app feedback, with a focus on language and images used within the app

TECC proposes a new approach to care that uses the most therapeutic elements of face-to-face mental health treatment with the accessibility and innovation of smartphone technology toward the goal of offering effective care that is accessible to all communities, including minority and underserved populations. Evidence suggests that short-term therapies—often 8-12 weeks in length—are as effective as longer-term treatments

in terms of both immediate and longitudinal outcomes [20]. However, these short-term therapies often fail to realize their potential because of clinician nonadherence to protocol and patient nonadherence to out-of-session exercises and homework. This nonadherence is not intentional by either party but rather a natural and well-documented pattern. Using technology, it is possible to help ensure treatment remains focused, with clear acknowledgment that overregulation and correction by technology would itself cause harm. This issue has already been raised by many mental health clinicians who report that some technology-based therapy programs limit the therapeutic approach and flexibility needed to help patients [21]. Thus, there is a need for technology to help guide care and ensure it remains on track while offering both patients and clinicians the autonomy to respond to unique care needs and clinical leads. The TECC protocol assessed in this study will offer such a hybrid approach and is informed by the research literature, focus groups with patients and clinicians, and our team’s experiences offering this form of care.

We realized the potential for this unique treatment while developing and implementing a *Digital Clinic*, an outpatient short-term mental health program based in Boston, Massachusetts. As outlined in previous publications, the Digital Clinic is a method of health care treatment that allows providers the ability to use digital technology to augment all aspects of care [22]. Initial successes of the digital clinic model are reflected in case reports, successful clinical outcomes, and positive patient feedback. However, the digital clinic framework offers a model for more complex care where the clinician uses digital tools like apps with less direct guidance and structure. This model is appropriate for many patients and especially those with treatment-resistant depression but requires more active investment from both clinician and patient. With this in mind, it may be possible to achieve the same outcomes for many patients who can benefit from brief and more structured evidence-based therapies while providing guidance for clinicians who seek more direction in using technology in care. Thus, although the theoretical model, hands-on experience, and actual framing of the Digital Clinic are imbued in this new protocol, the clinical focus of structured, educational, and guided care is what separates TECC from the original Digital Clinic model.

Taken from the Digital Clinic framework, this protocol will use a digital navigator (or technology specialist), a new team member who is able to offer technical support and assistance in ensuring the patient is able to thrive with technology use, so clinical visits remain focused on care needs. The digital navigators for this study will include research assistants who have completed the 10-hour digital navigator training. Briefly, the training consists of 5 modules: core smartphone skills, basic technology troubleshooting, app evaluation, clinical terminology and data interpretation, and engagement techniques. These modules will teach digital navigators how to perform their main responsibilities of selecting smartphone apps for care, troubleshooting technology issues for both client and clinician, and ensuring app data is understood by all parties [23].

Furthermore, TECC seeks to balance clinician and participant autonomy while providing some structure and treatment pathways. Thus, the protocol was specifically designed to



empower clinicians and participants to use smartphone technology by customizing data collection of both mental health surveys as well as sensor data (if agreed upon) toward ensuring each participant's unique experience is captured. Although each session of the protocol offers exercises related to aspects of the app, which the participant should complete between sessions, these activities are defined broadly to meet diverse clinical needs and offer clinicians therapeutic flexibility. For example, using the app toward goal setting and tracking will be applicable in almost any scenario.

The eight-session structure included in TECC will provide the flexibility for clients to learn about different treatment modalities to gain broad exposure to evidence-based therapeutic skills and techniques while still ensuring treatment is focused on personal needs. The clinical skills incorporated in TECC were chosen from current research done on short-term mental health treatments, studies designed specifically to understand marginalized communities, and app-based mental health interventions. The protocol consists of three main stages:

- Stage 1 “Creating the Clinical Foundation”: This stage will allow participants to learn and practice shared decision-making by cocreating treatment goals, identifying thought patterns, and identifying coping skills and defense mechanisms. The goal of this stage is for participants to develop a broad understanding of their thoughts and behaviors while beginning to identify strengths and need areas. Participants will also be introduced to clinical language and definitions for shared language to be established.
- Stage 2 “Building Clinical Skills”: Expanding from the skills learned in stage one, this stage will focus on teaching and practicing cognitive defusion and behavioral activation techniques. The goal for this stage is to expose participants to practical therapeutic skills that can be used across many situations and symptom management.
- Stage 3 “Solidifying Clinical Gains”: This stage introduces participants to mindfulness techniques, a diary card-like model, and patient activation and empowerment skills. The purpose of this stage is to ensure participants grasp all technical skills and clinical language reviewed throughout treatment to make informed autonomous decisions regarding treatment preferences.

This yearlong study will follow a prospective longitudinal cohort design where all participants will receive the same treatment and smartphone interventions. Based on our own Digital Clinic pilot data, we hypothesize participants will report a treatment response rate—defined as 50% symptom reduction—of improvements in anxiety and depression within the 8 weeks of treatment compared to their initial baseline. We also hypothesize that both rates of app engagement out of sessions, as well as therapeutic alliance measured during sessions, will be correlated with clinical improvements and suggest a mechanism of action for TECC. Furthermore the study will test the feasibility of providing technology-enabled mental health care within an outpatient clinical setting via virtual telehealth visits, explore the linguistic and cultural appropriateness of the smartphone app (mindLAMP) used in the study, and analyze the symptom changes of anxiety and depression for all study participants.

## Methods

### Study

The study will take place at Beth Israel Deaconess Medical Center (BIDMC), a Harvard affiliated teaching hospital in Boston, Massachusetts. The care team will include a psychiatrist, social worker, and digital navigator. The psychiatrist and social worker will provide clinical treatment, education, and support for all participants. The digital navigator, as previously discussed, will be available for technology support and mindLAMP training to other care team members and research participants.

For this study, 50 participants will be enrolled and will not be financially compensated for their participation in TECC. Given the success of the pilot Digital Clinic program, including 50 participants is feasible and necessary to collect a diverse sample and see significant effects of different techniques on clinical assessments of depression and anxiety. This study will be open to any adult (18 years or older) who is interested in using smartphone technology to augment their mental health care. Participants are required to meet the criteria for either mild to moderate depression or anxiety as measured on the Patient Health Questionnaire-9 (PHQ-9) or Generalized Anxiety Disorder-7 (GAD-7) scale. Participants must have daily access to a smartphone, be willing to download the mindLAMP app, use their smartphone for mental health care (both in and outside of session time), and be open to learning about an array of clinical modalities (dialectical behavior therapy [DBT], cognitive behavioral therapy [CBT], short psychodynamic therapies). For participants who do not own a smartphone, the care team will help individuals sign up for a free phone through the US Federal Government's Project Lifeline if they are eligible. Participants must also be affiliated with a BIDMC or Beth Israel Lahey Health provider and be available for eight clinical sessions (telehealth) over the course of 2-4 months. Until the Spanish language version of the mindLAMP app has been properly vetted, participants must be able to read, write, and communicate in English at an eighth grade level. Recruitment efforts for TECC include digital flyers and brief informational sessions for referring providers.

### Interventions

Interventions for TECC will be employed through a multipronged approach including in-session care from clinicians, exposure and education to evidence-based therapies, use of the mindLAMP app, and technology support from the digital navigator.

At least 1 week before the initial clinical visit, participants will meet with the digital navigator to download the mindLAMP app, receive app training, and will be asked to begin completing the mood surveys (PHQ-9 and GAD-7) in mindLAMP on a daily basis. During the meeting, participants will be informed the app will not be used to offer emergency services between sessions and app responses will not be monitored outside of clinical sessions. A signed waiver will be presented to reflect this understanding.

The format for TECC sessions will follow the pre-established Digital Clinic structure (Figure 1). Specifically, before each clinical session, participants will be required to complete a variety of clinical surveys. These surveys will be made available through the clinic’s secured, research-based survey platform (REDCap, Vanderbilt University). The surveys (see Figure 2 for more details) are designed to help clinicians develop a comprehensive understanding of each participants progress throughout the study. Once the clinical portion of the session starts, any mindLAMP data collected will be reviewed and discussed. This step will ensure the data in mindLAMP accurately reflects the participant’s lived experience and ensure the personalized nature of each patient’s care is reflected in the session. Next, the clinician will discuss a predetermined clinical

skill, and the clinician will work to relate the skill to the patient’s unique needs. The clinician will introduce the skill by describing its purpose, giving examples of when the skill can be used, and explain how the skill could impact the participants mental health needs. With clinician guidance, participants will then practice the skill, brainstorm scenarios in which the skill could be used, and review a skill-building activity (see Multimedia Appendix 1 for details). Activities will be conducted through skill-building modules (eg, mindfulness), informational worksheets, surveys, and free-writing opportunities that will be available through the app. Participants will be encouraged to complete the activities between sessions to strengthen their understanding and comfortability of use with each skill.

Figure 1. The Digital Clinic program structure including pre- and postclinical activities.

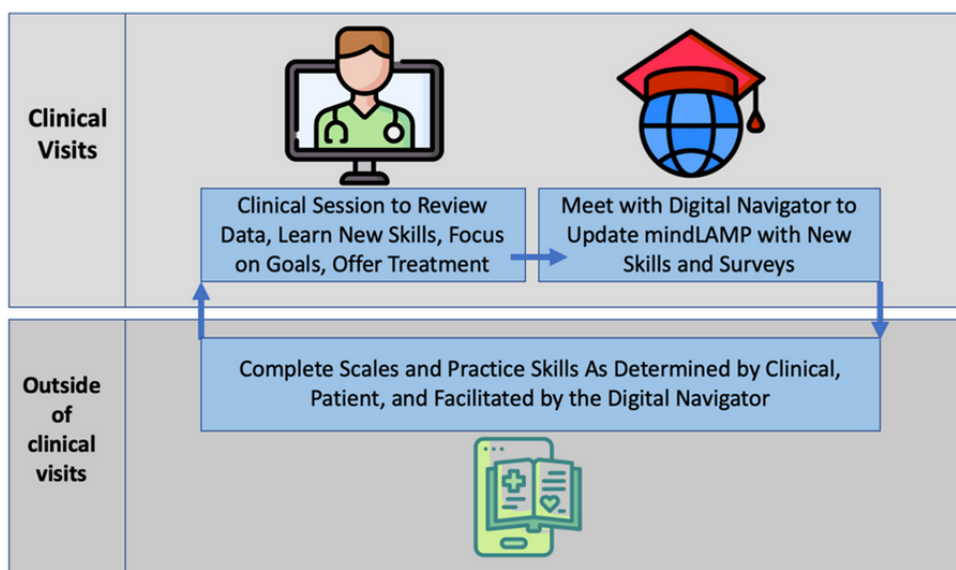
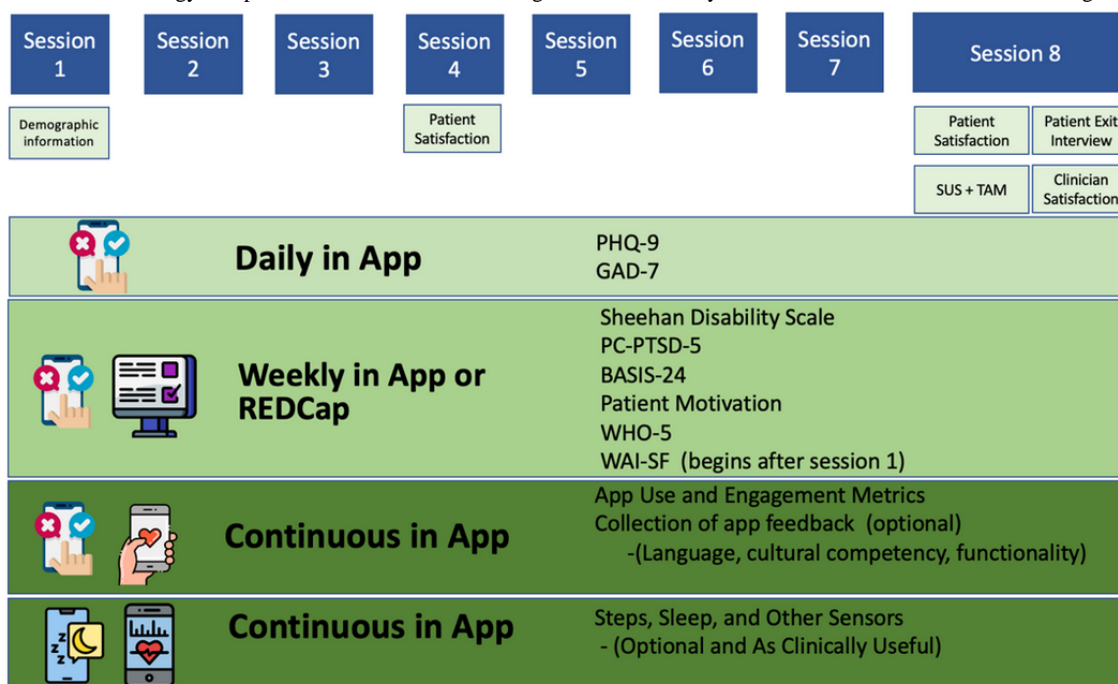


Figure 2. The Technology Enabled Clinical Care survey and data collection timeline. BASIS-24: Behavior and Symptom Identification Scale-24; GAD-7: Generalized Anxiety Disorder-7; PC-PTSD-5: Primary Care Posttraumatic Stress Disorder-5; PHQ-9: Patient Health Question-9; SUS: System Usability Scale; TAM: technology acceptance model; WAI-SF: Working Alliance Inventory–Short Form; WHO-5: World Health Organization Five.

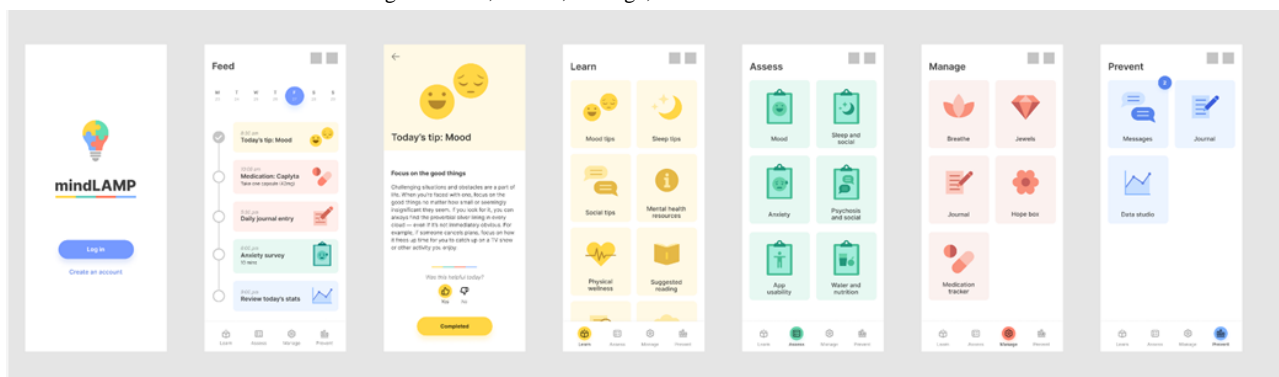


Upon completion of each clinical session, participants will meet with the digital navigator to address any technology-related questions or issues. The digital navigator will also work with participants to create any additional mood-tracking surveys and retrieve smartphone sensor data (if applicable). The mindLAMP app will be used in and outside of the session to allow participants to track their daily moods (PHQ-9 and GAD-7 scales) and practice clinical skills (through activities in the app).

As previously mentioned, the mindLAMP app will be used to provide digitally augmented care [24]. Cocreated with patients and clinicians, mindLAMP is designed not to drive care decisions or protocolize treatment but, rather, to serve as a flexible tool to be deployed in a personalized manner to customize care for each person. To support this flexibility, mindLAMP allows users to create unique surveys specific to their needs and assign a schedule of times to be reminded [25]. Likewise, mindLAMP can capture diverse sensor data from the smartphone, ranging from step count, sleep, geolocation, and screen time, and the user can determine which, if any, are useful to capture. As an example, some patients may wish to track mood and sleep to determine if changing their sleep pattern may improve their mood [26]. Any use of such data will be

determined by clinical needs and not the TECC protocol. mindLAMP also offers options for app interventions and supports a suite of resources that are customizable to the unique needs of users. The learning tab presents relevant tips and information, and the management tab has a series of tools and skill-building modules like mindfulness, defusion (from acceptance and commitment therapy [ACT]), goal setting, medication reminders, and emergency planning. Not all learning and management offerings will be relevant, or even useful, for all patients, and the goal of care is to help match the right elements of mindLAMP at the right time for each patient—much like in traditional medication management or therapy care. As a tool, mindLAMP aims to be accessible on Apple and Android smartphones as well as on an internet browser (ie, computers) and can support multiple languages including Spanish and English. In this protocol, mindLAMP is used in a structured manner, with each week using different aspects of the app, but personalization and customization are still part of each week's use, as outlined in later sections. Figure 3 provides several examples of the mindLAMP interface. A set of handouts is also included in Multimedia Appendix 1 that can be used as nondigital *backups*, in case a patient has a technical issue, and can be mailed or emailed to each patient in TECC.

**Figure 3.** Screenshots of mindLAMP showing the Learn, Assess, Manage, and Prevent functions.

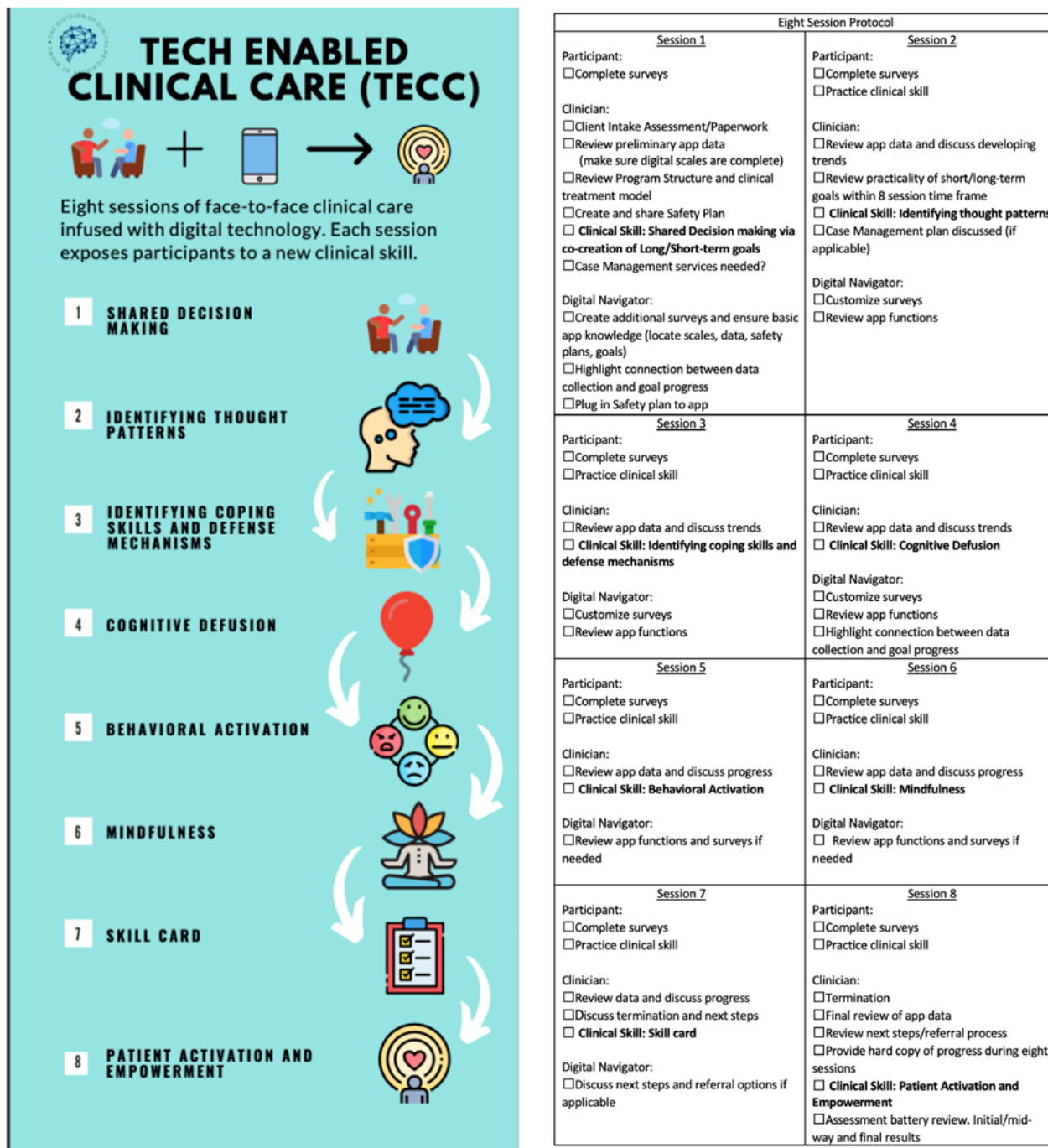


At the end of the study, participants will be provided a paper or electronic packet of all therapeutic skills learned, activities practiced, and mindLAMP data collected. Participants will also be allowed to keep using the app as a self-help tool or delete the app completely. A copy of clinical metrics and results will be offered to participants' referring provider to ensure transparency and continuation of care. In general, TECC clinical sessions and digital navigator meetings can be conducted in

person or through a video platform. However, due to COVID-19, all TECC-related participant meetings for the next year will be held over a Health Insurance Portability and Accountability Act-compliant video platform to maintain social distancing practices.

As previously mentioned, TECC follows an eight-session template (Figure 4), which provides a step-by-step guide for participants, clinicians, and digital navigators.

Figure 4. Overview of clinical sessions (left) and session-specific checklist (right).



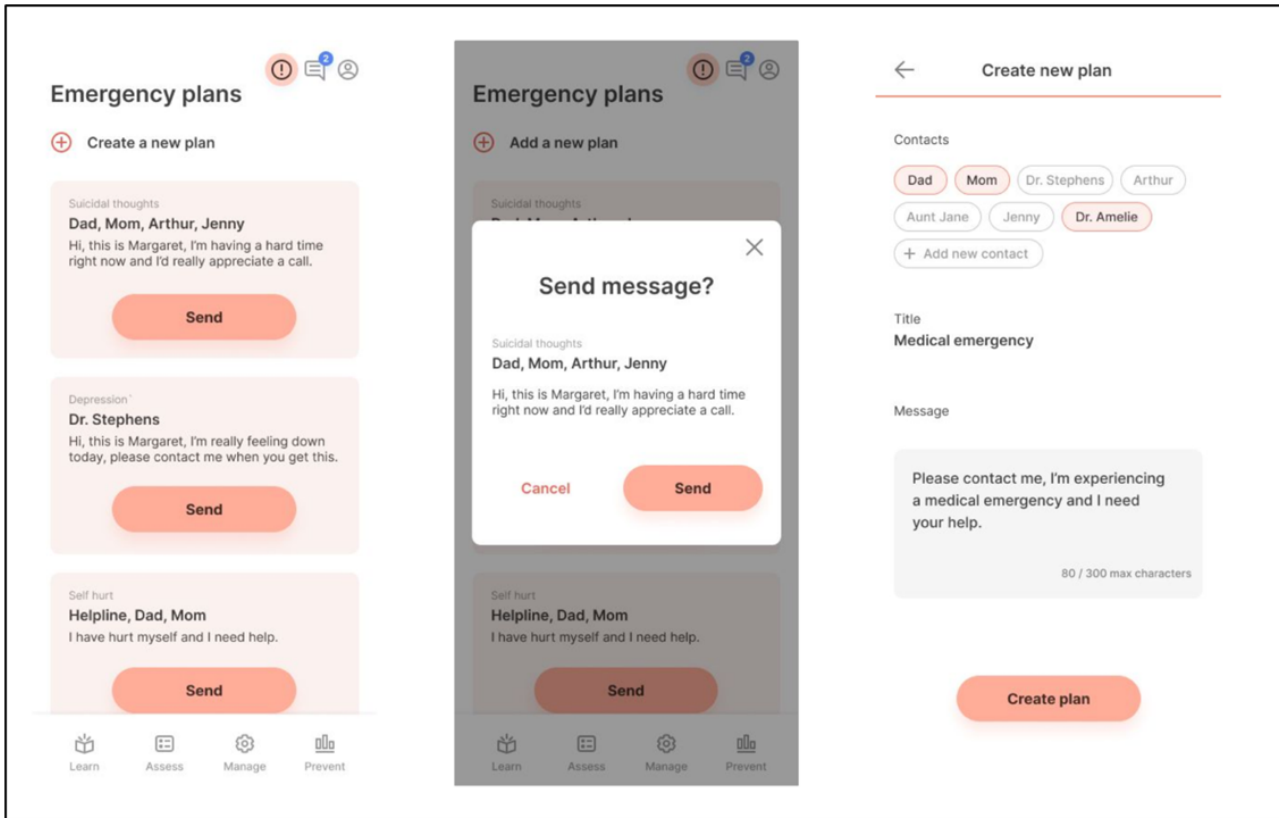
### Session One: Shared Decision Making

As with most initial therapeutic sessions, a client assessment will be completed, a safety plan created, and feasibility of short- and long-term goals will be addressed. (Please note, the safety plan used in TECC was not created by members of the research team and was borrowed from our affiliated hospital’s psychiatric department.) Figure 5 shows an example of how the safety plan

can appear in mindLAMP. After safety planning, the study time frame, expectations, and structure will be reviewed with participants. Since the study will be providing clinical treatment in a time-limited manner, the need for supplemental case management services will also be evaluated, and education and resources may be provided; however, connections to services cannot be guaranteed. For the remainder of the session, the skill of shared decision making (SDM) will be discussed.



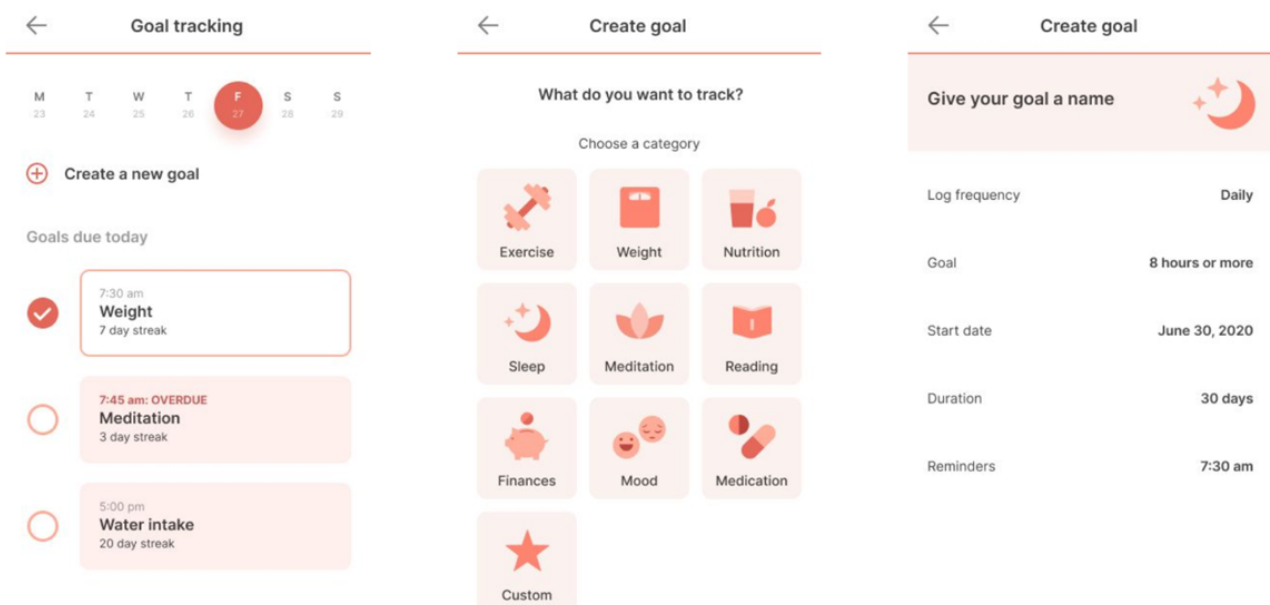
Figure 5. Example of one aspect of the safety planning activity as seen in mindLAMP.



For the purposes of this study, SDM will be defined as the process when provider and client review available treatment options and when clients are encouraged to select the treatment plan that best fits their personal preferences [27]. Previous studies combining app technology and SDM interventions have been mixed [28], and several limitations have been identified, such as time constraints and provider bias toward which patient

could benefit and which situation calls for the intervention [29]. However, our team will use this tool for the purposes of discussing and creating short-term therapeutic goals with participants. In addition to clinical conversations, SDM practices will be reinforced through out-of-session activities available through the app. Figure 6 provides an example of one goal-tracking activity as it appears in mindLAMP.

Figure 6. Goal tracking in mindLAMP.



Once each of the clinical visits are over, participants will meet with the digital navigator to review any app-related questions or concerns. The digital navigator will also work with

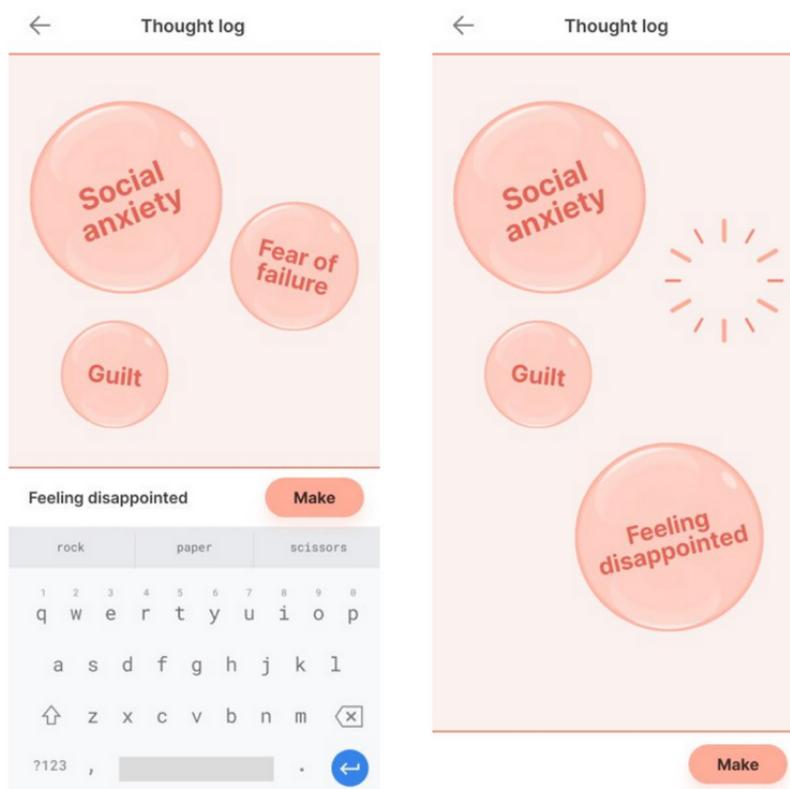
participants and clinicians to ensure that a connection between app data and clinical goals is clear.

## Session Two: Identifying Thought Patterns

The second skill will focus specifically on understanding and identifying thought patterns. CBT will be introduced using a core CBT principle, ensuring information is presented in a structured and educational method, which allows for in-the-moment focus and client participation [30]. Again, mindLAMP will assist in this process by providing clients with out-of-session education and activities. mindLAMP activities will include documenting, describing, and labeling different types of thinking patterns.

Studies have shown that CBT smartphone apps have therapeutic potential [31]; however, like many apps, high user engagement and sufficient long-term outcomes seem to be the top barriers for effective CBT app outcomes [32]. User engagement will be closely monitored through review of out-of-session activities, incorporating participant feedback when applicable, and monitoring participants overall engagement to care. Figure 7 provides an example of a mindLAMP activity that can be used for this skill.

**Figure 7.** The thought log allows participants to label and track thought patterns in real time.



## Session Three: Identify Coping Skills and Defense Mechanisms

In session one, a safety plan was cocreated using participant's language and clinician guidance. In this session, beneficial coping skills will now be identified and discussed in more depth, allowing coping skills to be the main clinical focal point.

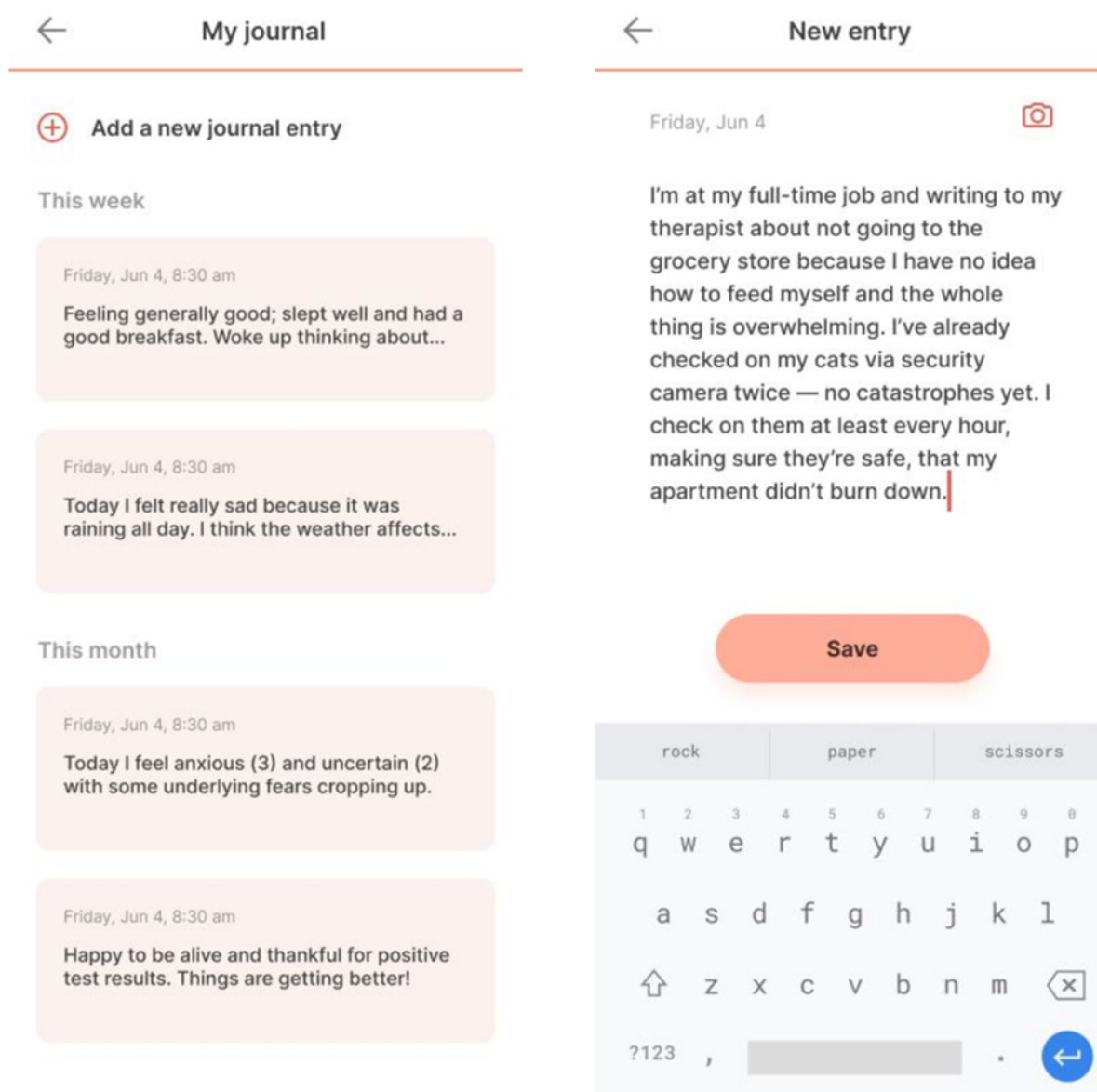
To the best of our team's knowledge, there are no psychodynamic mental health apps that have been widely tested and made available to the public. Providing short-term psychodynamic treatment presents many challenges (time constraints, adequate provider training, bias toward newer clinical modalities); however, recent studies continue to test new ways psychodynamic practices can be beneficial [33]. Therefore, this session will help participants learn and identify some defense mechanisms and help bridge the connection between defense mechanisms and coping skills. The mindLAMP activity will include a list of defense mechanisms (terms, definitions, and examples) and ask participants to link their preferred coping skill with a defense mechanism (if applicable).

## Session Four: Cognitive Defusion

In this session, participants will learn therapeutic skills that offer broad applicability. Specifically, they will learn cognitive defusion, an ACT intervention, which asks participants to notice their thoughts (nonjudgmentally and without identifying with them), acknowledge them, and then let those thoughts leave one's mind [34].

ACT techniques can be taught in a time-limited fashion, and the straightforward approach can be practiced independently once understood. In a 2-week trial, Levin et al [35] found that participants who used an app intervention to practice ACT skills believed the method was helpful and accessible; furthermore, participants' depression, anxiety, and psychological flexibility also showed significant improvement. Similar to other clinical skills, cognitive defusion will be practiced through the mindLAMP app by listing the steps of cognitive defusion, asking participants to practice the skill, and then providing space for participants to summarize their experience (see Figure 8 for example). Aspects of session four and the mindLAMP thought log (Figure 7) can be used as well.

**Figure 8.** Example of mindLAMP’s journal section, which allows participants space to freely reflect on experiences.



**Session Five: Behavioral Activation**

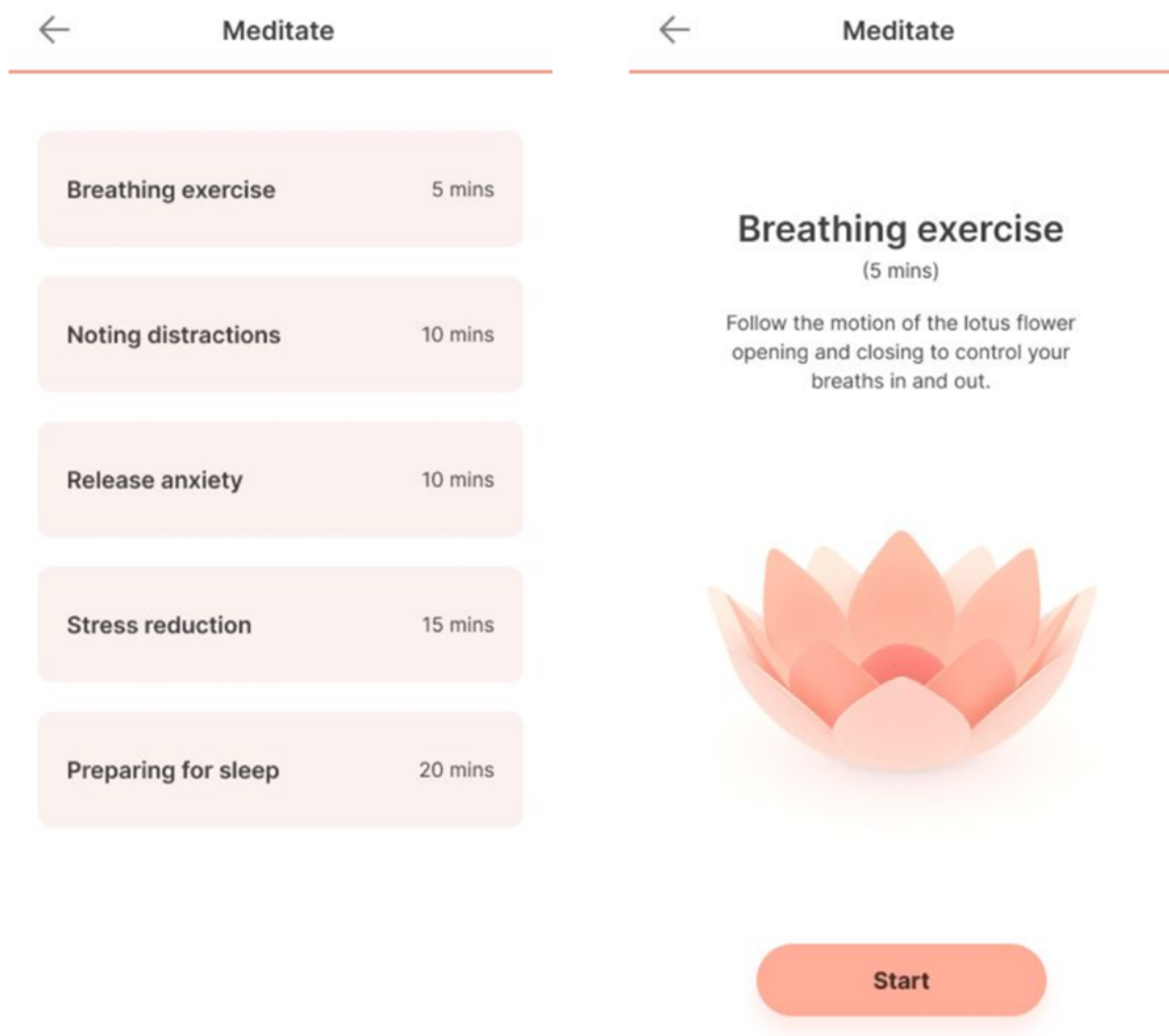
Session five will continue to develop participants’ tool kit of therapeutic skills. Modern day behavioral activation techniques include encouraging clients to become aware of avoidance behaviors and places extra emphasis on understanding environmental factors rather than thought patterns [36]. The broad applicability of these skills makes them ideal for TECC and meeting the needs for diverse populations.

Although research on behavioral activation through mobile apps is nascent, one qualitative study found that, when using app interventions, participants felt their treatment was more accessible, were more motivated to engage, and felt security [37]. The behavioral activation mindLAMP activity will include a list of step-by-step instructions and provide space for participants to share their experience.

**Session Six: Mindfulness**

Broadly, mindfulness skills ask participants to focus on aspects of their present state as well as factors in their immediate surroundings in a nonjudgmental way. Additionally, practicing mindfulness has been thought to enhance self-awareness, openness to new experiences, and provide users with a deeper understanding of self [38]. Mobile technology studies, including a 2018 randomized trial and a separate efficacy-based investigation, found mobile app interventions could reduce stress and irritability, and yielded statistically significant efficacy measures [39,40]. Mindfulness techniques will be practiced through mindLAMP by providing instructions on how to engage with the technique; participants will again have the option to document their experience (see Figure 9 for example).

**Figure 9.** Example of one of the guided mindfulness exercises offered in mindLAMP.



### Session Seven: Skills Card

This session introduces participants to a means to reflect on their mental health and build emotional self-awareness. Similar to a DBT diary card (where individuals document and monitor symptoms and behavioral skills used) participants will cocreate a skills card to help practice, identify, and monitor interventions learned and used in their daily lives. App-related DBT studies have shown potential in allowing users to learn and practice a wide range of skills; however, major barriers include app navigation challenges and difficulties understanding interventions without prior DBT exposure or clinical support [41,42]. Nonetheless, increasing symptom awareness and tracking, via diary cards, have been shown to be helpful for various conditions, including those in jeopardy of heart failure, chronic bronchitis, and pulmonary diseases [43,44].

### Session Eight: Patient Activation and Empowering

Based on the Right Question Project, this skill will empower participants to take an engaged role in care by actively asking questions that will encourage clients to participate in the decision-making process [45]. Additionally, the clinical team will pay special attention to ensure culturally appropriate

language and values are considered when practicing this skill. Research on apps that support this particular skill is limited. mindLAMP will provide support by encouraging participants to practice advocating for themselves in clinical care by using the skills they have learned throughout treatment and using them outside of clinical sessions.

### End of Study

At the end of the eight-session study, handouts of the data collected and skills learned throughout the study will be given to participants and briefly reviewed a final time. Participants will also be asked to complete a more extensive patient satisfaction survey, which will assess both the clinical sessions and general review of the mindLAMP app. Finally, before ending the study, participants will have a chance to provide verbal feedback to all care team members if they choose. Results and graphs created by participants in mindLAMP will also be made available to participant's referring provider to assist with continuation of care and build a connection between mental health and additional health care treatment.



### Study Measures

Since TECC was designed to collect a number of clinical surveys throughout treatment, the timeline for survey collection was carefully crafted to decrease oversaturation (see [Figure 2](#) for survey timeline). Specifically, participants will be asked to complete the PHQ-9 (which measures depression rates from minimal depression to severe depression) and the GAD-7 scale (a widely accepted anxiety scale that evaluates scores as either mild, moderate, or severe anxiety) on a daily basis [46,47]. Both the PHQ-9 and GAD-7 scales will be loaded on mindLAMP and become available to participants upon downloading.

Prior to each clinical visit, participants will briefly meet with a research assistant who will provide participants with a secure link (via REDCap) to weekly clinical surveys. This could be done via mindLAMP, but we will use a different platform for the purposes of this study. Those presession surveys include the Sheehan Disability Scale, which measures the effects of poor mental health across three domains: work and school, family, and social life [48]; the Primary Care Posttraumatic Stress Disorder-5, which assess for posttraumatic stress disorder [49]; the Behavior and Symptom Identification Scale-24, a symptom assessment scale [50]; a patient motivation scale, to assess participants commitment to change through treatment; the World Health Organization Five, a well-being assessment scale [51]; and the Working Alliance Inventory–Short Form, a scale to assess the alliance a patient feels toward the clinician that is known to be a predictor of treatment success (this scale will begin after session one) [52].

Additional nonweekly scales include a participant satisfaction scale, which will be given after session four and at the end of treatment, and the System Usability Scale, which is offered during the termination process and is a well-accepted tool to assess satisfaction around use of mindLAMP and TECC [53]. The technology acceptance model, a well-known implementation science framework, will also be used to assess feasibility of technology-infused care [54]. Since the mindLAMP app is able to automatically capture data about when and how it is used, the study will offer a unique data set on longitudinal use patterns

and engagement. A provider-specific satisfaction survey will be given to all referring providers at the end of the study to improve the referral process, assess the relevance of clinical data shared, and streamline continuation of care. Other metrics in this study include engagement with the app, as measured by number of log-ins each day, as well as time spent on each element of the app during each log-in. Basic demographics and measures of socioeconomic status will also be collected during the intake process.

### Further Study Details

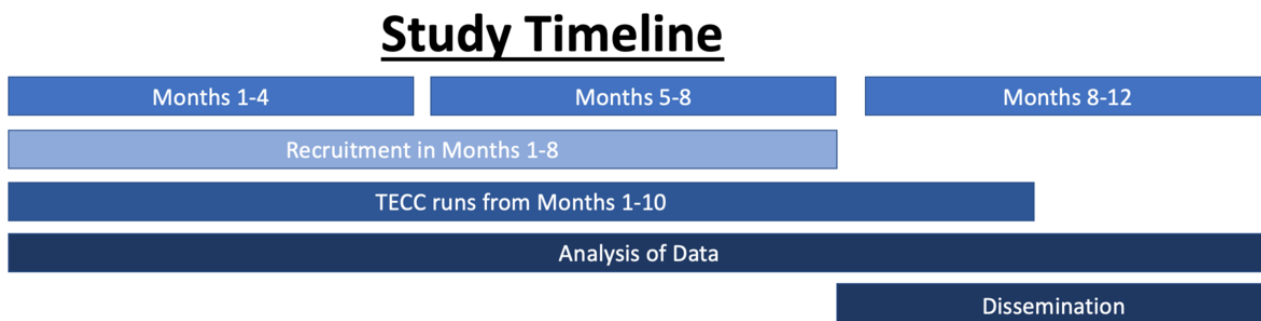
All participants will complete a written informed consent for this voluntary study. Participants will be able to withdraw from TECC anytime, just as they can withdraw from routine care at any time. Participants who miss four consecutive sessions will be asked to restart the protocol. During the study, if a participant’s clinical presentation significantly worsens, the clinical team will re-evaluate the participant’s involvement in the study. Intent-to-treat analysis will be applied so that data from all participants, even those who drop out, will be included in the outcomes.

The mindLAMP app meets federal privacy and security requirements, and has been institutional review board (IRB)–approved for use in clinical research. All data collected by mindLAMP will be securely transmitted directly to a server within the hospital network. Additionally, after receiving IRB approval, the TECC protocol will be registered with ClinicalTrials.gov.

### Results

The results of the TECC study will be used to support or adapt this model of care and create training resources to ensure its dissemination. The 1-year study timeline for TECC includes continuous recruitment and enrollment efforts until the sample size is reached; 10 months of clinical sessions, continuous collection of data, and in-session review of clinical metrics; several months spent analyzing data; and dissemination of study results (see [Figure 10](#) for details).

**Figure 10.** Study timeline. TECC: Technology Enabled Clinical Care.



### Analysis

Analysis will include calculation of the effect size of TECC to reduce symptoms related to stress, anxiety, and depression. Analysis will also focus on assessing association between baseline factors, race, language, and education, as well as dynamic factors like working alliance and technology

engagement patterns with changes in symptoms and use and adherence to the TECC protocol. We will assess relationships between these factors and clinical changes using generalized linear models and multiple regression analyses. Tests for dropout effects will be performed to see if outcome and covariate measures are associated with differences in engagement. If there are significant dropout effects, a logistic dropout probability

model will be fit using the significant dropout outcomes and covariates measured at the start of the stage, and inverse probability weighting will be used with these model probabilities to account for dropout in each of the models. The age-matched control group will be used to compare changes related to clinical scores and calculate effect sizes using means and SDs.

## Discussion

The eight-session TECC protocol outlined in this paper provides one solution for the ever-growing need for high-quality, evidence-based, time-limited mental health care. Specifically, the TECC protocol will use smartphone technology as a tool to enhance face-to-face (virtual) clinical sessions for clinicians and participants. TECC is designed to allow clinicians and participants a way to monitor customized information from surveys to sensors and bring this data into clinical visits toward improving outcomes. The mindLAMP app used in TECC also offers a flexible suite of app-based interventions that can be used to augment care outside of sessions. Given the digital nature of TECC, it is easy to share a comprehensive digital record of participant progress across the study and ensure transitions in care can be as seamless as possible. Results from this study will thus offer important data in understanding how to best share and implement TECC toward further improving access to care.

The bedrock of the TECC treatment protocol aims to improve clinical care by exposing participants to an array of different therapeutic modalities. With increased exposure to foundational clinical principles and basic understanding of how to use clinical skills, individuals will learn to identify the clinical modalities and interventions that are most effective for them. By the end of treatment, participants will have developed the skills needed to become more actively engaged in their mental health care and be better equipped to advocate for their mental health needs in the future. Even when the TECC study ends, patients can continue to use mindLAMP as a self-help tool and build off the skills and advances they made while in care.

By using the mindLAMP app, which will reside on a participant's personal mobile device, individuals will be continuously connected and engaged with treatment, something less feasible with nontechnology augmented care. Encouraging participants to frequently engage with treatment in an inconspicuous way (via their smartphone) may decrease mental health stigma, as treatment will be seamlessly woven into

already established behaviors (using smartphones in public). Additionally, by increasing app engagement, clinicians will be provided an array of individualized clinical measures and important participant narratives regarding treatment progress. These narratives will be reviewed with participants during clinical sessions and help clinicians customize activities for outside of the session by using individuals' preferred terminology and preferences. The customization and flexibility built into the model will help ensure high app engagement, as past research has shown high app engagement can correlate with higher clinical outcomes [55]. Furthermore, by allowing flexibility and customization of language used during skill-building activities, the study aims to limit dropout rates, as patients tend to drop out of care less when receiving treatment that matches their personal preferences [56].

TECC also offers unique potential for underserved populations. At the time of this writing, there were an estimated 10,000 mental health apps available to consumers [57]. Using digital tools, specifically smartphone apps, is a highly scalable solution to help ensure language-appropriate resources are available to all communities. Despite this promise, access to diverse language technology, especially in apps, continues to be limited. A 2018 review of diabetes-related Spanish language apps found only 25% of Android and 19% of IOS apps allowed users to fully interact with the app in Spanish [58]. Language barriers are not the only issue that contributes to health inequities, and much has been written about these factors that are collectively known as social determinants of health [59-62]; however, before fully incorporating a multi-language app into care, the team will ensure the Spanish Beta version of the app is culturally and linguistically appropriate for Spanish-speaking individuals. This will be done through feedback gathered from community members, participants, and providers who are well versed in the Spanish language and culture. Once the additional language version of the app is available in early 2021, the TECC protocol will be conducted again in Spanish.

It is undeniable that recent circumstances have forced providers and patients to use digital technologies for continued care, personalized treatment, and remote health care appointments to a degree that would not have been considered feasible in the pre-COVID-19 era. Since technology devices and digital platforms will continuously evolve over time, now is the moment to test this hybrid care model to offer innovative treatments that are effective and available to and for as many people as possible.

## Acknowledgments

The structure for this protocol manuscript was inspired by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (2013).

## Conflicts of Interest

None declared.

Multimedia Appendix 1  
Handouts.

[PDF File (Adobe PDF File), 1102 KB - [resprot\\_v10i1e23771\\_app1.pdf](#)]

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## Abbreviations

- ACT:** acceptance and commitment therapy  
**BIDMC:** Beth Israel Deaconess Medical Center  
**CBT:** cognitive behavioral therapy  
**DBT:** dialectical behavior therapy  
**GAD-7:** Generalized Anxiety Disorder-7  
**IRB:** institutional review board  
**PHQ-9:** Patient Health Questionnaire-9  
**SDM:** shared decision making  
**SPRIT:** Standard Protocol Items: Recommendations for Interventional Trials  
**TECC:** Technology Enabled Clinical Care

*Edited by G Eysenbach; submitted 22.08.20; peer-reviewed by B Rudd, C Yeager; comments to author 12.09.20; revised version received 27.09.20; accepted 08.12.20; published 14.01.21.*

*Please cite as:*

*Rauseo-Ricupero N, Torous J*

*Technology Enabled Clinical Care (TECC): Protocol for a Prospective Longitudinal Cohort Study of Smartphone-Augmented Mental Health Treatment*

*JMIR Res Protoc 2021;10(1):e23771*

*URL: <https://www.researchprotocols.org/2021/1/e23771>*

*doi: [10.2196/23771](https://doi.org/10.2196/23771)*

*PMID: [33296869](https://pubmed.ncbi.nlm.nih.gov/33296869/)*

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Protocol

# Mobile Health Intervention in the Maternal Care Pathway: Protocol for the Impact Evaluation of hAPPyMamma

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## Abstract

**Background:** Mobile health (mHealth) has great potential to both improve the quality and efficiency of care and increase health literacy and empowerment of patient users. There are several studies related to the introduction of mHealth tools for supporting pregnancy and the postnatal period, with promising but not yet rigorously evaluated impacts. This article presents the protocol for evaluating an mHealth intervention (hAPPyMamma) applied in the maternal and child care pathway of a high-income country (in a pilot area of Tuscany Region, Italy).

**Objective:** The protocol describes hAPPyMamma and the methods for evaluating its impact, including the points of view of women and practitioners. The research hypothesis is that the use of hAPPyMamma will facilitate a more appropriate use of available services, a better care experience for women, and an improvement in the maternal competencies of the women using the app compared to the control group. The protocol also includes analysis of the organizational impact of the introduction of hAPPyMamma in the maternal pathway.

**Methods:** A pre-post quasiexperimental design with a control group is used to undertake difference-in-differences analysis for assessing the impact of the mHealth intervention from the mothers' points of view. The outcome measures are improvement of maternal health literacy and empowerment as well as experience in the maternal care pathway of the control and intervention groups of sampled mothers. The organizational impact is evaluated through a quantitative and qualitative survey addressing professionals and managers of the maternal care pathway involved in the intervention.

**Results:** Following study recruitment, 177 women were enrolled in the control group and 150 in the intervention group, with a participation rate of 97%-98%. The response rate was higher in the control group than in the intervention group (96% vs 67%), though the intervention group had less respondent loss at the postintervention survey (10% compared to 33% of the control group). Data collection from the women was completed in April 2018, while that from professionals and managers is underway.

**Conclusions:** The study helps consolidate evidence of the utility of mHealth interventions for maternal and child care in developed countries. This paper presents a protocol for analyzing the potential role of hAPPyMamma as an effective mHealth tool for improving the maternal care pathway at individual and organizational levels and consequently helps to understand whether and how to scale up this intervention, with local, national, and international scopes of application.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/19073

(*JMIR Res Protoc* 2021;10(1):e19073) doi:[10.2196/19073](https://doi.org/10.2196/19073)

**KEYWORDS**

mHealth; maternal care pathway; impact evaluation; quasiexperimental study

## Introduction

### Background

Mobile health (mHealth) can play a disruptive role in transforming health promotion and health care service provision. mHealth refers to health-related practice supported by mobile and wireless devices, such as mobile phones, smartphones, and tablets, including mobile apps [1]. The growing spread of mobile devices has pushed the use of apps providing digital services, including for health care.

mHealth has great potential to both improve quality and efficiency of care [2,3] and to increase health literacy and empowerment of patient users [4]. Using mHealth apps, people can manage their health and well-being more actively and consciously [3]. Due to its characteristic of ubiquity and the possibility of personalization, it is expected to be a powerful tool for patient-centered care.

Nevertheless, there is contradictory evidence about the impacts of mHealth interventions on health promotion practice and health outcomes [5-8]. There are several studies focusing, in particular, on the introduction of mHealth tools for supporting pregnancy and the postnatal period, with promising but not yet rigorously evaluated impacts [9]. The evidence for effectiveness in behavioral change is also inconsistent, with both ineffective [10] and effective interventions [11,12] targeted at pregnant women and mothers. Furthermore, there is evidence of demonstrated positive outcomes from mHealth tools for pregnant women and future mothers, but also of the difficulties related to the routine integration of mHealth tools into established prenatal and newborn health services [13]. Nonetheless, it is worth pointing out that most of the research studies on mHealth interventions in the field of maternal, neonatal, and newborn care have been undertaken in low- and middle-income countries [14-29].

This protocol presents an mHealth intervention for maternal and child care in a high-income country, including the methods adopted for evaluating its impact at individual and organizational levels.

### Study and Policy Context Concerning mHealth and the Maternal Care Pathway

The context of this study is the region of Tuscany (Italy), which shows characteristics of eHealth diffusion in line with both the national and wider European contexts [30,31].

Within the framework of the Italian public health care system ensuring universal health care coverage, maternal care is

guaranteed for all women free of charge as an essential level of care [32,33]. Although this includes services provided by hospitals and family care centers along the entire maternal journey until the postpartum period, the majority of women prefer to be supported by a private gynecologist during pregnancy [34]; this may limit communication of the publicly available community services offered to pregnant women and new mothers. To standardize the prenatal visits and treatments within its territory, the Tuscany Region provides women with a pregnancy booklet, delivered by a midwife at the family care center. Despite such efforts to strengthen the maternal care pathway, some critical issues remain unresolved in Tuscany [35-38]. A first problem concerns the lack of coordination between services, especially where the maternal care pathway requires integration between local health authorities (LHAs) and teaching hospitals. A second issue is related to the communication channels: Tuscan women clearly expressed the preference to be informed using information and communication technology (ICT) such as text messages or emails [35]. A third issue concerns poorer health care service use by specific categories of women, such as foreign women and those with a low level of education [36]. Due to their weaker health literacy, these groups are often the least likely to exercise choice and to have a direct and appropriate relationship with health care services and consequently, equal access to antenatal and postnatal care [39]. A final issue regards infant vaccination coverage, which in 2016 was <90% for measles [40].

To address these weaknesses and gaps, Tuscany financed and promoted the development and pilot study of the mobile app hAPPyMamma in an LHA. hAPPyMamma was designed as a supportive tool for women and professionals who can provide women with information about the maternal care pathway and its services, also targeted at specific categories (such as low-income women). This may increase the opportunity for contact and interaction as well as women's self-management and can facilitate disadvantaged groups in accessing and using services [41].

### Design and Implementation of the Mobile App hAPPyMamma

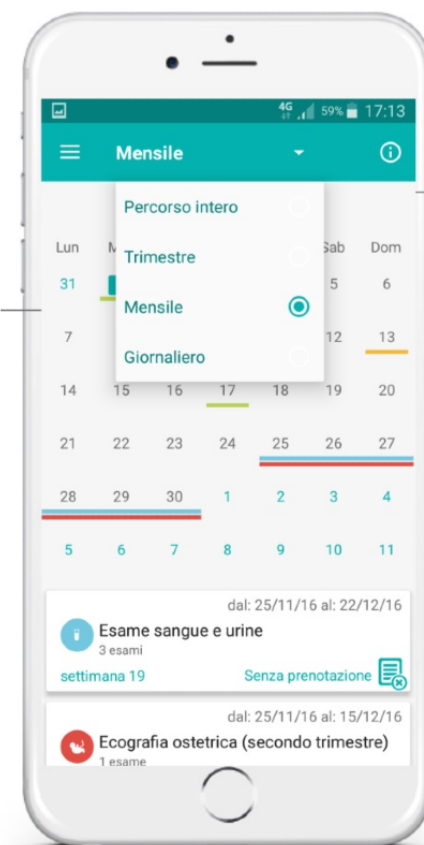
The mobile app offers different functionalities. From the home page, gestational age (during pregnancy) or newborn age (in the postpartum period) are addressed with personalized messages (Figure 1). It includes a digital translation of the pregnancy booklet and infant vaccination calendar into the planner within the app (Figure 2), including alert mechanisms to notify women about visits and diagnostic tests to reserve or, if reserved, to attend.



**Figure 1.** hAPPyMamma home page: identification of gestational age (during pregnancy) or newborn age (in the postpartum period), specific week-by-week messages, and memos for upcoming appointments.



**Figure 2.** hAPPyMamma agenda: digitization of the pregnancy booklet and infant vaccination calendar in the app planner, with different visualization options and alert mechanisms.



Women can digitally book, directly from the app, the 3 obstetric ultrasounds (the first visit in pregnancy and the postpartum visit; [Figure 3](#)), which are the mandatory touchpoints of the maternal care pathway in Tuscany.

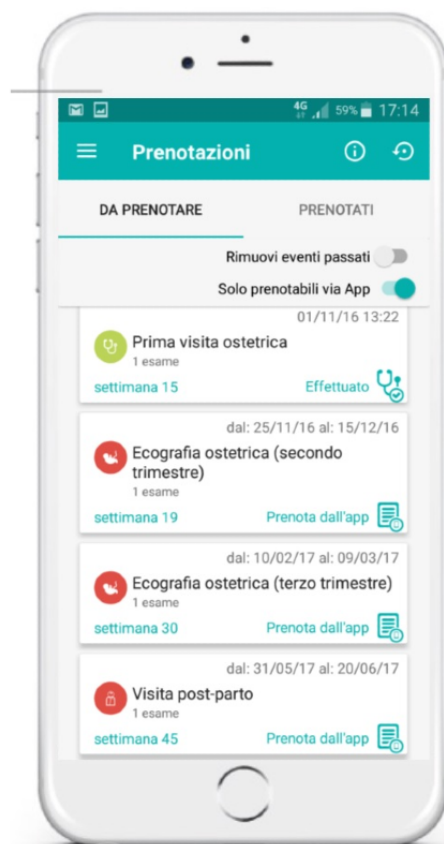
hAPPyMamma contains information on health promotion and prevention as well as on the health care services concerning pregnancy, childbirth, and the postpartum period, divided into thematic sections ([Figure 4](#)). It also proactively shows information through pop-up messages based on data reported by women (ie, smokers will receive pop-up messages on the specific topic of smoking during pregnancy).

hAPPyMamma includes a section with logistic details of primary care and hospital services along the maternity care pathway,

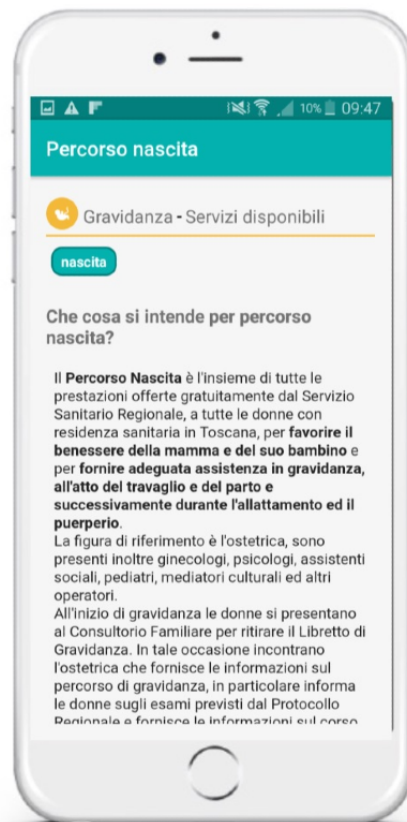
with a georeferencing system ([Figure 5](#)). It first presents services and providers related to the woman's residence area. Additionally, hAPPyMamma is integrated with the regional mobile app that allows access to personal health records developed by the Tuscan Regional Health System. Finally, women using the app can provide direct feedback and answer questionnaires proposed by the app to evaluate their experience in the maternity care pathway.

The design of hAPPyMamma was user-driven, as described, and its development was shared with the professionals involved at both the primary care and hospital levels and in both the maternal and child care areas. It involved the researchers of the Sant'Anna School, who facilitated the app design process and evaluated the results of this innovation.

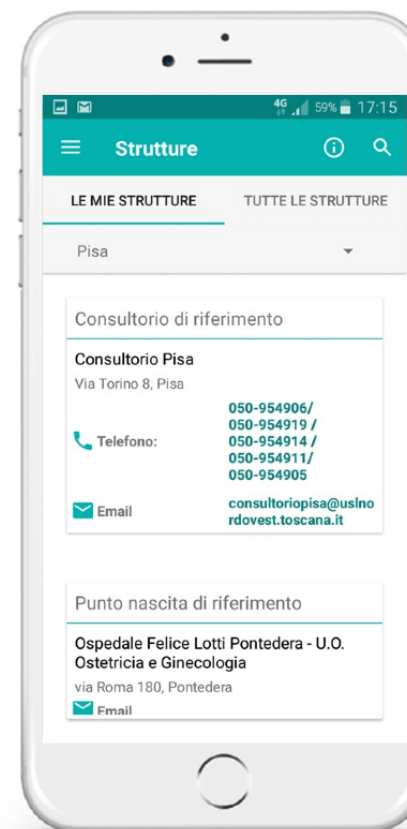
**Figure 3.** hAPPyMamma e-booking of visits and tests, integration into the app planner, and synchronization with the local health authority booking system.



**Figure 4.** hAPPyMamma information repository: provision of professionally validated information (in a frequently asked questions format) on health promotion, prevention, and health care services concerning pregnancy, childbirth, and the postpartum period, with information proactively suggested via pop-up messages.



**Figure 5.** hAPPyMamma facilities repository: information on family care centers and delivery hospitals, with logistic details, services provided, and georeferencing system embedded.



## Objectives

The aim of the study reported in this protocol is to evaluate whether and to what extent the mobile app hAPPyMamma is able to increase maternal health literacy (MHL) and empowerment of women as well as access to and utilization of health care services during the maternal care pathway. Our hypothesis is that implementation of the mHealth solution will bring a positive impact on the maternal care pathway, in terms of more appropriate use of the available services, a better experience for women, and an improvement in the maternal competencies of women using hAPPyMamma. To meet these objectives, the study proposes to compare pre-study and post-study differences in outcomes for the control group versus the intervention group using hAPPyMamma.

Moreover, the protocol includes an analysis of the use of hAPPyMamma for the intervention group and an analysis of the organizational impact of the introduction of the app in the maternal pathway from the professionals' perspectives.

## Methods

Impact evaluation of the hAPPyMamma mHealth intervention is provided in detail in this section.

### Study Design

In order to assess the impact of the use of hAPPyMamma in the maternal care pathway, this study uses a pre-post quasi-experimental design that compares 2 groups: women who use the app (intervention group) and women who do not use the app (control group). The manipulation of the independent variable (app use) is done by recruiting the 2 groups consequentially: control group before the app was available on the app stores and the experimental group when the app was introduced into the maternal care pathway. The ethical committee of the LHA where the mHealth intervention is implemented approved the research protocol (Authorization n. 42379 signed by the ethical committee on July 13, 2016 and registered with the approval number n. 0133972 on August 3, 2016).

The choice of not randomizing the samples using and not using the mobile app is in line with the ethical principles. Indeed, the mobile app can represent a potential tool to improve the quality of the maternity care pathway, and the randomization of women could have brought unfair advantages to women who use the app compared to the others. Therefore, the choice of a quasi-experimental study design also addresses this ethical principle.

The data concerning the measures of maternal health literacy and empowerment are collected prospectively through web-based pre-study and post-study surveys, enabling difference-in-differences analysis to assess the impact of the mHealth intervention [42]. In particular, there are 2 data collection moments through the web platform. The first data collection (pre-study survey) is carried out at the beginning of the maternal care pathway, when women receive the pregnancy booklet, corresponding to the beginning of the pregnancy. The second data collection (post-survey) is implemented around 6 months after childbirth in the postpartum period, when data on

women's experiences in the maternal care pathway are also collected. This second survey questionnaire also contains a section reserved for the intervention group on their experience with hAPPyMamma use.

The organizational impact will be evaluated through a quantitative and qualitative survey and in-depth interviews addressing professionals and managers of the maternal care pathway in the participating LHA and teaching hospital. Both data collection methods focus on the perceived changes the practitioners identify in their job activities due to the mHealth intervention. The survey uses a web questionnaire with close-ended and open-ended questions, in order to measure and assess practitioners' perceptions and opinions on the hAPPyMamma impact through rating questions and narratives. The survey results are discussed with some practitioners during the in-depth interviews. Considering that the organizational impact can be better evaluated through a midterm evaluation, this component of the study protocol is planned to be implemented after implementation of the data collection with mothers.

### Study Population and Sample Size

The sample size for the pre-post survey addressing mothers was estimated with respect to differences concerning some key measures considered within the study, namely MHL level and other experience measures such as access to maternal care services and satisfaction with the maternal care received. We determined the sample size required to detect a 10% difference between the 2 groups concerning the key measures considered within the study, when this difference genuinely exists in the populations of the mothers, with a power of 80% and an alpha error of 5%. With these parameters, a sample size of 300 pregnant women, divided equally between the control and intervention groups, was considered appropriate for a study population of around 2000 births in the pilot LHA yearly.

The quantitative and qualitative survey focusing on the organizational impact of the mHealth intervention uses a convenience sample of professionals and managers working in the LHA and teaching hospital of the study area. All midwives, obstetricians, pediatric doctors, and other professionals of the maternal care pathway are invited to fill in the web questionnaire. The results of this data collection are discussed with 15 practitioners during in-depth interviews.

### Eligibility Criteria

All women receiving the pregnancy booklet in the family care centers of the 3 districts of the participating pilot LHAs during the recruitment period were included. The only exclusion criterion is not speaking Italian, because the app does not have the multilanguage function activated during the experimentation phase. Finally, women without smartphones are not able to use hAPPyMamma and thus are unable to participate in the intervention group of the study.

### Outcomes

The study objectives are addressed in the following ways.



### ***Difference in Improvements in MHL and Empowerment Between the Control and Intervention Groups***

Key outcomes of the study concern MHL and empowerment of women involved in the maternity pathway, which may be particularly improved in the intervention group thanks to the use of the mobile app hAPPyMamma. In order to measure these outcomes, some items of internationally validated tools are used [43-45]. Table 1 shows the dimensions included in the MHL construct: critical, functional, self-efficacy, and social capital. The first 3 dimensions of MHL focus mainly on underlining the competence of mothers for promoting and protecting their health and that of their children, as well as orienting among health information and services. The fourth dimension concerns

social capital that can be considered both a demonstration and a consequence of MHL. In order to define the MHL items for the pre-post questionnaire, 2 different researchers translated the items from the international scales, compared and discussed the 2 different translations, and finally identified a shared version of the Italian items.

Empowerment is evaluated in our study in terms of self-efficacy on breastfeeding and duration of breastfeeding (total and exclusive). These measures that are internationally considered a proxy indicator of mother's empowerment can be positively affected by the more direct and easy access to information on breastfeeding through the app.

**Table 1.** Dimensions included in the pre-post survey questionnaires addressing sampled women in the maternal care pathway.

Dimensions	Description	Control group		Intervention group	
		Prestudy survey	Poststudy survey	Prestudy survey	Poststudy survey
Maternity pathway expectations	Expectations about pregnancy, delivery, and the postpartum period (1 item)	X	N/A <sup>a</sup>	X	N/A
<b>Maternal health literacy</b>					
Critical	Search of different sources of information, check of validity and reliability of information, use of information to make decisions on own health (7 items)	X	X	X	X
Functional	Ability to understand health information, difficulty in reading and interpreting health information materials, self-confidence to fill in modules with health information (4 items)	X	X	X	X
Self-efficacy	Self-confidence to follow health indications, self-confidence to be autonomous in taking care of own child, capability to identify different positive solutions facing obstacles (4 items)	X	X	X	X
Social capital	Support from someone in case of concerns or doubts on own condition, continuity of social life after pregnancy (2 items)	X	X	X	X
Intention to breastfeed	Expectations of breastfeeding and its duration (2 items)	X	N/A	X	N/A
Breastfeeding - empowerment	Total breastfeeding, exclusive breastfeeding, and its duration (3 items)	N/A	X	N/A	X
Experience in the maternal care pathway	Booking of exams during pregnancy, awareness of prenatal diagnostic tests, sources of information on prenatal diagnosis tests, attendance at antenatal classes, difficulties in accessing health services during pregnancy, awareness of labor and delivery, use of health services after delivery, orientation difficulties in maternal care pathway, satisfaction with the maternal care received, suggestions on maternal care pathway improvement (14 items)	N/A	X	N/A	X
Type of health care during pregnancy and delivery	Professionals and services involved in the pregnancy follow-up, number of visits and ultrasounds, characteristics of pregnancy and delivery (8 items)	N/A	X	N/A	X
Interest in ICT <sup>b</sup> services	Information and reminders for visits and exams, antenatal classes, and postpartum services; information on healthy lifestyle during pregnancy; health information records for pregnancy, delivery, and the postpartum period; communication with family pediatrician—by different ICT tools (8 items)	N/A	X	N/A	X
Experience with hAPPy-Mamma use	Duration and frequency of use, habits in smartphone and internet use, comparison with other apps concerning maternal care, utility of different app functionalities, suggestions to improve the app use (11 items)	N/A	N/A	N/A	X
Usability of hAPPyMamma	Learnability, memorability, understandability, attractiveness, errors, efficiency, evaluation of quality, satisfaction in terms of willingness to recommend (15 items)	N/A	N/A	N/A	X

Dimensions	Description	Control group		Intervention group	
		Prestudy survey	Poststudy survey	Prestudy survey	Poststudy survey
Sociodemographic characteristics	Age, citizenship, education level, employment status, gestational age, number of children (6 items)	X	N/A	X	N/A

<sup>a</sup>N/A: not applicable.

<sup>b</sup>ICT: information and communication technology.

### ***Control and Intervention Group Experiences in the Maternal Care Pathway***

The experience of women in the maternal care pathway is measured through a selection of the questions included in the validated questionnaires that have been used periodically in the Tuscany Region to evaluate the users' perspective in the maternal care pathway [35,36]. As shown in the Table 1, this dimension of experience concerns the use of health services during the maternal care pathway, such as prenatal care, antenatal classes, and postpartum care, and they explore particularly the difficulties in access to and orientation among the health services of the maternal care pathway. The questions focus also on the perceived quality of the maternal care pathway and the willingness to recommend its services to friends and family members. The use of the same survey tool ensures continuity in the research approach and the possibility to assess the trend in the outcomes measured.

### ***Intervention Group's Use of hAPPyMamma***

A specific section concerning the experience of the hAPPyMamma use and its usability is introduced in the post-survey questionnaire for the intervention group only (Table 1). The first dimension explores mainly the duration and frequency of the use of hAPPyMamma, perceived utility of the hAPPyMamma functionalities, and opinions of mothers concerning the comparison of hAPPyMamma with other apps related to maternity. The usability includes the principal criteria included in the scales used at the international level [46-49], such as learnability, memorability, understandability, attractiveness, errors, efficiency, quality, and satisfaction. Moreover, some questions focusing on the mothers' interest for ICT services are introduced in the post-survey questionnaire; these investigate mothers' possible interest in receiving—by email, message, or app—information on and reminders for visits and exams, antenatal classes, and postpartum services; information on a healthy lifestyle during pregnancy; health information records for pregnancy, delivery, and the postpartum period; and communication with the family pediatrician. They are submitted both to intervention and control groups in order to also assess the interest of mothers who are not using the mHealth solution. The intervention group has an additional option for answering these questions, namely that they already receive information and reminders via hAPPyMamma.

### ***Organizational Impact of the Introduction of the hAPPyMamma App in the Maternity Pathway From the Professionals' Perspectives***

The organizational impact is assessed through a web survey and in-depth interviews with the professionals and managers

of the maternal care pathway (midwives, obstetricians, neonatal doctors), focusing on the aspects of the experimental use of the mobile app affecting the health care process. In particular, the web survey and interviews explore their expectations before mHealth solution implementation, their perceived difficulties and worries, feelings of uncertainty, fear of replacement, desire to innovate, and the resistance to change that may characterize the opinions of the involved professionals. The descriptive analysis of the questionnaire allows elucidation of the experience of professionals and managers regarding the mHealth intervention. These results represent the basis of the discussion with some professionals and managers during the in-depth interviews. The implementation of the web survey and in-depth interviews after the end of the experimentation allow description of the impact of hAPPyMamma on health care services and practices from the points of view of professionals, with a certain period of distancing from the mHealth intervention to better appreciate its organizational impact.

### **Statistical and Qualitative Data Analysis**

Descriptive statistics will be used to characterize the study population to give an overview of the 2 groups concerning demographic characteristics and use of services during pregnancy, birth, and the postpartum period.

The impact of the app hAPPyMamma on the MHL will be evaluated through a difference-in-differences analysis, which allows measuring the difference in changes prestudy and poststudy between the 2 groups. In particular, the panel data of the study are used to measure the differences between the treatment and control group in the changes in the outcome variable (MHL) that occur over time. In particular, we will calculate the effect of the use of hAPPyMamma (ie, an explanatory variable or an independent variable) on MHL (ie, a response variable or dependent variable) by comparing the average change over time in the outcome variable for the treatment group and the average change over time for the control group. We will also verify the impact of the use of hAPPyMamma on the subdimensions of MHL.

Other multivariate analyses of variance will be carried out in order to evaluate empowerment related to breastfeeding results and the experience of women in the maternity pathway, specifically comparing the control and intervention groups.

Descriptive statistics and multivariate models will also be used to analyze the experience with hAPPyMamma use and its usability.

All statistical analyses are performed using SAS and Stata software.

Descriptive statistics will be performed for the web questionnaires completed by professionals and managers. These results will be presented to key practitioners involved in the in-depth interviews. Qualitative analysis of the in-depth interviews will be performed using QSR NVivo software. After importing the narrative answers to the web questionnaire and the transcriptions of the in-depth interviews, data coding will be implemented by 2 researchers. Content analysis will be carried out in order to identify emerging themes and patterns of the perceptions of professionals on the organizational impact of hAPPyMamma in the maternal care pathway [50].

## Results

Recruitment of the 2 samples of mothers (control and intervention groups) was carried out in sequence. Data collection with the control group started at the beginning of 2017. In May 2017, hAPPyMamma was made available on app stores, and recruitment of the intervention group started. Both groups were recruited using the same procedures. At the time of receiving the pregnancy booklet, women were informed about the study by midwives. Women who decided to participate signed a consent form, leaving their email address. For the control group, we sent an invitation by email to fill in the first web questionnaire at the beginning of the maternity pathway, while the intervention group received the invitation concerning the first web questionnaire directly from the app. The invitation for the second questionnaire was sent by email to both groups, with the intervention group also having the possibility to access the web questionnaire from the app.

The participation rate was high for both the control and intervention groups (around 97%-98%), since the consensus for attending the study was given by 177 women in the former group and by 150 women in the latter group. The response rate for the first questionnaire was different between the 2 groups: 96% (170/177) in the control group and 67% (100/150) in the intervention group. The difference in respondent loss in the follow-up questionnaires was reversed: 33% (56/170) in the control group and only 10% (10/100) in the intervention group. Data collection was completed in April 2018.

Data analysis as well as data collection with professionals and managers are currently underway.

## Discussion

This paper provides the protocol to evaluate the implementation of an mHealth intervention and its impact at individual and organizational levels in terms of improvement in maternal health literacy, mothers' empowerment, and access to and utilization of health care services in the maternal care pathway. We are collecting data to describe the experimental use of the app hAPPyMamma and report on benefits for the mothers using the app. This study is innovative in the Italian context and compared with other interventions worldwide. The mHealth intervention has been realized thanks to collaboration between university researchers and health professionals in maternal care and is promoted by the Regional Health Authority with the aim of improving the quality of the maternal care pathway. Therefore,

the study results assume an institutional perspective and will provide insights on the impact of hAPPyMamma use from the organizational as well as the user perspectives and on the perceptions on the provision of several services in the maternal care pathway through this mHealth channel.

Interviews with key professionals in the maternal care pathway will help to deeply understand their point of view alongside insights emerging from the quantitative and qualitative web survey. This will contribute to identifying and explaining factors positively and negatively affecting the implementation and deployment of hAPPyMamma from their perspectives and those that may facilitate or inhibit the normalization of the innovative tool within the maternal care pathway.

The findings of this study will be relevant for the academic community as well as for policy makers and practitioners. First, there is scarce empirical evidence of the real potential of mHealth in improving women's access to care, their literacy and self-management skills, and quality of services along the maternal pathway [9]. This is particularly true for western countries because the literature focuses on the impact of technologies in developing countries [14-29]. In high-income countries, technology-supported interventions targeted at pregnant women and new mothers are often aimed at improving their lifestyle-related behaviors [9,51]. Conversely, the current critical circumstances that impose social distancing and limit physical access to care have highlighted the need for evidence-based technologies to be introduced to support digital and at-distance health care services in a time of crisis, which could be maintained in normal times. This is the second key point that supports the need for evidence on the effectiveness of mHealth services for women in the maternal pathway in developed countries. Service innovation is urgently needed in health care [52], and hAPPyMamma is an innovative way of providing women-centered services along a pathway, also allowing the evaluation of several different outcomes.

There are several strengths in the design of this study. Its methodological approach as a quasiexperimental study allows overcoming the limitations of observational studies in measuring the effectiveness of interventions and their impact at the individual and organizational levels [53,54]. It is an appropriate method for evaluating policies or interventions, such as hAPPyMamma, collecting data before the recipients are exposed to policy or intervention activities [55]. The results of the study contribute to verifying the possibilities and potential of the scaling up of the mHealth intervention.

The study faces some potential methodological and practical challenges. The nonrandomization of the sample, which is an important aspect from an ethical point of view, represents a weakness of the study. Indeed, the noncontemporaneous recruitment of the intervention and control groups does not allow excluding the possibility of influencing factors due to environmental or organizational context [54,56].

Moreover, the differences in response rate and loss to follow-up among maternal samples have to be taken into account, and data analysis will verify if these affect the results [57].



In conclusion, this study contributes to defining the potential role of the mHealth intervention hAPPyMamma in the maternal care pathway. The findings of this study could provide valuable insights on the benefits of hAPPyMamma use for women's experiences in maternal care pathways. Therefore, this study could significantly support analysis to understand if scaling up hAPPyMamma implementation from the pilot area to the

Tuscany Region, as well as to the entire country, would be beneficial. As anticipated, the findings that will result from the evaluation of this mHealth intervention will also provide useful insights for supporting the introduction of mobile-based innovations in maternal and newborn care pathways in other (developed as well as developing) countries.

## Acknowledgments

We thank the CEO, Board of Directors, and staff of the local health unit and teaching hospital involved in the study, who supported the implementation of the mHealth intervention. We thank the members of the Maternal Care Pathway Committee of the local health unit involved in the study, in particular Patrizia Scida, Marta Lupetti, Massimo Srebot, Grazia Fazzino, Giuseppina Trimarchi, and Monica Funaioli, who collaborated on the implementation of the mobile app hAPPyMamma and its impact evaluation study. We thank all the women who participated in the study. Special thanks to Kendall Jamieson Gilmore for the support in the final revision for the English language. The study is part of the research activity plan of Laboratorio Management e Sanità, funded by the Tuscany Region Health Authority under the collaboration agreement signed in 2014 with the Sant'Anna School of Advanced Studies, renewed in 2016. The Tuscany Region Health Authority promoted the development of the mobile app hAPPyMamma and the relative study on its impact, but the Tuscany Region Health Authority was not involved in the study design, data collection, and analysis.

## Authors' Contributions

MB coordinated the design and implementation of the mobile app hAPPyMamma. MB, SDR, and MV designed the study, formulated the research question, and elaborated the study protocol. MB and SDR coordinated the implementation of the study. MB, SDR, and MV wrote, revised, and approved the final manuscript.

## Conflicts of Interest

None declared.

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## Abbreviations

**ICT:** information and communication technology

**LHA:** local health authority

**MHL:** maternal health literacy

*Edited by G Eysenbach; submitted 02.04.20; peer-reviewed by M allman-Farinelli, D Koutsouris; comments to author 04.05.20; revised version received 24.06.20; accepted 28.07.20; published 19.01.21.*

*Please cite as:*

*Bonciani M, De Rosis S, Vainieri M*

*Mobile Health Intervention in the Maternal Care Pathway: Protocol for the Impact Evaluation of hAPPyMamma*

*JMIR Res Protoc* 2021;10(1):e19073

URL: <http://www.researchprotocols.org/2021/1/e19073/>

doi: [10.2196/19073](https://doi.org/10.2196/19073)

PMID: [33464218](https://pubmed.ncbi.nlm.nih.gov/33464218/)

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Protocol

# A Shared Cancer Follow-Up Model of Care Between General Practitioners and Radiation Oncologists for Patients With Breast, Prostate, and Colorectal Cancer: Protocol for a Mixed Methods Implementation Study

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## Abstract

**Background:** The rising incidence of cancer and increasing numbers of cancer survivors have resulted in the need to find alternative models of care for cancer follow-up care. The acceptability for follow-up care in general practice is growing, and acceptance increases with shared-care models where oncologists continue to oversee the care. However, a major barrier to this model is the effective exchange of information in real time between oncologists and general practitioners. Improved communication technology plays an important role in the acceptability and feasibility of shared cancer follow-up care.

**Objective:** The aim of this study is to evaluate the feasibility and acceptability of a shared cancer follow-up model of care between patients, general practitioners and radiation oncologists.

**Methods:** This is a mixed methods, multisite implementation study exploring shared follow-up care for breast, colorectal, and prostate cancer patients treated with curative radiotherapy in New South Wales, Australia. This study uses web-based technology to support general practitioners in performing some aspects of routine radiotherapy follow-up care, while being overseen by a radiation oncologist in real time. The study has two phases: Phase 1 is designed to establish the level of agreement between general practitioners and radiation oncologists and Phase 2 is designed to implement shared follow-up care into practice and to evaluate this implementation.

**Results:** Recruitment of radiation oncologists, patients, and general practitioners commenced in December 2020 and will continue until February 2021. Data collection will occur during 2021, and data will be ready for analysis by the end of 2021.

**Conclusions:** Few studies have investigated the role of health technologies in supporting communication deficiencies for shared cancer follow-up care. The implementation and evaluation of models of care need to be conducted using a person-centered approach that is responsive to patients' preferences and needs. Should the findings of the study be acceptable and feasible to radiation oncologists, general practitioners, and patients, it can be quickly implemented and expanded to other tumor groups or to medical oncology and hematology.

**Trial Registration:** Australian New Zealand Clinical Trials Registry ACTRN12620001083987; <http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380057>

**International Registered Report Identifier (IRRID):** PRR1-10.2196/21752

(*JMIR Res Protoc* 2021;10(1):e21752) doi:[10.2196/21752](https://doi.org/10.2196/21752)

**KEYWORDS**

radiation oncology; general practice; health technology; communication; cancer; shared care; follow-up

## *Introduction*

The increasing incidence of cancer, coupled with improved survivorship, has resulted in higher demand for cancer follow-up care [1-3]. This has led to the sustainability of oncologist-led cancer follow-up care in the secondary health setting being questioned [4,5] and to a call for alternative models of cancer follow-up care [6,7]. There is a growing body of literature on the benefits of shared cancer follow-up models between general practitioners and oncologists [8]; however, this is yet to be integrated into routine practice.

Randomized controlled trials have shown that cancer follow-up care delivered by a general practitioner in the primary health care setting produces no difference in the rate of recurrence or quality of life compared to cancer follow-up with an oncologist [9-11]. General practitioners are willing to take a greater role in cancer follow-up care [12] provided they are supported by the oncologist [13-16] and the oncologist maintains overall responsibility [17].

Despite an acceptance by patients for their general practitioner to be involved in their follow-up care, barriers to shared care exist. The barriers are role clarification [18-20] and effective two-way communication [21-25]. There is a need for a robust information-sharing system that allows both the general practitioner and the overseeing oncologist to be involved in the follow-up care. Real-time and open access to patient information is crucial to coordinate the care of cancer survivors appropriately [26-28].

At present, cancer patients maintain follow-up with their oncologists in the secondary health care setting, and routine communication is transferred from the oncologist to the general practitioner via letter or secure email. In the case where a general practitioner has undertaken a cancer-specific follow-up, it is uncommon for the general practitioner to communicate their findings to the oncologist. This study will trial a web-based technology to breach the communication divide between the general practitioner and the oncologist so that they can work together collaboratively, should patients choose a shared-care model.

To our knowledge, there is currently no system that supports the involvement of general practitioners in shared cancer

follow-up care where the radiation oncologist can oversee the care. This study trials a web-based system that allows general practitioners to undertake routine aspects of cancer follow-up care, while sharing the data with oncologists at the hospital in real time so that they can continue to monitor, oversee, and maintain responsibility for the patient.

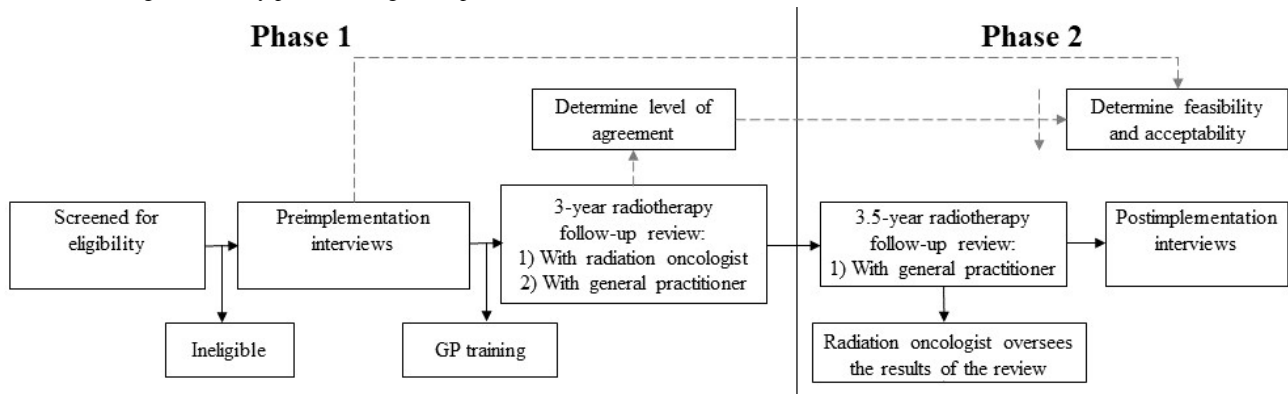
This research aims to evaluate the feasibility and acceptability of a shared cancer follow-up model of care between patients, general practitioners and radiation oncologists. The objectives of this study are to implement a model of care using a web-based system that transfers clinical information between the general practitioner and radiation oncologist in real time, to determine the level of agreement between general practitioners and oncologists completing a standardized follow-up assessment, and to establish the feasibility and acceptability of this model of care.

## *Methods*

### **Study Design**

This research is a mixed methods, multisite implementation study for breast, colorectal, and prostate cancer patients who have undertaken curative radiotherapy treatment. Mixed methods investigations involve integrating quantitative and qualitative data collection and analysis into a single study [29] and can strengthen the credibility of evidence and evaluation [30].

The study will implement the shared cancer follow-up model of care into practice at baseline (Phase 1) and at 6 months postrecruitment (Phase 2) (see [Figure 1](#)). During Phase 1, there will be a standard clinical review by the radiation oncologist as per the patient's routine follow-up schedule, plus an additional follow-up review by the general practitioner using the same standardized follow-up assessment. This first phase will determine the level of agreement between general practitioners and radiation oncologists when completing the same radiotherapy follow-up clinical assessment on the patient. This first phase is essential, as it informs the educational and training requirements for general practitioners. By demonstrating the level of agreement, it reassures both the general practitioner and radiation oncologist that the general practitioner can reliably conduct a cancer-specific follow-up review.

**Figure 1.** Flow diagram of study phases. GP: general practitioner.

The second phase of the study is the implementation of the shared cancer follow-up model of care into practice. The patient will visit their general practitioner at 3.5 years follow-up for a radiation oncology-specific follow-up appointment. The results will be transferred to the hospital, and the patient's radiation oncologist will be alerted by an automatic quality checklist to review the outcomes of the review in real time on the hospital's oncology information system. The system has a rapid referral built into it in the case of adverse events or should the general practitioner suspect cancer recurrence.

### Study Setting

The research will be conducted within the Illawarra Shoalhaven Local Health District (ISLHD) region in New South Wales, Australia. The ISLHD provides public health services to over 400,000 people and cancer services to almost 9000 people annually (ie, medical oncology, hematology, and radiation oncology). Radiation oncology outpatient services are provided at Wollongong Hospital (ie, tertiary hospital and regional care) and the Shoalhaven District Memorial Hospital (ie, secondary hospital and rural care).

The ISLHD radiation oncology service consults and treats over 1400 patients with radiotherapy and conducts over 5000 follow-up consultations annually. The service has experienced a 20% increase in follow-up consultations over a 5-year period (2015-2019), and treatment activity is projected to increase by 18% by 2031. A substantial proportion of radiotherapy treatment at each site is attributed to breast, colorectal, and prostate cancer.

The study will take place at the two hospital radiation oncology outpatient clinics and in the referring general practices. The relationship between general practice and local health districts in Australia is increasingly pivotal to the health system. General practice in Australia is typically comprised of small businesses with an average of three to five general practitioners, and a universal medical insurance scheme (ie, Medicare) covers all or part of a person's cost to visit a general practitioner [31].

### Local Follow-Up Guidelines

While there are many statements regarding "standard follow-up practices," postradiotherapy follow-up for patients varies greatly depending on the disease type, the oncologist's preference, and the patient's preference. At the ISLHD, a visit 6 weeks after radiotherapy is routine for most cases to review the settling of acute side effects. The pattern of remaining follow-up sessions

for all cancers will include a period of every 3 months for the first year and every 6 months for the second year, followed by yearly reviews and then, finally, discharge from follow-up. For many cancers, a 5-year period of follow-up is common.

At the ISLHD, an acceptable practice for breast cancer patients' postradiotherapy follow-up care would be a follow-up at 6 weeks, then every 3 months for 2 years, then every 6 months to 5 years, and then yearly to 10 years. An acceptable practice for colorectal cancer patients would be follow-ups every 6 months for the first year and then yearly to 5 years. An acceptable practice for prostate cancer patients would be follow-ups every 6 months or yearly to 5 years. However, the actual frequency depends on the individual patient's health, stage, and treatment and their preference for whom to see; in addition, there is currently no early discharge, transfer of care, or shared care for radiation oncology follow-up care to general practitioners.

### Health Technology

The free and open source software framework PROsaiq (Didymo Pty Ltd) will be used [32]. PROsaiq is based around a web server that extracts assessments from inside the oncology information system and encodes the assessment data into XForms (ie, an XML format used for collecting inputs from web forms), which is then presented as a webpage in a web browser. When the clinical assessment is completed on a smart device (ie, phone, computer, or tablet), the clinical assessment is returned to the web server and converted into a Health Level Seven (HL7) message; HL7 is an accepted international communication standard for clinical systems, such as those comprising laboratory information. The HL7 message is presented to the oncology information system MOSAIQ (Elekta AB), where it is imported to become part of the patient's oncological record.

Australia is equipped with reliable internet capability, and the webpage link will be made available to the general practitioner by integrating it into a current local system that they utilize. The general practitioner will complete the patient follow-up clinical assessments using PROsaiq, and the radiation oncologist will receive an automated alert in real time to review the results at the hospital. PROsaiq has been trialed for the collection of cancer patient-reported quality-of-life outcomes from patients and has demonstrated its operational feasibility [33].

## Eligibility Criteria

To be eligible for the study, patients must (1) have a previous diagnosis of colorectal, breast, or prostate cancer; (2) have completed curative-intent radiotherapy treatment and are due for their 3-year review; (3) be over 18 years of age; (4) be able to understand and speak English; and (5) have a general practitioner willing to participate. Patients who do not meet these criteria will be excluded, as will patients who have suspected or confirmed recurrence of cancer.

Patients 3 years posttreatment have been selected, as it was deemed a safe time period by the oncologists for a feasibility study, and the patients will have experienced the standard oncologist-led follow-up model. Participants can withdraw at any stage up until data analysis.

## Sample Size

The sample will consist of 20 triads comprising the patient, their radiation oncologist, and their general practitioner, for a total of 35 to 45 participants. A total of 10 patients will be from the Wollongong Cancer Centre (ie, regional) and 10 will be from the Shoalhaven Cancer Centre (ie, rural).

Sample size guidelines for qualitative interviews suggest that a range between 20 and 30 interviews is adequate for each group to reach data saturation [34]. The sample size for the quantitative level of agreement data requires a minimum of 5 samples; however, to increase the confidence interval, a higher sample is required [35].

## Recruitment

The radiation oncologists will review their follow-up clinic lists from both sites and screen for initial inclusion criteria. The researcher will invite each patient to participate via a postal letter on behalf of the radiation oncologist. Once each patient consents to participate, their general practitioner will be invited. General practitioners will be eligible for continuing professional

development points for participating. If the general practitioners do not consent to participate, the patient will not be eligible.

## Implementation

The foundation of this shared cancer follow-up model of care is that clinician communication exchange is two-way and in real time, while the radiation oncologist continues to oversee the follow-up care. The model includes real-time transfer of results, internal system alerts, and rapid referral to address any issues that may arise. During this study, patients maintain their current specialist standard follow-up care, with all relevant specialists, and will continue follow-up care with their radiation oncologist upon completion of the study.

General practitioners will complete a standardized online radiation oncology course developed by the Cancer Institute New South Wales [36]. The course developed for health professionals addresses the principles of radiation therapy, patient assessment grading systems of side effects, and supportive care management. General practitioners will receive one-on-one training by a radiation oncologist that includes localized radiotherapy-specific follow-up care, a review of the recruited patient's treatment background, and a demonstration of the clinical follow-up assessment that the general practitioner will use in the patient's follow-up review.

## Data Collection

### Overview

The PROsaiq software will be used to administer clinical assessments. The assessments were compiled internally at the ISLHD for follow-up of radiotherapy patients. These clinical assessments review physical items on a scale from 0 to 4 for items specific to radiotherapy follow-up care, such as pain, fatigue, physical performance, bowel issues, urinary issues, and appetite (see Table 1). The included scales were sourced from the Radiation Therapy Oncology Group scales [37] and the Common Terminology Criteria for Adverse Events, version 3.0 [38].

**Table 1.** Radiation oncology follow-up standardized clinical assessment.

Tumor type	Clinical assessments
Breast	Fatigue, ECOG (Eastern Cooperative Oncology Group) Performance Status, appetite, weight loss, chest and breast pain, telangiectasia, lymphedema-related fibrosis, and disease state (ie, local, regional, or distant)
Colorectal	Fatigue, ECOG Performance Status, appetite, weight loss, proctitis, pelvic pain, vomiting, and diarrhea
Prostate	Fatigue, ECOG Performance Status, erectile dysfunction, dysuria, and rectal hemorrhage

## Quantitative Data

The quantitative data will be collected from Phase 1. The radiation oncologist will enter the clinical assessment directly into the oncology information system, while the general practitioners will enter the clinical assessment on the webpage link that will be provided to the general practitioner. Both sets of data from these clinical assessments will be stored in the hospital oncology information system.

## Qualitative Data

At pre- and postimplementation, participants (ie, patients, general practitioners, and radiation oncologists) will participate

in semistructured interviews following a topic guide about radiotherapy follow-up care and their experience of shared care. Demographic data will be collected for all participants (ie, age, sex, level of education, and working years). The interviews will be audio-recorded and transcribed verbatim in preparation for thematic analysis in NVivo (QSR International).

## Data Analyses

### Quantitative Data

The clinical assessment data will be extracted from the oncology information system; the Cohen  $\kappa$  value and percent agreement for each variable from Table 1 will determine the level of



agreement between general practitioners and radiation oncologists. The agreement will assess the concordance between two measurements of each variable with the expectation that there will be near-perfect agreement on each item ( $>0.81$ ). The results of the analysis and level of agreement will be presented to the general practitioners and radiation oncologists to guide any additional education and training.

### *Qualitative Data*

Thematic analysis is a commonly used analytical approach for qualitative data in implementation studies [39]. This involves mapping the transcribed data and emergent themes onto a priori domains. The themes will be compared across the regional and rural sites (ie, Wollongong and Shoalhaven) and triangulated between radiation oncologists, patients, and general practitioners.

### **Ethics Approval and Trial Registration**

Ethics approval was received on May 12, 2020, from the Joint University of Wollongong and the ISLHD Human Research Ethics Committee (2020/ETH00301). The trial was registered with the Australian New Zealand Clinical Trials Registry on October 20, 2020 (ACTRN12620001083987).

### **Results**

Recruitment of radiation oncologists, patients, and general practitioners commenced in December 2020 and will continue until February 2021. Data collection will occur during 2021, and data will be ready for analysis by the end of 2021.

### **Discussion**

#### **Overview**

The important skill set and experience that oncologists have is undisputed. However, there appear to be limited alternate models of cancer follow-up care that address the principles of equity in access, connecting health services, and where the cancer survivor can make an informed decision about their cancer follow-up care. Cancer survivors are more likely to accept shared cancer follow-up care with a general practitioner if their care is overseen by their oncologist [15]. However, effective two-way communication between oncologists and general

practitioners is lacking. Improved communication is the strongest enabler to routine shared cancer follow-up care and is an area that is still being established [22,40-42].

Few studies have investigated the role of health technologies in supporting communication deficiencies for shared cancer follow-up care [43]. There have been no explicit recommendations of what type of health technology to use or how to use it. Health technology has been embraced for the collection of patient-reported outcomes of cancer patients during follow-up care, which utilizes the internet to complete online assessments that connect to the hospitals' patient medical files [44]. To our knowledge, using this type of technology between general practitioners and the oncologists is the first of its kind.

The body of literature on the benefits of general practitioner-led and shared cancer follow-up models of care is growing. Although shared follow-up care may not be desired or appropriate for everyone, Australia's oncologist-led model currently leaves limited patient choice as to when, where, and by whom their follow-up care is delivered. A well-informed patient can actively participate in the decision-making process about their care based on their personal circumstances, beliefs, and priorities.

Oncologists, general practitioners, and patients are supportive of a model of shared care [15,16,45]; however, any model developed needs to address the two-way communication barrier and be evaluated for acceptability [46]. The outcomes of this study may lead to a longitudinal implementation to measure patient satisfaction, cost-benefit analysis, health economic analysis, management of rapid referrals, and long-term outcomes of patients.

#### **Limitations**

Possible limitations of this research are the number of participants needed to determine the level of agreement; the research team will monitor this. Another limitation identified is that the general practitioners and radiation oncologists recruited may assess the same oncological patients from a different viewpoint due to differences in training. The researcher will assist in the coordination of appointments and try to minimize the impact on the patients and health professionals.

### **Acknowledgments**

We would like to thank the Radiation Oncology Department and Research Central at the ISLHD. This research is supported by an Australian Government Research Training Program scholarship.

### **Conflicts of Interest**

None declared.

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## Abbreviations

**HL7:** Health Level Seven

**ISLHD:** Illawarra Shoalhaven Local Health District

*Edited by G Eysenbach; submitted 02.07.20; peer-reviewed by ES Koh, S Pesälä; comments to author 18.09.20; revised version received 10.11.20; accepted 08.12.20; published 19.01.21.*

*Please cite as:*

Sandell T, Schütze H, Miller A

*A Shared Cancer Follow-Up Model of Care Between General Practitioners and Radiation Oncologists for Patients With Breast, Prostate, and Colorectal Cancer: Protocol for a Mixed Methods Implementation Study*

*JMIR Res Protoc* 2021;10(1):e21752

URL: <http://www.researchprotocols.org/2021/1/e21752/>

doi: [10.2196/21752](https://doi.org/10.2196/21752)

PMID: [33464209](https://pubmed.ncbi.nlm.nih.gov/33464209/)

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Protocol

# Technology to Improve Autonomy and Inform Housing Decisions for Older Adults With Memory Problems Who Live at Home in Canada, Sweden, and the Netherlands: Protocol for a Multipronged Mixed Methods Study

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## Abstract

**Background:** Understanding the mobility patterns and experiences of older adults with memory problems living at home has the potential to improve autonomy and inform shared decision making (SDM) about their housing options.

**Objective:** We aim to (1) assess the mobility patterns and experiences of older adults with memory problems, (2) co-design an electronic decision support intervention (e-DSI) that integrates users' mobility patterns and experiences, (3) explore their intention to use an e-DSI to support autonomy at home, and (4) inform future SDM processes about housing options.

**Methods:** Informed by the Good Reporting of A Mixed Methods Study (GRAMMS) reporting guidelines, we will conduct a 3-year, multipronged mixed methods study in Canada, Sweden, and the Netherlands. For Phase 1, we will recruit a convenience sample of 20 older adults living at home with memory problems from clinical and community settings in each country, for a total of 60 participants. We will ask participants to record their mobility patterns outside their home for 14 days using a GPS tracker and a travel diary; in addition, we will conduct a walking interview and a final debrief interview after 14 days. For Phase 2, referring to results from the first phase, we will conduct one user-centered co-design process per country with older adults with memory issues, caregivers, health care professionals, and information technology representatives informed by the Double Diamond method. We will ask participants how personalized information about mobility patterns and experiences could be added to an existing e-DSI and how this information could inform SDM about housing options. For Phase 3, using online web-based surveys, we will invite 210 older adults with memory problems and/or their caregivers, split equally across the three countries, to use the e-DSI and provide feedback on its strengths and limitations. Finally, in Phase 4, we will triangulate and compare data from all phases and countries to inform a stakeholder meeting where an action plan will be developed.

**Results:** The study opened for recruitment in the Netherlands in November 2018 and in Canada and Sweden in December 2019. Data collection will be completed by April 2021.

**Conclusions:** This project will explore how e-DSIs can integrate the mobility patterns and mobility experiences of older adults with memory problems in three countries, improve older adults' autonomy, and, ultimately, inform SDM about housing options.

**Trial Registration:** ClinicalTrials.gov NCT04267484; <https://clinicaltrials.gov/ct2/show/NCT04267484>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/19244

(*JMIR Res Protoc* 2021;10(1):e19244) doi:[10.2196/19244](https://doi.org/10.2196/19244)

## KEYWORDS

aging in place; co-design; cross-country comparison; electronic decision support intervention; housing decisions; memory problems; mixed methods; mobility patterns; shared decision making; technology

## Introduction

### Background

Estimates of life expectancy are increasing, yet age-related disability is still not decreasing [1,2]. Cognitive impairment, including memory problems, are increasingly considered a major public health, economic, social, and political challenge. Projected estimates are that over 75 million older adults worldwide will experience some form of dementia by 2030 [3]. Most older adults with dementia want to remain at home, in a familiar environment, as long as possible [4,5]. For those people with dementia who live at home, engaging in activities outside the home can predict vulnerability. For instance, one study found that 43% of people with dementia wander at some point [6]. Not all people with dementia, especially at the early stage of the disease, have a formal diagnosis or may feel stigmatized by the word [7-9]. Therefore, for the purpose of this research, the term “memory problems” will be used to identify participants rather than dementia. Further, in this protocol we refer to “housing decisions” as decisions about how to remain safely at home as well as decisions about whether to move elsewhere or not. Memory problems and other dementia-related behaviors, along with a need for more skilled health care services, can be a strong incentive to relocate people with dementia to residential care facilities, even against their will [10,11]. Whether to stay at home (ie, age in place) or move to a residential care facility is a frequent, and difficult, decision for older adults with health and memory problems and their informal and formal caregivers [12]. Moreover, the decision about whether it is time to relocate may have to be faced repeatedly as autonomy diminishes and the current housing situation may not provide enough support. Older adults with memory problems may express the desire to stay at home [5] but they and their caregivers are often unaware of options available to them that could support them to remain safely at home. Furthermore, older adults with memory problems are often unaware of their right to be engaged in the decision-making process, which undermines the quality of housing decisions for them and their caregivers [13-15].

New technologies could extend the period of time during which older adults with memory problems can remain mobile and autonomous [16]. Alarm bracelets with communication systems, assistive walking devices, support bars, and adaptive kitchen equipment are commonly used to support independence in indoor environments [17,18]. There is enormous potential for other technological interventions that are used extensively in other sectors, such as GPS tracking, indoor beacon technology, bed sensors, and personal activity monitors to measure movement (ie, acceleration, cadence, and steps) [19,20], detect falls [21], and measure activity inside and outside the home or

body metrics (eg, blood pressure and heart rhythm) [22]. These technologies could be enlisted to support mobility and autonomy in the home environment and hold great potential for older adults whose informed value-congruent decision is to stay home [23-26]. However, few technologies have been applied or tested with older adults in real-life settings outside of residential care facilities. Further, there have been limited attempts to use technologies to assist older adults with memory problems to stay at home longer, and data from such devices have not been used to inform housing decisions. This study builds on our current work [27,28].

To improve the quality of housing decisions among older adults with memory problems, team members of this study have performed systematic reviews [14,29] and created and evaluated electronic decision support interventions (e-DSIs) to inform and foster shared decision making (SDM) [14,30]. However, few studies have examined the relationship between the dynamics of mobility patterns and mobility experiences outside the home and how an understanding of mobility can inform SDM about housing options. Person-centered care promotes patient autonomy, empowerment, and value-congruent choice [31,32] and is key to the next generation of health reforms [33]. SDM is the cornerstone of person-centered care and a process whereby the people involved in decision making identify the decision to be made and discuss risks and benefits of the options, as well as the preferences of all involved [15,34-37]. In the case of older adults with memory problems and their caregivers, SDM requires conveying information in a way that will engage them in the decision-making process by helping to clarify what matters most to them. Preferred options need to be assessed and, if possible, tailored to meet the person’s understanding and needs. Decisions made in this way increase satisfaction, increase adherence to decisions made, and decrease decisional regret [38]. SDM is especially important in preference-sensitive decisions or in circumstances where decision making is plagued with uncertainty, such as housing decisions [29]. Housing decisions for older adults facing loss of autonomy are distinct in that their level of autonomy related to memory problems may be changing and their decisions can quickly be out of date. Thus, the decision-making process may need to be repeated and requires updated information on a regular basis. We hypothesize that an adapted e-DSI and the devices connected to it could play an important role in informing and updating this decision.

### Objectives

The overall aim of this research project is to understand the mobility patterns and experiences of older adults with memory problems living at home and how this data can improve autonomy and inform SDM about housing options. Our multidisciplinary and international team aims to address the

following research questions: (1) What are the mobility patterns and mobility experiences of older adults with memory problems? (2) How can an e-DSI be co-designed and adapted to integrate mobility patterns to improve autonomy? (3) What is the intention among older adults to use the e-DSI for future decision making about housing? and (4) How can this research inform SDM processes about housing decisions?

## Methods

### Overview of Study Design

The COORDINATEs (teChnology tO suppORt DecIision making about Aging aT homE) project is a multipronged study with four phases, each one under the leadership of team members in a different country. Our research questions will be addressed in three countries, with a diversified sample, using a mixed methods approach to provide rich insight into mobility patterns and decision making. Using an integrated knowledge translation approach, we will use iterative end-user consultation and feedback to tailor e-DSI technology to end users in Canada, Sweden, and the Netherlands.

Canada, Sweden, and the Netherlands all are advanced economies with welfare states with aging populations. However, each country has a different health and welfare system that influences policies and services dedicated to aging at home versus in institutions [39,40]. Canada's regime is liberal with a national health insurance system, while Sweden has a social-democratic welfare regime. The Netherlands has

characteristics of both conservative and social-democratic regimes and an etatist social health insurance system. We will take into account the intra- and intercountry differences between older adults and between urban and rural environments. Data collection for each phase will be carried out simultaneously and in collaboration with all country teams. The target population and recruitment strategy will vary for the three data collection phases (see Table 1). Phase 1 will be under the leadership of Dutch team members and will assess mobility patterns and experiences of older adults with memory problems in all three countries. Phase 2 will be under the leadership of a Swedish team and will support the co-design of an e-DSI that integrates mobility patterns and experiences generated from Phase 1 and end users' views and preferences for improving the usability and adaptability of technology [41]. Phase 3 will be under the leadership of Canadian team members who will oversee web surveys—one in each country—on the end users' intention to use personalized e-DSIs to improve autonomy and inform housing decisions. Lastly, for Phase 4, the leadership in all three countries will triangulate and compare results to develop an action plan for scaling up e-DSI development to improve autonomy among older adults with memory problems who live at home and inform their SDM processes about housing options. Informed by the Good Reporting of A Mixed Methods Study (GRAMMS) reporting guidelines [42], and applying an integrated knowledge translation approach [43], we will explore synergies between the data, inform the design of the sequential phases, and link the findings.

**Table 1.** Target population and recruitment strategy: Phases 1 to 3.

Project phase	Target population	Recruitment strategy
Phase 1	<ul style="list-style-type: none"> <li>Older adults with self-reported memory problems who live at home</li> </ul>	<ul style="list-style-type: none"> <li>Referrals from nurses and physicians</li> <li>Referrals from home health care teams</li> <li>Self-referrals from flyers in public spaces</li> <li>Self-referrals from media</li> </ul>
Phase 2	<ul style="list-style-type: none"> <li>Older adults with self-reported memory problems</li> <li>Caregivers</li> <li>Individuals with experience providing care to a person with memory issues</li> <li>Health care professionals</li> <li>Policy makers</li> <li>Information technology representatives</li> </ul>	<ul style="list-style-type: none"> <li>Network of the research team</li> <li>Reference group representing older people</li> </ul>
Phase 3	<ul style="list-style-type: none"> <li>Older adults with self-reported memory problems</li> <li>Caregivers</li> <li>Health care professionals</li> </ul>	<ul style="list-style-type: none"> <li>A survey firm in each country will recruit participants through web panels</li> </ul>

### Coordination and Management

An executive committee will oversee the operationalization of the project. The committee consists of the nominated principal investigator (FL), all coprincipal investigators in each country (AJ, LM, and ME), two representatives of older adults and caregivers (to be determined), one trainee (JS), and one research coordinator (DC). A steering committee consisting of team members and partners will oversee the development and implementation of all phases of the study and will meet annually in person or virtually. In accordance with the funding agencies,

our research team will attend the annual meetings of the project's funding agency, the More Years, Better Lives consortium [44].

### Phase 1: Mobility Patterns and Experiences

#### Participants

In each country, convenience samples of 20 older adults living at home with memory problems will be recruited using several methods, including distribution of flyers in the community and at health service sites, referrals from community physicians, home health care teams, and media. The research teams will

also provide a project overview presentation to local dementia case management teams as a way to elicit suitable referrals. Inclusion criteria for this phase of the study are (1) being over the age of 65 years; (2) living at home independently with a partner, family member, or alone; (3) and experiencing memory problems. Participants will be asked to self-identify as experiencing memory problems, and the severity of the problems will not be assessed by the research team. Our population target is older adults who live at home independently with a partner, family member, or alone. Thus, it is not necessary to have a caregiver to participate in this study. Although caregivers are not the target population for this phase of the research, if the research participant requests it, the caregiver will be asked to share their own personal experiences and to liaise between researchers and older adults if necessary. In situations where caregivers participate in the research, they will be asked to sign a consent form. We aim for a diverse group of participants (eg, sex, health status, and geographic region). Our mixed methods

approach is well-suited to gain in-depth insight into the mobility patterns and experiences of older adults experiencing memory problems.

### Data Collection

Data will be collected by using (1) a sociodemographic survey, (2) a walking interview, (3) GPS tracking, (4) travel diary entries, and (5) an in-depth interview (see Table 2). Each method provides unique data and, in combination, the data provide a comprehensive overview of mobility. For instance, the quantitative data collected through the survey will be analyzed to describe the sample. The qualitative data from the walking and debrief interviews will provide context for the mobility experiences, and the GPS data will provide insight into the spatial mobility patterns. While there may be gaps in the GPS data related to poor connectivity or if the participant forgets to take the GPS tracker with them to an activity, as seen in other studies with older adults and GPS data [28], the travel diary will be used to provide insight into the missing data.

**Table 2.** Data collection methods to assess mobility patterns and experiences.

Method	Description
Sociodemographic survey	A 21-item Likert scale-based questionnaire that includes questions on sociodemographics, living environment, social activities, and standardized self-rated health questions will be administered.
Walking interview	Participants will be asked to take the researcher on a walk of a typical route they take near their home. Throughout this participant-led interview, the researcher will ask questions about typical experiences the participants have when taking the route.
GPS tracking	We will provide participants with a GPS tracking device (eg, Qstarz BT-1000X) to track the routes and location of activities for a period of 14 days. GPS trackers collect spatial data, consisting of latitude, longitude, date, and time, in 5-second epochs.
Travel diary	To complement the GPS data, the participants will be asked to record daily activity information in a formatted travel diary. Activity information includes date, day of the week, time of departure, arrival time, location, purpose of the activity, mode of transportation, person with whom they traveled and did the activity, the use of a mobility aid, and whether the activity was planned.
Debrief interview	After 2 weeks of data collection, an audio-recorded debrief interview will be scheduled to review the participant's activities and mobility experiences.

The research team will carefully explain the data collection and storage process through oral and written information. The participants will then be asked to sign a consent form before the data collection begins. A research assistant will conduct the walking interviews with the participants to generate insights into the participants' movements in their neighborhoods [45]. The research assistant will walk along with each older adult and ask questions along the way, thereby capturing rich data on attitudes and feelings about their environment, special practices, social architecture, and biographies [46,47]. After 2 weeks of data collection, we will conduct debrief interviews to discuss participants' mobility patterns and experiences in relation to their self-reported well-being [16,28]. This last interview will more generally explore the participants' mobility experiences and motives for staying at home in their neighborhood.

### Data Analysis

In line with other studies using similar methods, the sample size of 20 participating older adults per country is based on the expectation that it should reach data saturation (eg, [28,48,49]). A database that includes quantitative data from travel diaries will be created in Microsoft Access 2016, and the data will be

cleaned, analyzed descriptively, and linked to the GPS data based on unique identifiers. All data, aside from the GPS data, will be anonymized and pseudonymized. The GPS data are extremely privacy-sensitive as they provide location information, so they will be securely stored in a virtual research workspace (VRW) created by the Center for Information Technology at the University of Groningen. Only project staff can access this environment via two-factor authentication (ie, password and text message). When analyzing the GPS data, we will work with the real location data within the VRW. The real locations are needed as the location and movement data need to be connected to other layers of information, such as roads, shops, and health care services. GPS data will be analyzed using the geographic information system programs V-Analytics and ArcMap 10.5.1 (Esri) to create maps with visited places and trajectories, including speed, duration, and length of time on an activity. The qualitative data generated through the walking interviews and debrief interviews will be transcribed verbatim, open content-coded using a grounded theory method [50], and analyzed thematically using the software package ATLAS.ti 8.4 (Scientific Software Development GmbH). All data sources will be compared and combined to check for incongruences



between the data sources to obtain a comprehensive overview of the participants' mobility in association with their respective environments. Furthermore, we will summarize the themes from the in-depth interviews, translate them into English, triangulate data from the three countries, and further compare differences between health care systems, geography, and regulations.

## Phase 2: Co-Design of an Electronic Decision Support Intervention

### *Participants in the Co-Design Process*

Using the research team members' extensive networks, we will recruit a convenience sample of 5 to 8 end users per country that will include (1) older adults, (2) caregivers, (3) professionals with experience caring for people with memory issues, and (4) technology developers. The group size and configuration is based on other co-design studies [51]. We will strive to have an equal proportion of each type of end user with a group size of 8 persons. The inclusion criteria for the older adults will be individuals over the age of 65 years with memory problems, who receive support at home from health services, and who have access to a computer and the internet at home.

### *Data Collection*

Based on data from Phase 1, we will conduct user-centered co-design workshops with older adults with memory problems and stakeholders. The aim is to co-design an adapted version of an existing e-DSI that could be used to improve autonomy and inform shared decision making for older people in frail health living at home, and to evaluate the co-design process. We will use the Double Diamond method [52] as a guide for the workshop facilitation. The Double Diamond method includes a three-step process: (1) idea generation, (2) modeling a prototype, and (3) testing and consensus discussions. Each country will facilitate their own workshops in keeping with the co-design approach.

### *Data Analysis*

The size of the groups is adequate for a user-centered process [53], ensuring optimal participation of the end users in the co-design group. The qualitative data generated through the group discussion will be transcribed verbatim, open content-coded, and analyzed thematically using the software package ATLAS.ti 8.4. We will compare data from the three working groups and try to find common ground with regard to the solutions mentioned. Based on the findings, we will develop recommendations as to how to integrate mobility patterns into an e-DSI and we will upload interactive video-based material developed in a previous study [54] with information about further options for staying independent at home.

## Phase 3: Exploring the Intention to Use an Electronic Decision Support Intervention

### *Participants*

We will hire a survey firm in each country that will recruit 70 older adults and/or caregivers. A total of 210 participants will be recruited from the survey firm's web panels and via end-user organizations, such as senior and caregiver associations. Inclusion criteria include the following: (1) older adult who is

65 years old or older or a caregiver of an eligible older adult, (2) older adult who self-identifies as having memory problems, and (3) older adult who has access to a computer with internet access. Facing a housing decision will not be an inclusion criterion, but participants will be asked if this is a current decision-making process they face. We have determined our sample size based on the mean behavioral intention taken from Delanoë et al [55]. With a power of 80% and an  $\alpha$  level set at .05, our survey will be able to detect a mean score of 5.6 (SD 0.14), 19 times out of 20 (margin of error equal to 0.14), within each country.

### *Data Collection*

For each country, based on sociocognitive behavioral change theories such as the theory of planned behavior [56], we will assess participants' opinions regarding factors [57] that could influence their adoption and intention to use an e-DSI to improve autonomy and make decisions about housing [13]. Participants will be invited to complete a self-administered web-based survey with closed-ended questions. The survey questions will be based on the integrative model of behavior [58] to assess participants' intention to use the e-DSI for future if they faced a housing decision [13]. Additionally, we will measure the psychosocial determinants of this behavioral intention [14] and explore their preferred role in decision making [59], their experience using technology [13], and sociodemographic variables (eg, age, sex, social economic status, and relationship between the older adult and the caregiver) [57,60].

### *Data Analysis*

Our primary outcome variable is the behavioral intention of a participant to use the e-DSI; this will be measured on a 7-point Likert scale, ranging from 1 to 7. We will assess the psychosocial determinants of this behavioral intention and participants' opinions regarding factors that could influence their use of an e-DSI by referring to questions in the domains of the NASSS (nonadoption, abandonment, scale-up, spread, and sustainability) framework [61]. We will compare data from people with and without experience using an e-DSI to explore how experience influences willingness to use it. Secondly, we will compare the data obtained in the three countries to identify any differences between health care systems, geography, and regulations.

## Phase 4: Inform Future SDM Processes

For the final phase of the project, we will synthesize, triangulate, and compare data from all project phases and collaboratively explore privacy issues. Validation and interpretation of data will be accomplished with consensus meetings between researchers and end users [62]. Data from the three countries—Canada, Sweden, and the Netherlands—will be triangulated and compared to assess differences in contextual factors (ie, health care system, policy, geography, and culture), and we will make recommendations for technology implementation to improve autonomy and inform SDM about housing in the three countries. At the end of Phase 4, end users in each country will participate in a workshop where project results will be presented and discussed. As an output, we will acquire knowledge about differences and similarities in mobility

patterns and experiences with using GPS and an e-DSI among older adults with memory problems and their caregivers, their respective assessments of its contribution to improving autonomy and emerging housing decisions, their willingness to continue using it, and factors that influence usage. After evaluating the impact of an e-DSI for continuing to age at home and for ongoing housing decisions among older adults and their caregivers, we will propose country-specific action plans to scale up e-DSIs and evaluate their implementation by home care services. We will explore opportunities to continue the consortium and form an infrastructure for continuous collaboration between the three countries.

### **Ethical Considerations and Trial Registration**

A review for issues regarding human subjects has been obtained from four research ethics committees. Ethics approval has been obtained by the Research Ethics Committee, Faculty of Spatial Sciences, University of Groningen; Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale, L'Université Laval; the Swedish Ethical Review Authority; and the Health Research Ethics Board, University of Alberta. For all phases of data collection, participants will be asked to sign an informed consent form. Where appropriate, we will ask informal caregivers to sign a consent form. This trial was registered at ClinicalTrials.gov (NCT04267484).

### **Results**

The study opened for recruitment in the Netherlands in November 2018 and in Canada and Sweden in December 2019. Data collection will be completed by April 2021. Given the COVID-19 pandemic and the different lockdown approaches taken by each country, data collection may be adapted using virtual methods.

### **Discussion**

We have described the methods for exploring how adding data about personal mobility patterns of older adults to an e-DSI has the potential to improve their autonomy and inform future SDM processes about housing options. Participants included older adults living at home with memory problems and their caregivers as well as a diverse group of stakeholders. This study will contribute to the mobility literature on older adults with memory problems and inform the development of technology that augments self-management among older adults affected by memory loss, their caregivers, health care professionals, and policy makers [13,14,16,30,60].

The proposed study is a highly original approach to the potential of technology use with older people with memory problems. First, this is an interdisciplinary, interprofessional, intersectorial, and international study. This question is often addressed in isolated contexts without the mutually enriching possibilities of working together with other disciplines, professions, technological traditions, and cultures. Second, while personalized medical care such as gene testing or drug treatment

selection is becoming the norm in specific contexts, personalized data have rarely been used to empower older people with memory loss. The results not only have the potential to keep older people safely at home for longer but will provide deep insights into their physical and emotional relationship with their surroundings and the consequences of displacing them into a new environment. Third, one of the persistent problems we have seen with decision making about housing among older adults is that their autonomy or mobility needs change from day to day. Thus, the information needed for decision making also changes from day to day. This technology could relieve the deep distress experienced by older people and their families facing this decision by providing reliable and relevant ongoing data that indicate the individual's changing needs for on-the-spot decision making.

Finally, new technologies such as GPS tracking can infringe on people's privacy, an issue that is highly relevant today. For example, more people are using apps that provide contact tracing for people infected with COVID-19. In our cross-country comparisons, we will investigate the ethical issues involved in working with tracking technologies with older adults in the three countries. There is little research on the ethical implications of these technologies with older adults and their caregivers [63-65]. Notably missing are discussions about translating general ethics and privacy principles into concrete guidelines in different national settings. Therefore, in accordance with guidance from our four ethics boards, we will advance the current state of the art in this domain by developing country-specific ethical guidelines for practice. There are some anticipated challenges and limitations of this research project. Although most of the data collection in each phase will take place in the language of each country, with Canada having two official languages, the overarching research process will be undertaken in English, and this may affect the capacity of team members, including older adults and caregivers, to fully participate. Communicating among different countries and time zones can be a challenge. Therefore, it is critical for this international team to have established solid lines of communication and formal institutional consortium agreements to ensure the success of the project. Second, despite the increasing computer literacy levels among older adults [66,67], some, especially those who are socioeconomically disadvantaged, do not have access to a computer with internet access and therefore will not be eligible to participate in Phase 2 of this project.

This protocol outlines an original approach to integrating mobility patterns and mobility experiences of older adults with memory problems into an e-DSI to improve their autonomy and ultimately inform SDM about housing options. The results will contribute to the development of technology that supports older adults' autonomy and housing decisions in general. Furthermore, the international collaboration with end users can provide valuable insights into the intention to use technology for housing decisions and barriers to its use.

## Acknowledgments

We thank Louisa Blair for kindly editing the manuscript. This research is a part of the COORDINATEs study (project No. 9003037412), which is funded by the Joint Programming Initiative More Years, Better Lives, represented by ZonMw in the Netherlands, the Canadian Institutes of Health Research, and Forte. We appreciate the support of Greybox Solutions in providing us with an in-kind contribution.

## Conflicts of Interest

None declared.

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## Abbreviations

**COORDINATEs:** teChnology tO suppORt DecIision making about Aging aT homE

**e-DSI:** electronic decision support intervention

**GRAMMS:** Good Reporting of A Mixed Methods Study

**NASSS:** nonadoption, abandonment, scale-up, spread, and sustainability

**SDM:** shared decision making

**VRW:** virtual research workspace

*Edited by G Eysenbach; submitted 09.04.20; peer-reviewed by L Lowenstein, M Jordan-Marsh, E Ding; comments to author 29.06.20; revised version received 20.10.20; accepted 08.12.20; published 21.01.21.*

*Please cite as:*

*Sturge J, Meijering L, Jones CA, Garvelink M, Caron D, Nordin S, Elf M, Légaré F*

*Technology to Improve Autonomy and Inform Housing Decisions for Older Adults With Memory Problems Who Live at Home in Canada, Sweden, and the Netherlands: Protocol for a Multipronged Mixed Methods Study*

*JMIR Res Protoc* 2021;10(1):e19244

URL: <http://www.researchprotocols.org/2021/1/e19244/>

doi: [10.2196/19244](https://doi.org/10.2196/19244)

PMID: [33475512](https://pubmed.ncbi.nlm.nih.gov/33475512/)

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Protocol

# Mapping, Infrastructure, and Data Analysis for the Brazilian Network of Rare Diseases: Protocol for the RARASnet Observational Cohort Study

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## Abstract

**Background:** A rare disease is a medical condition with low prevalence in the general population, but these can collectively affect up to 10% of the population. Thus, rare diseases have a significant impact on the health care system, and health professionals must be familiar with their diagnosis, management, and treatment.

**Objective:** This paper aims to provide health indicators regarding the rare diseases in Brazil and to create a network of reference centers with health professionals from different regions of the country. RARASnet proposes to map, analyze, and communicate all the data regarding the infrastructure of the centers and the patients' progress or needs. The focus of the proposed study is to provide all the technical infrastructure and analysis, following the World Health Organization and the Brazilian Ministry of Health guidelines.

**Methods:** To build this digitized system, we will provide a security framework to assure the privacy and protection of each patient when collecting data. Systems development life cycle methodologies will also be applied to align software development, infrastructure operation, and quality assurance. After data collection of all information designed by the specialists, the computational analysis, modeling, and results will be communicated in scientific research papers and a digital health observatory.

**Results:** The project has several activities, and it is in an initial stage. Initially, a survey was given to all health care centers to understand the technical aspects of each network member, such as the existence of computers, technical support staff, and digitized systems. In this survey, we detected that 59% (23/39) of participating health units have electronic medical records, while 41% (16/39) have paper records. Therefore, we will have different strategies to access the data from each center in the data collection phase. Later, we will standardize and analyze the clinical and epidemiological data and use these data to develop a national network for monitoring rare diseases and a digital health observatory to make the information available. The project had its financing approved in December 2019. Retrospective data collection started in October 2020, and we expect to finish in January 2021. During the third quarter of 2020, we enrolled 40 health institutions from all regions of Brazil.

**Conclusions:** The nature of rare disease diagnosis is complex and diverse, and many problems will be faced in the evolution of the project. However, decisions based on data analysis are the best option for the improvement of the rare disease network in Brazil. The creation of RARASnet, along with all the digitized infrastructure, can improve the accessibility of information and standardization of rare diseases in the country.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/24826

(*JMIR Res Protoc* 2021;10(1):e24826) doi:[10.2196/24826](https://doi.org/10.2196/24826)

## KEYWORDS

rare disease; digital health; health observatory; data science; health network

## Introduction

### Background

A rare disease (RD) is a medical condition with low prevalence compared to diseases prevalent in the general population, but there is no consensus on its definition [1]. The European Union describes a RD as a disease that affects no more than 1 person in 2000 [2]. In the United States, the Rare Disease Act of 2002 considers a RD any condition that affects less than 200,000 people across the country, or 1 person in 1500 [3]. In Japan, a RD is considered to affect less than 50,000 people (ie, 1 in 2500 people) [4]. On the other hand, in Latin America, there is no consensus on the definition of RDs in terms of numbers. Each country has its own definition according to its public policies, decrees, the existence of adequate treatments, or the severity of the disease [5].

Although individually rare, RDs collectively affect up to 10% of the population. Thus, rare diseases have a significant impact on health, and health professionals must be familiar with their diagnosis, management, and treatment [6]. It is estimated that there are up to 8000 rare diseases identified, 80% of which are of genetic origin [7]. In Brazil, the Ministry of Health defines a rare disease using the criteria of the World Health Organization (WHO), that is, 1.3 cases per 2000 individuals [8]. In 2014, the Brazilian Policy of Comprehensive Care for People with Rare Diseases was established within the scope of the Unified Health System (Sistema Único de Saúde [SUS]) [9].

To overcome this informational barrier, the WHO recommends that research involving the study of the process dynamics of RDs at the national level be financed by public agencies. The formation of large multidisciplinary networks is part of a fundamental process to encourage the collaboration of medical specialists, referral centers, and patient groups [10]. Providing an infrastructure for new mechanisms promoting the translation of basic research into clinically important products is still a priority. One of the most important opportunities addressed by the WHO reinforces support for “networks of excellence that focus on research infrastructures; research, infrastructure, and implementation of guidelines for medical and psychosocial care; [and] methods to provide easy access to health care available to patients, regardless of where they live” [11].

The first full version of a report relating to the concept of a health regionalized network emerged after World War I due to the consequent need for changes in the social protection system, presenting better ways for health services organization. Almost one century later, the original purpose remains very similar, as

many health systems around the world offer a specific organization of services to attend to their population. A need to establish a uniform system of clinical histories was declared a crucial reason for the better integration of different health service levels [12].

The proposal to integrate health networks gained momentum with the advent of health observatories. The emergence of these epidemiological monitoring centers is related to rapid changes in the health sector, including the need to monitor and assess the impact of health programs and public health policies, the advent of informational intelligence, digital health, and health knowledge management. The health observatories' functions include locating, gathering, analyzing, synthesizing, and disseminating data on the health status of a population, in addition to establishing partnerships and contacts with other agencies involved in the health of that region [13].

Independent of which model is used, the majority of countries today have digital systems to manage their data according to their health network structures. According to WHO recommendations, although digital health interventions are not enough on their own, when combined with health professionals, they are vital tools to promote health quality [11]. While data are still the main asset in the current digital world, many institutions do not yet fully understand the need and advantages of sharing their data with other organizations [14].

Cross-institutional sharing of health data is a challenge because many institutions are unwilling to share data due to privacy concerns or the fear of giving other institutions competitive advantages and, at an operational level, because of mistrust of technical barriers (there is no common platform for sharing these complex and heterogeneous data). On the other hand, overcoming this challenge may lead to better clinical effectiveness and improved clinical research [15]. Even if these concerns can be beaten, there is no consensus about the exact technical infrastructure needed to support such an effort.

Studies have shown that there remain a set of meaningful hurdles to achieving the desired benefits of health care data exchange. For example, failing to secure the patient record has financial and legal consequences as well as the negative potential to impact patient care. Thus, possible repercussions of a breach are a discouragement to swapping data. To avoid ethical and legal consequences for institutions, anonymization and privacy must be ensured for sensitive data, making them available only to authorized persons. Further, data anonymity could help improve the research area by removing identifiable information and sharing only limited data [15,16].



Another significant barrier that health networks need to face is adequate technological infrastructure. In addition to the scarce and fragmented availability of data on RDs [17], several technical aspects are common, like a centralized data source, which represents a high-security risk due to the susceptibility for malicious attacks to a nonredundant authority. A secure channel to send data to other organizations is another feature that institutions must address to avoid unauthorized access [14].

Due to the complexity of data in the health domain, achieving full interoperability is a hard task. Heterogeneous structures and data diversity decrease the accuracy of analysis and reduce understanding of information. To face this issue, several entities have created standards for data exchange. However, there is no consensus on the most adequate ones [18]. In Brazil, the Ministry of Health Ordinance 2073 of August 31, 2011, regulates the use of interoperability and health information standards for health information systems within the scope of the SUS; at the municipal, state, and federal levels; and in private systems and the private health sector [19].

In this sense, for there to be semantic interoperability between independent systems, it is necessary to standardize two aspects of information: the structure of the information and the semantic representation of the information. The information structure concerns the information and knowledge models that allow the systems to exchange data, formed in larger structures such as documents, correctly. The semantic representation of information includes terminologies, ontologies, and controlled vocabularies [20].

This framework can mitigate the several barriers preventing data access for research support agencies, academics, managers, and health professionals, such as the noncomputerization of processes, heterogeneity and duplicity of data in health information systems, and existence of a large amount of isolated data in databases accessible only in a certain context, usually to answer specific questions in particular research [17].

These factors often cause problems in the quality of information, making it difficult to coordinate and evaluate data in a research network linked to a rare disease patient care network, so it is not possible to use the data to assist in the decision-making process. Therefore, in health care, decision support tools are essential to guide the practice of health care and support the decisions of managers who will directly influence the quality of care provided to patients with RDs [21].

This paper presents a subproject belonging to the main project, entitled the Brazilian Rare Disease Network, funded by the Brazilian Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico [CNPq]), with a 2-year forecast. The main project is a mixed prospective and retrospective observational cohort study to map the landscape of rare diseases in Brazil. RARASnet is responsible for infrastructure and data analysis to provide health indicators and support the construction, organization, and monitoring of this patient network. Although the objectives are collaborative, different teams are responsible for specific parts.

## Related Work

RDs represent a major challenge for the organization of health care. The cooperation of health service professionals, civil society, and academia is essential to overcome this challenge. In recent years, different collaborative networking initiatives have emerged. Collaborative networks are of great value for science and technology institutions to share, generate, and disseminate new knowledge that can lead to innovations and form a solid basis for a national care network [22-24]. In this scenario, records represent an important tool in acquiring the necessary knowledge about the clinical form and natural history of patients with RD.

Maintaining records of epidemiological data also contributes to the planning of public health programs, which in some cases requires supranational coordination. Thus, European Reference Networks (ERNs) were organized, supported by a series of rules and guidelines that provide a cohesive structure for sharing good practices of diagnosis, treatment, and standardization of recommended approaches for RDs. The promotion of ERNs contributed to the identification of already established centers of expertise and encouraged the voluntary participation of health service professionals in ERNs dedicated to specific groups of RDs [22].

Italy was one of the first European countries to develop specific RD regulations. The success of the experience in Italy is exemplified by the regional network of Piedmont and Valle d'Aosta, where networked activities have provided several benefits, such as improvement of multidisciplinary knowledge, provision of quality care, and reduced cost of therapeutic mobility [22,23]. To produce epidemiological evidence on RDs and support health service policy and planning, Italy also assessed the integrity and consistency of procedures carried out from its national registry and found that the data quality still represents a limitation to any solid epidemiological estimate [22].

After comparing the outcome of patients with primary systemic amyloidosis in a referral center with the population of this same Italian network, another study in the country found that the patients observed by the network had a diagnosis 4 months earlier than those seen in the reference center. In addition to the rapid dissemination of knowledge pointed out as the main cause of this difference, important epidemiological differences were observed, which further reinforces the need for the standardization of reliable prognosis and the administration of clinical trial results [22,24].

According to the French National Plan for Rare Diseases, the first step in identifying patients with RD who are eligible for clinical trials or cohort studies is the definition of a minimum set of national data. In addition, providing reference centers with information technology (IT) tools contributes to the improvement of the service and research of RDs. Thus, according to international regulations on privacy and intellectual property and based on interoperability and semantics standards, the construction of the French model allowed data sharing in a national network composed of 131 centers specialized in RDs [22,24-26].

One of these French national reference centers went further and created a web-based medical archive of pediatric interstitial lung diseases. The construction of a national database made it possible to centralize and serve various stakeholders, such as researchers, clinicians, epidemiologists, and the pharmaceutical industry. Consequently, with the increasing engagement of new participants and the creation of committees to control data quality, there was an increase in the accuracy of the information provided, and several alternative solutions, depending on local possibilities, were configured [27]. Similar initiatives have also taken place in Germany [28] and the United Kingdom [29].

To not only collect records but also analyze them, a conceptual and digital framework based on the Asia-Pacific Economic Cooperation Rare Disease Action Plan has been articulated [26]. A proposal for a rare disease registry and analytical platform aims to assist in clinical decision making and improve the design and delivery of health services [30].

On the other side of the ocean, the National Center for the Advancement of Translational Sciences, one of the 27 departments of the US National Institutes of Health (NIH), maintains initiatives that aim to enhance the research of rare diseases, such as the promotion of information sharing and the construction of multidisciplinary collaborations. The Rare Diseases Clinical Research Network, for example, despite being formed by distinct clinical research consortia, shares the same data coordination and management center [31].

This management is only possible due to the availability of a genomic database maintained by the Genetic and Rare Diseases Information Center and the RD record program based on international standards and sharing (eg, Health Level Seven, Human Phenotype Ontology [HPO]) as well as the toolkit for the development of patient-focused therapies (National Center for Advancing Translational Sciences Toolkit), represented by an information portal with guidelines for the development process of research and partnerships with the NIH and the Food and Drug Administration [32].

Worldwide, these two actions integrated not only clinical and epidemiological data and records but also information from biorepositories of biological samples for rare biospecimens (RD-HUB) [33], and they created an integrated platform that connects databases, records, biobanks, and bioinformatics clinics for rare disease research (RD-Connect) [34]. To address the quality of these data, several models and tools have been developed worldwide [34,35]. An assessment approach for diagnosing rare diseases based on Unified Modeling Language and ontologies, called FindZebra, improves the quality of diagnosis compared with standard search tools [34-36].

To become more than a search engine, decision support systems for clinical diagnosis have incorporated artificial intelligence and natural language processing techniques to provide more accurate and useful systems [37]. By having the infrastructure established according to the Ministry of Health, we can focus on the data analysis. Data science has been playing a major role in retrieving insights from patient reports and human and technical resources. Thus, the main goals of this project are described in the following section.

## Objectives

The primary objective of this study is to identify the essential elements for mapping, infrastructure, and data analysis for the Brazilian Network of Rare Diseases. Secondary objectives are to (1) create and implement a system that allows the integration of data available in different systems of health care, social assistance, and epidemiology of RD cases (a shared electronic medical record), simplifying the access to patient data via the web by health care stakeholders; (2) promote interoperability between health information systems through the use of the Semantic Web combined with traditional communication and data exchange techniques for functional and semantic interoperability and the integration of databases to improve the management of health services data; (3) develop a single and complete database using cloud computing with an access hierarchy and well-defined security rules by building a ubiquitous platform capable of providing access services and adding syntactic and semantic value to data, covering innovative techniques such as the use of blockchain for cloud computing; and (4) develop an evidence-based portal with national protocols for monitoring and analyzing data collected or produced in several RD patient care settings, incorporating data processing, analysis, and machine learning techniques to assess the clinical situation and possible patient risks in real time.

## Methods

### Brazilian Rare Disease Network

Typically, information technology investigations can be distinguished as applied basic research. Basic research is scientific research focused on improving the understanding of phenomena and events [38]. Applied research uses scientific studies to develop technologies and methods to intervene in natural or other phenomena, aiming to improve human interaction with such phenomena [39].

As mentioned, the study described is part of a larger project, entitled the Brazilian Rare Disease Network, with a collection of quantitative data coupled with an innovation proposal, the creation of an epidemiological surveillance service network involving university hospitals, Reference Services for Neonatal Screening (Serviços de Referência em Triagem Neonatal [SRTNs]), and Reference Services for Rare Diseases (Serviços de Referência em Doenças Raras [SRDRs]) throughout the Brazilian territory.

Considering the goal of consolidating a national network of rare diseases that covers all regions of Brazil, this study has the participation of SRDRs, university hospitals that may or may not belong to the Brazilian Hospital Services Company (Empresa Brasileira de Serviços Hospitalares) network, and SRTNs. These centers are essential for building a national database that efficiently maps and represents the situation of the field of rare diseases in a country [40]. Brazil is divided into 5 regions (north, northeast, midwest, southeast, and south). The chosen participating centers are distributed across all Brazilian regions and are units of reference in health care for the population of their respective localities, according to the National Policy on Comprehensive Care of People with Rare Diseases [9].

Participating health centers are divided as follows by country regions: 6 centers in the north, 11 in the northeast, 6 in the midwest, 12 in the southeast, and 5 in the south. These include 16 Brazilian capitals that together have a total of 47 million people. In addition, as they are referral centers, they have the infrastructure to receive patients from smaller municipalities for the diagnosis and care of their population.

The area of care for people with rare diseases is structured into primary care and specialized care, following the Health Care Network (Rede de Atenção à Saúde) and the Guidelines for the Comprehensive Care for People with Rare Diseases plan of the SUS. SRDRs are responsible for preventive, diagnostic, and therapeutic actions for individuals with rare diseases or at risk of developing them, according to care axes. The SRDSs have a network of Specialized Rehabilitation Centers (Centros Especializados em Reabilitação [CERs]), which can receive patients referred from SRDSs and assist in the rehabilitation of these patients [41].

The CERs are structural components of the National Policy on Comprehensive Care of People with Rare Diseases. According to the integrality of care, these centers perform treatment, concession, adaptation, and maintenance of assistive technology, constituting a reference for the health care network in the territory [42]. SRDRs and CERs work together with university hospitals to promote comprehensive and universal care for rare disease patients.

The traditional concept defines a university hospital as an institution that is characterized by four traits: being an extension of a health teaching establishment (of a medical school, for example), providing university training in the health field, being officially recognized as a teaching hospital and subject to the supervision of competent authorities, and providing more complex medical care (tertiary level) to a portion of the population and being able to receive patients from SRTNs [42,43].

The SRTNs are units with multiprofessional health teams accredited and specialized in assistance, follow-up, treatment, and redirection of newborn patients diagnosed with pathologies such as phenylketonuria, congenital hypothyroidism, sickle cell diseases, biotinidase deficiency, congenital adrenal hyperplasia, and cystic fibrosis. Such pathologies are detected in the SRTN's own or an outsourced laboratory, according to the rules established in the National Neonatal Screening Program [44].

Initially, the 3 main collaborator groups consist of 17 university hospitals, 6 SRTNs, and 17 SRDRs. The effective consolidation of the Brazilian network of rare diseases, based on the mapping of these services, depends on 3 steps: (1) approval by the ethics committee of the coordinating institution of the project, (2) approval of the local ethics committees of each participating institution, and (3) consolidation of the human resources participating in each institution through the institutional consent form.

The first step has already been completed and the others are in progress. Any divergence in these steps results in the exclusion of the participating center from the project. While these steps are in progress, representatives of all participating institutions

meet monthly—on the second Saturday of the month in the morning—to discuss and structure the other activities of the project. Additionally, institutions must disseminate and invite partner services to participate in the initiative. The structuring and alignment of the final group of participants in the Brazilian network of rare diseases was finalized in August 2020.

### Ethical Considerations

The National Network of Rare Diseases project was approved (Edital No. 25/2019) from CNPq, with financial support from the Ministry of Health in the amount of R \$3.5 million (US \$662,139.10) [45]. Moreover, the main project was sent to the research ethics committee of Porto Alegre Clinical Hospital of the Federal University of Rio Grande do Sul (Hospital de Clínicas de Porto Alegre da Universidade Federal do Rio Grande do Sul) through Plataforma Brasil, a Brazilian platform of the Ministry of Health projects. The research ethics committee of Porto Alegre Clinical Hospital analyzed the research project (under code number 33970820.0.1001.5327 of Presentation Certificate for Ethical Appreciation). The research was approved (opinion number 4.225.579) on August 14, 2020.

To ensure the anonymity of patients while making it possible to track them if necessary, a password will be created for all patients, consisting of the first 2 letters of the city followed by the center number with 2 digits (from 01 for each city) and a 2-digit sequence for the patient's number. The rights, safety, and well-being of the subjects involved in the study will be the most important considerations and should prevail over the interests of science and society.

Considering the governmental efforts (ConecteSUS) [46,47], we similarly propose the use of a permissioned distributed blockchain solution that uses a key pair (private and public key) and a symmetrical consortium key for data encryption. A consortium distributed storage network will be established, consisting of research centers and other approved stakeholders throughout Brazil [48].

Authentication, authorization, integrity, and confidentiality verification mechanisms will be implemented through the establishment of a security layer. Thus, the security structure presented in this project aims to protect sensitive data for interoperability purposes. All computational techniques that support the solution, such as encryption and hashing, are well-known technologies that, when combined, can offer robust security features. In this way, each candidate system to interoperate with the rare disease ecosystem can easily meet all the necessary technical requirements.

All data collection processes will match the novel Brazilian General Law of Data Protection (federal law No. 13.709/18) [49]. The law refers to the respect to user privacy, transparency in the data collection, security, and prevention of damage in personal data. Since August 16, 2020, the law covers all national territory, and its violation can cause a warning, penalties, a data block, and suspension of the project [50]. As mentioned, the project will ensure the anonymity of the data during analysis. In addition, the IT team will present to all members of the network the definition and main aspects of the General Law on Protection of Personal Data (*Lei Geral de Proteção de Dados*



*Pessoais*) using supporting materials and a patient consent form for data collection and usage, with full transparency.

### **RARASnet Project Management**

The project management will include the cooperation and execution of several activities, including technological and technical implementation, that must be harmonized. The technical IT group will coordinate activities related to electronic resources, such as data collection instruments design, database management, and data analysis. The IT team is also responsible for maintaining a communication channel with the project's principal investigators to receive clinical administrative and clinical research input.

A set of practices that merge development and operations (DevOps) will be used as a reference to standardize the development process and align activities of software engineering, infrastructure operation, and quality assurance. As an agile methodology, DevOps allows quick delivery of a small set of requirements from concept to deployment. The method also creates efficiency in results monitoring due to continuous integration and the appreciation of high-value feedback from all stakeholders [51].

For project management and to increase collaboration across team members, Trello (Atlassian) [52] will be used, which provides easy visualization of tasks and priorities, as well as a macrovision of development stages. The workflow of a data analysis project will follow the classic steps of a knowledge discovery in databases process [53], detailed in the following subsections.

### **Data Collection Procedures**

Initially, the instruments to be used in data collection will be framed, validated, and tested. These instruments should serve as a basis for the steps that involve the survey of retrospective data in the participating institutions and as a model for the stage involving the prospective survey and analysis. Based on an initial report characterizing the informational maturity of the collaborating institutions, online training will be given to address the functioning of the data collection instrument developed, validated, and tested for the project's retrospective phase, and the same process will be carried out later in the prospective phase of the project.

The collection will be carried out through access to medical records, with data recording on portable computers acquired with funds from this proposal and carried out by fellows of the project with the support of researchers from each service. Data quality indicators will be monitored in this intervention, mainly about the difficulties encountered by institutions to codify the diseases in an interoperable way, ensuring the production of a reliable picture of the maturity of data collection of rare diseases in Brazil.

To ensure the monitoring of data quality indicators, an early hearing detection and intervention (EHDI) will be conducted, and dimensions such as completeness, uniqueness, timeliness, validity, accuracy, and consistency will be evaluated [54]. Elements not present in the EHDI, such as acceptability, reliability, and flexibility, will also be considered; the use of

dimensions will vary depending on the requirements of each center. These indicators were selected based on their importance in monitoring and evaluation in the National Policy on Comprehensive Care of People with Rare Diseases. It will also allow tracking results from the source to the national level and be indicative of data quality for all the indicators within a program area [55].

During data collection, phenotypic data will be described according to HPO terms, restricted to 5 terms per case, allowing the description of phenotypes of known syndromes. Information about the coding of the disease will also be presented, considering the name of the disease, the International Classification of Diseases 10th Revision (ICD-10), the Orpha number, and the gene name or symbol, thus allowing comparison with data from other platforms, such as Orphanet.

Data collection instruments (ie, case report forms [CRFs]) will be established by principal investigators and applied in distinct project phases, each with a specific objective. The development of all CRFs is guided by the National Policy of Comprehensive Care for People with Rare Diseases [56,57] in the context of the Brazilian Health Public System.

The main instruments are (1) a survey of the technical and technological resources of the participating research center, used to recognize needs and prepare and provide resources for data integration and collection across research centers; (2) a survey of procedures performed at participating centers, used to recognize the availability of technological resources for genetic diagnosis and human resources in the assistance of individuals with rare diseases; (3) a retrospective collection of clinical data, that is, the characterization of the clinical profile of patients with RDs treated throughout the country in the last 2 years; and (4) a prospective collection of clinical data, that is, the follow-up of patients with the defined RD clinical profile treated throughout the country, for the identification of changes in the clinical profile, such as in diagnosis and treatment.

After the initial development, the validation phase will take place. Key researchers, along with main investigators, will perform several rounds of revision and validation for each CRF. This process will occur until researchers reach a consensus. Then, the final version of an instrument (usually a paper-based one) will be translated into an electronic-based version.

### **Computational Infrastructure and Data Collection Resources**

The study will rely on a computational infrastructure to satisfy technological needs during all project phases. First, cloud computing resources were acquired as an infrastructure as a service. This makes it possible to quickly scale up and down with demand. Additionally, the expense and complexity of buying, managing, and maintaining physical servers and other data center infrastructure are avoided [58].

In this case, the University of São Paulo provides a private cloud computing environment (interNuvem USP) and manages the whole infrastructure, while the project's owners only need to install, configure, and manage their own software, operating systems, and applications. Several resources, such as web,



database, and data collection servers, will be available to help deliver this project outcome.

During the project, it will be necessary to collect data using CRFs. To facilitate the creation of electronic CRFs and their distribution, REDCap (Research Electronic Data Capture) and KoBo Toolbox will be used as electronic data capture systems. REDCap was built in 2004 by a team at Vanderbilt University to enable classical and translational clinical research, basic science research, and general surveys, providing researchers with a tool for the design and development of electronic data capture tools [59].

KoBo Toolbox, developed by the Harvard Humanitarian Initiative, is a free and open-source suite of tools for field data collection and basic analysis. It was initially built for use in challenging environments in developing countries, but it can be extended to any type of research [60]. Both electronic data capture systems are free, although licensing is necessary for REDCap. After applying for a REDCap license of use, the RARAS REDCap Server was established, which is now part of the REDCap Consortium, a community of experts and REDCap administrators [61]. KoBo Toolbox does not demand a licensing process and the software is publicly available for download and installation.

REDCap and KoBo Toolbox are integrated and can be used together. The first is used for data research, data storage, reporting, analysis, and management. The second is used exclusively in the data collection process as a front-end tool for final users, allowing responsive and offline data collection on any type of device without the need to install any third party or additional mobile app. After submitting a record in KoBo Toolbox, data are instantly synchronized with the REDCap database. This integration is possible due to a framework developed by the IT group.

### Database Modeling

By exploring the data sources of the Orphanet platform related to information on medicines and rare diseases, we started the modeling phase of the database. Additionally, materials were selected for the knowledge acquisition phase for the development of a computational ontology that will reuse the Orphanet Rare Disease Ontology (ORDO) [62], thus helping the classification and hierarchization of bibliographic data on the prevalence of these diseases. After this initial analysis to select the best attributes (variables) that represent this health domain and are aligned with the profiles of the participating centers, the second stage of modeling the database is expected to start [25].

The first step is important so that the system does not request variables that are not relevant to the study, reducing the time taken to collect patient data by the health professional. More specifically, conceptual modelers describe structure models in the form of entities, relationships, and constraints, as they can also describe behavioral or functional models in terms of states, transitions between states, and actions performed on states and transitions. Finally, they can describe interactions and user interfaces in terms of messages sent and received and information exchanged. At the end of the first stage, a system

requirements document must be prepared, detailing all functional and nonfunctional aspects of the implementation and application layers [31].

To facilitate the understanding of the information flow and operational processes of the participating institutions, auxiliary diagrams will be produced using the Business Process Management Notation approach. Such documents will be used during the project to validate the information from the services, which will also be useful for the implementation and maintenance phases of the database.

The second phase of the modeling, therefore, consists of mapping the model in the form of relational tables. To ensure data consistency, the mapping is done according to the rules of the relational model, which was chosen because of its simplicity and robustness and because it uses structured query language (SQL), which has become common in relational databases. To generate the first model of the proposed database, the MySQL Workbench (Oracle Corp) software will be used, which allows data management and SQL queries to be built and facilitates the administration, creation, and maintenance of several databases in the same location. In this way, the bank will be ready for use and its implementation will be dynamic, offering the scope for future updates and maintenance [32].

### Data Quality Assurance

As previously stated, both the retrospective and prospective phases will collect study data using the KoBo Toolbox electronic data capture tool and store them using the REDCap server hosted at the Ribeirão Preto Medical School, University of São Paulo, Brazil. The KoBo Toolbox online data entry system will minimize the data entry errors and facilitate the monitoring and quick resolution of queries and missing data.

The data collection tools will be reviewed by other researchers and pretested on a convenient sample of records and clinical settings. Reviewers will note their individual experience with both the definitional criteria and the time taken to collect and record data. Based on the final pretest, revisions will be made to both data collection instruments.

A manual of operations will be developed to minimize the need for judgment and interpretation by the data collectors and to increase the quality of data collection done by the health care center professionals. The manual of operations will include a description of the study in general terms, emphasize the importance of complete and accurate data, and foster the standardization of data collection.

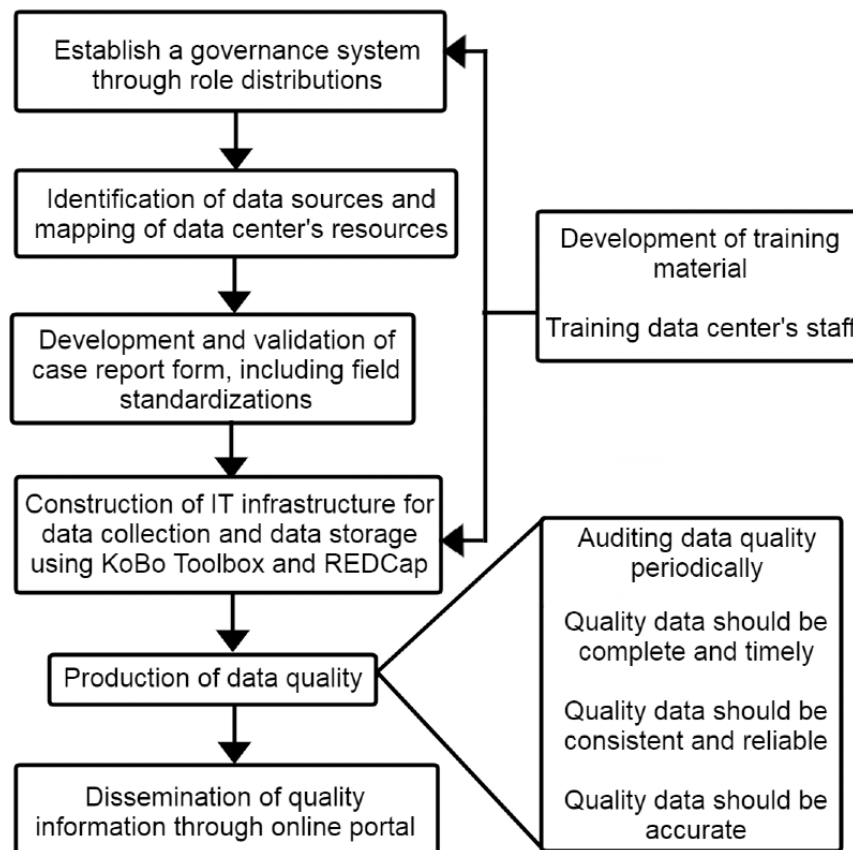
The responsible health care center staff member will maintain a problem logbook to document unanticipated problems. Technical questions encountered in the field will be resolved through consultation with the technical team and researchers responsible for the project.

To ensure that the record quality fulfills all prerequisites described in the literature and the normative documents previously mentioned, we will follow a set of recommendations described by the ERN in the RD-Connect framework, incorporating the indicators in each step of the process collection, storage, preprocessing, processing, and reporting

[63,64]. Our plan will consider aspects such as governance standards, infrastructure in compliance with the FAIR principles (findable, accessible, interoperable, and reusable for humans

and computers), didactic material, and informative documents, as well as personnel training and a data quality trail. The process and tools used for each level are presented in Figure 1.

**Figure 1.** Framework for quality management of rare disease registries. IT: information technology.



## Data Management

Trained research nurses at the participating health facilities will use KoBo Toolbox data collection tools to collect data for both retrospective and prospective phases. All entries will be deidentified at the stage of data collection, and participants will be identifiable only by unique identification codes that are only accessible and known to the hospital coordinator. A customized data entry and monitoring system will be developed in the REDCap platform for this study. This data entry system will be password protected and accessible only to the database managers and study team. The system will be developed and coordinated by the study data management unit at the University of São Paulo, Brazil.

## Portal Development and Data Analysis

After the identification and collection of the essential data, the IT team will be responsible for developing all the data analysis by the supervisors of specialists in the rare disease network. The analysis will serve as support for RARASnet specialists and patients to understand the main aspects of human and technical resources and the flow of rare diseases in Brazil. As retrospective and prospective data will be collected, they will serve as a base for the exploration of statistical and modeling computational methods, and with the validation of the results among specialists, the database will be incorporated into DATASUS and communicated in scientific reports and a web

portal. This web portal will be one of the main practical contributions of this work. It refers to the Brazilian Digital Atlas of Rare Diseases, available through a health observatory, which aims to integrate structural information about the referential institutions working in rare diseases in the country and clinical information about the individuals assisted by these institutions. This building process will be done according to the guidelines proposed by WHO for the development of health observatories [65].

From that data organization, the analysis tools will be made available, providing health indicators to the managers (hospital, municipal, and regional). The main analyses of the web portal will be (1) the flow of patients, which will present the displacement of patients according to the place of origin and the hospital care through georeferenced maps and tables; (2) hospital indicators, which will provide the automated calculation of 31 hospital indicators, such as mortality, morbidity, capacity, and usability, aiming to observe and compare these indicators among institutions; (3) nosological profiles, which will highlight the hospital care of individuals, allowing for the characterization of morbidities in the rare disease community; (4) diseases sensitive to primary care, which will describe hospitalizations for morbidities related to primary care, facilitating the identification of hospitalization rates that could be avoided by strengthening primary care; (5) prediction of risk of death by the Charlson Comorbidity Index, which will provide the risk

of death for patients according to their comorbidities; and (6) medical procedures, which will describe the surgical procedures performed, allowing the comparison between these procedures and the resources used [66-69].

The tools described will provide interactivity through consultation filters with spatial disaggregation (by region, health region, municipality, or a specific hospital) and temporal disaggregation. Thus, information will be able to be explored historically, geographically, and in real time, supporting different demands and decision making for rare diseases in Brazil. However, besides the web portal, which will contain general public information and resources, we will also provide all the knowledge through videos and talks using didactic language to facilitate understanding.

## Results

Considering the objective list and proposed conceptual and technical model, RARASnet presents some outcomes of interest, both specific and collaborative, in 9 steps:

1. Survey epidemiology, clinical procedures, and therapeutic resources, such as the number of individuals with rare disease according to each diagnostic group, age, race, sex, and other features.
2. Create a national rare disease network with the participation of important university hospital health services in rare diseases to create a database of national rare diseases.
3. Cover all regions of Brazil concerning the main rare diseases, with institutes and number of cases stratified according to each type of condition.
4. Create a standard in sociodemographic, epidemiological, clinical, and therapeutics data with the advice of the specialists in the national rare disease network. The data should follow patterns proposed by the Ministry of Health guidelines and HPO terms.
5. Identify the type of treatments being applied in each center and those funded by SUS or by supplementary health. The goal is to have a quantitative analysis for each type of treatment to understand the overall status of rare disease in Brazil and perform public health policies.
6. Map existing diagnostic and technological resources within the network.
7. Map human resources, such as the quantity of workers and specialists available in the network in each region of Brazil.
8. Establish a network of partners to underpin collaborative studies concerning rare diseases.
9. Develop the online Brazilian Atlas of Rare Diseases according to the guidelines of the WHO [70] to help professionals, the general public, and political decisions.

The present project is in its initial stages, and a survey was completed by each reference center to evaluate the technical

aspects of each health care center, such as the presence of computers, technical support staff, and a digitized system. Moreover, we are in the process of internally validating the collection instruments with specialists and principal investigators and preparing the pilot project to be carried out at the coordinating center for external validation. All the predicted methodological processes are shown in Figure 2.

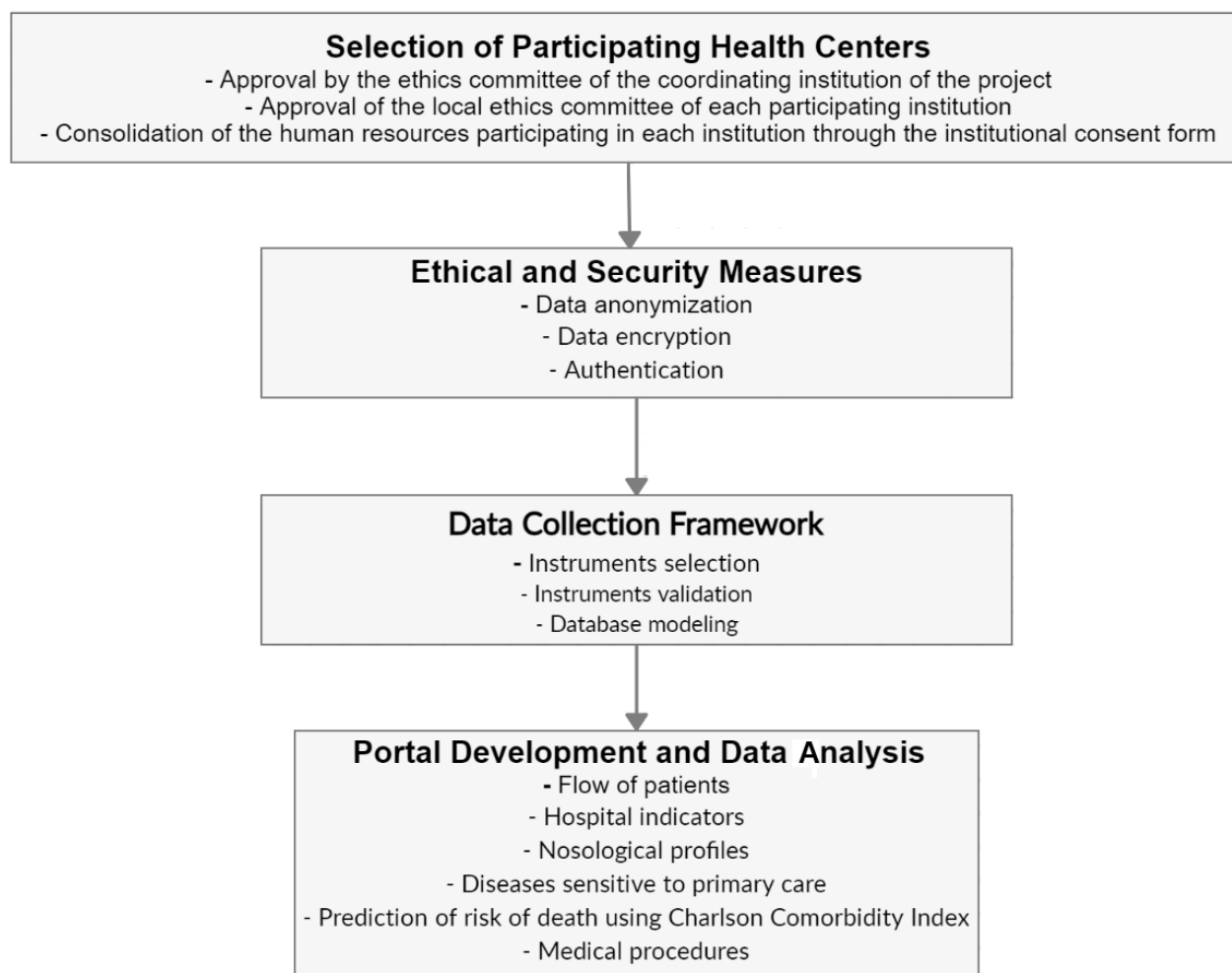
For the participating centers that have already obtained the project approval from their respective ethics committees, we developed an initial data collection instrument to verify the technological infrastructure of each center and the way these institutions capture information related to rare diseases. This survey aims to list and categorize these institutions according to their methods of data storage and retrieval, which can be digital, through electronic medical records and management software, or analog, through paper-based record management.

From a total of 40 participating centers so far, 39 have already responded to this initial survey, and among these, the results showed that 23 institutions (59%) have an electronic collection and recovery system and 16 institutions (41%) have a paper collection system. This initial survey is important for our IT team to plan the best clinical data collection approach for each institution during the project, aiming to minimize obstacles through an adequate and personalized collection proposal for each center.

One of the biggest challenges of this study is aligning data collection in all participating institutions so that the process of recovering data from medical records is standardized regardless of the storage support and the methods of retrieving information used in each health unit. In our scenario, based on 39 institutions, 14 (36%) health units extract information from medical records exclusively on paper, while 2 (5.1%) have a nonapplicable data recovery method; although they store their data in a system or on paper records, their recovery process does not fit into one of these methods (eg, using applications that are not for this purpose).

Later, we will standardize and analyze the clinical and epidemiological data and use these data to develop the national network for monitoring rare diseases, using the Digital Health Observatory to make the information available.

The project had its financing approved in December 2019. Retrospective data collection started in October 2020, and we expect to finish in January 2021. We will begin the prospective data collection in February 2021, and we expect to finish in June 2021. During the third quarter of 2020, we enrolled 40 health institutions from all regions of Brazil. We are currently receiving data to be analyzed. We expect the publication and dissemination of the findings in the second half of 2021.

**Figure 2.** Main activities of RARASnet.

## Discussion

This study is currently in its initial stage. We have performed a survey of technical aspects of health care centers (eg, support staff and technological infrastructure). A pilot data collection of clinical data carried out by specialists and principal investigators is planned to underpin the instruments' validation.

### Main Problems Anticipated and Proposed Solutions

The heterogeneity of the data is intrinsically connected to the type of information generated by the health services, which is considered diverse and complex. Some of the main problems normally encountered when handling health data are the highly heterogeneous and sometimes ambiguous nature of medical language and its constant evolution; the huge amount of data generated constantly by the automation of hospital processes; the emergence of new technologies; the need to process, analyze, and make decisions based on this information; and the need to ensure the safety of data related to patients [63].

To mitigate problems of heterogeneity and data standardization, we will make use of some semantic web technologies, which are presented as a fundamental approach to guarantee semantic interoperability and the integration of dispersed and isolated data sets. More specifically, we will use biomedical ontologies, which provide controlled vocabularies of scientific terminologies

used to assist in the annotation of produced data, such as basic terms and their relations in a domain of interest, as well as rules to combine these terms and relations [64]. As mentioned, some of the ontologies used will be ORDO and HPO.

Once the ontologies are defined, it will be possible to perform the semantic markup on the collected records present in our relational database and provide a SPARQL Protocol and RDF Query Language access point to execute queries on the data set, allowing us to make available a set of data that can be extracted by different information systems, as long as they are connected to the web.

For security reasons related to the sensitivity of the stored information, direct access by external systems to the data structure is blocked by default. Therefore, an authorization layer will be built to support the authentication processes (validation of the identity of external systems). The authorization and protection of the information transmitted will use digital signature and hybrid encryption techniques, that is, a combination symmetric (unique key) and asymmetric (public and private key pair) encryption.

We believe that through these planned solutions, obtaining information from the set of data related to rare diseases in Brazil will become possible, allowing data to be shared, reused, analyzed, and applied in other information systems, either to improve the completeness of other bases or to produce relevant



knowledge to support decision-making processes in the context of rare diseases.

### Applicability of the Results

In the development of digital products and services for this project, all tools must ensure that users have the freedom to interactively navigate and filter data to visualize the analysis according to personal interests. For this, the Brazilian Digital Atlas of Rare Diseases will have a filter that allows spatial disaggregation (queries by regions, health regions, municipalities, or a particular hospital) and temporal data. The filters will allow the user to set different visualization schemes without accessing the raw data and modifying the database.

It will also be possible to perform other types of data aggregation in queries, such as grouping by gender, age group, ICD-10, Orphacode, Online Mendelian Inheritance in Man (OMIM) [63], phenotypic characteristics, and other information that the health professionals involved consider relevant. It is important to emphasize that in the RD context, ICD-10 and OMIM are not able to cover all diseases with a unique identifier [71,72]. Thus, when ICD-10 is used as a filter, a further option box will be opened to distinguish between diseases with the same code. For OMIM, only genetic disorders are covered, and a note will be displayed on the website [63]. Orphacode [62], on the other hand, is the nomenclature that fits all RD diseases with a unique code due to its polyhierarchical nature [71].

This approach makes it possible to measure the performance of both the institution providing the health service and the care team. The analysis of efficiency and performance will be presented through dashboards and reports in real time, which can be used for the elaboration of new models based on the results.

The database of patients with rare diseases will allow an interactive epidemiological map and detail the care journey of the main rare diseases in Brazil. In this sense, it is expected that these developments can assist the evidence-based decision-making process for rare disease services in Brazil, bringing benefits to patients, health professionals, and managers.

### Plans for Validation, Dissemination, and Use of Project Results

The dissemination of the results will include the production of scientific papers in periodicals relevant to the area and the realization of scientific dissemination to the direct target audience and collaborators through workshops and training to the participating centers. Aiming for project integration and

sustainability, we will make the ontologies developed available in the international repository of biomedical ontologies, BioPortal. These artifacts will therefore be able to be used in other projects around the world and updated constantly. BioPortal is an open database that provides access to biomedical ontologies via web services, facilitating the participation of the scientific community in the evaluation and evolution of ontologies by suggesting additional resources for mapping terminologies and reviewing criteria and standards [73].

With the main results and interest topics, we intend to recruit a multidisciplinary panel for an e-Delphi [74] consensus-building exercise with the ad hoc team members. The e-Delphi method is an interactive structured communication technique to reach consensus on the responses, and it comprises an initial open round of questions to revise or suggest a list of potential items for scoring in the subsequent two scoring rounds.

Once results are validated, it is crucial “to design strategies and solutions to overcome bottlenecks that prevent proven and innovative public health interventions” from reaching the people who need them [75]. For this purpose, we intend to use the WHO toolkit for implementation research. One of the WHO toolkit topics describes how to plan a rigorous research project, including identifying implementation research outcomes, evaluating effectiveness, and making plans to scale up implementation in real-life settings [76].

Once we have the findings, we intend to analyze the implementation of these interventions and strategies. For this, the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework [77] will be used to organize reviews of the existing literature on health promotion and disease management in different settings. RE-AIM is a tool used to translate research into action for digital technologies by measuring 5 essential dimensions for successful implementation: reach, effectiveness, adoption, implementation, and maintenance.

The overall goal of the RE-AIM framework is to encourage program planners, evaluators, readers of journal articles, donors, and policy makers to pay more attention to essential program elements, including external validity, which can improve the sustainable adoption and implementation of effective, generalizable, evidence-based interventions [78]. Finally, by applying the RE-AIM framework, we can emphasize responses to improve the chances that recommendations will have a positive and sustainable impact on public health.

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### Acknowledgments

This study is supported by CNPq (No. 44303/2019-7). TMF is supported by CNPq (No. 306861/2019-4).

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### Conflicts of Interest

None declared.

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## Abbreviations

**CER:** Specialized Rehabilitation Center  
**CNPq:** Brazilian Council for Scientific and Technological Development  
**CRF:** case report forms  
**DevOps:** development and operations  
**EHDI:** early hearing detection and intervention  
**ERN:** European Reference Network  
**HPO:** Human Phenotype Ontology  
**ICD:** International Classification of Diseases  
**IT:** information technology  
**NIH:** National Institutes of Health  
**OMIM:** Online Mendelian Inheritance in Man  
**ORDO:** Orphanet Rare Disease Ontology  
**RD:** rare disease  
**RE-AIM:** reach, effectiveness, adoption, implementation, and maintenance  
**REDCap:** Research Electronic Data Capture  
**SQL:** structured query language  
**SRDR:** Reference Services in Rare Diseases  
**SRTN:** Reference Services for Neonatal Screening  
**SUS:** Unified Health System  
**WHO:** World Health Organization

*Edited by G Eysenbach; submitted 07.10.20; peer-reviewed by JA da Silva Freitas, A Benis; comments to author 26.11.20; revised version received 10.12.20; accepted 15.12.20; published 22.01.21.*

*Please cite as:*

Alves D, Yamada DB, Bernardi FA, Carvalho I, Filho MEC, Neiva MB, Lima VC, Félix TM  
Mapping, Infrastructure, and Data Analysis for the Brazilian Network of Rare Diseases: Protocol for the RARASnet Observational Cohort Study  
*JMIR Res Protoc* 2021;10(1):e24826  
URL: <http://www.researchprotocols.org/2021/1/e24826/>  
doi: [10.2196/24826](https://doi.org/10.2196/24826)  
PMID: [33480849](https://pubmed.ncbi.nlm.nih.gov/33480849/)

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Protocol

# Developing the Accuracy of Vital Sign Measurements Using the Lifelight Software Application in Comparison to Standard of Care Methods: Observational Study Protocol

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## Abstract

**Background:** Vital sign measurements are an integral component of clinical care, but current challenges with the accuracy and timeliness of patient observations can impact appropriate clinical decision making. Advanced technologies using techniques such as photoplethysmography have the potential to automate noncontact physiological monitoring and recording, improving the quality and accessibility of this essential clinical information.

**Objective:** In this study, we aim to develop the algorithm used in the Lifelight software application and improve the accuracy of its estimated heart rate, respiratory rate, oxygen saturation, and blood pressure measurements.

**Methods:** This preliminary study will compare measurements predicted by the Lifelight software with standard of care measurements for an estimated population sample of 2000 inpatients, outpatients, and healthy people attending a large acute hospital. Both training datasets and validation datasets will be analyzed to assess the degree of correspondence between the vital sign measurements predicted by the Lifelight software and the direct physiological measurements taken using standard of care methods. Subgroup analyses will explore how the performance of the algorithm varies with particular patient characteristics, including age, sex, health condition, and medication.

**Results:** Recruitment of participants to this study began in July 2018, and data collection will continue for a planned study period of 12 months.

**Conclusions:** Digital health technology is a rapidly evolving area for health and social care. Following this initial exploratory study to develop and refine the Lifelight software application, subsequent work will evaluate its performance across a range of health characteristics, and extended validation trials will support its pathway to registration as a medical device. Innovations in health technology such as this may provide valuable opportunities for increasing the efficiency and accessibility of vital sign measurements and improve health care services on a large scale across multiple health and care settings.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/14326

(*JMIR Res Protoc* 2021;10(1):e14326) doi:[10.2196/14326](https://doi.org/10.2196/14326)

**KEYWORDS**

health technology; remote monitoring; vital signs; patient deterioration

## Introduction

### Background

Vital sign measurements—also referred to as patient observations—are a widely adopted and integral component of clinical care. They involve the intermittent observation and measurement of a person's basic body functions. Traditionally, vital signs have included blood pressure, temperature, pulse rate, and respiratory rate measurements, although a number of other parameters are now also included. Changes in vital sign measurements may be the first and earliest indication of an abnormal physiological change in a patient, offering a source of essential information to the assessing clinician.

Within the hospital setting, and especially in high-dependency areas, vital sign measurements are undertaken regularly to support the recognition of clinical deterioration and the need for intervention and escalation of care; often, these measures are used within a multiparameter, early warning, scoring system [1,2]. In primary care services, vital signs measurements are similarly important, for example, in the assessment of infants and children [3] and in those with long-term conditions, while in community and residential care settings, home measurement of vital signs can be particularly useful in monitoring the health status of an increasingly aging population.

### Challenges, Gaps, and Inefficiencies

Despite their importance for clinical decision making, the accuracy and timeliness of vital sign observations is a recognized area in need of improvement [4-6]. There are several reasons behind the current challenges with vital sign measurements. First, a number of different methods of measurement of vital signs is available, both invasive and noninvasive, and a minimum level of training, skill, and competence is required by operators. A lack of standardized technique and the potential for operational errors can negatively affect measurement accuracy [7,8]. Second, the time required to take vital sign measurements can impact the frequency and quality of assessments, especially in an environment already experiencing a heavy workload and staff shortages. There is some evidence that complacency can develop when vital sign measurements become perceived as low-priority tasks [9]. Third, the quality of recording of vital sign measurements, including the accuracy and completeness of documentation, as well as the way in which this information is viewed in a clinical record, can all influence clinical management decisions [10]. Improvements in recording was one of the recommendations from the enquiry into poor care and high mortality rates among patients at the Mid-Staffordshire NHS Foundation Trust [11]: “The recording of routine observations on the ward should, where possible, be done automatically as they are taken, with results being immediately accessible to all staff electronically.”

Current standard of care methods for measuring vital signs can also be inconvenient and uncomfortable for patients. Most noninvasive techniques will still involve some form of contact, which can cause skin irritation [12]. Monitoring equipment can create hazards and interfere with patient care, mobility, and

sleep, while its conspicuousness can be emotionally upsetting, for example to visitors in critical care settings [13,14]. Stress or anxiety arising from the observation process itself can also result in misleading measurements, which may not be representative of the patient's clinical state; for example, the “white coat effect” may lead to raised blood pressure readings during clinical assessments despite normal blood pressure in other settings [15].

### Proposed Innovation and Delivery

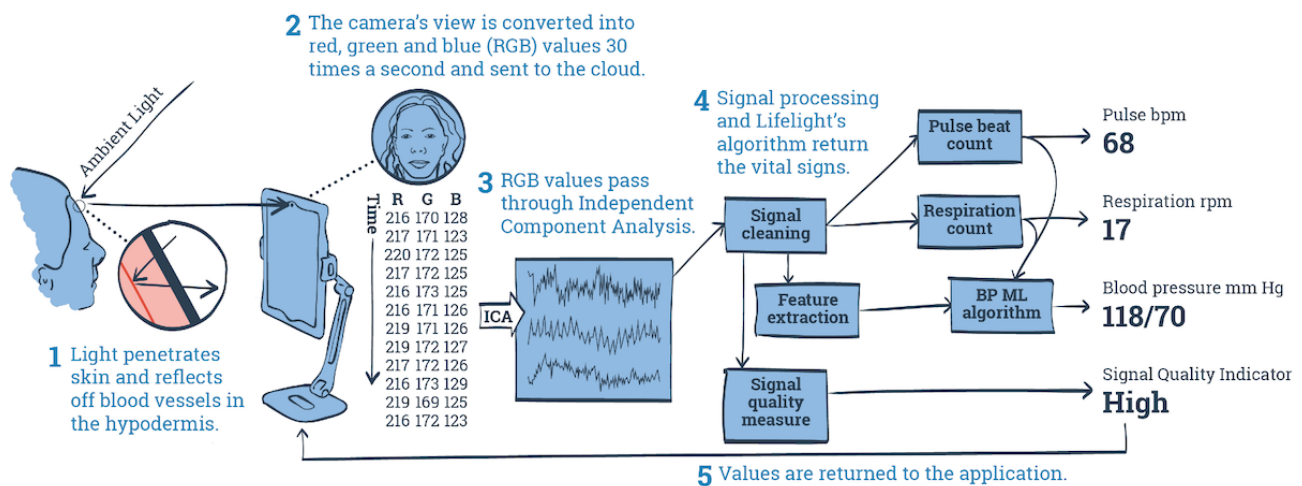
These identified challenges have led to significant research into the role that advanced technologies may play in improving the quality, timeliness, and accuracy of vital sign measurements. These advanced techniques have included using thermal imaging analysis [16,17], Doppler effect observations [18,19], and photoplethysmography [20]. There has been particularly rapid development in the use of image-based or video-based monitoring over the last decade [21] in a bid to improve the quality and accessibility of physiological monitoring.

Photoplethysmography is an optical measurement technique that uses changes in properties of the skin to detect blood volume changes in the microvascular tissue bed [22]. Photoplethysmography was originally shown to operate at red and near infrared wavelength but has since been found to also work effectively using ambient light as the illumination source [23]. Changes in the light reflected from the skin surface due to volumetric changes in the facial blood vessels can detect small variations in perfusion, providing valuable information about the cardiovascular system [24]. Photoplethysmography is now used to assess a number of physiological parameters, including heart rate, oxygen saturation [25], blood pressure [26], and respiratory rate [27,28]

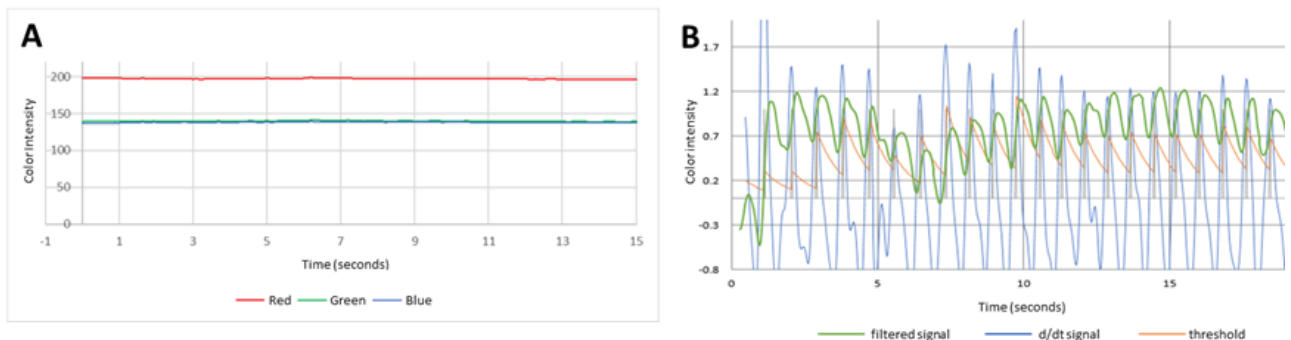
Lifelight is a software application that, when installed on a laptop, mobile device, or smartphone with an integral camera, uses remote photoplethysmography (rPPG) and live video capture to calculate these 4 most important physiological parameters (Figure 1). The application captures the average color of an area of the face (the “region of interest”) and sends this as red, green, and blue (RGB) color values to the server for further processing. The RGB data are recorded 30 times every second for 60 seconds until a full set of 1800 RGB points has been delivered. Having eliminated artefacts and interference, the application can derive a plethysmographic signal after 30-60 seconds of data collection (Figure 2). The strength of the pulsatile component of the raw video signal generated by the app is small (approximately 1%-2% of the signal). Highly tuned signal processing techniques are used to derive a pulse waveform that is further processed and counted to give heart rate, respiratory rate, and through comparison of color channel ratios, oxygen saturation. The shape of the pulse waveform undergoes additional analysis to derive features that describe the pulse's morphology, and the resulting morphological feature set is fed into an algorithmic model derived through machine learning to predict systolic and diastolic blood pressures. This technology has the potential to take noncontact measurements with a device that has minimal requirements for clinical skill or training.



**Figure 1.** Representation of the use of photoplethysmography in the Lifelight software application. BP: blood pressure; ICA: independent component analysis; ML: machine learning.



**Figure 2.** Chart of the (A) raw remote photoplethysmography (rPPG) signal received by the Lifelight algorithm and (B) some of the intermediate signal traces derived from that raw rPPG signal. These processed signals are used in turn to derive vital signs—in this example, pulse.



During this preliminary study, measurements predicted by the Lifelight software will be compared with standard of care measurements for a large population sample of inpatients, outpatients, and healthy people. The study will create a dataset for use in developing and testing the accuracy of the software. Predicted vital signs from recorded rPPG signals will be evaluated against measured vital sign values, and the success of changes to the underlying algorithm to improve the predictions will be gauged. This study will also explore how the performance of the algorithm varies with some patient characteristics including health condition and medication.

## Methods

### Aims of the Study

The overall aim of this study is to improve the accuracy of the estimated heart rate, respiratory rate, oxygen saturation, and blood pressure measurements predicted by the Lifelight software application through development of its algorithms. The primary objective is to compare the estimated Lifelight measurements with those from standard of care measurements. The secondary objective is to explore the impact of a range of variables (including age, sex, temperature, health condition, medication, skin tone, and ambient lighting) on the accuracy of the heart rate, respiratory rate, oxygen saturation, and blood pressure estimates made by the algorithm.

### Participants and Recruitment

Study participants will be recruited from a single study site in the United Kingdom (Queen Alexandra Hospital in Portsmouth Hospitals NHS Trust). Both adults and children will be included in the study population. Participants will include people who are attending the hospital, as an inpatient, an outpatient, a friend or relative of a patient, a visitor, or a member of hospital staff. Inpatients and outpatients will be approached about potential participation by study staff during their stay or while waiting for an appointment; in the case of pediatric potential participants, parents or guardians will be approached. Members of the public will be recruited through recruitment posters and information stands at public sites in the hospital. Members of the study team will be available to discuss the study with any interested individuals who approach the information stands or email or phone study staff. Hospital staff will be recruited through email recruitment campaigns, discussion in team meetings, posters in staff areas, and information stands.

Inclusion criteria include age over 3 years, sufficiently conversant in English language, and able and willing to comply with all study requirements and to provide written informed consent (either themselves or empowered by law to provide it). There are no exclusion criteria. Eligible potential participants interested in the study will receive written and verbal information on the study aims, what is involved, and the requirements for participation, including a participant

information sheet; in the case of pediatric potential participants, age-appropriate information will be provided to the child, and a parent information sheet will be available for their parents or guardians. Participation in the study will be entirely voluntary, refusal to participate will involve no penalty nor loss of medical benefits, and participants may withdraw from the study at any time.

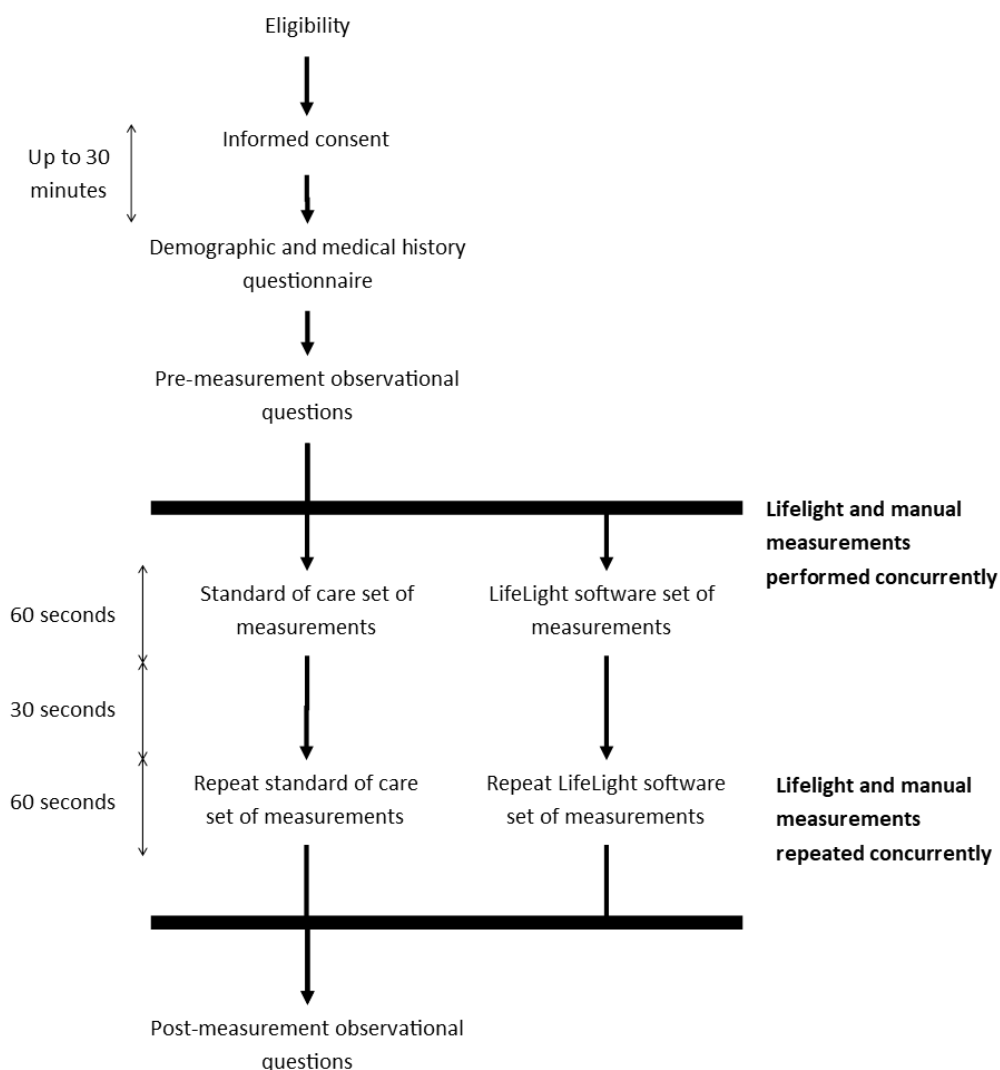
An estimated sample size of 2000 participants is planned to generate measurements for use in the training dataset. The final sample size of the study will depend upon the incremental improvement in accuracy of the Lifelight system, and the algorithm development cannot be predicted prior to enrollment. The intended study sample will be selected through cluster

sampling of the hospital population, including approximately equal proportions of inpatients, outpatients, and healthy control groups. The study sample will aim to capture a locally representative cohort regarding age, sex, health condition, and skin tone. Approximately 25% of participants will be children between 3 and 16 years old. Vital sign measurements from an additional 1000 patients will be taken at the end of the study period to be used for a validation dataset.

### Study Design

The study will adopt a prospective, observational design (Figure 3). The study will collect both training and validation datasets of vital sign measurements, which will be compared with the algorithm's estimated measurements.

**Figure 3.** Study flow diagram for VISION-D study participation.



### Data Collection and Outcome Measures

#### Measurements

Participation in the study will involve 2 methods of measuring 4 specific vital signs: heart rate, respiratory rate, oxygen saturation, and blood pressure measurements. One method of

measurement will be through manual direct physiological measurement of vital signs, while the other will be calculation of vital sign measurements from digitally captured changes in reflected light from the skin surface. Both sets of measurements will be taken concurrently by 2 members of staff during the same 60-second measurement period. Both Lifelight and manual measurements will then be repeated following the initial

observations, yielding a total of 4 sets of measurements for each participant. Once all measurements have been taken and recorded, the study staff member will complete the postmeasurement observation questions and record all answers manually on paper case report forms.

### Data Collection

Data collection will be face-to-face by trained study staff members. All measurements will be taken by adult or pediatric nursing staff, assisted by clinical trial assistants. All staff will receive appropriate competency-based training in the set-up, maintenance, and limitations before utilizing any of the medical

devices required for this study, including the Lifelight software and iPad device; all staff involved in data collection will also complete Good Clinical Practice training.

### Premeasurement Data Collection

Prior to any measurements being taken, the study staff member will complete a very brief set of demographic and medical history questions and a set of premeasurement observations with the participant. All answers will be recorded manually on paper case report forms; the information gathered is detailed in [Figure 4](#).

**Figure 4.** Observations and questions used for data collection during the study.

<p><b>Demographic and medical history</b></p> <p>Age</p> <p>Gender</p> <p>Ethnic background</p> <p>Background light</p> <p>Height and weight using height meter and scale or from patient's notes where measurement is not possible</p> <p>Temperature, measured using standard of care temperature probe</p> <p>Skin color by 6-point scale</p> <p>Current diagnosis of any medical conditions that might impact on skin perfusion and pigmentation and cardiovascular processes, including:</p> <ul style="list-style-type: none"> <li>• Liver conditions</li> <li>• Anemia</li> <li>• Renal failure</li> <li>• Skin conditions</li> <li>• Hypotension</li> <li>• Cardiovascular conditions</li> <li>• Respiratory conditions</li> </ul> <p>Prescription of medications for any of the above medical conditions</p>	<p><b>Pre-measurement observations</b></p> <p>Is there visible sweat on the participant's face? [yes/no]</p> <p>Does the participant have facial hair covering the skin on their cheeks? [yes/no]</p> <p>Does the participant have a tattoo, jewelry (not including earrings), birthmark, scar or other feature on their face? [yes/no]</p> <p>Is there visible (heavy) foundation/concealer make-up on the participant's cheeks and/or forehead? [yes/no]</p> <p>Participant declaration of wearing foundation/concealer (if not be visibly obvious)</p> <p><b>Post-measurement observation questions</b></p> <p>Did the participant move during the measurement period? [a lot/a little/no]</p> <p>In what position was the participant during the measurement period [lying/sitting/standing]</p> <p>Was the participant wearing glasses during the measurement period? [yes/no]</p> <p>Was the participant's hairstyle covering the skin on their cheeks and/or forehead during the measurement period? [yes/no]</p> <p>Was the participant wearing an item that obscured their face during the measurement period, e.g. headscarf? [yes/no]</p> <p>Did the software report "Face not found" at any time during the measurement period? [yes/no]</p>
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### Standard of Care Manual Measurements

The direct physiological measurement of vital signs will be taken manually using instruments normally employed during standard care. The following methods, which are already currently in routine use at the study site and are widely accepted as standard practice, will be adopted for vital sign measurements in this study.

The Welch Allyn Vital Signs Monitor device will be used to determine heart rate (pulse) measurements (primarily from the

oxygen saturation measurement methodology or, if unavailable, from the blood pressure measurement method).

Respiratory rate will be determined from manual counting of observed inspirations during the 60-second measurement period.

A standard clinical finger clip sensor (as part of the Welch Allyn Vital Signs Monitor device) will be used for oxygen saturation measurements. The average oxygen saturation measurement over the 60-second measurement period will be used as the final result, ensuring that the oximeter is picking up an appropriate waveform.

A standard clinical automatic sphygmomanometer with appropriately sized cuff (width at least two-thirds of upper arm length) on the participant's upper arm (on the side opposite the finger clip sensor) will be used for blood pressure measurements (as part of the Welch Allyn Vital Signs Monitor device). This will be operated at the start of the 60-second measurement period.

All equipment used in the study for direct manual vital signs measurements is newly purchased, is dedicated for study use, and has been serviced and calibrated in line with manufacturers' instructions. All medical devices have a CE marking, have been locally approved for use in the hospital setting, and have been cleaned in accordance with local infection control guidelines. The same protocol for measurement will be adopted for all direct manual measurements, to ensure standardization of data collection. The stopwatch integrated within the Lifelight

software application will be used to identify the beginning and end of the 60-second measurement period and to ensure that the measurements are taken exactly concurrently; this will be announced by the study nurse so that both the members of staff and the participant are aware of the measurement period. The results are automatically displayed on the Welch Allyn Vital Signs Monitor device and will be recorded manually at the time of measurement onto paper case report forms, before being later transcribed into a study-specific database, anonymized, and sent electronically to the Lifelight developer. For inpatients, these measurements will also be recorded in their electronic observations record, used by the clinical team responsible for their care; other participants, whose observations are outside of normal ranges and clinically significant, will be referred to their general practitioner or to an urgent care provider, as necessary, for further investigation (Table 1).

**Table 1.** Normal measurement ranges and ranges requiring referral for further investigation (adapted from ranges for physiological parameters as detailed in the Royal College of Physicians' National Early Warning Score).

Physiological parameter	Description	Normal range for adults	Range requiring referral to GP <sup>a</sup> for adults	Range requiring referral to urgent care for adults
Heart rate	Pulse rate or number of heart beats per minute	51-90 bpm	N/A <sup>b</sup>	<40 bpm, >120 bpm, or irregular
Systolic blood pressure	The pressure of circulating blood on the walls of blood vessels	111-219 mm Hg	>160 mm Hg	<90 mm Hg or >180 mm Hg
Oxygen saturation	The oxygenation of fresh arterial blood	≥96%	N/A	<92%
Respiratory rate	Breathing rate or breathing interval	12-20 breaths/minute	N/A	N/A

<sup>a</sup>GP: general practitioner.

<sup>b</sup>N/A: not applicable.

### Using the Lifelight Software

The digital measurement of changes in reflected light from the skin surface will be made using the Lifelight software on an Apple iPad (6<sup>th</sup> generation Wi-Fi, 32 GB, 9.7 inch [diagonal] display) mobile tablet device. Background light intensity will be determined using a handheld illumination, or lux, meter (URCERI MT-912 Light Meter) to measure the density of light in the area near the participant's face. Changes to the environment will then be made as necessary to ensure that the camera view of the participant is well illuminated, for example by turning on more lights or opening window blinds. The Lifelight software includes a face-tracking algorithm, which will detect the presence of a human face in the image and select a rectangular region of interest (usually on the forehead). Stepwise instructions from the Lifelight software will guide the operator and automatically start and stop the measurements, which will be taken throughout the 60-second measurement period. The measurements taken by the Lifelight software will not be displayed on the iPad screen, but will be recorded and stored locally on the mobile tablet device until it has internet connectivity, at which point anonymized data will be uploaded to the Lifelight developer's secure database. This will ensure that measurements will not be revealed to either the study staff or the participant, thereby reducing the risk of confounding.

The same protocol will be adopted for all measurements taken with the Lifelight software, to ensure standardization of data collection; in particular [29,30] the mobile tablet device will be held as still as possible, at a distance of approximately 1 meter away from the participant and angled towards their face. Participants will be requested to keep as still as possible during the measurement period and to refrain from moving their head, talking, or chewing. Participants will be requested to remove any garments (eg, hats, scarves) and arrange hair (including bangs) so that facial skin is not grossly obscured and the facial skin surface area is maximized. This excludes instances where garments or other features are of a sensitive nature (eg, worn for religious purposes). Participants will be repositioned as necessary to ensure adequate lighting to illuminate the facial skin and that there are no other people (including study nurses or assistants) coming into the line of sight of the device camera.

When these conditions are not achieved during the trial, because it is impractical to do so or because of participant nonconcordance, the study staff member will indicate so in their answers to the postmeasurement observation questions.

### Privacy and Data Protection

A unique sequential patient identifier will be generated for each participant in the study, and no identifiable data will be included



in the stored data. All documents will be stored securely and only accessible by study staff and authorized personnel. All transmitted data will be encrypted before sharing and stored in the developer's secure database.

Fully pixelated images without any video data will be uploaded during the study as default for both adult and pediatric participants. However, an option is available within the adult consent form for participants to increase the level of video data collected, sharing either data with identifying features obscured or sharing full face video if they wish.

### Data Analyses

Statistical analyses will use the Deming regression to assess the degree of correspondence between the vital sign measurements predicted by the Lifelight software and the direct physiological measurements taken manually using "gold standard" methods. Subgroup analyses will determine variability in the degree of correspondence for patient characteristics (specifically age, sex, BMI, temperature, health condition, medication, skin tone, ambient lighting, presence of visible sweat, and a 3-way comparison of confounding factors [cosmetics/moisturizer, presence of facial scars/tattoos, and none]). Subgroup analyses will also be carried out for participants with readings outside of normal clinical ranges (Table 1), as well as for groups formed according to measured values. The impact of any changes made to improve the performance of the algorithm will be analyzed by stratification of the data by each algorithm version. No changes will be made to the algorithm during analysis of the validation dataset.

All values will be log transformed for analysis. All statistical analyses will use *r* (version 3.5.0) via RStudio for Windows [31]. The total least squares approach of the Deming regression will be implemented via the *pca* functionality of *r* with appropriate corrections to account for the multiple sets of readings per participant.

Continuous variables will be categorized to allow comparison. BMI will be derived from height and weight measurements and separated into categories of underweight, normal, overweight, and obese. Categories will be based on internationally accepted classification for adults [32] and age-specific and sex-specific classifications for children [33].

All analyses will be completed per protocol, since there is no intention to treat. There will be no imputation of missing or implausible data, and any missing, implausible, or problematic readings will be excluded from analysis. Where height and weight data are not available, blood pressure will not be estimated. If the Lifelight software is unable to detect the participant's face during the measurement period, this will be recorded in the case report form, and the measurements will be deleted from the dataset.

## Results

The prototype Lifelight technology has been in development over the past 5 years. Recruitment of participants to this study

began in July 2018, and data collection will continue for a planned trial period of 12 months.

## Discussion

Digital health technology is a rapidly evolving area for health and social care. The monitoring of vital signs to provide early warning of critical health events is one area of clinical practice that is benefiting from the digital transformation currently being experienced across health care services, and in particular, image-based monitoring methods are undergoing significant research and development. For example, Shao et al [34] presented a noncontact method to monitor blood oxygen saturation, which gave results consistent with those measured using a reference contact oxygen saturation device, while Jain et al [35] used face video-based photoplethysmography to predict blood pressure and heart rate. A recent systematic review of image-based, noncontact methods of monitoring heart rate, blood pressure, respiratory rate, and oxygen saturation analyzed over 160 studies. However, 76% of these included 20 or fewer subjects, and only 20 of these studies were carried out in clinical (rather than academic) settings [36]. Use of the Lifelight software application for noncontact remote monitoring may provide an opportunity for increasing the efficiency and accessibility of vital sign measurements on a large scale across multiple health and care settings, and studying its performance in a very large cohort within a clinical environment is a crucial area of development.

There are some anticipated limitations that the study may encounter. Movement of the subjects can create noise in the readings, and technical requirements such as internet access and lighting are required for the application. Ensuring that a locally representative cohort of participants is involved in the study may also be challenging, and regular interim review of recruitment and targeted stratified sampling will therefore be carried out as necessary.

Anecdotal feedback during the design and development of this study has been very positive about the potential of this novel approach to patient observations, particularly its simplicity. However, concerns have been raised around how remote monitoring of vital signs might impact the interaction between patients and health care professionals, in particular nurses, and the risk it may present of missing other deterioration cues, thereby compromising the overall quality of the patient assessment. This will be an important area of research for future studies.

This initial exploratory study will enable the software application to be further developed as a preventative monitoring technology. Subsequent work will evaluate the performance of the application in healthy participants subjected to physiological perturbations and in participants with a range of health characteristics. The results of this study, alongside other extended validation trials, will be used to support the technology to gain CE marking. By demonstrating that the device is fit for its intended purpose and meets safety legislation requirements, the Lifelight software will become available for use across Europe as a medical device.

## Conflicts of Interest

None declared.

### Multimedia Appendix 1

Evidence of grant funding awarded.

[[PDF File \(Adobe PDF File\), 436 KB - resprot\\_v10i1e14326\\_app1.pdf](#)]

### Multimedia Appendix 2

Peer review completed and submitted to received Health Research Authority approvals to carry out the study in a UK NHS setting.

[[DOC File , 271 KB - resprot\\_v10i1e14326\\_app2.doc](#)]

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## Abbreviations

**RGB:** red, green, blue

**rPPG:** remote photoplethysmography

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*Edited by G Eysenbach; submitted 10.04.19; peer-reviewed by C Subbe, B Lebouche; comments to author 03.10.19; revised version received 20.01.20; accepted 21.10.20; published 28.01.21.*

*Please cite as:*

*Jones TL, Heiden E, Mitchell F, Fogg C, McCready S, Pearce L, Kapoor M, Bassett P, Chauhan AJ*

*Developing the Accuracy of Vital Sign Measurements Using the Lifelight Software Application in Comparison to Standard of Care Methods: Observational Study Protocol*

*JMIR Res Protoc 2021;10(1):e14326*

URL: <http://www.researchprotocols.org/2021/1/e14326/>

doi: [10.2196/14326](https://doi.org/10.2196/14326)

PMID: [33507157](https://pubmed.ncbi.nlm.nih.gov/33507157/)

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Original Paper

# Awareness, Information-Seeking Behavior, and Information Preferences About Early Childhood Allergy Prevention Among Different Parent Groups: Protocol for a Mixed Methods Study

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**Related Article:**

This is a corrected version. See correction statement: <https://www.researchprotocols.org/2022/9/e42011>

## Abstract

**Background:** In early childhood allergy prevention (ECAP), parents act on behalf of their children. Parental health literacy and the availability of high-quality information, both online and offline, are crucial for effective ECAP. Recent research highlights three main points. First, parents need sufficient health literacy to discriminate between high-quality and low-quality information. Second, ECAP information behaviors may vary between phases of childhood development and according to individual circumstances. Third, to strengthen user-centeredness of available services, a better overview of parents' information practices and needs and how they handle uncertainties is required.

**Objective:** This study aims to explore why, how, and when parents search for and apply ECAP-specific health information and which individual (eg, understanding of advice) and organizational challenges (eg, information services, information complexity, and changing recommendations) they perceive and how they handle them. This study also aims to assess the needs and preferences that parents express for future information formats and contents. The findings should inform the practical design of ECAP information as well as formats and channels specific to different parent groups.

**Methods:** The above-named issues will be explored with parents in four German cities as one element in our efforts to cover the spectrum of perspectives. Based on a mixed methods design, including qualitative and quantitative assessments, the first year serves to prepare focus groups, a piloted focus group guide, a short standardized survey adapted from the European Health Literacy Project, recruitment channels, and the recruitment of participants. After conducting 20 focus groups in the second year, data will be analyzed via a constant comparison method in the third year. Based on this, practice implications on channels (ie, Where?), formats (ie, How?), and contents (ie, What?) of ECAP-specific information will be derived and discussed with parents and associated project partners before its dissemination to relevant ECAP actors (eg, childcare institutions and pediatricians).

**Results:** The study began with preselection of recruitment channels, drafting of recruitment and study information for potential participants, and agreement on a first full version of the guideline. Then, a detailed contact list was compiled of health professionals, administrative and social institutions, and relevant social media channels (N=386) to be approached for assistance in contacting parents. The recruitment was postponed due to COVID-19 and will start in January 2021.

**Conclusions:** ECAP is a relevant example for assessing how users (ie, parents) handle not only health information but the various and continuous changes, uncertainties, and controversies attached to it. So far, it is unclear how parents implement the

respective scientific recommendations and expert advice, which is why this study aims to inform those who communicate with parents about ECAP information.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/25474

(*JMIR Res Protoc* 2021;10(1):e25474) doi:[10.2196/25474](https://doi.org/10.2196/25474)

## KEYWORDS

health literacy; allergy prevention; children; health information; parents

## Introduction

### Background

#### Overview

The overall prevalence of children with allergies or asthma remains high and is often considered to be rising, despite the fact that exact numbers vary between regions [1-4]. While research on, and responses to, allergic diseases retain their traditional focus on treatment, nowadays prevention, immune system stimulation, and tolerance induction are considered increasingly important [5]. Hence, infants and young children may be a particularly important focus for prevention, because a person's immune response to allergic triggers is formed early on in life [6]. For parents, this means that their role and the situation they find themselves in regarding early childhood allergy prevention (ECAP) has changed, particularly as new knowledge evolves continuously and often contradicts previous assumptions (eg, the effectiveness of deliberately exposing children to allergens, such as peanuts or eggs). This demands a more active, yet often less certain, parental role. Because of this and because recommendations given to parents change continuously [7-9], ECAP is a relevant example of how subject-specific health information is applied in daily (ie, regular) activities from four different perspectives, each with their own challenge.

#### Challenge 1: Information-Seeking Reasons and Motivations

Firstly, parents may search for information for different reasons and with varying motivations and individual circumstances [10]. Some may be concerned because of a known familial predisposition, some may have no particular risk but have more general concerns, while others may not have any specific interest. Apart from a particular risk status that triggers interest, different parental motivations may be evident at different stages of early childhood development. Also, a considerable proportion of parents may not seek ECAP-related information at all.

#### Challenge 2: Information Preferences

Secondly, evidence about parental information-seeking behavior and preferences regarding content, format, and delivery of information is crucial to adapt available services to parents' specific requirements [11,12]. While there is ample evidence that many individuals lack health literacy—the ability to access, understand, appraise, and apply health information [13-15]—information regarding parents' needs and preferences for ECAP-specific health information is scarce [16,17]. Research on needs and preferences relating to other topics suggests that available information is not tailored to target groups or according

to the respective subjects [18]. It is also assumed that search behavior and preferences vary across different subjects and that parents are selective in seeking information (eg, during their children's different developmental stages) [19].

#### Challenge 3: Information Formats

Thirdly, ECAP behavior and preferences may be influenced by available information formats. While the usage of online health information is increasing, the quality, safety, and reliability of available sources has been criticized in the past [20,21]. Further aspects, such as transparency, neutrality, appropriateness, and readability, may be equally important to ensure effectiveness [12,19,21,22]. This is also important because parents usually make use of more general information derived from public search engines rather than from specific sources for which a high degree of quality and a trustworthy evidence base can be assumed (ie, university- and health professional-authored sources) [12]. Another point of criticism of currently available online sources is that they are frequently overly technical, of limited accuracy, and contain too much information; in addition, there are no universal quality criteria for the development and provision of related services [18,23-28].

#### Challenge 4: Determinants of Information-Seeking Practices and Preferences

Lastly, parents' information-seeking behavior and the respective stages and tasks related to searching, finding, appraising, and applying available information is influenced by their specific level of health literacy (see Methods section). For Germany, recent research highlights the prevalence of inadequate levels of health literacy in the population [13]. The association between health literacy and parents' information and care practices has been discussed for other health issues (eg, obesity [29], food allergy [16], self-efficacy [30], weight control [31], and pediatric emergency utilization [32]). All studies highlight the negative effects of poor health literacy on parents' health behavior; these studies suggest adjusting information sources and health care practices to health literacy levels [29] and developing strategies to support parents [30,33]. To develop respective materials and strategies, a better understanding of parents' actual behavior and preferences is necessary [31]. In addition to the potential influence of health literacy, sociocultural habits, traditional beliefs, language barriers, past experiences, and routines regarding information use and access have been repeatedly described in the literature as important influencing factors. However, these aspects have not yet been assessed in the context of ECAP [34-37].

## Objectives

With the above-stated lack of empirical evidence on parental

ECAP needs, preferences, and practices, the objectives of the planned study are shown in [Table 1](#).

**Table 1.** Objectives and themes of the study.

Objective	Theme
Assess reasons and motivations for searching for early childhood allergy prevention (ECAP) information among different parent groups, and assess how these reasons are further influenced by parents' awareness of, trust and uncertainty with, and beliefs of risks and myths associated with allergy prevention	Reasons, motivations, awareness, and trust
Explore how parents search for and apply ECAP information and clarify the emphasis on digital vis-à-vis nondigital sources	Information behavior
Describe preferences for information formats	Information formats (ie, needs and preferences)
Describe parents' health literacy and sociocultural backgrounds and whether these create differences for the use of ECAP information	Influencing factors
Explore how sociocultural backgrounds may influence the above described aspects (ie, relevance, awareness, needs, preferences, and information behavior)	Sociocultural determinants
Summarize and disseminate key points for health professionals regarding parental handling of, and preferences for, ECAP information	Implications for practice

## Methods

### Study Design

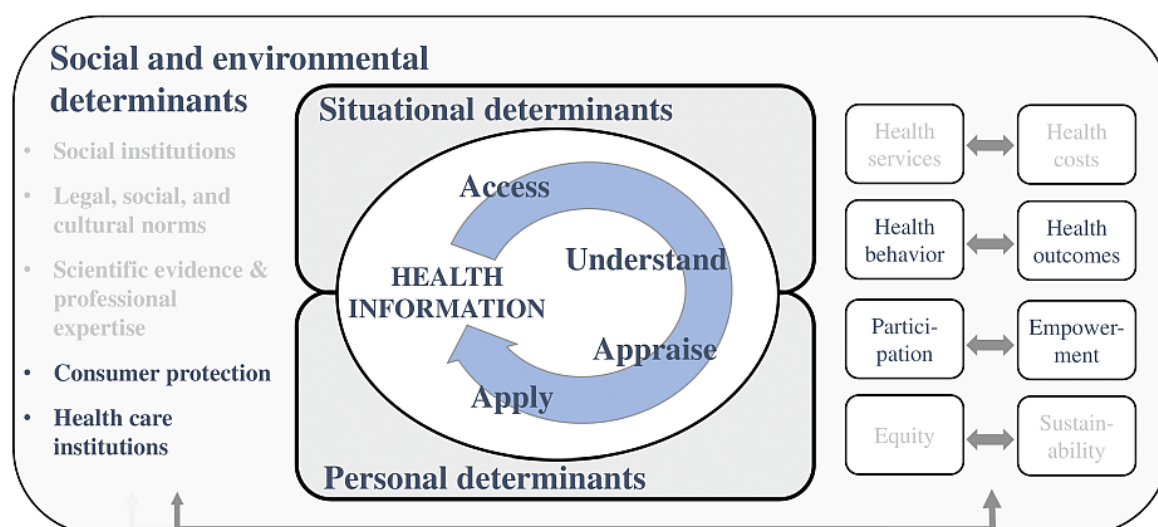
#### Theory and Framework

The study of health literacy has gained considerable momentum, both at national (ie, Germany) and international levels (eg, [38-42]), due to the many people who have difficulties with accessing, understanding, appraising, and applying health information [15,43]. In light of its growing importance, the National Alliance for Health Literacy published the German National Action Plan for Health Literacy in 2018 [14]; similar initiatives are in place internationally, for instance, in Scotland and the United States [44,45]. Since the aim is to assess parental handling of, and needs regarding, ECAP, health literacy is at

the core of each aspect of this study. The framework summarizes health literacy as a construct, with determinants of functional, interactive, and critical health literacy on a continuum from the individual to the population level, with the latter often being criticized for receiving too little attention [46,47].

The framework (see [Figure 1](#)) will be applied to (1) the development of the focus group manual, (2) data analysis (ie, development of coding categories; see [Data Analysis](#) section), and (3) formulation of recommendations, regarding both future ECAP information design and potential adjustments of the health literacy model. This framework has been slightly adapted from the original version by Sørensen et al [46] to emphasize the relevance of population-level determinants and the social embeddedness of health literacy.

Figure 1. Health literacy framework.



## Study Population

### Target Group

To gather insights about the range of potentially different parental ECAP information behaviors and preferences and to help develop tailor-made future information materials and communication channels, different groups of parents will be recruited: (1) risk-specific groups (ie, parents with or without a specific risk of their child developing an allergy, based on the parents having or not having a medically confirmed allergy) and (2) life stage-specific groups (ie, expectant, new, and experienced parents).

Overall, a self-developed sampling matrix will be employed for a better overview of the characteristics of recruited participants and to identify parental characteristics that are underrepresented in the overall sample. The matrix will account for the above-mentioned main identifiers—allergy risk and life stage—as well as further, more typical recruitment criteria, including age, gender, educational status, migration background, and familial status (ie, living with or without a partner). The respective information will be queried during the recruitment process using a short questionnaire.

### Recruitment Process

First, a list of contacts was compiled for health professionals (eg, pediatricians, gynecologists, and allergists) and for public and public health institutions (eg, kindergartens, family centers, and community offices) located in both urban and rural areas within a 10-km distance to the project sites in Germany (ie, Hanover, Magdeburg, Freiburg, and Regensburg) to reduce participants' travel time. Respective contacts were searched for via (1) entries in medical online registers (ie, mainly online physician registries like Arztauskunft Niedersachsen), (2) coordinating bodies within public health (eg, the German Society

for Allergy and Clinical Immunology, Landesamt für Gesundheit, and registries on insurance websites), and (3) general directories (eg, municipality websites, registries provided by municipalities for parents to find and choose a kindergarten or nursery, and local citizen administration and service offices). This will be complemented by (4) a Google search (eg, for further childcare institutions in specific cities) and (5) pre-established contacts (ie, mainly health professionals) from each project partner's previous networks and collaborators of the project lead. From the overall list of contacts, those who can be expected to have the most direct and/or most frequent contact with the target group will be contacted first, such as kindergartens; we will contact further individuals and institutions if necessary. After completion of the search for recruitment agents, health professionals and institutions will be contacted personally to inquire about their support and availability for recruitment.

### Recruitment Channels

As described above, parents will be approached via physician practices, public institutions, and a range of additional individual contacts from previously established project networks at the four project sites, in accordance with previous findings on the accessibility of lay target groups [48]. The first phase of recruitment is scheduled to take 1 to 2 months, followed by an assessment (ie, positive and negative recruitment channels) among the four project sites to identify difficulties. The second phase, expected to take 2 to 3 months, will then be conducted based on necessary adaptations.

Regarding recruitment via physician practices, access should be via (1) direct approach by the physician and/or nurses, for example, at the end of an appointment and (2) indirect approach via written information placed, for instance, at the clinic entrance or waiting room.



For recruitment via public institutions and offices, the main approach will be for an employee (eg, a nurse) to directly contact potential participants, for instance, for one hour in the morning, to limit the amount of staff time required. Again, an indirect approach via written information is also necessary to reach more potential participants. In settings where parents may best be reached at specific times of the day (eg, just before scheduled group meetings), project staff can support on-site recruitment. In addition, project sites' institutions and institutions doing on-site recruitment will also use social media channels to post short messages with links to the project website. In advance, a search for relevant groups and websites was conducted, particularly private groups on Facebook.

Project staff have prepared written information used to inform potential participants about the project across the various recruitment channels. Feedback regarding its appropriateness, structure, and content has been gathered from the partner project on health professionals' communication of ECAP information. Once participants have been selected, the initial short version of the project information document for participants used for recruitment will be adapted to an electronic version, using the online questionnaire tool SoSci Survey (SoSci Survey GmbH), to provide focus group participants with all necessary details. The electronic survey tool ensures full protection of personal data according to the German General Data Protection Regulation.

## **Data Collection**

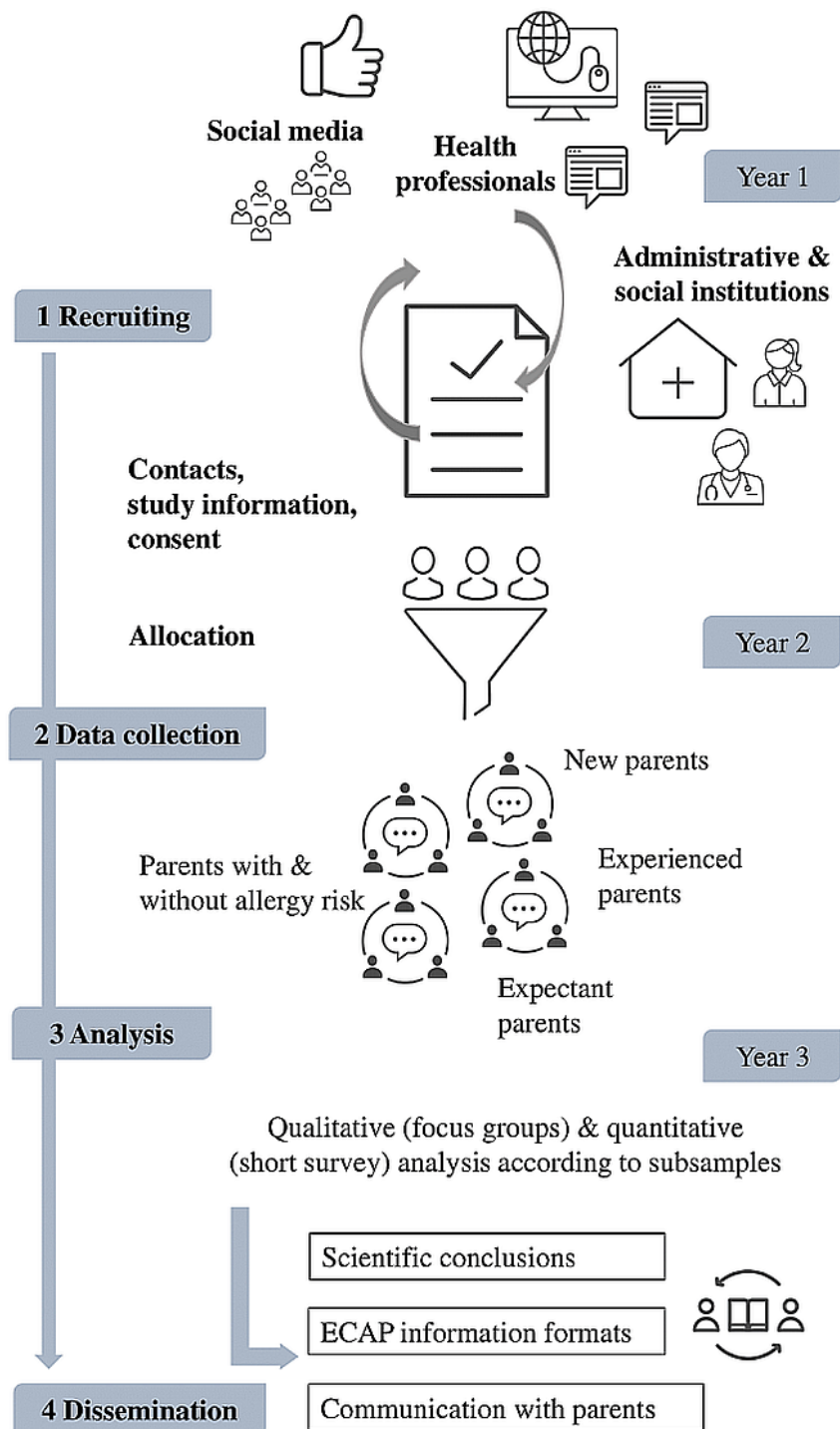
### **Qualitative Data Collection**

A focus group approach seems valuable as it enables exchange among peers [49,50], with the subject of allergy-related

prevention of health risks for the child being rather emotional and based on individual preferences, insights, and beliefs and, hence, worth discussing. In turn, this may help the target group reflect on their practices and needs based on others' contributions and, hence, may stimulate additional input, particularly regarding potential adaptations of ECAP information formats and contents. A focus group manual was drafted and revised according to available research on the overarching subjects of health literacy, parental information behavior, and focus group methodology (see [Multimedia Appendix 1](#)) [12-14,16,34,51-54]. From these sources, individual themes were reframed as relevant questions for parents and ECAP. For example, the item "ability to judge the relevance of the information" translates into "When you read ECAP-specific online information, what contributes to your judgement of this information being relevant or not?" A pilot test with focus group participants (n=6) recruited locally in Hanover is scheduled 4 to 8 weeks in advance of the actual start of data collection.

Following the preparation phase, four to five focus groups will be conducted at each project site, structured around the risk-specific and life stage-specific parent groups (see [Figure 2](#)). Focus groups will be led by the project staff assisted by two more researchers to ensure good methodological practice. Each group will be scheduled for about 90 minutes with additional time to complete health literacy surveys (see [Quantitative Data Collection](#) section). After the initial conduct of four to five focus groups, potential adaptations regarding format, process, and content will be discussed and the remaining focus groups will be conducted accordingly.

**Figure 2.** Main tasks and project phases. ECAP: early childhood allergy prevention.



### Quantitative Data Collection

To assess and compare health literacy levels among the focus group participants (approximately N=120), a short version of the European Health Literacy Survey containing 16 items [52] will be applied, distributed, and completed alongside the focus

group meetings. It covers three aspects of health along the four main health literacy dimensions, which appear suitable to assess health literacy in a group of parents. The survey comprises questions along the categories as shown in Table 2 as well as general information on each participant (eg, education status and health level), for a total of 25 questions.

**Table 2.** Subdimensions of health literacy, using the European Health Literacy Survey.

Health literacy subdimension	Information action			
	Access and obtain health information	Understand health information	Appraise and evaluate health information	Apply and use health information
Health care	Ability to access information on medical or clinical issues	Ability to understand medical information and derive meaning	Ability to interpret and evaluate medical information	Ability to make informed decisions on medical issues
Disease prevention	Ability to access information on risk factors	Ability to understand risk information and derive meaning	Ability to interpret and evaluate information on risk factors	Ability to judge the relevance of the information on risk factors
Health promotion	Ability to update oneself on health issues	Ability to understand health-related information and derive meaning	Ability to interpret and evaluate health-related information	Ability to form a considered opinion on health issues

## Data Analysis

### Parent Focus Groups

To account for potential differences in different parent groups (ie, risk-specific and life stage-specific groups), for instance, regarding when and how they seek ECAP information, the constant comparison method will be applied [55,56]. First, two focus groups will be selected from the risk-specific and life stage-specific parent groups, respectively, for detailed analysis and will be comprised of 6 participants each. Using established qualitative data analysis software, MAXQDA 2018 (Verbi GmbH), two researchers will independently apply open coding to attach codes (ie, descriptors will be applied to the various discussion sections). Codes will be broadly derived from the health literacy framework and focus group guideline items; additional codes will be added inductively as far as is relevant. Second, the various individual codes and respective text passages will be grouped into overarching categories. Next, the categories will be refined and structured around the initial research questions, again by two researchers, and core themes will be described for each. Any disagreement among the two researchers will be discussed with a third researcher, the project lead, to reach consensus. Each of the remaining focus groups will be analyzed using the set of previously built categories. Based on the final coding categories, key similarities and differences regarding information behavior, reasons for information searching, needs, and preferences, among others, will then be summarized and compared between groups.

### Differences Based on Sociocultural Backgrounds

While the main part of the analysis will focus on the different parent groups, a separate round will be conducted to determine differences due to sociocultural backgrounds. To do so, the respective original transcripts will be screened for specific mentions (eg, preferences for a certain kind of information).

### Health Literacy Survey

Data from the filled-in surveys will be entered into statistical data analysis software, SPSS Statistics, version 23 (IBM Deutschland GmbH), to allow for a descriptive portrayal of participant characteristics. This will be used mainly during the formulation of practice implications (see Expected Results section) (eg, specifying and characterizing parent groups that demand specific information formats and contents [ie, “Who

needs what?”]). Individual health literacy levels will be indicated as percentage shares for items rated as *very easy*, *rather easy*, *rather difficult*, *very difficult*, and *don't know*. Individual ratings will then be displayed as *excellent*, *adequate*, *insufficient*, and *problematic* according to the differentiation of health literacy levels [15]. Also, health literacy levels will be compared among the different parent groups based on mean values.

### Next Steps for Recruitment and Focus Group Discussion Manual

As of January 2020, the study started with a structured online search for (1) clinics, (2) general practitioners, (3) gynecologists, (4) pediatricians, (5) allergists, (6) midwives, (7) kindergartens, (8) public administration offices, and (9) local social institutions across the different local project sites, according to the plan described in the Recruitment Process section, to use these individuals and institutions for direct access to the target groups. Broad inclusion criteria were defined in cases where there were too many potential contacts. For example, general practitioners were included if they had a professional website, provided an email address, operated as a joint practice with at least two physicians, and had a medical degree. The contacts were further limited to a maximum of 15 per category to keep the subsequent contacting manageable. The current list entails 386 contacts across all project sites; further contacts may be added when necessary (eg, family centers and community offices with specific services for migrant parents).

Then, a manual for the focus group discussions was drafted, based on a search in PubMed and Google Scholar for available research on focus groups with parents on the subject of prevention measures for children (eg, [57-59]) and on established and alternative methods for the structure and conduct of focus groups [60-62]. All relevant sources were screened for input on methods and content of the planned focus groups. Summaries of each finding were implemented in the initial draft version of our manual following discussions among the project staff. A first complete version of the manual has been agreed on internally; further feedback will be gathered within the research unit once recruitment is underway. The manual shall also be sent to a small group of health professionals for content-related feedback (eg, an allergist from the allergy clinic of our host institution; a health literacy expert, to be identified from the scientific advisory board established as part of the

research unit; and a local public health or health care institution, such as the German Allergy and Asthma Foundation).

### *Transferring Results to Practice*

#### **Step 1: Participatory Development of Practice Implications**

Based on our findings, our aim is to determine (1) where ECAP-specific information should be placed to reach more users and what motivates parents to consider information, (2) the topics that create uncertainties (eg, recommendations on allergenic foods) and what parents consider helpful for navigating such challenges, and (3) the preferred information and learning formats and respective variations across parent groups.

To derive practice implications, relevant codes from the analysis will be grouped under each aspect. A preliminary set of implications will be drafted according to the categorization of codes, for which (1) volunteers from the focus groups (n=5) as well as (2) a group of health professionals (n=5) shall be invited to comment on, revise, and consent to the practice implications. The latter will be approached based on one of our neighboring projects within the Health Literacy in Early Childhood Allergy Prevention (HELICAP) research unit, which interviews health professionals from different disciplines regarding their ECAP communication with parents. A final version will be created based on the overall feedback; the exact format (eg, a user-friendly visualized brochure) will be consented to during the development process.

#### **Step 2: Dissemination**

Practice implications will primarily be disseminated to health professionals who inform and consult parents about ECAP (ie, midwives, pediatricians, and allergists) and providers of digital health information. Also, childcare service institutions, such as kindergartens and family centers, will be invited to offer short summaries of the main findings from both provider and user perspectives within their institution. Formats other than written summaries might be necessary here, which still must be agreed upon in the course of the project. To approach the above-mentioned individual actors, a combination of dissemination channels will be employed, particularly the following:

1. All actors and institutions for which contact details were collected for the recruitment of parents.
2. Established collaborations and networks by key German actors in the field of allergy-specific health information (eg, the German Allergy Information Service and the German Allergy and Asthma Foundation).
3. Umbrella organizations that reach out to allergy experts (eg, the German Society for Pediatric Allergology) and family and childcare institutions (eg, the Federal Association of Family Centers).

#### **Step 3: Preparing the Findings for Intervention Development and Testing in a Second Project Phase**

A final step is to transfer the study results and practice implications into a subsequent phase of intervention development and testing. At this point, a set of ECAP-specific information materials would be drafted based on the project

described here as well as on the recommendations for evidence-based health information (eg, [63-65]). This could then be piloted via a randomized controlled trial (ie, one group of parents receiving the intervention and another group receiving currently available ECAP information). A specific focus for the information materials (eg, suggestions for dealing with uncertainty) will be specified if the results of this study demonstrate a need for it. Besides constant patient and public involvement during the development stage by a group of parents, the development phase would be further supported by allergy prevention experts. These experts would be approached, for instance, via the associated university hospitals and respective allergy and pediatric clinics at each project site.

### *Ethical Considerations*

Besides a deeper reflection on the participants' own ECAP prevention and information practices and those of other focus group participants, as well as potentially controversial discussions, there are no likely risks to be expected from the conduct of focus groups. The study design, including the recruitment, conduct, and analysis, has been approved by the Ethics Committee of Hanover Medical School (ID 8161\_BO\_K\_2018).

### *Results*

The study began with preselection of recruitment channels, drafting of recruitment and study information for potential participants, and agreement on a first full version of the guideline. Then, a detailed contact list was compiled of health professionals, administrative and social institutions, and relevant social media channels (N=386) to be approached for assistance in contacting parents. Given the COVID-19 pandemic and, hence, the substantially limited access to potential participants as well as restrictions for direct meetings, it was decided, in accordance with the funding agency, to pause the recruitment and restart this process as of January 2021. Presumably, focus groups will commence in the first quarter of 2021, and an alternative to direct meetings is being considered in the case of continuing contact restrictions.

### *Discussion*

A major step toward successful focus group conduct is the recruitment of a sample diverse in individual backgrounds and perspectives, for example, by including parents with and without allergic predispositions, expectant and more experienced parents, single parents, and those who are not native German speakers. Hence, it will be important to sensitize recruitment agents to this issue, to contact institutions supporting disadvantaged people, and to ask all participants to inform peers.

The inclusion of hard-to-reach groups (ie, those that do not receive the call for study participation, those who do not use the internet, those who do not have the time or resources for participation, those who feel uncomfortable participating in group discussions, those with low reading levels, and those who have difficulties reading German) could prove difficult. While this potential challenge cannot necessarily be circumvented completely, we will make sure to address individual actors and



organizations with specific access to these groups, particularly family and childcare organizations with specific services (ie, *Familienhilfe*) and family centers located in social flashpoints. Also, recruitment could be done directly from low-education suburbs (eg, via distributing study flyers directly to each household). It will also be important to inform, for example, family centers' staff early, discuss potentially necessary adaptations of the recruitment material (eg, language), and ask them to approach potential participants more directly (ie, in their role as a reference person for hard-to-reach groups).

Experiences from similar, yet unpublished, studies on parental health literacy conducted by the research team in Hanover will provide valuable help for structuring the discussions on ECAP, addressing issues that deserve particular attention (eg, reasons for not adhering to certain sources and revising or changing less relevant topics). The challenge here may be to go beyond a discussion of general information behaviors (eg, Googling) and trusted sources (eg, scientific experts), though not neglecting these issues, and instead emphasize issues such as trust, decision making, and health literacy skill development.

As the COVID-19 pandemic continues to impede social contacts on-site, an alternative to this study's planned focus group methodology will have to be considered, particularly online (ie, video) meeting tools [62]. While the organizational and technical aspects (eg, unrestricted access to the tool, sending log-in details, providing usage information, and ensuring proper functioning) may all be implemented in advance, it is unclear if an online

meeting will be suitable, particularly regarding whether participants would contribute the same information as they would in a face-to-face meeting. For instance, it may be more difficult to react to another person's statement when not being able to observe the entire group and reactions by others. This would, in turn, impede group dynamics and result in a more passive discussion. However, reducing the size of participants per online focus group (eg, maximum of 5), thereby conducting more online focus groups overall, may contribute to improved perceptions of belonging and, hence, to participants contributing with greater confidence.

To conclude, with this study, the understanding of parents' information behavior and needs with respect to ECAP shall be improved, as allergies (ie, atopic diseases) are a major health issue in western industrialized societies that demand timely prevention strategies. It is hoped that we may not only develop a deeper understanding of individual influences regarding a person's ability to handle health information but also that we may gain insight into external organizational factors shaping individual health literacy, which have been largely neglected by previous attempts to create a comprehensive understanding of health literacy. The findings should also help generate practical advice for health professionals, public institutions, and public health institutions on providing user-centered information materials as well as for parents to access information resources that help them (1) to deal with uncertainty and risk, (2) not to be misled by inaccurate sources, and (3) to make informed choices about child health.

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## Acknowledgments

We would like to thank the steering committee (Christian Apfelbacher, Eva Maria Bitzer, Janina Curbach, Marie-Luise Dierks, Susanne Brandstetter, Markus Antonius Wirtz) as well as the initial members (Nina Egger, Christina Tischer, Jana Tempes, Uwe Mattered, Julia von Sommoggy, Maja Pawellek, Carolin Dresch, Anja Schulz) of the research group "Health Literacy in Early Childhood Allergy Prevention" (HELICAP, [66]). HELICAP is funded by the German Research Foundation (DFG FOR 2959, project-id: 409800133), of which this project is a part (grant number: DI 1757/2-1). The funder had no role in the design of the study, data collection, data analysis, or interpretation of the results. We also thank the external grant proposal advisers (Julika Loss, Kristine Sørensen) and the grant proposal reviewers who all provided valuable and critical feedback on the conceptualization of the study, its methodological design, and its integration into the overarching goals and structure of the research group. Lastly, we are grateful for the detailed language editing support provided by Roy Reuben Thomas.

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## Authors' Contributions

JL, MLD, and EB were responsible for the conceptualization of the study. JC and JVS were responsible for the study design and further revision of the manuscript. JL was responsible for writing the first draft of the manuscript. MLD, JC, JVS, and EB were responsible for writing, revising, and editing the manuscript. All authors read and approved the final version of the manuscript.

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## Conflicts of Interest

None declared.

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Multimedia Appendix 1

Focus group guideline.

[PDF File (Adobe PDF File), 131 KB - [resprot\\_v10i1e25474\\_app1.pdf](#)]

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## Abbreviations

**ECAP:** early childhood allergy prevention

**HELICAP:** Health Literacy in Early Childhood Allergy Prevention

*Edited by G Eysenbach; submitted 03.11.20; peer-reviewed by R Allison, C Cheng, R Ravangard; comments to author 28.11.20; revised version received 29.11.20; accepted 01.12.20; published 20.01.21.*

*Please cite as:*

*Lander J, Curbach J, von Sommoggy J, Bitzer EM, Dierks ML*

*Awareness, Information-Seeking Behavior, and Information Preferences About Early Childhood Allergy Prevention Among Different Parent Groups: Protocol for a Mixed Methods Study*

*JMIR Res Protoc 2021;10(1):e25474*

*URL: <http://www.researchprotocols.org/2021/1/e25474/>*

*doi: [10.2196/25474](https://doi.org/10.2196/25474)*

*PMID: [33470948](https://pubmed.ncbi.nlm.nih.gov/33470948/)*

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Proposal

# Morbidity and Complications of Diabetes Mellitus in Children and Adolescents in Ghana: Protocol for a Longitudinal Study

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## Abstract

**Background:** Diabetes is associated with premature morbidity and mortality from its many complications. There are limited data on the chronic complications of diabetes in children and adolescents in sub-Saharan Africa.

**Objective:** The study aims to determine the (1) burden and related factors of chronic systemic complications of diabetes, including diabetic and nondiabetic ocular conditions in children and adolescents, and (2) quality of life (QoL) of participants compared to healthy controls. This manuscript describes the study methodology.

**Methods:** Demographic information, medical history, anthropometric measurements, and laboratory characteristics were collected, and the participants were screened for microvascular and macrovascular complications as well as nondiabetic ocular disease. QoL questionnaires were administered to participants, their caregivers, and controls. Participants were followed up annually up to 3 years to determine the natural history of and trends in these conditions. SPSS Version 25.0 will be used for data analysis. Continuous and categorical data will be presented as mean (SD) and as percentages (%), respectively. t tests and analysis of variance will be used to compare means, and chi-square tests will be used to compare categorical data. Correlation, regression, and logistic regression analyses will be employed to establish linear associations and causal associations as appropriate. Relative risk and odds ratios will be used to estimate risk. QoL outcomes in Ghanaian children and adolescents with diabetes mellitus

compared with caregivers and healthy controls will be assessed using the Pediatric Quality of Life inventory. Significance will be set at  $\alpha=.05$ .

**Results:** Institutional approval from the Ethical and Protocol Review Committee of the University of Ghana Medical School was received on August 22, 2014 (Protocol Identification Number: MS-Et/M.12-P4.5/2013-2014). Funding for the project was received from the University of Ghana Research Fund (#UGRF/9/LMG-013/2015-2016) in March 2016. Patient recruitment, clinical examination, and data collection commenced in August 2016 and was completed in September 2019. A total of 58 children and adolescents with diabetes mellitus have been recruited. Blood samples were stored at  $-80^{\circ}\text{C}$  for analysis, which was completed at the end of July 2020. Data analysis is ongoing and will be completed by the end of December 2020. Investigators plan to submit the results for publication by the end of February 2021.

**Conclusions:** The prevalence, natural history, trends in diabetic complications and nondiabetic ocular disease, and QoL will be provided. Our data may inform policies and interventions to improve care given to children and adolescents with diabetes.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/21440

(*JMIR Res Protoc* 2021;10(1):e21440) doi:[10.2196/21440](https://doi.org/10.2196/21440)

## KEYWORDS

diabetes mellitus; type 1 diabetes; type 2 diabetes; microvascular; macrovascular complications; quality of life

## Introduction

Diabetes mellitus (DM), in general, is a challenge for all ages, as it leads to significant morbidity, especially kidney, eye, heart, and cerebrovascular disease, and premature mortality [1,2]. There are limited data on the epidemiology of DM in different sub-Saharan African (SSA) populations [3-6]. Danquah et al [7] reported the prevalence of type 2 DM as 6% among Ghanaian adults in an urban area. Notably, almost all the existing epidemiological data on DM pertain to adults [4-6]. The limited data available in children are relatively old [8-13], and studies have reported prevalence rates of 10.1 per 100,000 [9] to 0.33 per 1000 in a Nigerian hospital [14] for children younger than 15 years. However, considering the life expectancy of these persons, these rates are very high. The rapid epidemiological shift being experienced by western countries [15,16], where overweight and obese children and adolescents are increasingly being diagnosed with type 2 DM, may possibly also manifest in SSA. DM predisposes to the development of generalized microangiopathy, with clinical consequences affecting the kidneys, eyes, and nerves, and macrovascular disease in children and adolescents [15,17,18]. Populations of African origin have been reported to have the highest prevalence of microvascular complications of DM [19]. Type 1 DM is one of the most frequent chronic diseases in children and represents a public health challenge globally [20,21]. Reported estimates for the prevalence of nephropathy, retinopathy, and poor growth range between 10% and 33%, whilst hemoglobin (Hb)A1c levels averaged 7.5%-12.5% for children and adolescents in the western world [22-24]. However, there are limited data available for SSA.

Although children and adolescents with type 1 DM are faced with the threat of acute complications of hypoglycemia and ketoacidosis on a daily basis, in the long-term, the microvascular and macrovascular complications of the disease place them at greatest risk for serious morbidity and earlier-than-expected mortality [25]. The burden of both type 1 and 2 DM among Ghanaian children and adolescents and their attendant chronic complications have not been previously documented. Further, nondiabetic eye conditions have not been studied in Ghanaian

children with DM. There is also a lack of information on the natural history of diabetic complications in Ghanaian children or how these can be modified in the Ghanaian population. Currently, there is no national policy for the management of DM in Ghanaian children and adolescents.

It is known that clinical characteristics of type 1 and 2 DM in people from SSA may differ somewhat that in typical European populations [26]. Diabetic nephropathy and diabetic retinopathy (DR) are the leading causes of end-stage renal disease and blindness, respectively, in younger patients globally and pose major public health challenges. DM in children and adolescents is becoming a health problem in developing countries. Limited clinic-based data in Ghana suggest that the prevalence of childhood and adolescent DM is on the increase, a trend similar to that in ethnic minority populations in western countries [26]. To the best of our knowledge, there are limited or no data on the occurrence of ocular and kidney disease in children with DM in SSA including Ghana. There are no previous studies on the choroid and retina in these children.

It has been suggested that the age of onset of type 1 DM is later in African communities (22-29 years) including Tanzania (15-19 years), South Africa (21-30 years), and Ethiopia (20-25 years) compared to European populations [27]. Such an epidemiological shift from what occurs in the West is difficult to establish in Ghana currently, due to scarce data availability on the prevalence of type 1 or 2 DM in younger persons (<20 years).

DR is one of the long-term microvascular complications of DM in children and leads to debilitating effects on visual acuity and ultimately blindness in some cases [1,2]. The risk for development of DR is said to be variable but may be present at time of diagnosis of DM. The variability of the risk of retinopathy is corroborated by population-based studies from Australia and Sweden, where 24% [15] and 27% [28] of children and adolescents with type 1 DM develop retinopathy 6 and 13 years after DM diagnosis, respectively. The incidence of DR is dependent on age of diagnosis and duration [15,17]. Overall, DR affects 15%-55% of patients, with a high proportion of proliferative retinopathy and macular edema in type 1 DM. In

adults with type 2 DM, 21%-25% have retinopathy at diagnosis of diabetes compared with 9.5% of those with type 1 DM [19,29]. A nationwide Danish prospective cohort study of children and adolescents with type 1 DM followed up for 8 years investigated the effect of the prepubertal duration of DM on the development of early retinopathy and elevated albumin excretion rate ( $>20 \mu\text{g}/\text{min}$ ) [22]. This Danish study reported the prevalence of any level of retinopathy to be 17.7% in the age group 12-15 years, 45.4% in the age group 16-20 years, and increased to 67.6% after 20 years of age [22]. DR was significantly associated with poor long-term glycemic control (hemoglobin [Hb]A1c;  $P<.0001$ ) and with DM duration in patients with either a prepubertal or pubertal onset of disease ( $P<.001$ ). Prepubertal DM duration is significantly associated with the development of DR [22].

There are also significant nonvascular diabetic eye morbidities as younger DM patients are known to have increased risks of developing neurotrophic keratitis, cataracts, and cranial nerve palsies and may have refractive abnormalities, while adults may also develop retinal vascular occlusions [2,30-33].

This study aims to determine the burden of microvascular and macrovascular complications of diabetic and nondiabetic ocular conditions in Ghanaian children with DM and further, to evaluate different factors that may influence these complications or associations. Specifically, the study will:

1. Determine the hospital-based prevalence, incidence, onset, and trend of microvascular and macrovascular disease (retinopathy, nephropathy, and neuropathy; cardiovascular disease), as well as other ocular changes of diabetic (cataracts, corneal ulceration) and nondiabetic ocular disease in children and adolescents in Ghana.
2. Determine the relationship between the prevalence of these microvascular and macrovascular complications with age at diagnosis and duration of DM, HbA1c, lipid profile, and other inflammatory markers.
3. Determine differences in the patterns of presentation of microvascular and macrovascular complications with nutritional status (BMI-age-sex percentile or z-score).
4. Determine the clinical, social, and biochemical determinants of ocular, neuropathic, nephropathic, and cardiovascular complications of juvenile DM.
5. Investigate the quality of life (QoL) of children and adolescents living with DM compared to healthy controls and the perspectives of their carers.

## Methods

A multidisciplinary team of researchers from Europe and Ghana is assembled to achieve the study goals. These researchers have diverse experiences in clinic-based and population-based research in DM and other chronic disease in both adults and children.

### Study Design

The study was done in 2 phases comprising an initial cross-sectional study to determine the prevalence and characteristics of microvascular and macrovascular complications of juvenile DM as well as nondiabetic ocular

diseases among participants over a 3-year period. QoL, risks, and interaction with other diseases including sickle cell disease or trait will be evaluated. The second phase was a longitudinal study in which participants from the first phase were followed up annually for 3 years (with possible extension to 5-10 years, subject to funding) to determine the natural history of the studied conditions.

### Study Site

The study was conducted at the outpatient clinics of the Departments of Child Health, Medicine & Therapeutics, and Family Medicine; the Ophthalmology Unit; and the National Diabetes Management and Research Centre, all at Korle-Bu Teaching Hospital (KBTH), Accra, and Cape-Coast Teaching Hospital (CCTH) in the Central Region of Ghana. KBTH is the national referral hospital whereas CCTH serves mainly the Central, Western, and Western North regions of Ghana.

### Study Population

Children aged 4-19 years diagnosed with DM attending the outpatient clinics at the study sites who fulfil the inclusion criteria, their carers, and healthy controls consisting of children and adolescents from identified educational or religious facilities in Accra will be included.

### Case Definition

A case is defined as any child aged 4-19 years diagnosed with DM attending the KBTH or the CCTH. DM was diagnosed in a patient with classic symptoms and random plasma glucose  $\geq 11.1 \text{ mmol}/\text{L}$ . Type 1 DM was confirmed by the presence of glutamic acid decarboxylase (GAD) antibodies, insulinopenia, or low levels of C-peptide (stimulated C peptide values  $<0.6 \text{ pmol}/\text{mL}$ ), and type 2 DM was diagnosed by a negative test for type 1 DM-specific antibodies in association with elevated fasting insulin or C-peptide (stimulated C-peptide assay  $>0.6 \text{ pmol}/\text{mL}$ ) and the presence of acanthosis nigricans [34-36].

### Inclusion Criteria

For the children with DM, all patients aged 4-19 years with DM (ie, with classic symptoms of hyperglycemia or hyperglycemic crisis, random plasma glucose  $\geq 200 \text{ mg}/\text{dL}$  [ $11.1 \text{ mmol}/\text{L}$ ]) who consented, assented, or whose carers consented for inclusion were included. For the healthy controls, children without DM, any form of chronic and psychiatric diseases, or coexisting acute disease during the study period were included.

### Exclusion Criteria

Patients aged 4-19 years with DM who did not or whose parents or guardians did not give consent for inclusion in the study were excluded. Patients with diabetes diagnosed before 4 years of age or after 19 years of age were also excluded. Finally, patients with chronic disease, psychiatric disease, or coexisting acute disease during the study period were excluded.

### Sampling

Children and adolescents with DM who met the inclusion criteria were recruited consecutively after written informed consent was given by their carers or themselves or after assent given by the children aged  $\geq 8$  years, as applicable. Healthy controls who met



the inclusion criteria were also recruited conveniently after consent and assent, as applicable.

### Sample Size

The population of children and adolescents attending clinics at the study sites was expected to be low. As such, all available patients were recruited into the study. It was estimated from clinical data available from the proposed study sites that about 5-10 children were diagnosed with DM annually. From these available data, with a power of 80% at a significance level of .05, a sample size of at least 55 children was anticipated in this study. During the period of data collection, a total of 58 children with DM were recruited. A total of 80 age-matched healthy controls were recruited for the QoL outcomes study.

### Study Duration

An initial cross-sectional study was conducted in 2016 with follow-up in a longitudinal study over a period of 3 years (August 2016 to September 2019).

### Procedures

#### General

Written informed consent or assent (see [Multimedia Appendix 1](#)) was obtained from all subjects and their guardians. This was followed by the administration of predesigned structured questionnaires (see [Multimedia Appendix 2](#)) to collect all clinical data for the children and adolescents with DM. These included patient demography, past medical history, type of DM (type 1 or 2), features of any systemic complications (nephropathy, cardiac, neurological, fatty liver, peripheral vascular disease, leg ulcers, and other comorbid conditions recorded from case notes where available), and laboratory investigations (eg, blood glucose and HbA1c at diagnosis and during follow-up).

Blood pressure measurements and examination of all systems were recorded. Hb levels as well as Hb genotype status were determined by Hb electrophoresis.

#### Ocular

Ocular examination included visual acuity assessment using the appropriate LogMAR test type for age, anterior segment assessment using slit lamp binocular microscope, dilated funduscopy with binocular indirect ophthalmoscopy and a 20D or 28D lens, and fundus biomicroscopy using a 78D or 90D lens. Ocular ultrasound (B mode) examination of the posterior segment of the eye with a Tomey UD 1000 Model (Tomey, Germany) was undertaken where media opacity precludes fundus visualization. Ocular fundus photography acquiring 4-field stereocolor photos from each eye with a VISUSCOUT 100 portable retina camera system was done. All retinal images were graded independently (according to the Early Treatment Diabetic Retinopathy Study [ETDRS]) by WMA and VAE, with joint adjudication when there were discrepancies. The ophthalmic examination and investigations were repeated at every visit (at 12-month intervals).

### *Systemic, Microvascular, and Macrovascular Functional Evaluation*

A full physical examination was undertaken. Height and weight were measured, BMI was calculated in kg/m<sup>2</sup>, and BMI-age-sex z scores and percentiles were determined using Centers for Disease Control reference standards and Anthro Plus software.

Assessments of macrovascular and microvascular disease were performed at baseline and annually in all study subjects. Ankle brachial index (ABI) was measured according to the American Heart Association guidelines [37]. Huntleigh Doppler equipment with an 8-MHz Doppler probe (Huntleigh, UK) was used to determine flow reappearance during slow deflation of a blood pressure cuff. The systolic pressure of the posterior tibial and dorsalis pedis was measured in both ankles, and the higher of the 2 was used as the ABI numerator. The denominator was determined by the higher of the 2 systolic blood pressure readings, 1 taken from each arm. An ABI ≤0.90 was indicative of peripheral arterial disease. Assessment of coronary artery disease using a resting 12-lead electrocardiogram (Nova PC-based ECG system) was done and analyzed using the Minnesota Code. Clinical assessment of neuropathy included a physical examination as well as an assessment of vibration perception threshold (VPT) as recommended by the American Diabetes Association [38]. VPT was assessed using a hand-held neurothesiometer (Horwell Neurothesiometer, Scientific Laboratory Supplies Ltd, Nottingham, UK) according to the manufacturer's guidelines. VPT was assessed at the metatarsophalangeal joint of both feet in a 2-step manner starting from 0 V with increasing stimulation and then starting from 50 V with decreasing stimulation.

### *Laboratory Investigations*

Laboratory assessments were performed at the Diabetes Research and Chronic Disease Reference Laboratory, University of Ghana Medical School, and MDS-Lancet Laboratories Ghana Limited in Accra. Samples of serum and plasma aliquoted from appropriate collection tubes or whole blood from the collaborating regional hospitals were transported to the Diabetes Research and Chronic Disease Reference Laboratory on dry ice within 12 hours after sample acquisition and processed immediately or stored at -80 °C for later analysis. Type 1 DM was confirmed by the presence of GAD antibodies, insulinopenia, or low levels of C-peptide, and type 2 DM was diagnosed by a negative test for type 1 DM-specific antibodies in association with elevated fasting insulin or C-peptide and the presence of acanthosis nigricans. Blood C-peptide levels were determined by competitive enzyme immunoassay methods using ELISA kits (NovaTec Immundiagnostica GmbH, Dietzenbach, Germany). Islet cell antibodies were assayed using ICA Enzyme Immuno Assay Kits. Furthermore, GAD65 autoantibodies were assayed using another ELISA kit (Medizym anti-GAD Testkit 96 tests, Medipan GmbH, Blankenfelde-Mahlow, Germany). Presence and levels of thyroid antibodies were determined using a chemiluminescent microparticle immunoassay (Abbott Alinity, Abbott Park, IL). HbA1c was measured using the Tri-Stat Boronate Affinity System (Trinity Biotech, Ireland). Lipid profile was assayed by determining the total serum cholesterol (cholesterol oxidase, esterase), triglycerides (enzymatic end

point), high-density lipoprotein cholesterol (direct measure polymer-polyanion), and low-density lipoprotein cholesterol by enzymatic methods using an automated chemistry analyzer (AU480 Beckman Coulter, Brea, CA). Nephropathy was assessed by the measurement of albuminuria using immunochromatography on fresh spot urine, and serum beta 2 macroglobulin was assessed by an immunoassay method (Siemens Immulite, Washington DC). Blood urea (urease UV method), electrolytes (ion selective electrodes [ISE] and enzymatic method for bicarbonates), and creatinine (Jaffe IDMS-traceable method) were assayed with the Beckman Coulter AU480. Hb electrophoresis was performed to determine the Hb type using the cellulose acetate paper method (tris-EDTA boric acid [TEB] buffer, pH 8.4). Urinalysis and microscopic examination of urine deposits were performed. Hematological examination included a complete blood count using a 3-part Mindray hematology autoanalyzer (Shanghai, China).

### **Other Investigations**

Abdominal ultrasound (B mode) was performed on patients found to have abdominal masses on clinical examination at baseline then yearly using a Hitachi EUB-7500 (Japan-made, 2009-2010). Where there was a pathology detected on ultrasound, magnetic resonance imaging was performed with the Hitachi Airis Elite (Ibaraki, Japan).

### **Quality of Life Outcome**

Children and adolescents with DM and healthy controls completed the Pediatric Quality of Life Inventory (PedsQL, Mapi Research Trust, Lyon, France; [Multimedia Appendix 3](#)). In addition, children and adolescents with DM completed the disease-specific (diabetes) module. Parents and carers also completed the proxy reports for the PedsQL 4.0 Generic Core Scales and the disease-specific (diabetes) modules, the PedsQL 2.0 Family Impact Module, and the PedsQL Family Information Form. Permission was sought from Mapi Research Trust for the use of the inventories ([Multimedia Appendix 4](#)). Each questionnaire took approximately 5-10 minutes to complete.

The PedsQL 4.0 Generic Core Scales has a set of questions for the participants and their parents or carers and healthy controls. For the participants and controls, the PedsQL asks questions about how they felt and what they thought about their health. For the parent, the PedsQL assesses the health-related QoL (HRQoL) of their children and adolescents. It contains questions about the child's physical, emotional, social, and school functioning in the past 1 month. It is a 5-point Likert scale ranging from 0 (Never) to 4 (Almost Always) without weighting of items on the scale.

The PedsQL 3.2 Diabetes Module is a 33-item diabetes-specific, HRQoL instrument that is made up of 5 scales measuring diabetes symptoms (15 items), treatment barriers (5 items), treatment adherence (6 items), worry (3 items), and communication (4 items). The scale is made up of patient self-report and parent proxy report formats for ages 5-25 years and a parent proxy report format for ages 2-4 years, which analyzes the patient's and parent's perceptions of the patient's diabetes-specific symptoms and management challenges. The patient self-report aspect was designed specifically for ages 5-7

years, 8-12 years, 13-18 years, and 18-25 years, while the parent proxy report forms are specific for ages 2-4 years (toddler), 5-7 years (young child), 8-12 years (child), 13-18 years (adolescent), and 18-25 years (young adult). The instrument seeks to know how much of a problem each item has been during the past 1 month. Items on the scale are reverse-scored and linearly transformed to a 0-100 scale (where 0=100, 1=75, 2=50, 3=25, 4=0). Lower scores indicate more diabetes symptoms and management problems, meaning lower diabetes-specific HRQoL. Summary scores are calculated as the sum of all the items divided by the number of items answered. When more than 50% of the items in the scale are missing, the summary score is not calculated.

The PedsQL 2.0 Family Impact Module is a 36-item tool that examines parents' self-reported HRQoL and family functioning due to their child's health condition. The tool is made up of physical functioning (6 items), emotional functioning (5 items), social functioning (4 items), cognitive functioning (5 items), communication (3 items), worry (5 items), daily activities (3 items), and family relationships (5 items) of the parent or carer.

The PedsQL Family Information Form was completed by the parent or carers. The form is made up of the demographic characteristics of the child and parent and an impact scale assessment. Demographic characteristics such as age, sex, and ethnicity of the child and marital status, highest level of education, and occupation of both parents are documented. For the impact scale assessment, the presence of a chronic condition (defined as a physical or mental health condition that has lasted or is expected to last at least 6 months and interferes with the child's activities) in the past 6 months, any overnight visit to the hospital or an emergency room or urgent care in the past 12 months, absenteeism from school in the past 30 days due to physical or mental health conditions, number of days in the past 30 days the child was sick in bed or too ill to play and needed someone to care for them due to a health condition, and parent's absenteeism from work due to child's ill health were all documented.

### **Preliminary or Pilot Data**

Our anecdotal clinical experience is that the prevalence of childhood and adolescent DM is on the increase and that complications including DR and nephropathy may be severe. This is based on the collective experiences of the physicians and ophthalmologists involved in this project as well as national projections.

### **Primary Outcome Measures**

The primary outcomes are the prevalence of DM in the young (4-19 years old) and occurrence of organ-specific complications (ie, nephropathy, retinopathy, and neuropathy) in this population.

### **Secondary Outcome Measures**

Secondary outcomes include incidence of diabetic complications from baseline to the end of the second year of the study, QoL and type of comorbid conditions, weight and height (for nutritional status using BMI-age-sex percentile and z-score), Hb levels and genotypes, and duration and number of follow-ups in the study.

Disease progression will also be evaluated, including incidences of nephropathy, retinopathy, visual loss, neuropathy, and peripheral arterial disease. Changes in the macular, retinal, and choroidal thickness at onset of DR and with time will be assessed and correlated with other parameters.

### Treatment of Identified Cases

All children with diseases or complications requiring treatment were treated or will be treated by the relevant specialty using medication and other treatment modalities used and prescribed routinely in Ghana as per Ghana Health Service or Teaching Hospital treatment policies as well as those of the National Health Insurance Scheme. There is currently no national policy for the management of DM in Ghanaian children and adolescents. As such, international guidelines for the management of children and adolescents with DM were also referred to, as necessary, including the American Diabetes Association Guidelines [36] and the Diagnosis and Management Guideline for Diabetes (type 1 and type 2) in children and young people (NICE, NG18) [39].

### Follow-Up of Patients in the Longitudinal Study

Follow-up visits for participants without ocular complications were scheduled annually. For participants with ocular complications at baseline or diagnosed during annual follow-up visits, subsequent follow-up examinations were scheduled for every 6-12 months as determined by the type and severity of the findings.

### Study Status

Currently, patient recruitment, clinical examinations, and some laboratory analysis have been completed. Blood samples are stored at  $-80^{\circ}\text{C}$  for analysis. Data captured to date have been cleaned for analyses.

### Ethical Approval

This study was approved by the Ethical and Protocol Review Committee of the College of Health Sciences, University of Ghana (protocol identification number: MS-Et/M.12-P4.5/2013-2014).

### Data Analysis

Data captured using Microsoft Office Access will be cleaned for analysis. Analysis will be done using SPSS Version 25.0. Continuous numerical data will be presented as mean (SD) and categorical data as percentages (%). For continuous variables that may be skewed, median and interquartile ranges will be used for their summary. Data will be presented as frequency, proportions, and percentages either in tables or pie and bar charts as appropriate. Chi-square tests will be used to compare proportions and tests for independence or associations of conditions among the categories of patients. *t* tests and analyses of variance will be used to compare means where appropriate. Correlation analysis will be used to establish linear associations for scale and ordinal variables, while regression and logistic regression analyses will be employed to establish causal associations in the data. Relative risk and odds ratios will be used to estimate risk in the samples. Significance will be set at  $\alpha=.05$ .

QoL outcomes in Ghanaian children and adolescents with DM compared with parents or carers and healthy controls will be assessed using the PedsQL 4.0 Generic Core Scales inventory. In scoring the process, items on the inventory will be reverse-scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. When  $>50\%$  of the items in the scale are missing, the scale scores will not be computed. When  $\geq 50\%$  items are completed, the mean of the completed items in the scale will be computed by summing the items over the total number of items answered. The Psychosocial Health Summary Score will be obtained by the summation of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. The total score will finally be obtained by summing all the items over the number of items answered on all the scales.

To examine parents' self-reported HRQoL and family functioning due to their children's health condition, the PedsQL 2.0 Family Impact Module will be used. The overall total score will be obtained by averaging all 36 items. To obtain the HRQoL summary score of a parent, the average of the 20 items comprising the Physical, Emotional, Social, and Cognitive Functioning scales will be computed. The Family Functioning Summary score will be calculated by averaging the 8 items comprising the Daily Activities and Family Relationships scales. The items on the Family Impact Module will be reverse-scored and transformed linearly to a 0-100 scale where the higher scores will show better (a less negative impact of the child's health on the parent or family) HRQoL.

## Results

Institutional approval from the Ethical and Protocol Review Committee of the University of Ghana Medical School was received on August 22, 2014 (protocol identification number: MS-Et/M.12-P4.5/2013-2014). Funding for the project was received from the University of Ghana Research Fund (#UGRF/9/LMG-013/2015-2016) in March 2016.

Patient recruitment, clinical examination, and data collection commenced in August 2017 and were completed in September 2019. A total of 58 children and adolescents with DM has been recruited. Blood samples are stored at  $-80^{\circ}\text{C}$  for analysis, which was completed at the end of July 2020.

Data analysis is ongoing and will be completed by the end of December 2020. Investigators plan to submit the results for publication by the end of February 2021.

## Discussion

The population of SSA is rapidly expanding. Similarly, the prevalence of DM is reported to be on the increase, increasing the risks associated with increased population growth compared to the risk reduction in higher-income economies [40]. This increase in DM prevalence is faster in low-income and middle-income populations than in high-income populations in all age groups [41].

Clinical studies in adults from South Africa [42], Tanzania [12], Ethiopia [43], and Ghana [7,44] reviewed by Hall et al [26]

suggest that the characteristics of type 1 and 2 DM in people from SSA may differ somewhat from typical European populations. It is suggested that the present study, when completed, will help elucidate any such differences in childhood and adolescent DM in SSA including Ghana. Children and adolescents with type 1 DM are threatened by acute complications of hypoglycemia and ketoacidosis on a daily basis. However, the long-term microvascular and macrovascular complications of the disease place them at greatest risk for serious morbidity and early mortality [25].

Although it is estimated that the prevalence of DM in the adult population of Ghana is approximately 10%, no data are available on childhood and adolescent DM in Ghana. However, when DM is coupled with the number of years ahead of persons in childhood and adolescence, morbidity and the drain on the individuals, their families, and society become very immense and require quantification. In order to establish the importance of this growing problem, it is important to determine the hospital-based prevalence, incidence, onset, and trends of neuropathy, microvascular and macrovascular diseases (retinopathy, nephropathy, and neuropathy; cardiovascular disease), and other changes of diabetic (cataracts, corneal ulceration) and nondiabetic ocular disease in children and adolescents in Ghana. Potential estimates of hospitalization and mortality may also be gleaned from this study. This will serve

as a preamble to further investigate the population prevalence and trend of DM in Ghana. To the best of our knowledge, there are no data on the QoL of children and adolescents with DM in SSA. This study, when completed, will provide some data to fill such a void. The associations with obesity, as well as QoL of people with DM and their carers, will be of immense importance in national and SSA planning of health education programs on DM and other childhood morbidities.

Furthermore, nondiabetic eye diseases have not been previously studied in Ghanaian children with DM. In addition, there is a lack of information on the natural history of DM complications in Ghanaian children or how these can be modified in the Ghanaian population. Currently, there is no national policy for the management of DM in Ghanaian children and adolescents. Data from this study would therefore lead to the development of policy briefs and guidelines that will be submitted to the Ministry of Health to help with the planning and implementation of effective policies for DM screening and the early detection of diabetic complications and nondiabetic eye disease in children, for improved care.

The study may also offer an opportunity for training and mentorship of resident doctors and biomedical scientists to augment in building capacity toward clinical care and research in children and adolescents with DM.

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## Acknowledgments

We would like to acknowledge the executives and members of Diabetes Youth Care-Ghana (DYC-Ghana), including all the children and adolescents with DM enrolled into the study and their caregivers for their support during the recruitment and examination processes. Special thanks to the staff of the Paediatric Eye Unit at the KBTH, staff of the Eye Department at the CCTH, and National Diabetes Management and Research Centre, all at KBTH, for their cooperation during the conduct of this study. This study received financial support from the University of Ghana Research Fund.

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## Authors' Contributions

VE and WA conceptualized and supervised the study, performed the validation and visualization, and wrote the original manuscript draft. VE acquired the funding and provides the resources. VE, WA, TN, and BA curated the data. TN and BA will perform the formal analysis. VE, NT, JA, AE, AS, CH-B, GA, AA, and IO-A conducted the investigation. VE, JA, AE, AS, CH-B, GA, BA, AA, TN, and WA developed the methodology. VE, BA, and WA perform project administration. All authors reviewed and provided feedback on the manuscript.

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## Conflicts of Interest

None declared.

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### Multimedia Appendix 1

Participants informed consent form.

[[DOCX File, 87 KB - resprot\\_v10i1e21440\\_app1.docx](#) ]

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### Multimedia Appendix 2

Study questionnaires.

[[DOCX File, 67 KB - resprot\\_v10i1e21440\\_app2.docx](#) ]

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### Multimedia Appendix 3

PedsQL 4.0 questionnaires.

[[PDF File \(Adobe PDF File\), 513 KB - resprot\\_v10i1e21440\\_app3.pdf](#) ]



## Multimedia Appendix 4

Permission to use PedsQL 4.0 inventory.

[\[PDF File \(Adobe PDF File\), 56 KB - resprot\\_v10i1e21440\\_app4.pdf \]](#)

## Multimedia Appendix 5

Ethical clearance letter.

[\[PDF File \(Adobe PDF File\), 603 KB - resprot\\_v10i1e21440\\_app5.pdf \]](#)

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## Abbreviations

**ABI:** ankle brachial index  
**CCTH:** Cape-Coast Teaching Hospital  
**DM:** diabetes mellitus  
**DR:** diabetic retinopathy  
**ETDRS:** Early Treatment Diabetic Retinopathy Study  
**GAD:** glutamic acid decarboxylase  
**Hb:** hemoglobin  
**HRQoL:** health-related quality of life  
**KBTH:** Korle-Bu Teaching Hospital  
**PedsQL:** Pediatric Quality of Life Inventory  
**QoL:** quality of life  
**SSA:** sub-Saharan Africa  
**VPT:** vibration perception threshold

*Edited by G Eysenbach; submitted 15.06.20; peer-reviewed by G Silvestri, H Barahimi; comments to author 23.09.20; revised version received 21.10.20; accepted 10.11.20; published 06.01.21.*

*Please cite as:*

Essuman VA, Tagoe NN, Akpalu J, Essuman A, Sackey AH, Hayfron-Benjamin CF, Asare G, Abaidoo B, Amoah AGB, Ndanu T, Ofori-Adjei IDB, Barnes NA, Appiah-Thompson BL, Amoaku WM

*Morbidity and Complications of Diabetes Mellitus in Children and Adolescents in Ghana: Protocol for a Longitudinal Study*  
*JMIR Res Protoc* 2021;10(1):e21440

URL: <https://www.researchprotocols.org/2021/1/e21440>

doi: [10.2196/21440](https://doi.org/10.2196/21440)

PMID: [33404517](https://pubmed.ncbi.nlm.nih.gov/33404517/)

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Protocol

# Reducing Ethnic and Geographic Inequities to Optimise New Zealand Stroke Care (REGIONS Care): Protocol for a Nationwide Observational Study

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## Abstract

**Background:** Stroke systems of care differ between larger urban and smaller rural settings and it is unclear to what extent this may impact on patient outcomes. Ethnicity influences stroke risk factors and care delivery as well as patient outcomes in nonstroke settings. Little is known about the impact of ethnicity on poststroke care, especially in Māori and Pacific populations.

**Objective:** Our goal is to describe the protocol for the Reducing Ethnic and Geographic Inequities to Optimise New Zealand Stroke Care (REGIONS Care) study.

**Methods:** This large, nationwide observational study assesses the impact of rurality and ethnicity on best practice stroke care access and outcomes involving all 28 New Zealand hospitals caring for stroke patients, by capturing every stroke patient admitted to hospital during the 2017-2018 study period. In addition, it explores current access barriers through consumer focus groups and consumer, carer, clinician, manager, and policy-maker surveys. It also assesses the economic impact of care provided at different types of hospitals and to patients of different ethnicities and explores the cost-efficacy of individual interventions and care bundles. Finally, it compares manual data collection to routine health administrative data and explores the feasibility of developing outcome



models using only administrative data and the cost-efficacy of using additional manually collected registry data. Regarding sample size estimates, in Part 1, Study A, 2400 participants are needed to identify a 10% difference between up to four geographic subgroups at 90% power with an  $\alpha$  value of .05 and 10% to 20% loss to follow-up. In Part 1, Study B, a sample of 7645 participants was expected to include an estimated 850 Māori and 419 Pacific patients and to provide over 90% and over 80% power, respectively. Regarding Part 2, 50% of the patient or carer surveys, 40 provider surveys, and 10 focus groups were needed to achieve saturation of themes. The main outcome is the modified Rankin Scale (mRS) score at 3 months. Secondary outcomes include mRS scores; EQ-5D-3L (5-dimension, 3-level EuroQoL questionnaire) scores; stroke recurrence; vascular events; death; readmission at 3, 6, and 12 months; cost of care; and themes around access barriers.

**Results:** The study is underway, with national and institutional ethics approvals in place. A total of 2379 patients have been recruited for Part 1, Study A; 6837 patients have been recruited for Part 1, Study B; 10 focus groups have been conducted and 70 surveys have been completed in Part 2. Data collection has essentially been completed, including follow-up assessment; however, primary and secondary analyses, data linkage, data validation, and health economics analysis are still underway.

**Conclusions:** The methods of this study may provide the basis for future epidemiological studies that will guide care improvements in other countries and populations.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/25374

(*JMIR Res Protoc* 2021;10(1):e25374) doi:[10.2196/25374](https://doi.org/10.2196/25374)

## KEYWORDS

stroke; protocols; stroke units; rehabilitation; Māori; Pacific people; health inequities; cost-efficacy; rural; observational study

## Introduction

Stroke is the second leading cause of death and disability globally [1]. In New Zealand, the overall burden of stroke is expected to rise by 40% over the next decade, largely due to an aging population [2]. Considerable effort has gone into implementing best practice stroke care across New Zealand in the past two decades; however, substantial variation in stroke service provision continues to exist [3-5].

The low population density of New Zealand has led to concessions in the organization of best practice stroke care being accepted for small- and medium-sized hospitals that serve geographically dispersed urban populations of less than 100,000 people [6]. For example, smaller hospitals are not required to have a designated stroke unit or stroke-specific rehabilitation service, and patients are often managed by clinicians without specific training or regular skill maintenance in stroke care [5]. It is unclear whether equitable patient outcomes can be achieved with these compromises.

Māori, the indigenous population of New Zealand, and Pacific people make up 16.5% and 8.1% of the total population, respectively, and have a greater incidence of modifiable stroke risk factors, including obesity, smoking, hypertension, and diabetes mellitus, compared to other New Zealanders [7,8]. This may explain these populations' higher age-adjusted incidence of stroke as well as the younger age at first stroke [9], but secondary health service factors that may impact on disparities in stroke outcomes have not been fully explored. Research from other countries shows that ethnic inequities exist in stroke service access and outcomes [10,11], and interpersonal and institutional racism have been shown to exist in general health care in New Zealand [12,13]. Several New Zealand studies have assessed the impact of ethnicity on functional outcomes poststroke, but results are conflicting [14,15]. Therefore, it remains unclear to what extent inequities in access for different

ethnic groups may affect patient outcomes beyond differences in baseline risk factors.

Here we describe the design and methods of the *Reducing Ethnic and Geographic Inequities to Optimise New Zealand Stroke Care* (REGIONS Care) study, an investigator-driven, multicenter observational study.

## Methods

### Study Aims

The primary aim of this study is to determine whether there is significant inequity in access to best practice stroke care and patient outcomes in New Zealand, based on the geographic location of health care facilities and the ethnicity of patients. Secondary aims include an exploration of current stroke service access barriers and the impacts of ethnicity, hospital location, and various care pathways on treatment costs and their association with patient outcomes. A further secondary aim is to compare and validate three different stroke data sources to determine the optimal use of health service resources to support data-driven, ongoing service improvement. These data sources include the following: (1) prospective individual patient data collected as part of a formal study involving patient consent for extended patient outcome assessment and data linkage, (2) prospective individual patient data collection as part of a routine national clinical registry that does not involve extended outcome data collection or data linkage and does not require individual patient consent, and (3) use of routinely collected health and other government data involving the New Zealand Integrated Data Infrastructure (IDI) maintained by Stats NZ.

### Primary Hypotheses

We have two primary hypotheses, as follows:

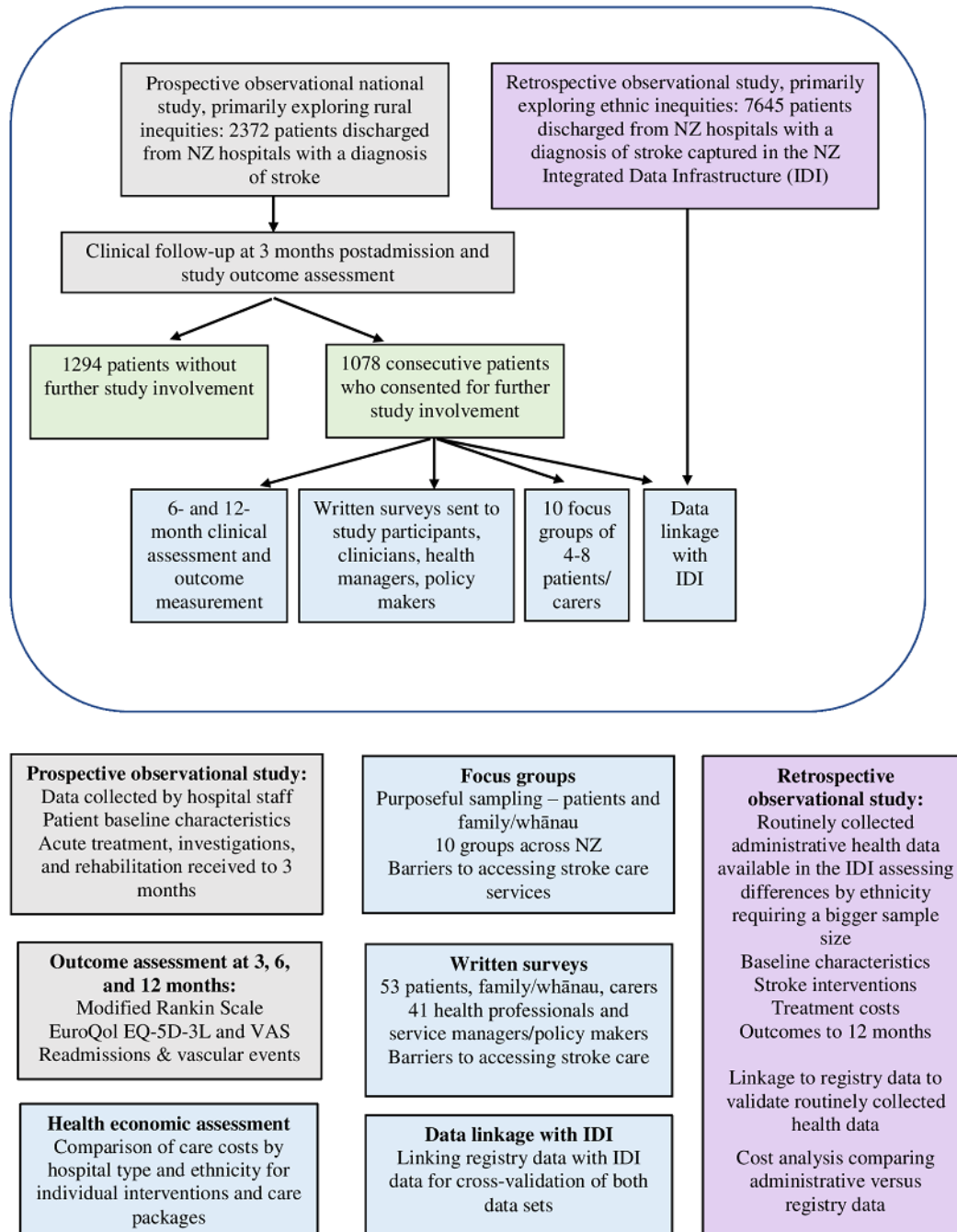
1. Stroke service location and size affects access to optimal stroke care and patient outcomes.

2. Ethnicity affects access to optimal stroke care and patient outcomes.

**Design**

This study consists of two large, complementary cohort studies with several nested substudies comprising surveys, focus groups, and an economic evaluation (see Figure 1).

**Figure 1.** Study flow diagram and components. EQ-5D-3L: 5-dimension, 3-level EuroQol questionnaire; NZ: New Zealand; VAS: Visual Analogue Scale.



**Part 1**

The two complementary cohort studies are described as follows:

1. Study A is a nationwide, prospective observational study of 2372 consecutively admitted stroke patients cared for at any New Zealand public hospital. The study collects information on individual patient baseline data, to allow for appropriate case-mix adjustments; acute and rehabilitation interventions; treatment costs; and poststroke

outcomes up to 12 months. It focuses primarily on differences associated with geographic location of the health service provider.

2. Study B is a nationwide, retrospective observational study of 7645 patients discharged from New Zealand hospitals with a diagnosis of stroke. The study uses routinely collected administrative health data available through Stats NZ's IDI. The IDI is a longitudinal meta-data set linked at the individual level, consisting of deidentified data from

government agencies [16,17]. Baseline characteristics, stroke interventions, treatment costs, and poststroke outcomes up to 12 months will be extracted and validated against a subset of patients recruited as part of Study A from Part 1. This study will focus primarily on differences based on ethnicity for which the greater sample size will provide sufficient power.

## Part 2

A mixed methods evaluation of access barriers will be carried out. This includes qualitative data derived from 10 focus groups involving face-to-face interviews with selected patients and carers from patients involved in Study A from Part 1; a survey of 50 stroke patients, family members, and/or carers; and a survey of 40 clinicians, health service managers, and/or policy makers.

## Patient Population

For Part 1, Study A, all patients discharged from New Zealand hospitals managing acute stroke between May 1 and July 31, 2018, with a discharge diagnosis of ICD-10-AM (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification) codes I61, I63, or I64, were captured prospectively into a national stroke registry database. To boost the sample size from smaller hospitals, smaller centers continued data collection until October 31, 2018, or until 100 patients had been recruited, whichever happened first. To boost the tertiary clot-retrieval center sample, tertiary centers collected patients until at least 150 patients had been captured. Nonreperfused patients with complete symptom resolution by 24 hours and no evidence of stroke on imaging (ie, transient ischemic attacks) were excluded. All patients in Part 1, Study A, were invited to consent to further follow-up at 6 and 12 months and data linkage until a preset sample size target (n=1078) was met. Collection of all consecutively admitted patients during the first 3 months, and then until targets are reached, will address the risk of selection bias.

For Part 1, Study B, all patients with the above discharge diagnoses admitted between November 1, 2017, and October 31, 2018, were captured via health administrative data. The only additional inclusion criterion was the requirement for patient consent for study-related follow-up and data linkage.

## Data Collection and Measures

For Part 1, Study A, baseline data include patient demographics, vascular risk factors, premorbid level of function (ie, the modified Rankin Scale [mRS]) [18], employment status, domiciliary information, and level of disability at time of hospital presentation (ie, six simple variable [SSV] model [19]). The mRS is a 6-point scale measuring independence and physical disability, ranging from 0 (no symptoms) to 6 (death) [20]. The SSV model includes six variables: age, living alone prestroke, independence in activities of daily living prestroke, the verbal component of the Glasgow Coma Scale, arm power, and ability to walk on hospital admission. Postadmission data include best practice acute stroke investigations and interventions during acute hospital admission and up to 3 months; in-hospital complications; hospital length of stay; prescription of appropriate secondary prevention medications

prior to discharge; if transferred to inpatient rehabilitation, the length of time to transfer and number and duration of therapy contacts during the admission; if referred for community rehabilitation, the time to first assessment and number of therapy contacts in the first 3 months; documentation of interdisciplinary meetings, goal setting, and patient and carer education; provision of culturally appropriate care and support services; and referral to the Stroke Foundation of New Zealand community stroke advisor. The 3-, 6-, and 12-month follow-up assessments captured data from the mRS, the EQ-5D-3L (5-dimension, 3-level EuroQol questionnaire) [21], doctors' visits, hospital readmissions, work status, and domiciliary status. The complete data collection form can be viewed in [Multimedia Appendix 1](#), Table S1.

For Part 1, Study B, baseline data include patient demographics and risk factors that can be ascertained from available administrative data (see [Multimedia Appendix 1](#), Table S2). Other data include health status at 3, 6, and 12 months poststroke (ie, alive, employed, change in domiciliary address, or deceased) and stroke-related interventions that are captured by administrative data (eg, carotid endarterectomy, endovascular thrombectomy, inpatient rehabilitation, length of hospital stay, and prescriptions filled). A subset of participants from Part 1, Study A, will have their data linked to IDI data to assess the accuracy of the administrative data set.

For Part 2 of the study, health professionals, managers, policy makers, and consented patients and/or their family member or carer were sent an online survey or, where requested, a paper copy. The survey asked participants to rate the accessibility of key stroke interventions and to comment on any barriers to accessing care and potential solutions (see [Multimedia Appendix 2](#) for a sample survey). A subset of patients were also invited to participate in one of 10 focus groups of 4 to 8 people to discuss barriers they have to accessing optimal stroke care and potential solutions. The focus groups were facilitated by experienced research staff and focused on overall experience of stroke care received, description of difficulties in accessing required services, perceived barriers to accessing services, and any suggestions to reducing these barriers. Focus group recruitment was aimed at maximizing diversity in regard to both ethnicity and geographic location.

## Primary Outcome

The primary outcome for Part 1 is *whether there was a favorable outcome at 3 months*. For Part 1, Study A, the favorable outcome will be assessed using both an ordinal or *shift* analysis and a dichotomous approach using the mRS. For the dichotomous analysis, a *favorable outcome* is defined as having an mRS score of 0 to 2, and an *unfavorable outcome* is defined as having an mRS score of 3 to 6 [20]. Results will be adjusted for important predictors of outcome, such as stroke severity (ie, SSV model), baseline level of function (ie, mRS), and age. For Part 1, Study B, the mRS is unavailable and a composite measure will be used instead. Here, a favorable outcome is defined as meeting all of the following criteria: being alive; being employed, if employed prestroke; and having no change in domicile location. The latter is intended to capture patients who shifted from home to institutional care or to live with a family member for support,



indicating a significant decline in independence. These outcomes are available via the IDI and have been used in previous stroke research [22,23].

### Secondary Outcomes

For both Study A and Study B from Part 1, the mRS at 6 and 12 months comprises the main secondary outcomes. However, best practice stroke care will also be considered as largely based on the Australian Stroke Standards [19]. For Part 1, Study A, this will look at reperfusion therapy, acute stroke unit admission, optimal secondary prevention prescription, transfer to rehabilitation within 7 days of admission, review by a community rehabilitation team member within 7 days of discharge, documented patient-centered goals, documented individualized care plan, and referral to the Stroke Foundation of New Zealand. Other secondary outcomes, which will be measured at 3, 6, and 12 months, where applicable, include the following: hospital readmissions, stroke recurrence, any vascular event or death, discharge destination, treatment costs, quality-of-life assessment using the EQ-5D-3L score, and other interventions received during the hospitalization, such as undergoing relevant imaging, swallow assessment, or a documented continence plan. In addition, the impact of other patient factors on outcome (eg, sex and baseline vascular risk factors) will be assessed. For Part 1, Study B, best practice stroke care measures will include being managed in an acute stroke unit and, if transferred to inpatient rehabilitation, being transferred within 7 days of admission to hospital. These measures align with the New Zealand Ministry of Health quality indicators for optimal stroke processes of care and can be extracted from the National Minimal Dataset, which is a national collection of public and private hospital discharge information, including coded clinical data for inpatients and day patients [24]. Other secondary outcomes that will be obtained from administrative data include the following: the provision of endovascular thrombectomy and the prescription and maintenance of secondary prevention therapies.

### Sample Size Estimates

The main variable of interest is *favorable outcome* as a function of hospital location and ethnicity. Part 1, Study A, of the study is powered on the assumption that favorable stroke outcomes can be achieved among 50% of patients if high-quality care is provided [25]. A sample size of 514 patients per group would identify a discrepancy in favorable outcomes of 10% at 90% power with an  $\alpha$  value of .05 between groups. We powered the study to conduct analysis at four geographic levels—tertiary, urban secondary, provincial secondary, and rural secondary hospitals—and aimed to collect data for a minimum of 514 patients from each of these four subgroups. However, because of uncertainty around optimal and suboptimal stroke outcome rates in the New Zealand setting, we chose to make our primary outcome a dichotomous comparison of *urban* versus *nonurban*, and with a sample of 1028 patients per group, the study is powered to allow detection of an intergroup difference of just 7%. To account for a loss to follow-up of 15% to 20%, we aimed for a total sample size of 2400 patients. Due to budgetary constraints, this larger cohort is followed up for 3 months, while a subset of around 1100 patients are followed up for 6 and 12

months, while still meeting the requirements of the primary power calculation assumptions for dichotomous geographic comparisons.

In 2015, there were 944 Māori and 466 Pacific people presenting to hospital with stroke [2,26]; study power will be increased by also capturing all stroke patients admitted to New Zealand hospitals over a 12-month period using the IDI (ie, Part 1, Study B, sample). In 2015, a total of 8495 stroke patients were admitted to hospital with stroke [21]. Allowing for 10% missing or incomplete data, a sample size of 7645 was expected to include 850 Māori and 419 Pacific patients, providing over 90% power to detect a 10% difference in favorable stroke outcomes between Māori and non-Māori patients and over 80% power to detect a difference in favorable stroke outcomes between Pacific and non-Pacific patients.

For the focus groups, the aim is to assemble 10 groups of 4 to 8 participants at locations across New Zealand, covering small, medium, and large district health boards (DHBs) (ie, New Zealand districts). Purposeful sampling according to age (ie, <65 years and ≥65 years), gender, ethnicity (ie, Asian, Māori, Pacific, and European), and place of residence (ie, rural versus urban) was used. The number of planned focus groups is expected to be sufficient to allow for saturation of themes.

### Economic Evaluation

We will describe the costs of stroke in New Zealand using patient-level data. The costs and consequences of those who did and did not receive best practice stroke care based on ethnicity and hospital location will be determined using care pathway analysis methods. Resource use and costs will be obtained as part of the data collection of clinical information for each individual participant. Simulation techniques will be used to assess the identified alternate models of care applied to the New Zealand population. The robustness of results from the incremental cost-effectiveness analyses of each identified care pathway will be assessed using one-way sensitivity analyses and multivariable uncertainty simulations as appropriate for the distribution of the data. Determination of the costs will include the following: index event hospitalization; costs of additional procedures, specifically endovascular thrombectomy; cost of intravenous thrombolysis, if administered; prescriptions; readmissions; aged residential care costs; and lost economic contribution.

### Statistical Analyses

Study A and Study B from Part 1 will examine associations between hospital location, ethnicity, and access to best practice care and stroke outcomes. We will use logistic regression for dichotomous outcome measures and linear regression for continuous outcomes. In Part 1, we will also use ordinal regression to assess associations with the mRS scores. Analyses will be conducted for 3-, 6-, and 12-month posthospital admission, with case-mix adjustments to reduce bias, controlling for important predictors of outcome, including premorbid level of function, level of function at presentation, and age. We will also include baseline characteristics and variables that are associated with the outcome in univariate analyses ( $P < .10$ ) in regression modeling using a backward elimination technique.



For Part 1, Study B, stratified analyses will be conducted by age group, ethnicity, domiciliary DHB, treating hospital, premorbid level of function, and domicile.

Regression analyses from Study A and Study B from Part 1 will aid the identification of some potential barriers to accessing best practice stroke care. Barriers will also be assessed in more detail using quantitative and qualitative data from the surveys and focus groups in Part 2. Quantitative survey data will be analyzed using descriptive statistics. Qualitative data from the free-text questions and focus groups will undergo data-driven thematic analysis. Data will be coded to identify thematic patterns. Key themes will be named according to scope and will be defined and described. Results from all data sources will be triangulated to inform conclusions.

### Study Organization, Funding, and Ethics

The study is funded by the Health Research Council of New Zealand (reference 17/037). Ethics approval was received by the Central Health and Disability Ethics Committee (reference 17/CEN/164). The registry-based data collection and 3-month follow-up assessments met New Zealand ethics criteria for *audit*, where data were collected as part of routine care for the purpose of service improvement. In New Zealand, audits do not require individual patient consent. However, the extended follow-ups at 6 and 12 months went beyond routine clinical care and required individual participant consent, which was obtained at the 3-month follow-up assessment. Where a patient was unable to provide consent themselves, consent from someone who carries the responsibility for the participant's welfare was permitted. Patients approached for consent were also asked for permission to submit their data to Stats NZ for data linkage with other routinely collected government data for validation purposes. Ethics approval included the linkage of patient data to anonymized IDI data for patients who died prior to the 3-month follow-up assessments and who, therefore, were not able to provide consent for data linkage. All data linked via IDI are fully anonymized.

### Results

As of December 2020, data collection was nearly completed. A total of 2379 patients have been recruited for Part 1, Study A; 6837 patients have been recruited for Part 1, Study B; 10 focus groups have been conducted and 70 surveys have been completed in Part 2. Data collection is still underway for Part 1, Study B, and primary and secondary analyses, data linkage, data validation, and health economics analysis are expected to be completed by March 2021.

### Discussion

The study design is significant for several reasons. It involves two concurrent, large observational studies using different but

overlapping data sources to ensure sample sizes are achieved in order to answer the main questions while optimizing data quality. The use of Stats NZ's IDI, an internationally unique and powerful research tool that integrates routinely collected health data and allows linkage to research data, is unprecedented in stroke research. The availability of both data sets within a single study allows for cross-validation, which will provide important information to guide optimal resource use for ongoing and future data collection to continuously drive nationwide stroke service improvement. Involvement of every single stroke hospital in the country is a significant achievement that will provide high-quality epidemiological data and demonstrates that this approach is feasible for future stroke research. Furthermore, the inclusion of patient data from prehospital (eg, arrival mode and detailed premorbid level of function) and following patients through the completion of community rehabilitation adds considerable depth to the data, with the longer-term follow-up of up to 12 months offering important insights into outcomes that are meaningful to consumers. The research team includes academic and nonacademic clinicians from a variety of professional backgrounds (ie, primary, secondary, and tertiary medical care; nursing; therapy; and rural care), epidemiologists, consumers, and stroke support organization representatives. The strong focus on approaching stroke care from an interdisciplinary and overall system perspective, keeping the patient at the center, and recognizing the important contributions that are made throughout the patient's journey at all of the involved facilities has contributed to our recruitment success and will add valuable insights during the analysis and dissemination phases of the study. Potential limitations include the observational nature of the study, which risks bias, but bias is minimized through the collection of all consecutively admitted patients; the fact that nonhospitalized patients are not included, but fortunately we know that number is very low (~2%) [14]; and the fact that while this is a complete national cohort, this single-nation sample will not be generalizable to all other settings. However, we do expect that findings will be widely informative given many shared resource and ethnic inequity challenges globally.

The results from this study will inform whether changes to New Zealand stroke services are required, with the goal of ensuring that patients receive optimal stroke care and achieve favorable outcomes poststroke, irrespective of ethnicity or geographic location. In addition, the focus groups and surveys will provide information on how to best tackle identified inequities. The health economic analysis will aid DHBs with funding prioritization around proposed service improvements. Finally, the data validation part of the project will provide the New Zealand Ministry of Health with vital information to guide future investments into optimal data-driven, ongoing, stroke service improvement efforts.

### Conflicts of Interest

None declared.

## Multimedia Appendix 1

Part 1 data dictionary and baseline information from administrative data.

[[DOCX File, 52 KB](#) - [resprot\\_v10i1e25374\\_app1.docx](#) ]

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## Multimedia Appendix 2

Part 2 patient survey.

[[DOCX File, 18 KB](#) - [resprot\\_v10i1e25374\\_app2.docx](#) ]

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## Multimedia Appendix 3

Peer review comments from the Health Research Council of New Zealand - Reviewer #97.

[[PDF File \(Adobe PDF File\), 133 KB](#) - [resprot\\_v10i1e25374\\_app3.pdf](#) ]

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## Multimedia Appendix 4

Peer review comments from the Health Research Council of New Zealand - Reviewer #47.

[[PDF File \(Adobe PDF File\), 135 KB](#) - [resprot\\_v10i1e25374\\_app4.pdf](#) ]

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## Multimedia Appendix 5

Peer review comments from the Health Research Council of New Zealand - Reviewer #45.

[[PDF File \(Adobe PDF File\), 136 KB](#) - [resprot\\_v10i1e25374\\_app5.pdf](#) ]

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## Abbreviations

**DHB:** district health board

**EQ-5D-3L:** 5-dimension, 3-level EuroQol questionnaire

**ICD-10-AM:** International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification

**IDI:** Integrated Data Infrastructure

**mRS:** modified Rankin Scale

**REGIONS Care:** Reducing Ethnic and Geographic Inequities to Optimise New Zealand Stroke Care

**SSV:** six sample variable

*Edited by T Derrick; submitted 16.11.20; this is a non-peer-reviewed article; accepted 19.11.20; published 12.01.21.*

*Please cite as:*

Ranta A, Thompson S, Harwood MLN, Cadilhac DAM, Barber PA, Davis AJ, Gommans JH, Fink JN, McNaughton HK, Denison H, Corbin M, Feigin V, Abernethy V, Levack W, Douwes J, Girvan J, Wilson A  
*Reducing Ethnic and Geographic Inequities to Optimise New Zealand Stroke Care (REGIONS Care): Protocol for a Nationwide Observational Study*

*JMIR Res Protoc* 2021;10(1):e25374

URL: <https://www.researchprotocols.org/2021/1/e25374>

doi: [10.2196/25374](https://doi.org/10.2196/25374)

PMID: [33433396](https://pubmed.ncbi.nlm.nih.gov/33433396/)

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Protocol

# Self-Care Index and Post-Acute Care Discharge Score to Predict Discharge Destination of Adult Medical Inpatients: Protocol for a Multicenter Validation Study

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## Abstract

**Background:** Delays in patient discharge can not only lead to deterioration, especially among geriatric patients, but also incorporate unnecessary resources at the hospital level. Many of these delays and their negative impact may be preventable by early focused screening to identify patients at risk for transfer to a post-acute care facility. Early interprofessional discharge planning is crucial in order to fit the appropriate individual discharge destination. While prediction of discharge to a post-acute care facility using post-acute care discharge score, the self-care index, and a combination of both has been shown in a single-center pilot study, an external validation is still missing.

**Objective:** This paper outlines the study protocol and methodology currently being used to replicate the previous pilot findings and determine whether the post-acute care discharge score, the self-care index, or the combination of both can reliably identify patients requiring transfer to post-acute care facilities.

**Methods:** This study will use prospective data involving all phases of the quasi-experimental study “In-HospiTOOL” conducted at 7 Swiss hospitals in urban and rural areas. During an 18-month period, consecutive adult medical patients admitted to the hospitals through the emergency department will be included. We aim to include 6000 patients based on sample size calculation. These data will enable a prospective external validation of the prediction instruments.

**Results:** We expect to gain more insight into the predictive capability of the above-mentioned prediction instruments. This approach will allow us to get important information about the generalizability of the three different models. The study was approved by the institutional review board on November 21, 2016, and funded in May 2020. Expected results are planned to be published in spring 2021.

**Conclusions:** This study will provide evidence on prognostic properties, comparative performance, reliability of scoring, and suitability of the instruments for the screening purpose in order to be able to recommend application in clinical practice.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/21447

(*JMIR Res Protoc* 2021;10(1):e21447) doi:[10.2196/21447](https://doi.org/10.2196/21447)

**KEYWORDS**

discharge planning; forecasting; logistic models; patient transfer; post-acute care discharge score; protocol; self-care index; sensitivity; specificity; validation study

## Introduction

Delays in hospital discharge are associated with deterioration in the performance of activities of daily living (ADL), especially among frail patients [1,2], and other negative patient outcomes like hospital-acquired infection (pneumonia, urinary tract infection, or sepsis), short- and long-term mortality [3], and negative economic outcomes like hospital costs [4].

In frail elderly patients, nonmedical reasons accounted for nearly one-third of prolonged hospitalization, with nursing facility placement delay [5] and waiting time for post-acute care (PAC) institutions being the most common reasons [4,6,7]. Delayed hospital discharge is therefore caused to a relevant extent by non-medical reasons (288/960, 30% [7]; 392/1221, 32.1% [8]), such as no free beds being available in a nursing home or PAC facility, discharge to home not being possible, or delivery of nursing/medical equipment at home being delayed) [7-9]. In hospitalized patients with respiratory tract infections, organizational issues caused delayed discharge [10], even with structured discharge planning [11]. Furthermore, prolonged hospital stays due to nursing and organizational reasons were evident in patients with decompensated heart failure [12].

Several studies concur on a list of risk factors of discharge to follow-up care institutions: advanced age, living alone, functional disability, and preexisting ADL and instrumental ADL limitations [13-15].

The fact that so many discharges of medically stable patients are delayed due to lack of resources in PAC institutions indicates a need to refine the processes of both triage and early interprofessional discharge planning [6,10-12,16-18].

Two instruments have been developed to identify patients requiring transfer to PAC facilities (the post-acute care discharge score [PACD]; see [Multimedia Appendices 1 and 2](#)) or to predict postdischarge care needs (the self-care index [SPI]; see [Multimedia Appendix 3](#)). The PACD scores were developed to identify medical patients requiring transfer to a PAC facility [6]. Patients who score less than 8 points on the PACD are considered at low risk for requiring post-acute care. A score of 8-15 points defines medium risk, and more than 15 points indicates a high risk for requiring post-acute care [6]. Two versions, PACD day-1 (15 items) and day-3 (5 items), were published [6]. Both showed good performance (day-1 area under the curve (AUC)=0.81; day-3 AUC=0.82). Our team further developed the score, and in patients with respiratory tract infections (n=240), biopsychosocial risk (PACD day-1) correlated significantly with discharge to a PAC facility [19]. Both versions showed an acceptable sensitivity and specificity (cutoff at  $\geq 8$ , PACD day-1: sensitivity 82%, specificity 55%, AUC=0.90; PACD day-3: sensitivity 86%, specificity 69%, AUC=0.79) [20]. In patients admitted from home with urinary tract infections, falls/syncope, or heart failure (n=308), PACD day-1 showed a sensitivity of 90% and a specificity of 62%, and PACD day-3 showed a sensitivity of 80% and a specificity of 60%, with cutoff at  $\geq 8$  [21]. The accuracy was good for both the day-1 (AUC=0.82) and the day-3 (AUC=0.79) versions [21]. Validated in a prospective cohort study with 1432 medical and 464 neurological patients, PACD day-1 and day-3 provided

AUCs of 0.77 and 0.82, sensitivities of 72.6% and 83.6%, and specificities of 66.5% and 70.0% with cutoff at  $\geq 8$ . Neurological patients' scores showed lower accuracy both days: AUCs were 0.68 and 0.78, sensitivities were 41.4% and 68.7%, and specificities were 81.4% and 83.4% [22].

The SPI was developed to identify a possible care deficit after hospitalization (former name: "CaseManagementScore," CMS) and is widely used as a patient assessment instrument in hospitals across German-speaking regions. Patients who scored more than 32 points on the SPI are considered at low risk for having a care deficit after a hospital stay. A score of less than or equal to 32 points on the SPI indicates a high risk for having a care deficit. In a consecutive sample of 620 hospital patients (cutoff $\leq 32$ ), the SPI yielded 85.5% sensitivity and 92.3% specificity [23].

In a cohort of 1342 medical and 402 neurological patients, both PACD and SPI predicted transfer to PAC facilities ( $P<.001$ ). SPI sensitivity was 64% and the specificity was 84%, with cutoff $\leq 32$ . The PACD combined with SPI (AUC=0.83, +7.8%; 0.78, +14.7%) identified patients at risk significantly better than the PACD alone (AUC=0.77; 0.68). Also, sensitivities (68%, -6.8%; 55%, +37.5% vs. 73%; 40%) and specificities (82%, +26.2%; 85%, +4.9% vs. 65%; 81%) were mostly higher than with the PACD alone. Patients who scored less than 16 points on the PACD-SPI combination are considered at low risk for requiring post-acute care. A score of 16-25 points was considered as medium risk, and more than 25 points is considered a high risk for requiring post-acute care. The net reclassification index (28.6%) and integrated discrimination index (4.8%) both showed significant ( $P<.001$ ) improvement [24]. The results indicate that self-care abilities are an independent predictor for the risk of PAC facility discharge [24].

In the described preceding studies, PACD scores accurately predicted transfer to PAC facilities, indicating potential as screening instruments to improve discharge planning and shorten hospital length of stay. A review on prediction of support services after hospital confirmed the particular need for external validation studies [25]. As the results were replicated in a monocenter study only, the predictive accuracy requires further validation in other hospitals and regions in a multicenter setting with a larger and more varied sample of medical patients.

The research proposed in this study protocol aims to explore the ability of SPI to predict post-acute care discharge, develop scoring, and then test whether PACD (day-1), SPI, or the combination of PACD and SPI can reliably identify patients requiring transfer to PAC facilities in order to replicate previous findings and allow generalization.

## Methods

### Overview

We follow the recommended procedures by the Prognosis Research Strategy (PROGRESS) Group [26-28] and report according to the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement [29,30]. The PROGRESS guidelines on

predictive modelling [28] advise testing of scores in new settings. In our research we apply the scores in different hospital types (urban, rural) and other geographical areas. Therefore, the proposed multicenter external validation results are needed to test the calibration and, depending on the results, suggest a recalibration of the scores.

### Study Design

This study is embedded in a 3-phase pre-post quasi-experimental study called “Integrative hospital treatment in older patients to benchmark and improve outcome and length of stay – the In-HospitoOL study,” conducted at secondary and tertiary hospitals in both urban and more rural areas in the German-speaking part of Switzerland, aiming to safely reduce hospital length of stay by implementing an interprofessional discharge management tool [31,32].

### Study Population (Sample and Setting)

We will include consecutive, unselected adult medical patients admitted to the hospitals through the emergency department within the In-HospitoOL study, using both the PACD and SPI instruments for patient assessment (4 hospitals). We will exclude patients admitted from PAC facilities (eg, nursing homes), patients transferred from or to another hospital, and patients who die during the study period. We estimate that we will include a patient sample of 3000 in the observation period (6 months) to check the scoring for the SPI and 6000 in the subsequent period (12 months) with both the PACD and SPI instruments during the data collection phase.

### Data Collection

Data will be collected by health professionals from July 1, 2017, to February 8, 2019, from eligible medical patients admitted to hospital during the study period as part of routine clinical care documentation. Health professionals will be trained by an instruction video and one-hour on-site workshop. Data will then be exported from the clinical information system to the study database. The physicians who initially assess the patients will indicate the number of active medical problems at admission, defined as International Classification of Diseases diagnoses with diagnostic or therapeutic consequence for actual treatment, increased monitoring needs, or both. The treating physicians and nurses will assess the PACD day-1 scores in the emergency department or on the ward, depending on their hospital's processes within 24-48 hours. The SPI will be collected by the staff nurse as part of the standard nursing assessment (“ergebnisorientiertes Patientenassessment–Acute Care” [ePA-AC]) within the first 2 days of admission. The medical coding department will provide data on pre-admission and postdischarge residence and length of stay from Diagnosis Related Group coding data collected for the Swiss Federal Statistical Office.

### Predictors

#### PACD

The PACD includes information on the patient's age, active medical problems, and support situation at home within the last 14 days, while integrating his or her abilities in ADL and instrumental ADL [21] (see [Multimedia Appendix 1](#)). The

PACD was translated from French to German by the research team [19] and pilot-tested regarding comprehensibility and clinical practicability on 10 medical patients in the emergency department setting. After the test, we adapted the PACD's phrasing accordingly [19].

In the original PACD day-1, no scoring was defined, because only the PACD day-3 was implemented at the study site in Geneva, Switzerland. Therefore, for the PACD day-1's first tests, conducted at the Aarau Cantonal Hospital (a 600-bed teaching hospital in Switzerland), the principles for point definition used by the authors for the scoring of the day-3 version [6] were applied [19,21]. After comparing the predictors in the logistic regression model, we allocated points depending on how much larger or smaller the other standardized regression coefficients were [19]. Proportional points per answer were defined based on their value in relation to each other. The one exception, based on clinical considerations, was the decision to allocate 1 risk point for each 10 years of age, starting at 60 (1 point), with a maximum of 5 points for patients 100 years or older (see [Multimedia Appendix 1](#)) [19].

Based on this analysis, two adaptations were made [22]. First, “transfer within the hospital” (part of the original PACD day-1) [6] was omitted because it was not significantly predictive of PAC facility transfer [22]. Second, “partner to provide help” was modified to “someone living with the patient to provide help” [10,19,22].

#### SPI

The SPI assesses the degree of patients' self-care, and Grosse Schlarman [23] examined this part of the “Result-Oriented Nursing Assessment–Acute Care” (52-item ePA-AC version 1.0) as a screening tool to identify postdischarge nursing care deficits.

The SPI includes 10 items with 4 Likert-type answer categories: mobility, personal hygiene (upper/lower body), dressing and undressing, eating and drinking, excretion of urine/ stool and cognition. The categories are completely dependent (1 point), requirement of extensive support (2 points), requirement of minor support (3 points), and independent (4 points), summing up to a total with a possible range of 10-40 points, where a score of 10 points corresponds to completely dependent. The SPI is usually measured as part of the standard nursing assessment within the first days after admission [19]. The cutoff point indicating a risk for PAC deficit was defined by the developer at less than or equal to 32 points [23].

### Outcome Measure

The primary outcome will be discharge destination, defined as transfer to a PAC facility (ie, temporary care, transient nursing care, health resort treatment, rehabilitation or nursing home) or discharge home. This information will be extracted from the discharge summary by the medical coding staff. They will be blinded to the scores.

### Power Calculation

To provide 60-100 degrees of freedom for our multivariable models, we aim to include a total of 6000 patients over the course of 12 months (both instruments implemented), with an

expected 10% rate of PAC facility transfers ( $n=600$ ). The expected rate is based on previous studies in Switzerland, where we found PAC transfer rates of 10.6% (152/1432) [22], 11.2% (150/1342) [24], and 16.7% (62/371) [21]. These percentages are lower than in 150 out of 752 patients (19.9%) discharged to facilities in an American hospital setting [33]. For all phases, the expected rate of outcome events (non-home discharge) exceeds the recommended 250 [34]. Power calculations for these models indicate that this sample size will have enough power to provide sufficiently precise confidence intervals regarding AUC, sensitivity, specificity, and positive and negative likelihood ratios, as well as for intergroup comparisons (power=80%) and logistic regression models.

### Data Handling

Data will be checked for patterns of missing responses and outliers. Patients with missing data will be compared based on discharge destination, age, active medical problems, and length of stay. Depending on the amount of missing data and their nonrandomness, they will be replaced by multiple imputation, or only complete cases will be included in the analysis.

### Data Availability

Data set will be made available on Dryad [35].

### Statistical Analysis

Patient characteristics will be analyzed descriptively using frequencies, percentages, medians, means, and standard deviations based on the data types and variable distributions, and we will compare the distribution of important variables (demographics, predictors, and outcome) between data sets (development and validation). The number of outcome events will be reported.

In order to validate the SPI for the purpose of screening and identifying patients likely to need institutional aftercare, the first step needed is to check the relation between SPI items and the transfer to a PAC facility and define optimal scoring of the SPI. This scoring combines the different self-care abilities with specific weights into a new risk score, which then needs to prove prognostic accuracy following a formative proceeding. For predictive scores, formative evaluation is recommended [36,37]. Therefore, we will derive a SPI model. To develop or refine the scoring if necessary, logistic regression models including the items of both scores as formative indicators will be analyzed, and the coefficients will be compared with existing data or examined for the need of weighting the items differently depending on their specific impact regarding transfer to a PAC facility.

Logistic regression models will be used to investigate the instruments' individual and combined scores' predictive capacities. We will present the full prediction model. The geographical external validation will take place in different hospitals in Switzerland.

We will use receiver operating characteristic analysis to estimate various cut-off points for sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios.

As the PACD and SPI are under consideration as screening tools for implementation in clinical practice, they would ideally identify every potential patient at risk of requiring PAC facility transfer and, therefore, comprehensive further assessment. While they do not achieve this standard, for their intended purpose, high sensitivity and adequate specificity are indicated.

Model calibration will be evaluated graphically and by test [30]. A calibration plot will be used to compare predicted transfer probability to observed transfer frequency. We will test for agreement between predicted and observed probabilities using the Hosmer-Lemeshow goodness-of-fit test [30,38]. To judge discrimination, we will calculate AUC (C statistic) with confidence intervals [39]. To test AUC differences between various scores, we will use a nonparametric approach including the "roccomp" procedure (Stata) [40].

We plan to assess the incremental prognostic value of SPI when added to the PACD score and therefore updating the prognostic model by the likelihood ratio test [30]. Classifications from the two models will be compared for changes by cross-table or scatterplot with smooth curve fitted by Loess [39]. The reclassification calibration will compare observed and predicted values within cross-classified categories [39]. Weighted net reclassification improvement [41] will be calculated. An integrated discrimination improvement analysis [42] will be performed and visualized by box plots [39].

To assess overall predictive performance in comparison, we will use the  $R^2$  Brier score and a validation graph [39]. We will judge overfitting by calibration slope [34,43].

Clinical usefulness will be judged by decision analytic measures. We will calculate the net benefit of using the models at a defined threshold (cross-table) with sensitivity analysis on different other thresholds [41], plot a decision curve [44], and determine the change in relative utility [41]. Decision curve analysis will provide evidence over a range of thresholds [39].

Values of  $P<.05$  will be considered statistically significant. Reporting the 95% confidence intervals allows the reader to estimate the precision of the values [45]. Statistical analyses will be performed using SPSS Version 24.0 (IBM Corporation) and Stata Version 15.1 (StataCorp).

## Results

The study was approved by the institutional review board on November 21, 2016, and funded in May 2020. Expected results are planned to be published in spring 2021 (see [Multimedia Appendix 4](#)).

## Discussion

Evidence-based knowledge regarding implementation of an early assessment test is warranted to support clinical teams, accelerate discharge management, and determine the most appropriate post-acute care transfer destinations for patients at risk. The interprofessional PACD score and the SPI nursing score will serve as bases for discussion between health care professionals, with the potential to strengthen cultures of interprofessional teamwork. In addition to patient's risk scores



for PAC transfer, decision-making regarding discharge relies upon a mix of subjective clinical experience and objective data. If hospital stays can be shortened via a more process- and patient-oriented screening approach, the benefits will far outweigh the cost (in time) of assessing the scores.

We expect several potential limitations: as the PACD is newly implemented into routine care, and data collection depends on the completeness of documentation, there is a rate of missing data of at least 20%-30% anticipated. The PACD is combining the information of physician and nurses, which also increases the risk of gaps in information. Furthermore, to test the combination score, both measures need to be completed. The PACD, SPI, and combined (PACD/SPI) scores will be included in patient records as part of discharge planning by physicians,

nurses, and social workers. All centers already worked routinely with the SPI; the PACD was newly introduced, and instructions were given for its use as basic information for discharge planning. Given this method of data collection, it is impossible to blind the study. Like other studies with similar population and sample size (n=885 to 1055) [46,47], the unselected and extensive patient data in other hospitals will provide a sufficient basis for robust analysis.

The instrument's reliability and ability to reliably predict PAC facility transfer needs have to be tested in diverse populations to enhance the level of evidence, which is needed before safe recommendation and large-scale implementation. This external validation study will provide evidence on the incremental value of combining PACD and SPI for prediction of PAC transfer.

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## Acknowledgments

This work is supported by the Swiss National Research Foundation [grant number 407440\_167376]; the Forschungsrat [Grant 1410.000.086] and the "Wissenschaft & Weiterbildung" (W&W) Fonds [140.000.495] of the Kantonsspital Aarau AG; the "Hugo und Elsa Isler Fonds" of the Argovian Department of Health and Social Affairs; the Stiftung Pflegewissenschaft Schweiz [grant number 2236-2018]; and the Bank Vontobel Charitable Foundation.

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## Conflicts of Interest

None declared.

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### Multimedia Appendix 1

PACD day-1.

[[DOCX File , 20 KB - resprot\\_v10i1e21447\\_app1.docx](#) ]

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### Multimedia Appendix 2

PACD day-3.

[[DOCX File , 19 KB - resprot\\_v10i1e21447\\_app2.docx](#) ]

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### Multimedia Appendix 3

SPI Self-care index.

[[DOCX File , 12 KB - resprot\\_v10i1e21447\\_app3.docx](#) ]

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### Multimedia Appendix 4

Project timeline.

[[DOCX File , 13 KB - resprot\\_v10i1e21447\\_app4.docx](#) ]

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## Abbreviations

**ADL:** activities of daily living

**AUC:** area under the curve

**ePA-AC:** ergebnisorientiertes Patientenassessment–Acute Care (Result-Oriented Nursing Assessment–Acute Care)

**PAC:** post-acute care

**PACD:** post-acute care discharge score

**PROGRESS:** Prognosis Research Strategy

**SPI:** self-care index

**TRIPOD:** Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis

*Edited by G Eysenbach; submitted 16.06.20; peer-reviewed by J Li, A Rovetta, L Genaro; comments to author 21.07.20; revised version received 14.09.20; accepted 01.12.20; published 14.01.21.*

*Please cite as:*

*Conca A, Koch D, Regez K, Kutz A, Bächli C, Haubitz S, Schuetz P, Mueller B, Spirig R, Petry H*

*Self-Care Index and Post-Acute Care Discharge Score to Predict Discharge Destination of Adult Medical Inpatients: Protocol for a Multicenter Validation Study*

*JMIR Res Protoc 2021;10(1):e21447*

*URL: <http://www.researchprotocols.org/2021/1/e21447/>*

*doi: [10.2196/21447](https://doi.org/10.2196/21447)*

*PMID: [33263553](https://pubmed.ncbi.nlm.nih.gov/33263553/)*

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Protocol

# Health Professional Student Placements and Workforce Location Outcomes: Protocol of an Observational Cohort Study

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## Abstract

**Background:** The successful recruitment and retention of health professionals to rural and remote areas of Australia is a health policy priority. Nursing or allied health professional students' learning placements in the Northern Territory (NT) of Australia, most of which is considered remote, may influence rural or remote work location decisions.

**Objective:** The aim of this study is to determine where allied health professionals and nurses who have had a student placement in the NT of Australia end up practicing.

**Methods:** This research is an observational cohort study, with data collection occurring at baseline and then repeated annually over 10 years (ie, 2017-2018 to 2029). The baseline data collection includes a demographic profile of allied health and nursing students and their evaluations of their NT placements using a nationally consistent questionnaire (ie, the Student Satisfaction Survey). The Work Location Survey, which will be administered annually, will track work location and the influences on work location decisions.

**Results:** This study will generate unique data on the remote and rural work locations of nursing and allied health professional students who had a placement in the NT of Australia. It will be able to determine what are the most important characteristics of those who take up remote and rural employment, even if outside of the NT, and to identify barriers to remote employment.

**Conclusions:** This study will add knowledge to the literature regarding rates of allied health and nursing professionals working in remote or rural settings following remote or rural learning placements. The results will be of interest to government and remote health workforce planners.

**Trial Registration:** Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620000797976; <https://www.anzctr.org.au/ACTRN12620000797976.aspx>

**International Registered Report Identifier (IRRID):** PRR1-10.2196/21832

(*JMIR Res Protoc* 2021;10(1):e21832) doi:[10.2196/21832](https://doi.org/10.2196/21832)

**KEYWORDS**

remote health; students; training; workforce retention; workforce location; workforce; allied health; allied health professionals; Northern Territory of Australia; rural; nursing; rural employment

## Introduction

### Background

Australia's population predominately lives in its major cities (72%), with another 26% living in regional areas and just 2% living in remote or very remote areas [1]. However, 73% of the Australian landmass is considered *very remote* and a further 13% as *remote* [2], with the *outer regional* and *inner regional* categories respectively covering 11% and 3% of Australia's land area. The Northern Territory (NT) of Australia is one of the least densely populated areas in the world, with 0.16 people per square kilometer, compared to the overall Australian rate of 3.3 people per square kilometer, 4.1 people per square kilometer in Canada, and 36 people per square kilometer in the United States [3].

The health status of residents in rural and remote Australia is well-known to be worse than that of residents of major cities. Chronic disease and mortality rates are higher and access to health services are poorer [4]. One of the key factors that influences access to health services in rural and remote Australia is the ability to recruit and retain skilled and qualified clinicians [5-8]. There is a maldistribution and shortage of the health workforce, with a lack of health professionals outside major centers being one of the reasons often cited for lower health outcomes of remote and rural Australians. In addition, practicing as a health professional in remote areas is significantly different from practicing in metropolitan centers [9,10]. However, frequently, the curriculum in health professional training programs pays scant attention to preparing students for remote practice [11-13].

The NT has the highest proportion (approximately 30%) of Indigenous residents in Australia, with many living in remote and very remote locations. Aboriginal Australians also carry a higher burden of disease and have greater challenges in accessing health services [14].

The National Strategic Framework for Rural and Remote Health [2] workforce profile demonstrates the difficulties for rural and remote residents in accessing health professionals. For example, it estimates that in rural and remote Australia there are 589 registered nurses per 100,000 population compared to 978 per 100,000 in major cities, and only 64 allied health workers per 100,000 population compared to 354 per 100,000 in major cities [2]. Internationally, the value of the health workforce and the need to significantly increase it has been recognized by the World Health Organization [15].

Undertaking workplace-based learning placements is foundational throughout health professional training programs [16]; in addition, there is a growing body of literature from Australia, Canada, and New Zealand on the value of quality student placements in rural and remote areas and the ways in which placements might positively influence recruitment and retention [17-20]. The successful recruitment and retention of health professionals to rural and remote areas has also become a focus of current health policy. The Australian Commonwealth Government introduced Rural Health Multidisciplinary Training (RHMT) Expansion Program funding in 2016 with a specific

focus on nursing and allied health professions. The RHMT Program is designed to encourage the recruitment and retention of rural and remote health professionals by "supporting effective rural training experiences" for health students [21].

Research into the effects of undertaking placements in rural and remote areas and students' intentions to return to take up positions after graduation has found a positive association between exposure to rural practice and the intention to consider working in a similar situation [7,22-29]. One study also found a positive relationship between rural exposure and return to rural practice, even among those who had taken up positions in a metro area: "there did seem to be a widespread disposition to working in rural areas...even if they were not currently doing so" [30]. Critically, however, there is little known about how intention translates into the uptake of positions in rural and remote places over time.

The career decisions that early-career health professionals make are influenced by a range of factors (eg, [31-34]). Many of these, such as family location and personal career goals, are beyond the control or influence of universities and workplaces. Equally important, the quality of placements in rural and remote areas can be directly influenced by the work of the RHMT Program and the support provided to students, workplaces, and supervisors [29]. The impact of large-scale but locally delivered placement support on long-term remote career location decisions by nursing and allied health professional students has not been investigated.

Internationally, there are relatively few studies on the effects of rural or remote health placements on allied health professionals' decisions to work in a remote setting. The bulk of the literature regarding work location outcomes focuses on medical students, with most studies reporting that an "organised, well-funded, rural placement or rural clinical school program produced positive associations with increased rural intentions and actual graduate rural employment" [35]. Considerable work also focuses on challenges associated with remote nursing [36].

### Context

Flinders University in Adelaide, Australia, has a long history of delivering education and training to develop the Australian NT health workforce [37,38]. In 2016, Flinders University was awarded a national federal government grant, the RHMT Expansion Program, to provide NT-wide support for work-integrated learning placement students from nursing and allied health professions. The grant encourages rural and remote placements as a strategy for recruitment of health professions to the rural and remote workforce. To evaluate the effectiveness of this program, the planned study will track the career location decisions of former placement students and explore the impact of their NT placements on their work choices.

This research is a 10-year tracking study of the work practice locations of all nursing and allied health students who complete an NT work-integrated learning placement. The study will also investigate the factors that contribute to the work location decisions of the participants and will determine if and how an NT placement influenced career decision making.

## Research Question and Objectives

The overarching research question for this study is as follows: Where do nursing and allied health professionals who have had a student placement in the NT end up practicing? The primary objective of this study is to identify the workplace locations, annually, of nursing and allied health students who completed an NT work-integrated learning placement; this will be conducted for 10 years postgraduation. The secondary objectives of this study are as follows: (1) investigate factors that contribute to work location decisions and (2) determine if and how an NT placement influenced career decisions.

## Methods

### Theoretical Framework and Study Design

The research will use a pragmatist theoretical framework [39-41]. This research is an observational cohort study with data collection occurring at baseline and repeated annually over 10 years, from 2017-2018 to 2029 (see [Table 1](#)). The baseline data collection includes a demographic profile of nursing and allied health students and their evaluations of their NT placements (ie, Survey 1: Student Satisfaction Survey). The Student Satisfaction Survey is used nationally by University Departments of Rural Health across Australia [42]. The annual survey (ie, Survey 2: Work Location Survey) has been purpose developed to track work location and the influences on work location decisions.

**Table 1.** Study design showing timing of recruitment and data collection.

Participant cohort	Study activity by year				
	2020	2021	2022	2023-2028	2029
Retrospective recruitment of 2017-2019 students (Cohorts 1-3)	Access to Flinders University Northern Territory (NT) database of completed placements Recruit and obtain consent using last known phone number and email address Survey 1 <sup>a</sup> : already undertaken as part of routine quality assurance Survey 2.1 <sup>b</sup>	Survey 2.2	Survey 2.3	Survey 2 taken annually up to and including 2026 for Cohort 1 and up to and including 2027 for Cohort 2	Completed
Recruitment of 2020 students (Cohort 4)	Access to Flinders NT database of commencing placements Recruit and obtain consent when sent Survey 1	Survey 2.1	Survey 2.2	Survey 2 taken annually up to and including 2028	Completed
Recruitment of 2021 students (Cohort 5)	N/A <sup>c</sup>	Access to Flinders NT database of commencing placements Recruit and obtain consent when sent Survey 1	Survey 2.1	Survey 2.2	Survey 2 taken annually until 2029 Cohort 5 tracked for 8 years in the workforce
Recruitment of 2022-2027 students (Cohorts 6-11)	N/A	N/A	Access to Flinders NT database of commencing placements Recruit and obtain consent when sent Survey 1	Survey 2.1	Survey 2 taken annually until 2029 Cohort 6 tracked for 7 years in the workforce Cohort 7 tracked for 6 years in the workforce Cohort 8 tracked for 5 years in the workforce Cohort 9 tracked for 4 years in the workforce Cohort 10 tracked for 3 years in the workforce Cohort 11 tracked for 2 years in the workforce
Recruitment of 2028 students (Cohort 12)	N/A	N/A	N/A	Access to Flinders NT database of commencing placements Recruit and obtain consent when sent Survey 1	Survey 2.1

<sup>a</sup>Survey 1 is the Student Satisfaction Survey and is a student evaluation of their placement.

<sup>b</sup>Survey 2 is the Work Location Survey. Note that 2.1 refers to participants' first year in the workforce or postgraduation, 2.2 is their second year, etc. Participation ends after 10 years in the workforce or postgraduation.

<sup>c</sup>N/A: not applicable; no study activities were performed in this year for these cohorts.

## Participants and Eligibility

Study participants will be students or graduates, over the age of 18 years, of an Australian allied health or nursing training program and will have undertaken an NT placement as a student. Their placement, including any assessment of competence, will be concluded by the time of participation. Individuals who were

already employed as a nursing or allied health professional and undertaking a placement as part of a postgraduate qualification will be excluded.

Framed by our pragmatist approach and as part of our due diligence around appropriate research designs, we considered using Australian Health Practitioner Regulation Agency



(AHPRA) registration data rather than participant survey data. However, only about half of the professions of interest are registered through the AHPRA: Aboriginal and Torres Strait Islander Health Practitioner, Chinese medicine, chiropractic, dentistry, medical radiation, nursing and midwifery, occupational therapy, optometry, osteopathy, pharmacy, physiotherapy, podiatry, and psychology. Disciplines that are not registered include audiology, dietetics and nutrition, disability, exercise physiology, medical laboratory science, orthotics and prosthetics, paramedicine, social work, and speech pathology. Therefore, relying on AHPRA data to answer our primary question will not provide coverage of all the professions of interest.

The research design relies on access to the contact details of health professional students known to have undertaken work-integrated learning placements in the NT from 2017 onward. Flinders NT holds a secure database with the contact details of the placement students. These details were obtained for the purpose of supporting the placement; however, students consent to the use of their information for educational research purposes, such as our standard quality-improvement Student Satisfaction Survey regarding placement. Access to the database will allow the researchers to recruit participants to the study by contacting current and former students and inviting them to participate in the research.

### Ethics and Trial Registration

Ethics approval was provided by the Flinders University Social and Behavioural Research Ethics Committee (project No. 8245, expiring December 31, 2029). This study was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) (ACTRN12620000797976).

### Sample Size

In 2017, Flinders NT supported 462 students on placement from more than 20 universities across Australia. The average response rate to the standard quality assurance Student Satisfaction Survey regarding placement is about 30%. Based on 450 students per year undertaking placements and a conservative 15% response rate in the first year from students in the first three cohorts, approximately 203 participants will be added in the first year. Each year, another 450 students will be added to the sampling pool; however, over a 10-year period, we assume that the response rate will decline logarithmically by 1% each year, so that in the tenth year the response rate will be 6%. This equates to a total possible pool of 5400 participants who will each be offered up to 10 surveys, depending on the year they commenced in the study; however, with the declining response rates, we anticipate a final sample of 3175.

### Participant Recruitment

The recruitment process comprises an email invitation to participate. If a message bounces back from an email address, we will contact the participant seeking an email address via the last known telephone number in the database.

The research is comprised of annual online surveys, or phone surveys at the participant's request. Survey 1 (ie, the Student Satisfaction Survey) is the first survey and is an evaluation of

the student placement. The following year, Survey 2 (ie, the Work Location Survey) is sent, which comprises a 10-minute online survey asking about current work location and work location history and includes several questions regarding the influences on work location decisions. All subsequent years will use Survey 2 (ie, the Work Location Survey) to ask about work location and work location history, but this survey will not repeat the initial questions regarding demography and the NT placement.

Participation is voluntary and former students can also opt out of receiving any further surveys. In order to maximize the response rate while avoiding harassment of potential participants, we will send an email invitation to complete the survey, followed by two reminders that also contain the survey link. The reminders will include an option to cease receiving communications from Flinders NT.

We will also advertise the research on our social media sites (ie, Facebook, blog page, and website) in order to maximize exposure of potential participants to the study. This advertising will not contain a link to the survey but will simply describe the study and invite potential former placement students to contact us if they have not received an email invitation to participate.

To summarize, participants will be recruited in one of two ways, depending on their year of NT student placement:

1. Cohorts 1 and 2, which include health professional students known to have undertaken a Flinders NT-supported work-integrated placement during 2017 or 2018, will be contacted via their last recorded email address or phone number and invited to participate.
2. Cohorts 3 to 12, which include health professional students undertaking Flinders NT-supported work-integrated placements from January 2019 and onward, will be emailed an invitation to participate at the conclusion of their placement.

Participants who complete Survey 1 will have their names placed in a random draw to win one of four vouchers valued at Aus \$50 (US \$38). Participants who complete Survey 2 will have their names placed in a random draw to win one of 10 vouchers valued at Aus \$100 (US \$76).

### Student Training and Placement

In this study, the intervention is having undertaken a student placement in the NT of at least one week in length. As part of standard accreditation processes, university-level health professional courses are required to demonstrate graduate competence in the application of knowledge and skills to patients and consumers of health care. Workplace-based placements, sometimes known as work-integrated learning activities, are a cornerstone of the curriculum because the students are working in health care workplaces under the supervision of a qualified health professional, learning to deliver the graduate competencies of the profession [43,44].

The supervision requirements, length, curriculum, and assessment of student placements vary according to the needs of the specific profession [12]. Whether the university pays the

workplace or the workplace supervisor for providing the placement also varies. We recognize that the intervention includes student placement experiences that are not homogenous. From the perspective of workplaces, it is commonly assumed that student placements are a mutually beneficial recruitment strategy, allowing both the workplace and the student to consider the suitability and attractiveness of employment once they graduate [23,24,27,42,45].

### Retention Strategies

To maximize participation in the study, we will use a set of effective cohort retention strategies tested in previous cohort studies (eg, the Communicating Healthy Beginnings Advice by Telephone [CHAT] trial [46]). For example, we will send a thank-you e-card and birthday card to all participants. The relationship of the student with the placement coordinator or workplace supervisor may also influence survey participation, and we will seek ways to incorporate individual anecdotes into communications with students.

### Outcomes

The primary outcome of the study is the workplace location, assessed using the Modified Monash Model (MMM) [47], with MMM 4 and 5 considered rural and MMM 6 and 7 considered remote. The MMM defines whether a location is urban, rural, remote, or very remote, based on the Australian Statistical Geography Standard—Remoteness Areas (ASGS-RA) framework. The model measures remoteness and population size on an MMM category scale, ranging from MMM 1 to MMM 7. MMM 1 is a major city and MMM 7 is very remote. Any health service provision in areas classified as MMM 4 to 7, whether full time or part time, in the previous 12 months will be considered a rural or remote workplace location.

Baseline data (ie, Survey 1: Student Satisfaction Survey) will be collected following student placements and will include age, gender, degree program in which student is enrolled, length of placement, placement location, Indigenous status, NT residency, and rural origin.

### Data Analysis

To clarify the representativeness of the sample participants who respond each year, we will compare the distribution of the responders with the nonresponders in terms of age, gender, profession, length of placement, and Indigenous status. Descriptive analysis of deidentified aggregated data is planned. This will include survey response rates; number of student placements by profession and location, using the MMM and not town location; length and number of placements; gender; rural origin; NT residency; and influences on placement. Changes in work location will be analyzed by location. Factors associated with remote work location (ie, MMM 4 to 7 versus MMM 1 to 3) will be analyzed using logistic regression.

## Results

This study will generate unique data on the remote and rural work locations of nursing and allied health professional students

who will have had placements in the NT of Australia. It will be able to determine what are the most important characteristics of those who take up remote and rural employment, even if outside the NT, and identify barriers to remote employment.

## Discussion

The question of how many allied health and nursing students, as well as their characteristics, who have had a remote student placement go on to work remotely is a gap in the literature on remote work locations, which more typically focuses on medical students and to a lesser extent on nursing students. Filling this gap is important, given the federal funding invested in the RHMT Expansion Program as a strategy to grow a local remote health workforce. Given the national policy priority to recruit and retain health professionals in remote and rural areas, new insights into strategies to achieve this are needed. It is recognized internationally that building a remote and rural health workforce is a common challenge [48].

The analyses will be able to determine what are the most important characteristics of those who take up remote and rural employment, even if outside the NT, while adjusting for potential confounders, and will identify independent barriers to remote employment. A meta-synthesis of recruitment and retention of occupational therapists and physiotherapists in rural areas found that the availability of, and access to, practice supports; opportunities for professional growth; and an understanding of the context of rural practice were important [20]. Further, the calculation of the proportion of students who have had a placement in a remote setting and went on to work remotely is important for workforce planning. One study reported that 1 year after graduation, half of the allied health students who had had a rural placement were working in a rural or remote location, compared to 23.7% of all graduates from these disciplines [49]. It remains to be determined what proportion of students undertaking a remote placement will be working in a remote location in the short, medium, or long term after graduation.

The very low population density in the NT makes it a unique context to study remote health workforce issues. How the factors influencing the selection of remote health workplace locations compared to rural settings needs further study.

Possible limitations of this study revolve around potential low participation rates, which could bias outcomes. Prompts, reminders, and acknowledgements (eg, birthday cards) will assist, but it may be that those most interested in rural and remote work will respond and that those who either had a negative experience of remote work while on placement or in some other context will choose not to participate. General information provided to the wider pool of nursing and allied health professional students about the study and the importance and benefits of rural and remote work will encourage participation in the study and will, more generally, promote interest in placements in the NT.

## Conflicts of Interest

None declared.

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## Abbreviations

**AHPRA:** Australian Health Practitioner Regulation Agency  
**ANZCTR:** Australian New Zealand Clinical Trials Registry  
**ASGS-RA:** Australian Statistical Geography Standard—Remoteness Areas  
**CHAT:** Communicating Healthy Beginnings Advice by Telephone  
**MMM:** Modified Monash Model  
**NT:** Northern Territory  
**RHMT:** Rural Health Multidisciplinary Training

*Edited by G Eysenbach; submitted 26.06.20; peer-reviewed by S McRoy, S Pit; comments to author 23.10.20; revised version received 08.11.20; accepted 17.11.20; published 14.01.21.*

*Please cite as:*

Campbell N, Farthing A, Witt S, Anderson J, Lenthall S, Moore L, Rissel C  
*Health Professional Student Placements and Workforce Location Outcomes: Protocol of an Observational Cohort Study*  
*JMIR Res Protoc* 2021;10(1):e21832  
URL: <http://www.researchprotocols.org/2021/1/e21832/>  
doi: [10.2196/21832](https://doi.org/10.2196/21832)  
PMID: [33443482](https://pubmed.ncbi.nlm.nih.gov/33443482/)

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Protocol

# Mental Health and Burnout Syndrome Among Postgraduate Students in Medical and Multidisciplinary Residencies During the COVID-19 Pandemic in Brazil: Protocol for a Prospective Cohort Study

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## Abstract

**Background:** The COVID-19 pandemic has led to high levels of physical, psychological, and social stress among health care professionals, including postgraduate students in medical and multidisciplinary residencies. This stress is associated with the intense fear of occupational exposure to SARS-CoV-2, the virus known to cause COVID-19. These professionals are at risk of developing physical and mental illnesses not only due to the infection but also due to prolonged exposure to multidimensional stress and continued work overload.

**Objective:** This study aims to evaluate the prevalence of symptoms suggestive of mental disorders and burnout syndrome and determine the risk factors for burnout among postgraduate students in medical and multidisciplinary residencies in Brazil during the COVID-19 pandemic.

**Methods:** For this prospective cohort study with parallel groups, participants were recruited between July and September 2020 to achieve a sample size of at least 1144 participants. Research instruments such as Depression, Anxiety, and Stress Scale; Patient Health Questionnaire; Brief Resilient Coping Scale; and Oldenburg Burnout Inventory will be used to collect data. Data will be collected in 2 waves: the first wave will include data related to sample characterization and psychosocial evaluation, and the

second wave will be launched 12 weeks later and will include an evaluation of the incidence of burnout as well as correlations with the potential predictive factors collected in the first wave. Additionally, we will collect data regarding participants' withdrawal from work.

**Results:** The recruitment took place from July 29 to September 5, 2020. Data analyses for this phase is already in progress. The second phase of the study is also in progress. The final data collection began on December 1, 2020, and it will be completed by December 31, 2020.

**Conclusions:** We believe the findings of this study will help evaluate the impact of the COVID-19 pandemic on the mental health conditions of health professionals in Brazil as well as contribute to the planning and implementation of appropriate measures that can alleviate these mental health challenges.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/24298

(*JMIR Res Protoc* 2021;10(1):e24298) doi:[10.2196/24298](https://doi.org/10.2196/24298)

## KEYWORDS

burnout syndrome; medical residency; multidisciplinary residency; COVID-19; mental health; burnout; stress; anxiety; prospective; cohort; health care professional; medical student

## Introduction

The first COVID-19 outbreak occurred in Wuhan, China, at the end of 2019, and it rapidly spread across the world. On January 30, 2020, the World Health Organization declared that the outbreak constituted a public health emergency of international importance and characterized COVID-19 as a pandemic on March 11, 2020 [1].

During this pandemic, health care professionals, including postgraduate students in medical residency and multidisciplinary programs, have been directly involved in disease management, and consequently, they are exposed to an increased risk of infection due to direct contact with infected patients [2]. Additionally, most of these professionals are likely to develop psychological distress and other mental health-related symptoms, which may be attributed to the lack of security in the face of the unprecedented scenario, increase in the number of confirmed COVID-19 cases, work overload, shortage of diagnostic tests and personal protective equipment (PPE), and the lack of specific drugs for treatment, among other factors [3].

Mental disorders among health care professionals have been the focus of many scientific studies in recent years. A high prevalence of mental health conditions has been reported among the professionals, with a wide spectrum of manifestations correlated to the intense emotional demands and adverse working conditions experienced by them. Physicians and nursing professionals, especially nurses [4], are particularly more susceptible to the development of these problems, in addition to the high levels of work-related stress [5].

In this context, the burnout syndrome stands out. It is defined as a state of physical and mental exhaustion resulting from work activities or care provision, reflected through emotional change and irritability. Burnout is characterized as a psychological syndrome resulting from a continuous response to chronic stressors and interpersonal factors at work. Consequently, psychiatric problems may develop, featuring as emotional exhaustion, depersonalization, and reduced personal achievement [6].

Medical and multidisciplinary residency programs have high workloads and demands; these programs call for many hours of dedication from postgraduate students to fulfill the established requirements. In addition, there can be a significant degree of burnout, which can interfere with the students' decision-making. In general, burnout syndrome is associated with a number of unfavorable consequences such as depression, risk of medical errors, and patient safety risks [5]. Moreover, an increased workload during this critical period of residency has been found to be associated with a decline in the mental health of the residents [6]; these findings have important implications especially in the ongoing pandemic situation.

In recent years, several studies related to burnout syndrome in health care professionals have been published; however, data published in the scientific literature referring to residents are limited [7]. Studies addressing mental health and burnout syndrome among health care professionals in Brazil and worldwide are quite restricted with regard to the number of residents (ie, medical residents and multidisciplinary residents). Additionally, no studies on these disorders have been performed during the COVID-19 pandemic. Therefore, this study aims to evaluate the prevalence of symptoms suggestive of mental disorders and burnout syndrome as well as determine the risk factors for burnout among postgraduate students in medical and multidisciplinary residencies in Brazil during the COVID-19 pandemic.

## Methods

### Study Design and Data Collection

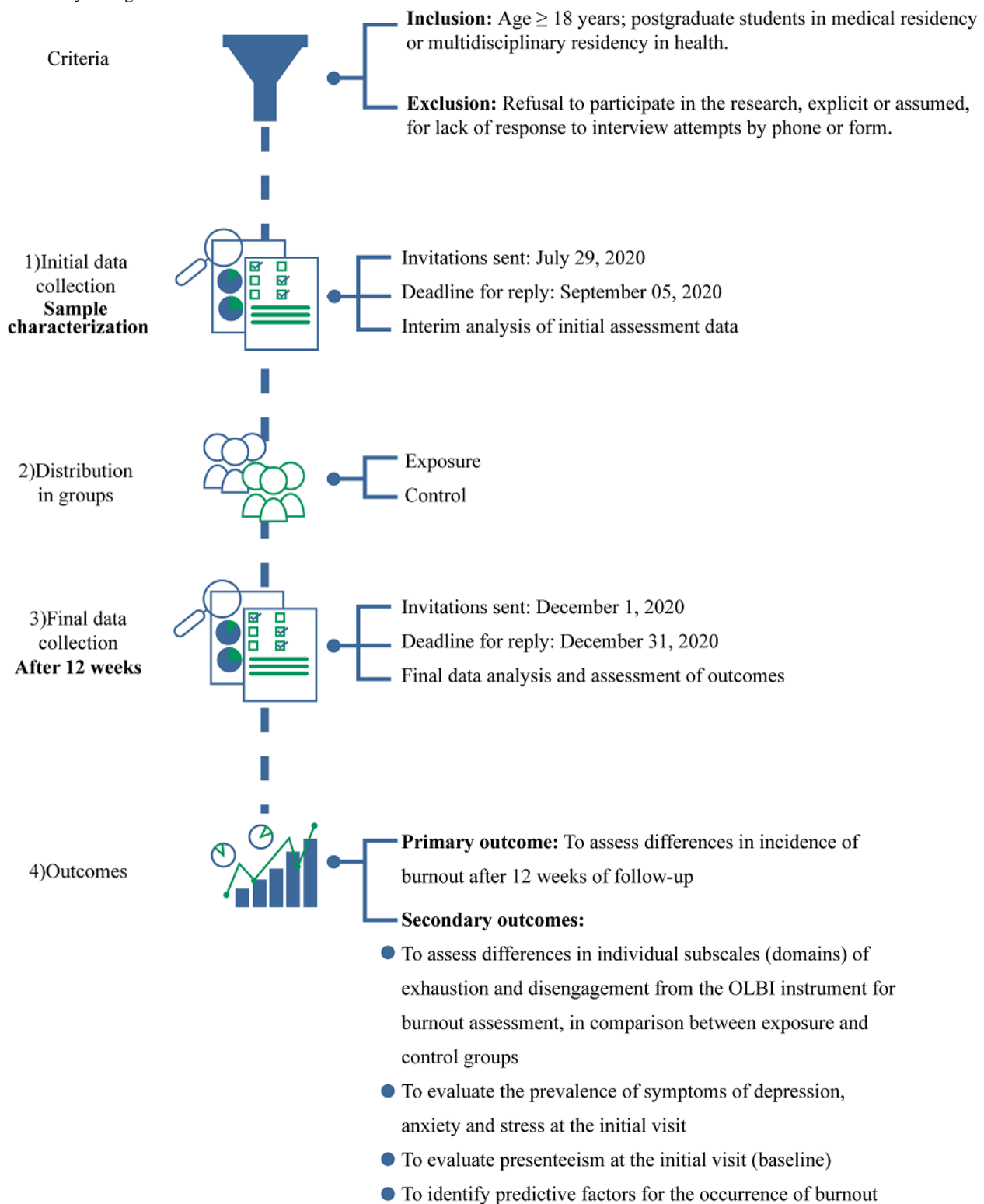
This is a prospective cohort study comprising 2 parallel groups. Baseline evaluation will be performed at the time of recruitment of study participants and will serve as cross-sectional data to estimate the prevalence of symptoms indicative of mental disorders and professional burnout. A longitudinal follow-up will also be performed to enable estimation of the incidence and identification of predictive factors of burnout among the study participants.

Individuals were recruited from July to August 2020 via electronic invitations sent out through the Microsoft Forms

platform (Microsoft Corp). Two waves of data collection were programmed, including initial data collection and a 12-week follow-up (Figure 1). In the first wave (July 29 to September 5, 2020), all data related to the characterization of the study sample, including psychosocial assessment and potential predictive factors related to the research outcomes, were

collected. In the second wave of data collection (ie, at the 12-week follow-up), the incidence of burnout will be evaluated, which will then be correlated with the potential predictive factors collected during the first wave. Additionally, we will collect data on participants' withdrawal from work.

**Figure 1.** Study fluxogram.





## Research Instruments

### *Depression, Anxiety, and Stress Scale*

The Depression, anxiety, and stress scale–21 items (DASS-21) scale has been translated and validated in Portuguese [8] and consists of 3 subscales with 7 items each. Responses are given

on a 4-point scale, ranging from 0 (strongly disagree) to 3 (totally agree). The DASS-21 covers 3 symptom domains: depression, anxiety, and stress. The cutoff points for each of these domains are as follows: depression >9, anxiety >7, and stress >14 (Textbox 1, [9]).

**Textbox 1.** Depression, Anxiety, and Stress Scale–21 items (DASS-21) [9]

<p><b>DASS-21</b></p> <p><b>Responses:</b></p> <p>0: Did not apply to me at all</p> <p>1: Applied to me to some degree, or some of the time</p> <p>2: Applied to me to a considerable degree or a good part of the time</p> <p>3: Applied to me very much or most of the time</p> <p><b>Items:</b></p> <ol style="list-style-type: none"> <li>1. I found it hard to wind down.</li> <li>2. I was aware of the dryness of my mouth.</li> <li>3. I couldn't seem to experience any positive feeling at all.</li> <li>4. I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion).</li> <li>5. I found it difficult to work up the initiative to do things.</li> <li>6. I tended to overreact to situations.</li> <li>7. I experienced trembling (eg, in the hands).</li> <li>8. I felt that I was using a lot of nervous energy.</li> <li>9. I was worried about situations in which I might panic and make a fool of myself.</li> <li>10. I felt that I had nothing to look forward to.</li> <li>11. I found myself getting agitated.</li> <li>12. I found it difficult to relax.</li> <li>13. I felt down-hearted and blue.</li> <li>14. I was intolerant of anything that kept me from getting on with what I was doing.</li> <li>15. I felt I was close to panic.</li> <li>16. I was unable to become enthusiastic about anything.</li> <li>17. I felt I wasn't worth much as a person.</li> <li>18. I felt that I was rather touchy.</li> <li>19. I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat).</li> <li>20. I felt scared without any good reason.</li> <li>21. I felt that life was meaningless.</li> </ol>
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### *Patient Health Questionnaire*

Patient Health Questionnaire–9 items (PHQ-9) is a rapid assessment tool that has been translated and validated in Portuguese. It has advantages over other instruments currently

validated for use in Brazil [10]. It consists of 9 questions for screening depression, with respondents expected to mark responses in relation to the frequency of symptoms they have experienced in the last 2 weeks: 0, no day; 1, less than 1 week; 2, 1 week or more; and 3, almost every day (Textbox 2, [11]).

**Textbox 2.** Patient Health Questionnaire–9 items (PHQ-9) [11].

<p><b>PHQ-9</b></p> <p><b>Responses:</b></p> <p>0: Not at all</p> <p>1: Several days</p> <p>2: More than half the days</p> <p>3: Nearly every day</p> <p><b>Items:</b></p> <ol style="list-style-type: none"> <li>1. Little interest or pleasure in doing things</li> <li>2. Feeling down, depressed, or hopeless</li> <li>3. Trouble falling or staying asleep, or sleeping too much</li> <li>4. Feeling tired or having little energy</li> <li>5. Poor appetite or overeating</li> <li>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</li> <li>7. Trouble concentrating on things, such as reading the newspaper or watching television</li> <li>8. Moving or speaking so slowly that other people could have noticed? Or, so fidgety or restless that you have been moving a lot more than usual?</li> <li>9. Thoughts that you would be better off dead, or thoughts of hurting yourself in some way</li> </ol>
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### ***Brief Resilient Coping Scale***

Brief Resilient Coping Scale (BRCS) is a 1D instrument comprising 4 items to assess an individual's ability to deal with stress in an adaptive way [12]. The responses to the questionnaire items are provided on a 5-point scale: 5, almost

always; 4, very often; 3, often; 2, occasionally; and 1, almost never. Total scores on the scale range from 4 and 20, and according to its developers, respondents who score less than 13 are considered to have a low level of resilience (Textbox 3, [13]).

**Textbox 3.** Brief Resilient Coping Scale (BRCS) [13].

<p><b>BRCS</b></p> <p><b>Responses:</b></p> <p>1: Does not describe me at all</p> <p>2: Does not describe me</p> <p>3: Neutral</p> <p>4: Describes me</p> <p>5: Describes me very well</p> <p><b>Items:</b></p> <ol style="list-style-type: none"> <li>1. I look for creative ways to alter difficult situations.</li> <li>2. Regardless of what happens to me, I believe I can control my reaction to it.</li> <li>3. I believe I can grow in positive ways by dealing with difficult situations.</li> <li>4. I actively look for ways to replace the losses I encounter in life.</li> </ol>
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### ***Autonomy Degree Scale to Decide Conduct at Work***

This visual analog scale (VAS) assesses an individual's perception of autonomy at their job. Response options range from 0 to 10, with 0 indicating "I have no autonomy" and 10 indicating "I have total autonomy." Total scores  $\leq 4$  indicate a low level of perceived autonomy at work [14].

### ***Perception of Availability of Personal Protective Equipment***

This single-item instrument was used to assess the availability of personal protective equipment (PPE) for health professionals on a scale of 1 to 5. The question was "In your professional practice, in patient care, for which period of time did you have sufficient and adequate personal protective equipment (PPE) available?" The response options were as follows: 1, no time;

2, less than half the time; 3, half the time; 4, more than half the time; and 5, all the time.

### **Oldenburg Burnout Inventory**

The Oldenburg Burnout Inventory (OLBI) is used to assess burnout through the development of a cross-culturally adapted version for both Brazil and Portugal [15]. The OLBI is a 5-point self-reported scale: 5, strongly agree; 4, agree; 3, neither agree

nor disagree; 2, disagree; and 1, strongly disagree. This 2D scale covers disengagement and exhaustion, and each dimension comprises 8 items. The disengagement dimension refers to the distancing from work in terms of object and content and the development of cynical and negative attitudes and behaviors toward work. The exhaustion dimension refers to feelings of physical fatigue, need for rest, feeling of overload, and emptiness in relation to work (Textbox 4, [16]).

**Textbox 4.** Oldenburg Burnout Inventory (OLBI) [16].

<p><b>OLBI</b></p> <p><b>Responses:</b></p> <p>1: Strongly disagree</p> <p>2: Disagree</p> <p>3: Neutral</p> <p>4: Agree</p> <p>5: Strongly agree</p> <p><b>Items:</b></p> <p><b>Disengagement</b></p> <p>1. I always find new and interesting aspects in my work.</p> <p>3. It happens more and more often that I talk about my work in a negative way.</p> <p>6. Lately, I tend to think less at work and do my job almost mechanically.</p> <p>9. I find my work to be a positive challenge.</p> <p>11. Sometimes I feel sickened by my work tasks.</p> <p>13. This is only type of work that I can imagine myself doing.</p> <p>15. I feel more and more engaged in my work.</p> <p><b>Exhaustion</b></p> <p>2. There are days when I feel tired before I arrive at work.</p> <p>4. After work, I tend to need more time than in the past in order to relax and feel better.</p> <p>5. I can tolerate the pressure of my work very well.</p> <p>8. During my work, I often feel emotionally drained.</p> <p>10. After working, I have enough energy for my leisure activities.</p> <p>12. After my work, I usually feel worn out and weary.</p> <p>14. Usually, I can manage the amount of my work well.</p> <p>16. When I work, I usually feel energized.</p>
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### **External Work Contract**

This instrument comprises a single “yes” or “no” item to assess the existence of an employment relationship rather than that of a residency.

### **Providing Care for Patients With COVID-19**

This instrument forms a single “yes” or “no” item to assess whether the respondent provides direct assistance to patients with COVID-19.

### **Stanford Presenteeism Scale**

The Stanford Presenteeism Scale (SPS-6) exclusively assesses presenteeism. This instrument helps evaluate the relationship between presenteeism, health problems, and productivity among workers. It consists of 6 items, with responses for each item ranging from 1 (strongly disagree) to 5 (strongly agree) (Textbox 5, [17]).

**Textbox 5.** Stanford Presenteeism Scale (SPS-6) [17].

**SPS-6**

**Directions:**

Please describe your work experiences in the past month. These experiences may be affected by many environmental as well as personal factors and may change from time to time. For each of the statements below, please check one of the following responses to indicate your agreement or disagreement with the statement in describing your work experiences in the past month.

**Responses:**

Please use the following scale for evaluation:

1: I strongly disagree with the statement.  
 2: I somewhat disagree with the statement.  
 3: I am uncertain about my agreement with the statement.  
 4: I somewhat agree with the statement.  
 5: I strongly agree with the statement.

**Items:**

1. Because of my (health problem)\*, the stresses of my job were much harder to handle.
2. Despite having my (health, problem)\*, I was able to finish hard tasks in my work.
3. My (health problem)\* distracted me from taking pleasure in my work.
4. I felt hopeless about finishing certain work tasks, due to my (health problem)\*.
5. At work, I was able to focus on achieving my goals despite my (health problem)\*.
6. Despite having my (health problem)\*, I felt energetic enough to complete all my work.

\*Note: the words “back pain,” “cardiovascular problem,” “illness,” “stomach problem,” or other similar descriptors can be substituted for the words “health problem,” in any of these items.

**Participants and Eligibility Criteria**

The eligibility criteria used for the inclusion of participants was as follows: aged 18 years or above and postgraduate student in a medical residency or multidisciplinary residency program who has been designated for activities that involve direct patient care during the COVID-19 pandemic. The exclusion criteria have been defined as the explicit or assumed refusal to participate in the study as indicated by no response to telephone or electronic form interview attempts.

**Study Groups**

For longitudinal tracking purposes, the exposed groups (parallel to each other) will comprise participants who are farther away from normal or reference ranges, in an unfavorable sense. This will be determined based on the following cutoff points defined for each of the instruments selected (ie, scales to assess burnout, depression, anxiety, stress, and resilience):

- DASS-21 scores
  - Depression >9
  - Anxiety >7
  - Stress >14
- PHQ-9: scores  $\geq 9$  indicate depression
- BRCS: scores  $\leq 13$  indicate low resilience

In the exposed groups, we will also include participants with lower scores on the evaluation instruments for measuring autonomy at work, availability of PPE, and subjective perceptions of pedagogical adequacy of the residency program,

according to the cutoff points listed below. Participants who have a work contract outside the residency program and who are directly involved in care provided to patients with COVID-19 will also be part of the exposed group. The following elements will be considered as predictors of burnout:

- Autonomy degree scale to decide conduct at work (VAS): score  $\leq 4$
- Availability and adequacy of PPE for assistance activities (5-point Likert scale): score  $\leq 3$
- Proper pedagogical organization of the medical residency program or multidisciplinary (VAS): score  $\leq 5$
- External working contract: yes
- Providing care to patients with COVID-19: yes

The corresponding control groups will include participants who present burnout levels considered to be minimally satisfactory or close to the normal or reference values based on the following cutoff points defined for each of the instruments. Participants who do not have a working contract external to the residency program and who are not directly involved in the care provided to patients with COVID-19 will also be part of the control group.

- DASS-21 scores
  - Depression  $\leq 9$
  - Anxiety  $\leq 7$
  - Stress  $\leq 14$
- PHQ-9: score <9
- BRCS: score >13



- Autonomy degree scale to decide conduct at work (VAS): score >4
- Availability and adequacy of PPE for assistance activities (5-point Likert scale): score >3
- Proper pedagogical organization of the medical residency program or multidisciplinary (VAS): score >5
- External working contract: no
- Providing care to patients with COVID-19: no

### Sampling Size

In estimating the required sample size, a general prevalence of about 28% for burnout syndrome among health care professionals was taken as the starting point [18]. Nevertheless, higher burnout prevalence should be expected among individuals with relevant predisposing factors. In order to identify such risk factors, we considered a difference of at least 10 percent points in the prevalence of burnout between the exposed and nonexposed groups as clinically relevant. Therefore, aiming to detect at least a 10-percent-point difference between the groups after 12 weeks of follow-up, the total sample size was initially calculated at  $N=686$  (ie,  $n=343$  for each group). However, only about 72% of the participants initially included (ie. those who did not exhibit burnout at the initial assessment) should enter the longitudinal phase and be analyzed after 12 weeks. Moreover, a dropout rate of up to 20% was expected during this longitudinal follow-up. To compensate for these expected losses, the minimum sample size was thus recalculated to be  $N=1144$  ( $n=572$  in each group). Electronic forms were sent to all participants to collect relevant data for the research, with additional clarifications sought from the participants by telephonic contact, if necessary.

### Clinical Data and Outcomes

The primary outcome will assess the differences in the incidence of burnout (determined using the OLBI instrument) between the exposure and control groups at 12 weeks of follow-up. Participants will be classified as “experiencing burnout” if their exhaustion score is  $\geq 2.25$  and their disengagement score is  $\geq 2.10$ , considering the achieved outcome (clinically relevant difference) in case of a  $\geq 10\%$  (relative risk  $\geq 1.10$ ) difference in the occurrence of burnout between groups.

Secondary outcomes will assess differences in exhaustion and disengagement scores, as determined using the OLBI instrument to assess burnout between the exposure and control groups, with 12 weeks of follow-up. The outcome will be considered if relative risk  $\geq 1.15$ , resulting in scores of  $\geq 2.25$  and  $\geq 2.10$  for exhaustion and disengagement, respectively. The prevalence of depression, anxiety, and stress symptoms at the initial visit, as measured by DASS-21 and PHQ-9 and based on previously defined cutoff scores, will also be considered as secondary outcomes. Furthermore, SPS-6 will be administered at the baseline, with a cutoff score for clinical relevance  $< 18$ , in case of a difference of  $\geq 15\%$  ( $OR \geq 1.15$ ) when comparing the exposure and control groups. Absence from work in the previous 12 weeks will be evaluated descriptively through a survey (administered via Microsoft Forms) at the final evaluation stage (Figure 1). Risk factors for the occurrence of burnout will also be evaluated at the 12-week follow-up and compared between the exposure and control groups, as evaluated by relative risks

and 95% CIs. An interim analysis with data from the initial assessment (ie, cross-sectional data) will be performed to estimate the prevalence as soon as the recruitment of participants is completed.

### Statistical Analysis

Outcomes based on proportions will be compared between the exposed and control groups by using the chi-square test (or Fisher exact test). Outcomes based on continuous variables will be compared by Student  $t$  test (or Mann-Whitney U test). The predictive factors for burnout among the candidates will be evaluated using a generalized linear model log-binomial.

For the longitudinal follow-up, participants with scores indicative of burnout at the baseline assessment will be excluded from incidence analyses at the 12-week follow-up. Primary and secondary outcomes will be compared between participants of different professional categories (ie, medical residents and multidisciplinary residents), and potential imbalances observed between groups (ie, exposed vs control groups) will be adjusted by multiple linear regression, logistically or log-binomial, as appropriate.

### Ethics and Dissemination

This study was approved by the Research Ethics Committee from the Medical School (CEP/FM) of the University of Brasília (CAAE: 33493920.0.0000.5558), through the CEP/CONEP system - Plataforma Brasil in 05/07/2020. An informed consent form will be obtained from all participants included in the study. As this is an observational study, one of the biggest risks perceived by the participants is the eventual discomfort in the face of any personal questions that may be part of the initial clinical interview conducted to determine the application of research instruments. The protocol will be registered in the Brazilian Clinical Trials Registry (Registro Brasileiro de Ensaios Clínicos) as an observational study. Undergraduate students in medicine and other undergraduate health courses will participate in the study as collaborating researchers.

### Results

Data collection for this study is currently in progress. Recruitment (for the first phase) started on July 29, 2020, and ended on September 5, 2020. Analyses of data collected during this first phase is already in progress, and we estimate this to be completed by January 2021. The second phase of data collection was launched on December 1, 2020, and we expect it to be completed by December 31, 2020; thereafter, we will begin analyses of the data collected in this phase.

### Discussion

This prospective cohort study will help evaluate the prevalence of symptoms that are suggestive of mental disorders and burnout syndrome among postgraduate students of medical and multidisciplinary residencies in Brazil, as well as to determine the predictors of burnout during the COVID-19 pandemic. It is known that health care workers, in general, have encountered worsened mental health and well-being as a result of the COVID-19 pandemic [19]. Moreover, since studies on this topic

are quite limited especially with regard to this study population, we believe that our dataset will help to better understand and evaluate the impact of the ongoing pandemic on the mental health of these professionals; this is extremely relevant not only

to scale the consequent losses but also to contribute to the planning and implementation of appropriate measures that can potentially alleviate these challenges in the near future.

## Acknowledgments

We would like to thank the University Hospital of Brasília, especially the Superintendency and the Division of Teaching and Research, and EBSEH for the support provided to this study.

## Conflicts of Interest

None declared.

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## Abbreviations

**BRCS:** Brief Resilient Coping Scale  
**DASS-21:** Depression, anxiety, and stress scale, 21 items  
**OLBI:** Oldenburg Burnout Inventory  
**PHQ-9:** Patient Health Questionnaire, 9 items  
**PPE:** personal protective equipment  
**SPS-6:** Stanford Presenteeism Scale  
**VAS:** visual analog scale

*Edited by G Eysenbach; submitted 15.09.20; peer-reviewed by W Zhang, J Hoogervorst; comments to author 06.10.20; revised version received 14.10.20; accepted 27.10.20; published 19.01.21.*

### *Please cite as:*

Pinho RDNL, Costa TF, Silva NM, Barros-Areal AF, Salles ADM, Oliveira AP, Rassi C, Valero CEB, Gomes CM, Mendonça-Silva D, Oliveira F, Jochims I, Ranulfo I, Neves JDBS, Oliveira L, Dantas MN, Rosal M, Soares M, Kurizky P, Peterle VU, Faro YF, Gomides AP, da Mota L, Albuquerque C, Simaan CK, Amado VM  
*Mental Health and Burnout Syndrome Among Postgraduate Students in Medical and Multidisciplinary Residencies During the COVID-19 Pandemic in Brazil: Protocol for a Prospective Cohort Study*  
*JMIR Res Protoc* 2021;10(1):e24298  
URL: <https://www.researchprotocols.org/2021/1/e24298>  
doi: [10.2196/24298](https://doi.org/10.2196/24298)  
PMID: [33290246](https://pubmed.ncbi.nlm.nih.gov/33290246/)

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Protocol

# Effects of the Argus II Retinal Prosthesis System on the Quality of Life of Patients With Ultra-Low Vision Due to Retinitis Pigmentosa: Protocol for a Single-Arm, Mixed Methods Study

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## Abstract

**Background:** Retinitis pigmentosa is an incurable, degenerative retinal condition causing progressive sight loss, significantly affecting patients' quality of life. The Argus II Retinal Prosthesis is a surgically implanted medical device that delivers electrical stimulation to the retina. It is intended to produce a form of artificial vision for blind people with severe-to-profound retinitis pigmentosa by stimulating the remaining viable retinal cells to induce visual perception. This study has been initiated by National Health Service England's Commissioning through Evaluation program and funded through the National Institute of Health Research of the United Kingdom.

**Objective:** The aim of this study was to assess the effect of the Argus II device on patient's daily activities and quality of life.

**Methods:** This protocol is a prospective, single-arm, open-label, mixed methods study on 10 consecutive participants receiving the Argus II device. The patient representatives played an integral role in the design of this study. Eligibility criteria include ultra-low vision in both eyes as a result of end-stage retinitis pigmentosa and a willingness and capacity to complete the postimplantation rehabilitation program. Participants will be interviewed by independent researchers at baseline and 12 months later by using a semistructured, in-depth approach, alongside validated questionnaires (Impact of Vision Impairment-Very Low Vision, 5-level EuroQoL-5 dimensions scale, EuroQoL-visual analog scale, and Hospital Anxiety and Depression Scale) and a bespoke device-related questionnaire, which includes questions about users' experiences with the procedure, the device, and rehabilitation. The effect of the device on patients' functional vision and activities of daily living will be assessed by vision rehabilitation specialists using a set of tests measured on an ordinal scale (eg, ability to locate objects and avoid obstacles). Clinical outcomes include full-field stimulus light threshold, square localization, direction of motion, grating visual acuity, Landolt-C, procedural success, and adverse events. Qualitative and quantitative outcomes will be linked in a single database to enable individual participant measures to be considered in toto, comparing baseline to the final review.

**Results:** This study was approved by the local ethics committee on April 24, 2019 (London-Camberwell St. Giles Research Ethics Committee, reference 19/LO/0429). It has also been approved by the Health Research Authority and Health and Care



Research Wales. At the time of protocol writing, Argus II was available for use in the United Kingdom; however, the manufacturer recently withdrew the Argus II device from sale in the United Kingdom. Therefore, the study is not going ahead at this time.

**Conclusions:** The mixed methods approach provides a rich and in-depth assessment of the effect of the device on participants' quality of life. Despite the work not going ahead, the publication of this publicly funded protocol is important for researchers planning similar work.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/17436

(*JMIR Res Protoc* 2021;10(1):e17436) doi:[10.2196/17436](https://doi.org/10.2196/17436)

## KEYWORDS

patient-reported outcomes; quality of life; qualitative methods; artificial vision; visual function; functional vision; ultra-low vision; low vision; visual function questionnaire

## Introduction

### Background

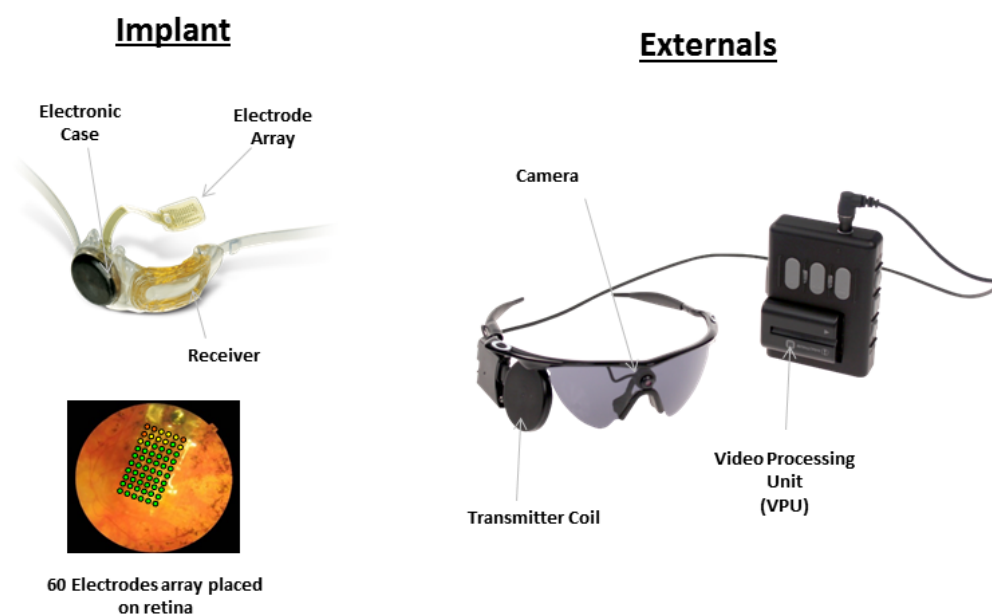
Retinitis pigmentosa is a term for a group of genetically determined degenerative eye conditions that cause progressive loss of retinal photoreceptors. It typically starts with mild loss of peripheral vision, but as the disease advances, vision reduces to a small island of central vision, which may be lost at the end stages of the disease. It is the leading cause of inherited blindness in the United Kingdom, affecting 1 in 4000 people [1]. Although gene therapy has recently been approved for a single genetic subtype [2], there is currently no cure for most forms of retinitis pigmentosa.

### Argus II Retinal Prosthesis System (Argus II)

The Argus II Retinal Prosthesis is a medical device that is surgically implanted into only 1 eye and it delivers electrical stimulation to the retina. It is intended to produce a form of

artificial vision to blind people with severe-to-profound retinitis pigmentosa by stimulating the remaining viable retinal cells to induce visual perception. It aims to provide functional vision, which enables patients to perceive light, movement, and shapes. The core element of the Argus II system is a spectacle-mounted video camera that records real-time images and a video processing unit that converts the images into data that are wirelessly transmitted to an episcleral receiver unit (Figure 1). This then relays data to the electrode array, which produces electrical impulses that bypass damaged photoreceptors and stimulate the retina's remaining cells. Visual information is then transmitted by the optic nerve to the brain, creating a visual percept. Through the help of vision rehabilitation professionals, the user learns to interpret these visual patterns to regain some visual function such as perceive light, gain mobility, and identify shapes. Patients require a program of device training coupled with postprocedural rehabilitation to achieve optimal results from the Argus II device [3].

**Figure 1.** Argus II retinal prosthesis components.



## Current Evidence of the Effects of Argus II

### *Efficacy of Argus II*

In 2015, the National Institute for Health and Care Excellence (NICE) published interventional procedure guidance on the insertion of a retinal prosthesis for retinitis pigmentosa [4]. The available evidence was based primarily on 1 prospective multicenter case series of 30 participants [5]. At 5 years after implantation, 12 (40%) patients experienced 24 serious adverse events, including conjunctival erosion, hypotony, conjunctival dehiscence, and endophthalmitis. By 5 years, 2 (6.7%) Argus II devices failed. In both cases, the reason was progressive loss of the radiofrequency link between the external antenna and the implant.

### *Effect on Visual Function*

There is evidence that Argus II produces improvements in visual function and observer-rated functional vision tasks, albeit in a small number of patients in a clinic environment, when comparing the device in its “ON” and “OFF” position [5-8]. Functional vision was assessed using the Functional Low-Vision Observer Rated Assessment tool, a multicomponent questionnaire consisting of 35 observer-rated tasks organized into 4 domains: visual orientation, visual mobility, daily life, and interaction with others. On average, patients were able to complete 24 of the 35 tasks (69%) more easily with the Argus II device switched ON than when the Argus II device was switched OFF; 2 tasks (6%) were harder to complete on average, and 9 tasks (26%) showed no significant change between the ON and OFF positions (the authors did not report the number of patients who showed a change) [7]. Using orientation and mobility tasks (“find the door” and “follow the white line”), all patients performed better with the device switched ON than when the device was switched OFF at all time points (28 patients at 1, 2, and 3 years; 22 patients at 4 years; and 20 patients at 5 years) [5]. Patients performed better at 3 real-world functional vision tasks: in a sock sorting task (bare table), 21 of the 28 patients (75%) performed better with the system ON; in the sidewalk tracking task, 18 of the 27 patients (67%) performed better with the system ON; and in the walking direction discrimination test, 18 of the 27 subjects (67%) performed above chance with the system ON and 6 (22%) did so with system OFF [8].

### *Effect on Quality of Life*

Currently, there is limited evidence on the effect of Argus II on patients’ quality of life (QoL), with 1 study reporting scores from a vision-specific, multi-attribute utility instrument. The Vision and Quality of Life Index (VisQoL) consists of 6 dimensions (injury, life, roles, assistance, activity, and friendship) and was completed by patients before and after receiving Argus II at 3, 6, 12, 18, 24, and 36 months [9]. Composite VisQoL scores at follow-up (presumably all follow-up time points although the authors do not specify this) showed no statistically significant change from the baseline. In 3 of the 6 VisQoL dimensions (injury, life, and roles), there was a significant and lasting improvement after implantation with Argus II in patients whose blindness was affecting their QoL at baseline [9]. No published qualitative studies have been

carried out on patients who have received Argus II; a recent report by Health Quality Ontario reports narrative accounts but does not report a full methodology, and this work is not published in a peer-reviewed journal [10].

NICE’s Interventional Procedures Guidance (IPG519) [4] has recommended further research focusing on “...the impact on quality of life and activities of day-to-day living, and durability of implants.” The committee “wanted evidence that any changes in metrics of vision result in improved QoL and activities of daily living.” These recommendations have been reflected in National Health Service (NHS) England’s Clinical Commissioning Policy on Argus II retinal prosthesis for retinitis pigmentosa [11].

This study was initiated by NHS England as part of Commissioning through Evaluation, which is part of their Evaluative Commissioning Program. Commissioning through Evaluation enables a limited number of patients to access treatments that are not routinely funded by the NHS, but nonetheless show significant promise for the future, while new clinical and patient experience data are collected within a formal evaluation program. This study was commissioned to develop evidence on the effect of Argus II on patients’ QoL, in order to inform the NHS England commissioning policy for the procedure.

## Methods

### **Aim, Design, and Setting of the Study**

This study aims to assess the impact of the Argus II Retinal Prosthesis System (Second Sight) on the QoL of participants with ultra-low vision as a result of retinitis pigmentosa. This protocol is for a single-arm, prospective, open-label, mixed methods, multicenter, before versus after study on 10 participants. All participants will receive Argus II as part of the research study and will be required to take part in the rehabilitation program following surgery. A mixed methods approach is required because neither qualitative nor quantitative methods alone would support the in-depth analyses of the effect of Argus II on participants’ QoL. The study will take place in several settings. The retinal prosthesis will be implanted and fitted in a specialist eye hospital, where clinical examinations will also take place. The vision rehabilitation training and assessments will take place in an outpatient clinic and in participants’ homes. Recruitment is expected to take 12 months, and each participant will be followed up for 12 months.

### **Study Population**

The population will be adults with ultra-low vision in both eyes as a result of retinitis pigmentosa. Participants must have severe-to-profound outer retinal degeneration (not including age-related macular degeneration), with some residual light perception or with retinal response to electrical stimulation and with history of useful form vision. Eligible participants must provide consent for the procedure, a program of rehabilitation, clinical data collection, and agree to take part in qualitative interviews and questionnaire completion (administered and analyzed by independent researchers from an NHS research center, Cedar, Cardiff & Vale University Health Board).

The exclusion criteria for the patients would be as follows: (1) ocular diseases or conditions that could prevent Argus II from working, (2) ocular structures or abnormalities that could prevent the successful implantation of the Argus II implant or adequate healing following surgery, (3) ocular diseases or conditions (other than cataracts) that prevent adequate visualization of the inner structures of the eye (eg, corneal opacity), (4) predisposition to eye rubbing, (5) inability to tolerate general anesthesia or the recommended antibiotic and steroid regimen associated with the implantation surgery, and (6) any disease or condition that prevents understanding or communication of informed consent, study demands, testing protocols, and qualitative interviews.

Eligible participants will be provided with an information pack at or before their initial study visit and the clinical investigators will read all of the written information to the participant. Participants will be offered an audio recording and electronic version of the participant information sheet and informed consent form.

### Sampling

Ten participants will be recruited over a 1-year period to take part in the study. The recruitment rate is based on UK recruitment experience during a previous clinical trial of the Argus II implant [5]. The procedure is a highly specialized treatment and large numbers of participants would be difficult to recruit. In addition, NHS England (the commissioning body) recognized that approximately 10 people per year would be eligible for the Argus II procedure [11]. Consecutive participants who meet the eligibility criteria will be invited to take part. The choice of a sample size of 10 participants is also based on pragmatic considerations of time and budget (ie, convenience). The aim will be to reach or at least approach data saturation by the end of follow-up of the tenth participant. This approach is supported by the work of Francis et al (2010) [12], whereby an initial analysis sample of 10 interviews was chosen. We accept that limiting our sample size to 10 may not identify every key theme, but we expect to identify those most important to the majority of the participants.

If a participant withdraws prior to receiving the implant, they will be replaced by another participant. If a participant withdraws after the implant is fitted, they will retain the device but will no longer be required to complete any subsequent study visits.

### Study Device

The Argus II Retinal Prosthesis System is an active implantable medical device. It received a CE mark in 2011. It is intended to “provide electrical stimulation of the retina to induce visual

perception in blind individuals” (from Second Sight Instructions for Use). The Argus II system has 2 key groups of components (Figure 1): (1) the external components comprising a small video camera mounted on a pair of spectacles, which is connected via a cable to a video processing unit worn on a belt or a shoulder strap. The video camera captures images, which are converted by the video processing unit into stimulation commands. These are wirelessly transmitted to the internal components and (2) the implanted components, which include an episcleral receiver unit, electronics, and an electrode array that are surgically implanted in and around the eye. The array is attached to the retina over the macula. When the system is functioning, data from the video processing unit is received by the subconjunctival receiver unit, which communicates directly with the electrode array through a permanent sclerotomy. The electrodes emit electrical impulses to stimulate the sensory neurons of the surviving retinal cells, which send visual information to the brain via the optic nerve.

### Schedule of the Procedures and Assessments

#### *Insertion and Fitting of the Retinal Prosthesis*

Argus II is intended to be implanted in a single eye and should be implanted in the worse-seeing eye. If both eyes have equivalent residual vision and are equally suitable for implantation, the participant’s preference for the implanted eye should be respected (from Second Sight Instructions for Use). Insertion of the implanted device components is performed with the participant under general anesthesia, usually in a single procedure taking several hours. The surgeon performs core and peripheral vitrectomies, followed by dissection of any retinal membrane in the area where the electrode array will be placed. The electrode array is inserted through a superotemporal sclerotomy and secured on the retina using a retinal tack. It is connected to the receiver unit by a cable that penetrates the sclera in the pars plana. This cable is sutured flat against the external sclera at the point of exit and is covered with a piece of donor sclera (Tutoplast) to avoid exposure and erosion. Intraoperative adverse events and complications will be recorded as part of this study.

Following implantation (typically 1 week after surgery), the device will be customized by a fitting technician in an outpatient clinic where the video processing unit is programmed specifically for use by the subject (Table 1). The basic fitting process involves implant diagnostics (eg, electrode impedance measurements), array scanning (ie, determination of stimulation thresholds for each single electrode), and the creation of one or more video configuration files, which contain the information of how the video signal is mapped to the electrical signal of the electrode array.

**Table 1.** Schedule of the study procedures and assessments.

Role, study procedure/assessment	-60 to -1 days	Day 0	Day 1	Week 1	Week 2	Month 1	Month 3	Month 6	Month 12
<b>Clinical teams</b>									
Enrolment/consent	✓								
Patient history	✓								
Clinical examinations including eye examination, retinal photography, visual acuity	✓		✓	✓	✓	✓	✓	✓	✓
Functional vision, including square localization test, direction of motion test	✓					✓	✓	✓	✓
Adverse events (including relatedness to device)		✓	✓	✓	✓	✓	✓	✓	✓
Resource use	✓	✓	✓	✓	✓	✓	✓	✓	✓
<b>Researchers independent of the clinical team</b>									
Semistructured interviews	✓ <sup>a</sup>								✓
<b>Quantitative QoL outcomes</b>									
IVI-VLV <sup>b</sup>	✓							✓	✓
EQ-5D-5L and EQ-VAS <sup>c</sup>	✓							✓	✓
HADS <sup>d</sup>	✓							✓	✓
Bespoke device-related questionnaire <sup>e</sup>							✓	✓	✓
<b>Rehabilitation staff</b>									
Training and visual rehabilitation reports							Sessions in clinic and at patient's home		
Visual function tests	✓								✓

<sup>a</sup>5-30 days prior to implantation.

<sup>b</sup>Changes in vision-related QoL (quality of life) will be measured using the IVI-VLV (Impact of Vision Impairment-Very Low Vision) questionnaire.

<sup>c</sup>Changes in general health-related QoL will be measured using the EQ-5D-5L (5-level EuroQoL 5-dimension scale) and EQ-VAS (EuroQoL visual analog scale) questionnaires.

<sup>d</sup>Changes in symptoms of anxiety and depression will be measured using the HADS (Hospital Anxiety and Depression Scale) questionnaire.

<sup>e</sup>The overall impact of Argus II as well as pain/discomfort from the device, perceived complications, satisfaction with results of procedure, and satisfaction with rehabilitation will be measured using a bespoke questionnaire.

### Clinical Follow-up

Clinical follow-up visits are planned at 1 day postimplantation, at weeks 1 and 2, and then at 1, 3, 6, and 12 months after the implantation (these visits will be modified in line with local routine practice, [Table 1](#)). In the event that COVID-19 precautions are in place, some clinical follow-ups may be carried out remotely where the treating clinician deems it is appropriate. Most of the visual function tests and measures will be conducted in both the implanted and fellow eye to provide data on the natural course of the participants' vision loss and as a control for measurements of visual function. Testing will also compare visual function in the study eye with the device ON versus that in the study eye with the device OFF. The number of follow-up visits will be recorded. Unscheduled visits such as those required to address potential adverse events will also be recorded.

### Baseline Assessments

At the baseline visit (60 days to 1 day prior to the implantation procedure and after consent has been given), clinical data will be recorded in a clinic setting, including complete eye

examination, medical evaluation, retinal photography, and optical coherence tomography, ultrasound A-scan and B-scan, photographic flash test (using a camera flash to assess whether a patient has perception of light; the flash is set off in front of the patient's eye to confirm any residual response to light), visual acuity tests, as well as a psychosocial evaluation in order to ensure that the subject has realistic expectations about the system ([Table 1](#)).

### Participant Interviews and Questionnaires

Participants will be interviewed by independent researchers at baseline (approximately 5-30 days prior to the implantation procedure) and at 12 months follow-up ( $\pm 1$  month). More frequent in-person interviews were ruled out as being overly burdensome to patients. Interviews will be semistructured (using a topic guide, [Multimedia Appendix 1](#)) with opportunities for unstructured conversation. Structure is required to ensure that certain areas of interest are explored during the interviews, but the approach will be kept flexible enough to explore the impact of the device on all aspects of participants' lives and allow for unexpected findings. Interviews will be preferentially carried



out in-person at participants' homes. Where this is not possible (such as in cases where COVID-19 precautions are in place), interviews can be carried out by phone. An interview/prompt guide will be finalized and piloted on participants who have received the Argus II device already. Each researcher will use the same prompts to guide their interview and to cover the same topic areas. A series of questionnaires will be read aloud to participants by independent researchers in person or by telephone at 6 and 12 months follow-up (the bespoke

device-related questionnaire will also be administered at 3-month follow-up) (Table 1 and Table 2).

The questionnaires will be Impact of Vision Impairment-Very Low Vision (IVI-VLV) [13], 5-level EuroQoL-5 dimension (EQ-5D-5L) scale, EuroQoL visual analog scale (EQ-VAS) [14], Hospital Anxiety and Depression Scale (HADS) [15], and bespoke device-related questionnaire to obtain structured responses from participants to questions related to the device and the participant experience.

**Table 2.** Qualitative and quantitative outcome measures.

Outcomes	Qualitative measures	Quantitative measures
<b>Participant-reported outcomes</b>		
Impact of device on quality of life	Semistructured/unstructured interviews (in-person or by phone) at baseline and 12 months	<ul style="list-style-type: none"> <li>Vision-related QoL<sup>a</sup> using the Impact of Vision Impairment-Very Low Vision validated questionnaire at baseline, 6 months, and 12 months.</li> <li>General health-related QoL measured using EQ-5D-5L<sup>b</sup> and EQ-VAS<sup>c</sup> questionnaires at baseline, 6 months, and 12 months.</li> </ul>
Device-related experience	Semistructured/unstructured interviews (in-person or by phone) at baseline and 12 months	Bespoke questionnaire, which includes questions about pain/discomfort from the device, perceived complications, satisfaction with the results of the procedure, satisfaction with rehabilitation, and overall impact of the device at 3 months, 6 months, and 12 months
Psychological measures	N/A <sup>d</sup>	HADS <sup>e</sup> -validated questionnaire at baseline, 6 months, and 12 months
<b>Outcomes reported by rehabilitation staff</b>		
Delivery/implementation of rehabilitation and device training	Semistructured interviews with rehabilitation staff to record rehabilitation and training strategies, fidelity of delivery, satisfaction with rehabilitation and training program, barriers and facilitators after 5 patients received Argus II and at the end of the study	N/A
Impact of device on activities of daily living	Short "session report" by rehabilitation staff, which records number of visits, length of visit, and "training" strategies delivered at each visit	Semiquantitative: Visual function tests assessed by rehabilitation staff and recorded on an ordinal scale at baseline and 12 months
<b>Clinical outcomes</b>		
Safety outcomes	N/A	<ul style="list-style-type: none"> <li>Procedural success</li> <li>All-cause adverse events and serious adverse events</li> <li>Management and outcome of adverse events</li> <li>Device explanation rate</li> </ul>
Visual function	N/A	<ul style="list-style-type: none"> <li>Full-field stimulus light threshold</li> <li>Square localization test</li> <li>Direction of motion test</li> <li>Grating visual acuity test</li> <li>Landolt-C test</li> </ul>
Resource use	N/A	<ul style="list-style-type: none"> <li>Proforma for clinical teams, including number of consultations, staff grade, length of procedure, additional interventions, adverse event management</li> <li>Rehabilitation use costed separately from device-related resource</li> </ul>

<sup>a</sup>QoL: quality of life.

<sup>b</sup>EQ-5D-5L: 5-level EuroQoL 5-dimension scale.

<sup>c</sup>EQ-VAS: EuroQoL visual analog scale.

<sup>d</sup>N/A: not applicable.

<sup>e</sup>HADS: Hospital Anxiety and Depression Scale.

The IVI-VLV questionnaire, developed by Finger et al [13] in 2014, has been chosen as a vision-related QoL outcome in this study to assess the true effect of the Argus II device on participants' QoL. The IVI-VLV is a self-rated 28-item questionnaire for use in participants with severe vision loss. Questions are split into 2 subscales: (1) 12 items in the emotional well-being subscale and (2) 16 items in the activities of daily living, mobility, and safety subscale. The tool has been validated and is suitable for use as an outcome measure in trials attempting sight restoration [13]. It can differentiate between different levels of vision-related QoL in participants, and its results are unaffected by levels of self-perceived general and mental health. This was chosen over VisQoL used in a previous Argus II study [9] because the latter is a much shorter (6-item) vision-related utility instrument for the health economic evaluation of eye care and rehabilitation programs rather than a tool to obtain in-depth patient-focused feedback. A generic tool, EQ-5D-5L, is proposed to collect non-disease-specific measures by using a well-established and cross-specialty questionnaire. The EQ-5D-5L comprises the widely used global health questionnaire that provides a simple descriptive profile and a single index value for health status [14].

HADS will be used in the study to examine the effect of Argus II on depression and anxiety. The HADS is a validated and widely used self-rating scale that measures anxiety and depression in both hospital and community settings [15]. This is an important outcome, as mental health issues are prevalent in this patient group. The questionnaire is composed of 14 items (7 for the anxiety subscale and 7 for depression subscale) and can be answered within 2-5 minutes.

A short bespoke (nonvalidated) questionnaire is proposed to provide a structured survey response to questions related to the device and the participant experience. Likert scales or check boxes will be used to assess the following: frequency and duration of device use in the past week, tasks performed with help of the device, pain/discomfort due to the device, perceived complications from the device/procedure, satisfaction with the results of the procedure, and overall effect of the device. The device-related questionnaire will also include a free-text section to capture other information that participants consider important.

### **Vision Rehabilitation Assessments**

The impact of the device on participants' functional vision and activities of daily living will be assessed by vision rehabilitation specialists using a set of visual function tests recorded on an ordinal scale at baseline and 12 months (Table 1 and Table 2). Vision rehabilitation specialists will complete a short "session report," which describes the actual "training" strategies delivered to the participants, the duration, and the setting of the visit. The proforma will record whether the vision rehabilitation specialists delivered the rehabilitation program as planned and any deviation or adaptations to the planned intervention. Independent researchers will carry out semistructured interviews with vision rehabilitation specialist staff at the study halfway point (after 5 participants have received Argus II) and then at the study end. These interviews will record rehabilitation and training strategies, fidelity of delivery, satisfaction, context, barriers, and facilitators. Once subjects have completed the 1-year

follow-up, they will continue to use the device and will be followed per the standard of care (ie, follow-up visits every 12 months).

### **Outcomes**

The outcome measures are described in Table 2.

### **Data Management and Analysis**

#### **Qualitative Data**

Audio recordings of each interview will be transcribed verbatim into a standard word processing document by independent researchers. All potentially identifiable participant data will be deidentified in the transcript. Transcripts will be imported and coded using computer-assisted qualitative data analysis software (NVivo, QSR International). Analysis of the qualitative data will use a mainly iterative-inductive approach, whereby emergent categories and ideas are generated based on specific observations and measures, rather than *a priori* concepts. This approach is committed to retaining diversity and complexity in the analysis. Furthermore, we aim to respect the uniqueness of individual cases as well as identifying comparative themes and patterns. Inductive thematic analysis (using elements of Grounded Theory as a set of procedures for coding data) will be used to identify themes in the data and to combine them to achieve a coherent interpretation of how the Argus II device affects participants' QoL.

#### **Quantitative Data**

Clinical data collected at the treating sites will be transferred to a secure electronic study database. Responses from the participants to questionnaires will be recorded on paper copies by independent researchers and then transferred to the study database. Data will be reidentified to enable linkage with qualitative data to provide richness. The aim of this mixed methods approach will be to investigate not only "did the implant improve vision and quality of life" (from quantitative data sources) but also "how" and "why" and most importantly the patients' own perception of the impact on their QoL (from qualitative data). For instance, questionnaires may point toward measurable improvements between baseline and follow-up in vision and QoL; when linked to qualitative interview data, we can better understand the factors that influenced this result such as previous patient strategies for dealing with vision loss, existence of mental health issues, home living arrangements and support network, perception of the impact of the device, perception of rehabilitation support, and patient engagement with rehabilitation service. Individual participant measures will be presented in a case report format where appropriate, with a focus on changes from baseline to follow-up. Descriptive statistics will be generated across all measures. No statistical comparisons will be carried out due to the small sample size.

#### **Adverse Events**

All participants who have been exposed to the study treatment will be evaluated for adverse events at each visit. All adverse events, regardless of the severity or seriousness and whether they are ascribed to the study treatment, will be recorded in the source documents and case report form by using standard medical terminology and coded using the Medical Dictionary

for Regulatory Activities Preferred Terms. The adverse event severity, action taken, outcome, follow-up, and relatedness to study device will be recorded and escalated appropriately.

### Patient and Public Involvement

Two patient representatives sat on the Steering Group for this study, which had met regularly since the project's inception. Both have been treated with the Argus II device in a previous study and they provided valuable insights to the research teams regarding the acceptability of the planned research and how best to design the study from a patient perspective. Both patient representatives reviewed the participant information sheet and informed consent form and provided feedback.

### Ethical Considerations

This study is a clinical trial of a CE-marked active implantable medical device being used as per the manufacturer's intended purpose. The manufacturer's instructions for use will be followed at all times. Previous studies suggest that there is a material risk of adverse events associated with the implantation of Argus II. Clinical teams and rehabilitation specialists will monitor participants closely following implantation of the device to ensure that adverse events are identified and treated promptly. Risks to participant data confidentiality will be mitigated through transfer of only deidentified participant data between treatment sites (questionnaire and interview data will be deidentified). Protocol adherence will be monitored at both clinical sites by the sponsor (King's College London). This study has been reviewed by and given favorable ethical opinion by London Camberwell St. Giles Research Ethics Committee (REC Reference: 19/LO/0429). It has also been approved by the Health Research Authority and Health and Care Research Wales. Written informed consent will be obtained from eligible patients prior to enrolment.

### Results

This study was approved by the local ethics committee on April 24, 2019 (London-Camberwell St. Giles Research Ethics Committee, reference 19/LO/0429). At the time of protocol writing, Argus II was available for use in the United Kingdom; however, during preparation for study initiation, the manufacturer (Second Sight) suspended worldwide production of the device, resulting in the suspension of commercialization in the United Kingdom and other international markets (to direct resources to development of the Orion cortical implant). We felt it important to publish this protocol so that the publicly funded work to develop the protocol is made publicly available and that researchers planning similar research on other retinal or low vision devices could learn from our work.

### Acknowledgments

This study is funded through NHS England's Commissioning through Evaluation program and a grant from the National Institute for Health Research (grant reference: NIHR 128190). Cedar has also been funded by NICE to undertake nonresearch activities. NICE and NHS England have been involved in the design of the study. None of the funding bodies will be involved in the

## Discussion

### Overview

Retinitis pigmentosa is a disabling disease, which currently has no cure. Insertion of a retinal prosthesis offers a potentially important treatment by restoring perception of light, movement, and shapes, but the effect of this relatively basic visual function on QoL is unknown. This study was part of NHS England's Commissioning through Evaluation program, which is part of its Evaluative Commissioning Program. Commissioning through Evaluation enables a limited number of patients to access treatments that are not routinely funded by the NHS, but nonetheless show significant promise for the future, while new clinical and patient experience data are collected within a formal evaluation program. NHS England's clinical commissioning policy states that there is not sufficient evidence to support the routine commissioning of Argus II for retinitis pigmentosa and that, based on the recommendation by the Rare Diseases Advisory group, further evaluation is required before making the treatment available. In addition, NICE IPG519 recommends further research on this technology, including outcomes on the impact on QoL and activities of day-to-day living and durability of implants. The proposed Commissioning through Evaluation study has been designed to fill this evidence gap by providing first-hand narrative accounts of patients about the effects on their daily activities and QoL before and after receiving a prosthesis.

### Strengths and Limitations

The key strength of this study is the mixed method design, which used both qualitative and quantitative outcomes to provide a rich and in-depth evaluation of the effect of the Argus II device on the quality of patients' lives. Patients previously treated with Argus II have sat on the Steering Group and have been integral to the study design and production of patient-facing documentation and assessment tools. The involvement of independent researchers to gather qualitative data from patients and vision rehabilitation specialists lends credibility to the research. Furthermore, collecting data on the provision of a rehabilitation service adds a unique and important insight to this research on a complex intervention.

The main limitation of this study is the small sample size. Only 30 patients have previously received this technology in the United Kingdom in a research context. We accept that limiting our sample size to 10 may not identify every key theme when interviewing participants, but we expect to identify those most important to the majority of the participants. Purposive sampling, which aims to select the most information-rich cases (eg, extreme sampling or maximum variation sampling), is not appropriate for this study because of the ethical problems of denying the Argus II intervention to eligible participants.

collection, analysis, or interpretation of the study results. The authors sincerely thank the patient representatives for their time and contribution to the design of this study. We thank Andy Fisher (Focal Point UK) for his contributions to the rehabilitation program delivery and evaluation planning. Contributors from NHS England are also acknowledged.

### Authors' Contributions

JW, LK, and TLJ led the design of the protocol. KW, H Patrick, H Powell, and LB provided input to the protocol design and study set-up. TLJ, LdC, and PS provided clinical input to the protocol. JW and TLJ wrote the first draft of the manuscript with input from KW and all of the coauthors. All authors have reviewed and approved the final manuscript

### Conflicts of Interest

LdC and PES were investigators and surgeons in the Argus II feasibility study (NCT00407602). PES has undertaken consultancy for Second Sight. The remaining authors (JW, LK, LdC, H Patrick, H Powell, LB, KW, GCR, and TLJ) report no financial or nonfinancial interest related to this project.

Multimedia Appendix 1

Interview topic guide.

[[DOCX File, 18 KB - resprot\\_v10i1e17436\\_app1.docx](#)]

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## Abbreviations

**EQ-5D-5L:** 5-level EuroQoL 5-dimension scale  
**EQ-VAS:** EuroQoL visual analog scale  
**IVI-VLV:** Impact of Vision Impairment-Very Low Vision  
**NHS:** National Health Service  
**NICE:** National Institute for Health and Care Excellence  
**QoL:** quality of life  
**VisQoL:** Vision and Quality of Life Index

*Edited by G Eysenbach; submitted 12.12.19; peer-reviewed by BM Kyaw, N de Jong; comments to author 21.08.20; revised version received 15.09.20; accepted 17.11.20; published 20.01.21.*

*Please cite as:*

*White J, Knight L, da Cruz L, Stanga PE, Patrick H, Powell H, Berry L, Withers K, Carolan-Rees G, Jackson TL  
Effects of the Argus II Retinal Prosthesis System on the Quality of Life of Patients With Ultra-Low Vision Due to Retinitis Pigmentosa:  
Protocol for a Single-Arm, Mixed Methods Study  
JMIR Res Protoc 2021;10(1):e17436  
URL: <http://www.researchprotocols.org/2021/1/e17436/>  
doi: [10.2196/17436](https://doi.org/10.2196/17436)  
PMID: [33470946](https://pubmed.ncbi.nlm.nih.gov/33470946/)*

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Protocol

# Health-Related Quality of Life in European Childhood Cancer Survivors: Protocol for a Study Within PanCareLIFE

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## Abstract

**Background:** Survival after childhood cancer has improved to more than 80% during the last few years, leading to an increased number of childhood cancer survivors. Cancer itself, or its treatment, may cause chronic health conditions, including somatic and mental sequelae, which may affect survivors' health-related quality of life (HRQoL).

**Objective:** The project PanCareLIFE aims to establish a large database with comprehensive data on childhood cancer survivors from different European countries, including data on HRQoL. Within PanCareLIFE, this study aims to describe HRQoL in survivors, investigate predictors of HRQoL, and describe the association of HRQoL with hearing and female fertility impairment.

This paper describes the design of the HRQoL study, the origin of data, strategies for data collection, and sampling characteristics of survivors from each contributing country.

**Methods:** A total of 6 institutions from 5 European countries (the Czech Republic, France, Germany, the Netherlands, and Switzerland) provided data on HRQoL assessed with the Short Form 36 and on relevant predictors. The central PanCareLIFE data center aggregated the data and harmonized the variables between the institutions. Survivors were eligible if they received a diagnosis of cancer according to the 12 main groups of the International Classification of Childhood Cancer, 3rd edition, or Langerhans cell histiocytosis; were aged  $\leq 18$  years at the time of diagnosis; were residents of the respective country at the time of diagnosis; had survived  $\geq 5$  years after cancer diagnosis; were aged  $\geq 18$  years at the time of the questionnaire survey; and did not refuse to registration in the national or local childhood cancer cohort.

**Results:** We identified 24,993 eligible survivors. Of those, 19,268 survivors received a questionnaire and 9871 survivors participated, resulting in response rates of 9871/24,993 (39.50%) of eligible survivors and of 9871/19,268 (51.23%) invited survivors. Most participants were diagnosed with cancer between the ages of 10 and 14 years (3448/9871, 34.93%) or  $< 5$  years (3201/9871, 32.43%). The median age was 8 years. Of the 9871 participants, 3157 (31.97%) were survivors of leukemia, 2075 (21.02%) lymphoma, and 1356 (13.7%) central nervous system (CNS) tumors. Most participants (9225/9871, 93.46%) had no history of a subsequent tumor; 77.45% (7645/9871) received chemotherapy with or without other treatments. More than half (5460/9871, 55.31%) were aged 25 to 34 years at the time of the HRQoL study. Participating survivors differed from nonparticipants; participants were more often women, survivors of leukemia or lymphoma, and less frequently, survivors of CNS tumors than nonparticipants.

**Conclusions:** PanCareLIFE successfully assessed HRQoL and its predictors in 9871 European survivors of childhood cancer. This large population will permit detailed investigations of HRQoL after childhood cancer, particularly the impact of hearing and female fertility impairment on HRQoL.

**International Registered Report Identifier (IRRID):** RR1-10.2196/21851

(*JMIR Res Protoc* 2021;10(1):e21851) doi:[10.2196/21851](https://doi.org/10.2196/21851)

## KEYWORDS

children; adolescents; neoplasms; quality of life; health status; Europe; epidemiology; survivors of childhood cancer

## Introduction

At present, more than 80% of children diagnosed as having cancer in Europe survive [1]. Almost half a million childhood cancer survivors are estimated to live in Europe in 2020 [2]. However, cancer itself, or its treatment, causes chronic health conditions, including a broad spectrum of somatic [3] and mental sequelae [4]. In the St. Jude Lifetime Cohort Study, nearly all childhood cancer survivors had at least one chronic health condition by the age of 50 years and twice the burden of disease than the general population [5]. Chronic health conditions such as heart failure, second neoplasms, or pulmonary dysfunction can be life threatening; other health conditions such as fertility and hearing impairment can affect survivors' life planning and daily life, which may reduce their health-related quality of life (HRQoL) [6-8].

HRQoL is a multidimensional concept that includes elements of physical, functional, social, and psychological health as well as perceived health status and well-being [9]. Many studies assessing HRQoL in childhood cancer survivors used different questionnaires or different reference groups or varied in characteristics of the study population (eg, treatment era, age of survivors, cancer diagnostic groups), making it difficult to compare results between studies [10]. Results from large childhood cancer survivor studies in the United Kingdom (British Childhood Cancer Survivor Study, BCCSS) [11], the United States (Childhood Cancer Survivor Study) [12], and Switzerland (Switzerland Childhood Cancer Survivor Study, SCCSS) [6] suggest that, on average, childhood cancer survivors

have similar HRQoL compared with the general population. However, there were significant differences in HRQoL between subgroups of survivors. Women, survivors with low educational background, survivors of brain tumors, and survivors who had undergone radiotherapy had the lowest HRQoL [6,11,12]. It is still unclear which other factors influence HRQoL and whether HRQoL in childhood cancer survivors differs among European countries.

Within the PanCareLIFE project, funded by the European 7th Framework Program (FP7), we aim to study HRQoL in a large database of childhood cancer survivors from 5 European countries using a homogeneous approach to assess and analyze HRQoL. In particular, we aimed to compare HRQoL in European childhood cancer survivors with normative data and between European countries to determine predictors of HRQoL and describe the effect of hearing and fertility impairment on HRQoL [13]. This study provides an overview of the design, data origin, and data collection strategies and summarizes the characteristics of survivors who participated in this study.

## Methods

### The PanCareLIFE Research Framework

The European FP7 project PanCareLIFE (grant agreement no. 602030) started in 2013 [14]. Institutions from 10 countries provided data on more than 15,000 childhood, adolescent, or young adult cancer survivors. Within the PanCareLIFE framework, this study focused on long-term HRQoL in childhood cancer survivors [13]. It was based in the University Hospitals of Münster (2013-2015) and Bonn (2016-2018). The

Institute of Social and Preventive Medicine at the University of Bern provided methodological support and conducted the analyses. Each institution obtained ethical approval according to their local and/or national authority regulations before collecting the data. For all survivors, either written informed consent was obtained or the ethics committee agreed that an individual's consent was not required for this questionnaire study.

## Origin of Data and Inclusion Criteria

The PanCareLIFE HRQoL study population was composed of 6 national or regional cohorts, which had slightly different inclusion criteria. [Table 1](#) provides an overview of the countries and institutions that provided data for the PanCareLIFE HRQoL study.

**Table 1.** Sources of eligible survivors for the PanCareLIFE health-related quality of life study.

Country	Data provider	National or regional cohort	Source of baseline data	Identification (prospective or retrospective)	Estimated national or regional coverage (%)
Switzerland	UNIBE <sup>a</sup>	SCCSS <sup>b</sup> [15]	National population-based registry	Prospective	95 [16]
The Czech Republic	FNMC <sup>c</sup> and UHB <sup>d</sup>	N/A <sup>e</sup>	Hospital-based cohort	Retrospective	95
France	CHU-SE <sup>f</sup>	Rhone-Alpes Cohort	Regional population-based registry	Prospective and retrospective	95
The Netherlands	DCOG LATER <sup>g</sup> Registry with data from 7 pediatric oncology hospitals	DCOG LATER [17]	Registry based on nationwide hospital cohorts [18]	Retrospective	>95
Germany	VIVE <sup>h</sup> group (UKB <sup>i</sup> /UKM <sup>j</sup> )	VIVE	National population-based registry [19]	Prospective	>95 [20]

<sup>a</sup>UNIBE: University of Bern.

<sup>b</sup>SCCSS: Swiss Childhood Cancer Survivor Study.

<sup>c</sup>FNMC: Motol Teaching Hospital, Prague, the Czech Republic.

<sup>d</sup>UHB: University Hospital Brno, the Czech Republic.

<sup>e</sup>N/A: not applicable.

<sup>f</sup>CHU-SE: Centre Hospitalier Universitaire de Saint-Étienne, St Étienne, France.

<sup>g</sup>DCOG LATER: Dutch Childhood Oncology Group Survivor study.

<sup>h</sup>VIVE: First Basic Survey on Life Situation, State of Health, and Quality of Life of Childhood Cancer Survivors in Germany.

<sup>i</sup>UKB: Universitätsklinikum, Bonn, Germany.

<sup>j</sup>UKM: Universitätsklinikum, Münster, Germany.

We combined data from Brno and Prague to 1 Czech cohort. The identification of eligible survivors depended on the respective cohort. Switzerland and Germany prospectively identified the survivors from the national childhood cancer registry, the Czech Republic and the Netherlands retrospectively identified the survivors and France implemented both ways of identification ([Table 1](#)) [15,17-19]. The identification of survivors was population-based in Switzerland, the Rhone-Alpes

region (France), and Germany. In the Netherlands and the Czech Republic, it was hospital-based, with an estimated coverage of 95% of the national childhood cancer population. Switzerland, Germany, and the Netherlands enrolled their cohorts before and France and the Czech Republic after the launch of PanCareLIFE. Details on the period of data collection and sample characteristics of each cohort are listed in [Table 2](#).

**Table 2.** Number of eligible patients, time period of cancer diagnosis, age of survivors at diagnosis, time period of the health-related quality of life (HRQoL) survey, and age of survivors at HRQoL survey, by country.

Country	Number of eligible survivors	Years of diagnosis	Age at diagnosis (years)	Years of study	Age at study (years)
Switzerland	3023	1976-2010	≤18	2007-2016	18-47
The Czech Republic	3127	1967-2010	≤18	2013-2017	18-51
France	1060	1987-1999	≤15	2005-2016	18-43
The Netherlands	5639	1963-2001	≤17	2016-2017	18-70
Germany	12,144	1980-2003	≤15	2014-2015	25-47

Survivors were eligible for the study if they were aged ≤18 years at the time of diagnosis, had been residents of the respective country at the time of diagnosis, had a cancer diagnosis according to the International Classification of Childhood

Cancer, 3rd edition (ICCC-3) [21] or had been diagnosed as having Langerhans cell histiocytosis, had survived ≥5 years after cancer diagnosis, were aged ≥18 years at the time of the questionnaire survey, were not undergoing treatment for cancer



at the time of the study, and did not refuse to registration in the national or local childhood cancer cohort. The last criterion did not apply to Czech survivors because patients were identified in a clinical routine. We could not calculate the exact age at the time of survey and the survival time, as we did not receive information on the day of birth, day of diagnosis, and day of survey from the institutions because of PanCareLIFE data protection rules. Therefore, we allowed for a tolerance of 2 months and included survivors who were 2 months older than 18 years at the time of cancer diagnosis, those who survived 2 months less than 5 years, and those who were 2 months younger than 18 years at the time of the survey.

In addition to the general eligibility criteria, there were country-specific reasons for the exclusion of eligible survivors and not all reasons applied to all cohorts. The Czech Republic, France, and the Netherlands excluded survivors with severe mental sequelae. In Switzerland and the Czech Republic, survivors were excluded from invitation because of physicians' decisions mainly because of palliative care or relapsed disease. France, the Czech Republic, and Switzerland did not exclude survivors because of competing surveys. In the Netherlands and Germany, 2.21% (552/24,993) of survivors could not be included because they were already enrolled in competing surveys (Table 3). The French cohort did not include leukemia survivors.

**Table 3.** Overview of eligible, invited, and participating survivors in the health-related quality of life Short Form 36 questionnaire study, overall and by country.

Overview	Country					
	All data providers combined (n=24,993), n (%)	Switzerland (n=3023), n (%)	The Czech Republic (n=3127), n (%)	France (n=1060), n (%)	The Netherlands (n=5639), n (%)	Germany (n=12,144), n (%)
<b>Eligible cohort</b>						
Died before questionnaire mailing	2088 (8.35) <sup>a</sup>	252 (8.34) <sup>a</sup>	6 (0.19) <sup>a</sup>	74 (6.98) <sup>a</sup>	677 (12.00) <sup>a</sup>	1079 (8.89) <sup>a</sup>
Severe mental sequelae	28 (0.11) <sup>a</sup>	0 (0) <sup>a</sup>	15 (0.48) <sup>a</sup>	2 (0.19) <sup>a</sup>	11 (0.20) <sup>a</sup>	0 (0) <sup>a</sup>
Living abroad	489 (1.96) <sup>a</sup>	95 (3.14) <sup>a</sup>	8 (0.26) <sup>a</sup>	0 (0) <sup>a</sup>	127 (2.25) <sup>a</sup>	259 (2.13) <sup>a</sup>
No address or lost-to-follow-up	854 (3.42) <sup>a</sup>	148 (4.90) <sup>a</sup>	259 (8.28) <sup>a</sup>	122 (11.51) <sup>a</sup>	16 (0.28) <sup>a</sup>	309 (2.54) <sup>a</sup>
Physician's decision not to invite the survivor <sup>b</sup>	118 (0.47) <sup>a</sup>	14 (0.46) <sup>a</sup>	104 (3.33) <sup>a</sup>	0 (0) <sup>a</sup>	0 (0) <sup>a</sup>	0 (0) <sup>a</sup>
Competing surveys	552 (2.21) <sup>a</sup>	0 (0) <sup>a</sup>	0 (0) <sup>a</sup>	0 (0) <sup>a</sup>	266 (4.72) <sup>a</sup>	286 (2.36) <sup>a</sup>
Other <sup>c</sup>	1596 (6.39) <sup>a</sup>	1 (0.03) <sup>a</sup>	1159 (37.06) <sup>a</sup>	11 (1.04) <sup>a</sup>	292 (5.18) <sup>a</sup>	133 (1.08) <sup>a</sup>
<b>Invited cohort</b>						
Did not respond to the invitation	8277 (42.96) <sup>d</sup>	775 (30.84) <sup>d</sup>	461 (29.25) <sup>d</sup>	418 (49.12) <sup>d</sup>	2074 (48.80) <sup>d,e</sup>	4549 (45.14) <sup>d</sup>
Refused to participate	914 (4.74) <sup>d</sup>	148 (5.89) <sup>d</sup>	30 (1.90) <sup>d</sup>	42 (4.94) <sup>d</sup>	0 (0) <sup>d,e</sup>	694 (6.89) <sup>d</sup>
Short Form 36 information incomplete for full scoring	206 (1.07) <sup>d</sup>	5 (0.20) <sup>d</sup>	56 (3.55) <sup>d</sup>	6 (0.71) <sup>d</sup>	30 (0.71) <sup>d</sup>	109 (1.08) <sup>d</sup>
Participating cohort	9871 (51.23) <sup>d</sup>	1585 (63.07) <sup>d</sup>	1029 (65.29) <sup>d</sup>	385 (45.24) <sup>d</sup>	2146 (50.49) <sup>d</sup>	4726 (46.89) <sup>d</sup>

<sup>a</sup>Proportions of survivors from the eligible cohort.

<sup>b</sup>Physician's decision not to invite the survivors because of psychosocial reasons or family problems.

<sup>c</sup>Other reasons were as follows: patients could not be approached during the study period (the Czech Republic, n=1156), ethical approval not obtained in time (the Netherlands, n=279), moved to another center (the Netherlands, n=3), unknown case at the time of the study (France, n=1), transgender (the Netherlands, n=1), did not understand the local language (Switzerland, n=1), unknown reasons (the Czech Republic, n=3; the Netherlands, n=9; France, n=11; Germany, n=133).

<sup>d</sup>Proportions of survivors from the invited cohort.

<sup>e</sup>Dutch survivors who refused to participate were included in the category *Did not respond to the invitation* because the Netherlands did not distinguish between nonresponse and refusal.

## Variables

Exposure variables and confounders covered the following topics: demographic characteristics, socioeconomic measures, lifestyle, cancer diagnosis, cancer treatment, hearing impairment, and female fertility impairment.

The outcome variables were the 36 HRQoL questions from the Short Form 36 (SF-36, version 1 or 2). The Netherlands, Germany, and the Czech Republic used version 1 of the SF-36, and Switzerland and France used version 2 [22,23]. Both versions differ only slightly in a few items, whereas the psychometric properties are comparable [24]. With the exception of variables concerning demographic characteristics, cancer diagnosis, and cancer treatment, all variables were self-reported.

Self-reported confounder variables included living with a partner (yes or no), education, occupational status, migration background, alcohol consumption, smoking, and body mass index. Another substudy of the PanCareLIFE research project investigated female fertility impairment and coded the data using 8 different criteria into a binary variable (fertility impairment: yes or no). The detailed procedure is outlined by

van den Berg et al [25]. Fertility impairment data on male survivors were unfortunately not available in most of the cohorts; therefore, we will analyze female survivors only.

Hearing impairment data (yes or no) were collected together with information on HRQoL via questionnaires. Questions on hearing impairment differed slightly between data providers. Data on hearing impairment were not available for the Dutch cohort. All relevant variables (outcomes, exposures, and confounders) are listed in [Multimedia Appendix 1](#).

The central PanCareLIFE data center defined a baseline variable list, including sex, cancer, and treatment-related variables and a minimal set of information provided for nonparticipants. The data center collected and harmonized the variables from each institution. We also recoded a few variables used specifically for the HRQoL study (eg, on hearing impairment) in cooperation with the institutions. All partners transferred the data according to the PanCareLIFE data protection standards.

The sources of cancer-related and treatment information, sources of self-reported data, and the methods of written questionnaire assessments differed slightly among the 5 cohorts ([Table 4](#)).

**Table 4.** Sources of cancer-related and treatment data and logistics of paper-pencil questionnaire assessment of health-related quality of life, by country.

Country	Source of cancer-related data	Source of treatment data	Logistics of questionnaire mailing to assess HRQoL <sup>a</sup> and sociodemographic data
Switzerland	Forms sent by clinical sites to Swiss Childhood Cancer Registry	ITT <sup>b</sup> -based information complemented with AT <sup>c</sup> information; AT data retrospectively collected from medical records	Coordinated centrally by SCCSS <sup>d</sup> . Survivors were approached by email and phone call reminders.
The Czech Republic	Clinical records in UHB <sup>e</sup> and FNM <sup>f</sup>	AT information, retrospectively collected from medical records	Coordinated either by UHB or FNM. Survivors were approached during clinical visits, by email or phone calls, followed by mailed questionnaire.
France	Forms sent by clinical sites of the Rhône-Alpes region to the Rhône Alpes Regional Childhood Cancer Registry	AT information, retrospectively collected from medical records	Coordinated by CHU-SE <sup>g</sup> . Survivors were approached mainly by email and phone call reminders, sometimes during clinical visits, followed by mailed questionnaire.
The Netherlands	DCOG <sup>h</sup> LATER Registry [17,18]	AT information, retrospectively collected from medical records	Coordinated by DCOG LATER <sup>i</sup> clinics. Most survivors were approached by email and few during clinical visits.
Germany	Forms sent by clinical sites to the German Childhood Cancer Registry	ITT-based information	Coordinated centrally by UKM <sup>j</sup> or UKB <sup>k</sup> and GCCR <sup>l</sup> . Survivors were approached by mailed questionnaire.

<sup>a</sup>HRQoL: health-related quality of life.

<sup>b</sup>ITT: intention to treat.

<sup>c</sup>AT: as treated.

<sup>d</sup>SCCSS: Swiss Childhood Cancer Survivor Study.

<sup>e</sup>UHB: University Hospital Brno, the Czech Republic.

<sup>f</sup>FNM: Motol Teaching Hospital, Prague, the Czech Republic.

<sup>g</sup>CHU-SE: Centre Hospitalier Universitaire de Saint-Étienne, Saint-Étienne, France.

<sup>h</sup>DCOG: Dutch Childhood Oncology Group.

<sup>i</sup>DCOG LATER: Dutch Childhood Oncology Group Survivor study.

<sup>j</sup>UKM: Universitätsklinikum, Münster, Germany.

<sup>k</sup>UKB: Universitätsklinikum, Bonn, Germany.

<sup>l</sup>GCCR: German Childhood Cancer Registry.

Data on HRQoL and HRQoL-specific exposure variables and self-reported confounders were assessed using the same questionnaire. An exception were the Dutch survivors, who answered the questionnaire on HRQoL on average 4 years later than the questions on sociodemographic characteristics and lifestyle for the purpose of their national Dutch Childhood Oncology Group Survivor (DCOG LATER) study.

### SF-36 Data From the General Population

Country-specific reference data from the general population did not exist for Switzerland, France, and the Czech Republic at the time of the study. We used the German SF-36 version 1 normative data from 1998 for norm-based scoring of data from all participating countries [26]. This norm-based scoring allowed us to compare the HRQoL between countries [24]. We also scored HRQoL raw data with more recent SF-36 version 2 normative data from Germany (2008-2011) [24] and from Switzerland (2015-2016) [27].

### Statistical Analyses

We compared survivors who participated in the survey with those who did not participate using chi-square tests. We used the software package Stata (version 14, StataCorp) for all analyses.

For all future analyses, we documented the planned statistical approaches for all HRQoL-related research questions of PanCareLIFE in a statistical analysis plan before we received the data from the central data center. In brief, SF-36 consists of 36 items (questions), which use a 2- to 6-point Likert scale, depending on the item. Between 2 and 10 items can be summarized into 1 of the 8 scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and further into 2 summary scores (Physical Component Summary and Mental Component Summary). Because we will perform comparisons with both version 1 and version 2 normative data, we will transform all scales into the respective version with an algorithm provided by the developer of SF-36 [23,24,26]. We will convert raw scores into *T*-scores (mean 50, SD 10), and depending on the normative data used, we will stratify for subgroups, for example, age and sex. Higher scores indicate better HRQoL. Survivors with >50% missing data in any of the SF-36 scales will be excluded from the analyses. We will implement appropriate measures to deal with missing values, including imputation procedures. We will use regression analyses with HRQoL as an outcome variable to address all research questions to (1) compare HRQoL in European childhood cancer survivors with

normative data and between European countries and to determine predictors of HRQoL, (2) describe the effect of hearing impairment on HRQoL, and (3) describe the effect of fertility impairment on HRQoL. We will include country, gender, and age in all multivariable models. We will also include the most important risk factors as defined by a selection criterion of  $P < .05$  in the univariable regression. [Multimedia Appendix 1](#) gives an overview of the variables that we plan to include in the regression analyses. If HRQoL scores have a skewed distribution, we will run logistic regressions (poor HRQoL vs normal or high HRQoL) and define poor HRQoL and high HRQoL, respectively, as scores below [11] and above the 10th percentile of the control population.

We will analyze subcohorts depending on the research question ([Multimedia Appendix 2](#)). For the analyses of differences in HRQoL between participating countries and predictors of HRQoL and for the analyses of the effect of hearing on HRQoL, we will use 2 main subsets for the analysis. In the first, we will include all survivors aged  $\geq 25$  years at the time of the study from all participating countries. The second subset will include survivors aged <25 years from all countries except Germany because Germany did not collect data in this age group. For the analyses on the effect of fertility impairment on HRQoL, we will investigate female survivors aged  $\geq 25$  years only. We will describe the detailed procedure in the respective publication of each research question.

## Results

We identified 24,993 eligible 5-year childhood cancer survivors ([Table 3](#)). Of those, 5725 had died before the questionnaire survey, had severe mental problems, were living abroad at the time of the study, had no available contact data (lost to follow-up), were enrolled in competing surveys, their physicians decided not to invite them, or for other reasons. Of the 19,268 survivors who received an invitation to the HRQoL survey, 9192 did not respond or refused to participate and 206 had incomplete SF-36 information, preventing full scoring. In total, 9871 survivors (4725 men and 5146 women) participated in the HRQoL analyses, thus resulting in response rates of 39.50% (9871/24,993) of eligible survivors and of 51.23% (9871/19,268) of invited survivors. Of the 9871 participating survivors, almost half were from Germany 4726 (47.88%), 2146 (21.74%) from the Netherlands, 1585 (16.06%) from Switzerland, 1029 (10.42%) from the Czech Republic, and 385 (3.90%) from France ([Table 5](#)).

**Table 5.** Sociodemographic and medical characteristics of participating survivors, by country.

Country	All data providers combined (N=9871), n (%)	Switzerland (n=1585), n (%)	The Czech Republic (n=1029), n (%)	France (n=385), n (%)	The Netherlands (n=2146), n (%)	Germany (n=4726), n (%)
<b>Sex</b>						
Male	4725 (47.87)	824 (51.99)	347 (33.72)	167 (43.38)	1076 (50.14)	2311 (48.90)
Female	5146 (52.13)	761 (48.01)	682 (66.28) <sup>a</sup>	218 (56.62)	1070 (49.86)	2415 (51.10)
<b>Age at the time of survey (years)</b>						
18 to <25	1636 (16.57)	725 (45.74)	427 (41.50)	131 (34.03)	353 (16.45)	0 (0)
25 to <30	2997 (30.36)	374 (23.60)	275 (26.72)	123 (31.95)	346 (16.12)	1879 (39.76)
30 to <35	2463 (24.95)	239 (15.08)	164 (15.94)	93 (23.90)	402 (18.73)	1566 (33.14)
35 to <40	1437 (14.56)	146 (9.21)	104 (10.11)	33 (8.57)	363 (16.92)	791 (16.74)
40 to <45	833 (8.44)	63 (3.97)	49 (4.76)	6 (1.56)	301 (14.03)	414 (8.76)
45-69	505 (5.12)	38 (2.40)	10 (0.97)	0 (0)	381 (17.75)	76 (1.61)
<b>Age at cancer diagnosis (years)</b>						
0 to <5	3201 (32.43)	424 (26.75)	289 (28.09)	173 (44.94)	936 (43.62)	1379 (29.18)
5 to <10	2572 (26.06)	352 (22.21)	196 (19.05)	97 (25.19)	595 (27.73)	1332 (28.18)
10 to <15	3448 (34.93)	540 (34.07)	336 (32.65)	115 (29.87)	468 (21.81)	1989 (42.09)
15-18	650 (6.58)	269 (16.97)	208 (20.21)	0 (0)	147 (6.85)	26 (0.55)
<b>Period of cancer diagnosis</b>						
1963 to <1985	2086 (21.13)	340 (21.45)	53 (5.15)	0 (0)	711 (33.13)	982 (20.78)
1985 to <1995	4680 (47.41)	721 (45.49)	283 (27.50)	261 (67.79)	764 (35.60)	2651 (56.09)
1995 to <2005	2792 (28.28)	403 (25.43)	501 (48.69)	124 (32.21)	671 (31.27)	1093 (23.13)
2005-2010	313 (3.17)	121 (7.63)	192 (18.66)	0 (0)	0 (0)	0 (0)
<b>Time since cancer diagnosis (years)</b>						
5 to <10	455 (4.61)	291 (18.36)	164 (15.94)	0 (0)	0 (0)	0 (0)
10 to <15	835 (8.46)	281 (17.73)	226 (21.96)	4 (1.04)	0 (0)	324 (6.86)
15 to <20	2179 (22.07)	397 (25.05)	283 (27.50)	134 (34.81)	450 (20.97)	915 (19.36)
20 to <25	2503 (25.36)	332 (20.95)	160 (15.55)	209 (54.29)	439 (20.46)	1363 (28.84)
25 to <30	2023 (20.49)	183 (11.55)	130 (12.63)	38 (9.87)	393 (18.31)	1279 (27.06)
30 to <35	1302 (13.19)	84 (5.30)	43 (4.18)	0 (0)	331 (15.42)	844 (17.86)
35-54	574 (5.82)	17 (1.07)	23 (2.24)	0 (0)	533 (24.84)	1 (0.02)
<b>Cancer diagnosis (ICCC-3)<sup>b</sup></b>						
I Leukemias	3157 (31.97)	492 (31.04)	267 (25.95)	0 (0) <sup>c</sup>	724 (33.74)	1673 (35.40)
II Lymphomas	2075 (21.02)	351 (22.15)	266 (25.85)	83 (21.56)	349 (16.26)	1026 (21.71)
III CNS <sup>d</sup> tumors	1356 (13.74)	236 (14.89)	125 (12.15)	96 (24.94)	256 (11.93)	643 (13.61)
IV Neuroblastoma	440 (4.47)	51 (3.22)	46 (4.47)	52 (13.51)	118 (5.50)	174 (3.68)
V Retinoblastoma	172 (1.74)	32 (2.02)	19 (1.85)	9 (2.34)	10 (0.47)	103 (2.18)
VI Renal tumors	738 (7.48)	80 (5.05)	81 (7.87)	52 (13.51)	239 (11.14)	286 (6.05)
VII Hepatic tumors	61 (0.62)	9 (0.57)	11 (1.07)	9 (2.34)	16 (0.75)	16 (0.34)
VIII Bone tumors	588 (5.96)	94 (5.93)	62 (6.03)	30 (7.79)	116 (5.41)	286 (6.05)
IX Soft tissue sarcomas	654 (6.63)	99 (6.25)	55 (5.34)	26 (6.75)	164 (7.64)	309 (6.54)



Country	All data providers combined (N=9871), n (%)	Switzerland (n=1585), n (%)	The Czech Republic (n=1029), n (%)	France (n=385), n (%)	The Netherlands (n=2146), n (%)	Germany (n=4726), n (%)
X Germ cell tumors	386 (3.91)	60 (3.79)	60 (5.83)	15 (3.90)	88 (4.10)	163 (3.45)
XI Epithelial neoplasms and melanomas	130 (1.32)	23 (1.45)	20 (1.94)	13 (3.38)	30 (1.40)	44 (0.93)
Other malignant neoplasms <sup>e</sup>	114 (1.15)	58 (3.66)	17 (1.65)	0 (0)	36 (1.68)	3 (0.06)
<b>Subsequent tumor<sup>f</sup></b>						
Yes	646 (6.54)	45 (2.84)	64 (6.22)	14 (3.64)	149 (6.94)	374 (7.91)
No	9225 (93.46)	1540 (97.16)	965 (93.78)	371 (96.36)	1997 (93.06)	4352 (92.09)
<b>Cancer treatment</b>						
Surgery only	642 (6.50)	190 (11.99)	66 (6.41)	92 (23.90)	213 (9.93)	81(1.71)
Radiotherapy only	49 (0.50)	2 (0.13)	2 (0.19)	2 (0.52)	26 (1.21)	17(0.36)
Chemotherapy only	2086 (21.13)	354 (22.33)	176 (17.10)	35 (9.09)	639 (29.78)	882 (18.66)
Surgery and radiotherapy	285 (2.89)	77 (4.86)	32 (3.11)	13 (3.38)	113 (5.27)	50 (1.06)
Surgery and chemotherapy	1737 (17.60)	348 (21.96)	214 (20.80)	129 (33.51)	529 (24.65)	517 (10.94)
Radiotherapy and chemotherapy	1975 (20.01)	145 (9.15)	249 (24.20)	30 (7.79)	257 (11.98)	1294 (27.38)
Radiotherapy, chemotherapy, and surgery	1847 (18.71)	367 (23.15)	261 (25.36)	79 (20.52)	343 (15.98)	797 (16.86)
No surgery, chemotherapy, or radiotherapy	46 (0.47)	16 (1.01)	3 (0.29)	3 (0.78)	18 (0.84)	6 (0.13)
Complete treatment information not available	1204 (12.20)	86 (5.43)	26 (2.53)	2 (0.52)	8 (0.37)	1082 (22.89)
<b>Hematopoietic stem cell transplantation</b>						
Unknown	307 (3.11)	51 (3.22)	3 (0.29)	0 (0)	4 (0.19)	249 (5.27)
Yes	307 (3.11)	65 (4.10)	120 (11.66)	25 (6.49)	50 (2.33)	47 (0.99)
No	9257 (93.78)	1469 (92.68)	906 (88.05)	360 (93.51)	2092 (97.48)	4430 (93.74)

<sup>a</sup>The Czech cohort included a higher proportion of women than other countries, because women were prioritized during recruitment as they were also part of an associated PanCareLIFE study on female fertility.

<sup>b</sup>ICCC-3: International Classification of Childhood Cancer, 3rd edition.

<sup>c</sup>Percentages of French cohort varied from those of other countries because the French cohort did not include survivors of leukemia and CNS tumors represented the largest of diagnostic groups.

<sup>d</sup>CNS: central nervous system.

<sup>e</sup>ICCC-3 main group XII (Other and unspecified malignant neoplasms) and Langerhans cell histiocytosis but not benign and in situ tumors and tumor-like lesions or unclassified survivors.

<sup>f</sup>All subsequent tumors registered in national registry until the start of the study.

Most survivors were diagnosed as having cancer between the ages of 10 and 14 years (3488/9871, 34.93%) or <5 years (3201/9871, 32.43%). Almost half (4680/9871, 47.41%) were diagnosed as having cancer between 1985 and 1994, most were survivors of leukemia (3157/9871, 31.97%), lymphoma (2075/9871, 21.02%), or CNS tumors (1356/9871, 13.74%),

had no history of a subsequent tumor (9225/9871, 93.46%), and received chemotherapy with or without surgery and/or radiotherapy (7645/9871, 77.45%). More than half (5460/9871, 55.31%) of the participants were aged 25 to 34 years at the time of the HRQoL study.

Response rates differed between countries. The proportions of eligible survivors who were invited to participate were 83.13% (2513/3023) in Switzerland and 82.99% (10,078/12,144) in Germany, 80.28% (861/1060) in France, 75.37% (4250/5639) in the Netherlands, and 50.40% (1576/3127) in the Czech Republic (Table 3). The proportion of responders was highest in the Czech Republic, with 65.3% (1029/3127) and lowest in France (385/1060, 45.2%).

Participants were more often women, slightly younger at the time of the survey, and slightly older at cancer diagnosis; their

cancer diagnosis tended to be in more recent years, and they were more often survivors of leukemia or lymphoma and less often survivors of CNS tumors than nonparticipants (Table 6). The Czech participants had the highest proportion of women (682/3127, 66.3%) because women were prioritized during recruitment as they were also part of an associated PanCareLIFE study on female fertility [25]. In other countries, the proportion of women ranged between 48.0% (761/3023, Switzerland) and 56.6% (218/1060, France).

**Table 6.** Comparison of participants and nonparticipants.

Characteristics	Participants (n=9871), n (%)	Nonparticipants (n=15,179), n (%)	P value <sup>a</sup>
<b>Sex</b>			<.001
Male	4725 (47.87)	9058 (59.67)	
Female	5146 (52.13)	6121 (40.33)	
<b>Age at the time of survey (years)</b>			<.001
18 to <25	1636 (16.57)	2245 (14.79)	
25 to <30	2997 (30.36)	4355 (28.69)	
30 to <35	2463 (24.95)	3886 (25.60)	
35 to <40	1437 (14.56)	2496 (16.44)	
40 to <45	833 (8.44)	1399 (9.22)	
45-69	505 (5.12)	798 (5.26)	
<b>Age at the time of cancer diagnosis (years)</b>			.005
0 to <5	3201 (32.43)	5075 (33.43)	
5 to <10	2572 (26.06)	4055 (26.71)	
10 to <15	3448 (34.93)	4977 (32.79)	
15-18	650 (6.58)	1072 (7.06)	
<b>Period of cancer diagnosis</b>			.004
1963 to <1985	2086 (21.13)	3500 (23.06)	
1985 to <1995	4680 (47.41)	7064 (46.54)	
1995 to <2005	2792 (28.28)	4128 (27.20)	
2005-2010	313 (3.17)	487 (3.21)	
<b>Time since cancer diagnosis (years)</b>			<.001
5 to <10	455 (4.61)	679 (4.47)	
10 to <15	835 (8.46)	1024 (6.75)	
15 to <20	2179 (22.07)	2986 (19.67)	
20 to <25	2503 (25.36)	3738 (24.63)	
25 to <30	2023 (20.49)	3513 (23.14)	
30 to <35	1302 (13.19)	2335 (15.38)	
35-54	574 (5.82)	904 (6.96)	
<b>Cancer diagnosis (ICCC-3)<sup>b</sup></b>			<.001
I Leukemias	3157 (31.97)	4398 (28.97)	
II Lymphomas	2075 (21.02)	3015 (19.86)	
III CNS <sup>c</sup> tumors	1356 (13.74)	2659 (17.52)	
IV Neuroblastoma	440 (4.47)	696 (4.59)	
V Retinoblastoma	172 (1.74)	320 (2.11)	
VI Renal tumors	738 (7.48)	983 (6.48)	
VII Hepatic tumors	61 (0.62)	101 (0.67)	
VIII Bone tumors	588 (5.96)	983 (6.48)	
IX Soft tissue sarcomas	654 (6.63)	954 (6.28)	
X Germ cell tumors	386 (3.91)	644 (4.24)	
XI Epithelial neoplasms and melanomas	130 (1.32)	279 (1.84)	
Other malignant neoplasms <sup>d</sup>	114 (1.15)	147 (0.97)	

Characteristics	Participants (n=9871), n (%)	Nonparticipants (n=15,179), n (%)	P value <sup>a</sup>
<b>Treatment</b>			<.001
Surgery only	642 (6.50)	1240 (8.17)	
Radiotherapy only	49 (0.50)	87 (0.57)	
Chemotherapy only	2086 (21.13)	2551 (16.81)	
Surgery and radiotherapy	285 (2.89)	431 (2.84)	
Surgery and chemotherapy	1737 (17.60)	2048 (13.49)	
Radiotherapy and chemotherapy	1975 (20.01)	2580 (17.00)	
Radiotherapy, chemotherapy, and surgery	1847 (18.71)	2075 (13.67)	
No surgery, chemotherapy, or radiotherapy	46 (0.47)	76 (0.50)	
Complete treatment information not available	1204 (12.20)	4091 (26.95)	

<sup>a</sup>P values were derived from Pearson chi-square tests.

<sup>b</sup>ICCC-3: International Classification of Childhood Cancer, 3rd edition.

<sup>c</sup>CNS: central nervous system.

<sup>d</sup>ICCC-3 main group XII (other and unspecified malignant neoplasms) and Langerhans cell histiocytosis but not benign and in situ tumors and tumor-like lesions or unclassified survivors.

## Discussion

### Central Message

PanCareLIFE has successfully constructed a large population of 9871 childhood cancer survivors with comprehensive data to assess HRQoL and its predictors. This rich data set of survivor cohorts from 5 different countries will allow in-depth investigation of the differences in HRQoL between countries, including the effect of female fertility and hearing impairment on HRQoL. The sample size and the wide range of treatment era, type of diagnosis, and age at diagnosis provide an excellent basis for risk stratification. It will thereby provide new scientific information on risk factors for impaired HRQoL after childhood cancer. This study will be the first to estimate the association between well-defined female fertility information and HRQoL with ample statistical power. Our results will help caregivers to identify survivors at risk for decreased HRQoL and will contribute to the development of evidence-based interventions toward better HRQoL of future childhood cancer survivors. Our data allow us to investigate similar predictors of HRQoL as in previous studies [6,11] (except for annual income) and, in addition, the role of female fertility impairment.

### Strengths and Limitations

This study is one of the largest studies worldwide to examine HRQoL and its predictors in childhood cancer survivors. It is, in terms of size, comparable with large studies from the United States (CCSS) [12] and the United Kingdom (BCCSS) [11]. This study combines a series of population-based or regionally well-defined cohorts from different European countries or regions. This will allow comparisons between national cohorts and representative in-depth analyses of HRQoL in survivors and their influencing factors. The central data center processed the raw data from all institutions to minimize coding and data cleaning errors before data pooling.

We faced some challenges when assembling the data from 6 institutions from 5 countries, as recruitment and study design

differed between countries. Some countries had specific exclusion criteria before they invited the survivors to the survey, which may have led to selection biases. The Netherlands, the Czech Republic, and France excluded survivors with severe mental sequelae and other severe impairments. However, these were only a few patients (only 0.1% of eligible patients, n=28), and therefore, a potential bias toward an overestimation of HRQoL in these countries is negligible. Germany did not contact survivors <25 years on the date of the survey, France did not include survivors of childhood leukemia, and the Netherlands did not send data on hearing impairment. Depending on the research question, we will stratify the overall data set by age at survey (18-24 years and ≥25 years) and/or by country (including or excluding Germany and/or France and/or the Netherlands). The time elapsed between diagnosis and survey differed between countries. In Switzerland and the Czech Republic, survivors received a questionnaire already ≥5 years after diagnosis, whereas in Germany, France, and the Netherlands, it was much longer (≥10 years). However, in the SCCSS, the time since diagnosis did not influence HRQoL after adjusting for age at the time of the study [6]. We will, therefore, include age at the time of diagnosis and age at the time of the survey in all multivariable analyses. The Motol Teaching Hospital in Prague preferred female survivors to participate in the study. A high proportion of women may lead to the underestimation of HRQoL because women reported lower HRQoL than men in both CCSS [12] and BCCSS [11]. We will adjust for sex in all regression models and stratify the results by sex.

Of all countries, France had the highest percentage of survivors who were lost to follow-up and the Netherlands had the lowest. In the Netherlands, the proportion of 5-year survivors who died before the mailing of the questionnaire was highest, most probably because the Dutch cohort had the longest follow-up. Age at the time of study was a predictor for some domains of HRQoL in the SCCSS [6] and in a study from the European Organization for Research and Treatment of Cancer [28] pooling data from the general population. In future analyses, we will



adjust for age at the time of the survey in multivariable regression models.

Different assessment logistics among the countries may have influenced response rates. In the Czech cohort, where most survivors were asked to participate during clinical follow-up visits, the participation rate was higher than in Switzerland, the Netherlands, or Germany, who invited all eligible participants via letters. Survivors who have a high risk for late effects are followed up with clinical visits more often than those with lower risk [29]. In the SCCSS, survivors with late effects were at risk for low HRQoL [6]. Therefore, the different sampling procedures in the Czech cohort could have resulted in a lower HRQoL score compared with the other countries. Differences in mentality and general willingness to take part in surveys may also explain the differences in response rates.

The participating survivors differed only slightly from those who did not respond, suggesting that bias from selective response may not be large. The higher proportion of participating women than men reflects a commonly observed self-selection bias in questionnaire health surveys [30]. The frequencies of observed diagnostic groups are similar to those reported from population-based cancer registries, with the following exceptions: more survivors of lymphoma and less survivors of brain tumors participated, reflecting a prognosis-based disease bias.

The countries contributing to this study assessed treatment data differently: most countries collected *as-treated* data

retrospectively from medical records. Switzerland complemented intention-to-treat (ITT) data, with retrospective data from medical records. Germany used solely ITT data from a study protocol database, which did not have treatment data information for 23% of the survivors.

Overall, the limitations refer to different aspects of the data and are mostly specific for each country; therefore, we will provide overall and country-specific results and perform sensitivity analyses excluding countries with specific properties. We will also include a careful evaluation of the differences in data ascertainment and data quality between countries when interpreting the results for specific research questions.

### Conclusions and Prospects for Further Research

With careful interpretation, the large data set of this PanCareLIFE study provides a unique opportunity to study long-term HRQoL among childhood cancer survivors across Europe. It will contribute to the knowledge on HRQoL after childhood cancer while acknowledging the differences between countries in treatment traditions and long-term care. It will also allow the investigation of the role of female fertility and hearing impairment on HRQoL. The results may uncover unknown risk factors for reduced HRQoL and will help inform clinicians about certain groups of survivors who have greater needs for counseling and psychological support to obtain the best possible HRQoL.

### Acknowledgments

The authors gratefully acknowledge the participation of survivors of childhood and adolescent cancer and their families in this research. They would also like to thank in Switzerland, the Swiss Pediatric Oncology Group Scientific Committee: RA Ammann (Bern), M Ansari (Geneva), M Beck Popovic (Lausanne), E Bergstraesser (Zurich), P Brazzola (Bellinzona), J Greiner (St Gallen), M Grotzer (Zurich), H Hengartner (St Gallen), T Kuehne (Basel), J Roessler (Bern), F Niggli (Zurich), F Schilling (Lucerne), K Scheinmann (Aarau), and N von der Weid (Basel). In addition, they thank the team of the Swiss Childhood Cancer Registry (SCCR): Meltem Altun, Erika Berclaz-Brantschen, Katharina Flandera, Elisabeth Kiraly, Verena Pfeiffer, and Shelagh Redmond, and the team of the Swiss Childhood Cancer Survivor Study: Rahel Kasteler, Jana Remlinger, and Annette Weiss. They also thank Marcel Zwahlen for the statistical advice.

At the University Hospital of Brno, the authors thank the team of collaborators from the Children's Hospital in Brno, Masaryk University in Brno, and Brno survivors' association Together Toward a Smile: H Hrstková, V Bajčiová, D Hošnová, Z Kuttnerová, M Blanářová, R Mazúr, I Mikulec, E Bučková, L Červinková, E Bařinová, I Krupková, E Novotná, P Chloupková, Z Wimmerová, L Štrublová, and many other external collaborators and supporters.

At the University Hospital of Prague LTFU Care Registry, the authors thank the team of the Prague Childhood Cancer Survivor Study: P Keslová, M Ganevová, V Reichlová, J Bašeová, L Nováková, M Douchová, and M Čepelová.

In the Netherlands, they thank the DCOG LATER Consortium: LCM Kremer, E van Dulmen-den Broeder, MM van den Heuvel-Eibrink, WJE Tissing, J Loonen, D Bresters, B Versluijs, MA Grootenhuys, M van der Heiden-van der Loo, F van Leeuwen, SJC Neggers, HJH van der Pal, CM Ronckers, ACH de Vries, J den Hartogh, HM van Santen, MA Veening, M Louwerens, and SMF Pluijm.

In France, the authors thank the team of the long-term follow-up study (SALTO): C Faure-Conter (Lyon), N Corradini (Lyon), D Plantaz (Grenoble), E Tarral (Grenoble), I Durieu (Lyon), I Guichard (Saint-Etienne), F Odier (Saint-Etienne), N Gauthier (Lyon), P Métral (Lyon), M Mercier (Lyon), S Billet (Grenoble), C Celette (Grenoble), I Schiff (Grenoble), and A Loubier (Saint-Etienne).

In Germany, they thank the VIVE group and members of the GCCR: U Creutzig (Hannover), T Langer (Lübeck), J Dobke (Berlin), I Jung (Mainz), I Kerenyi (Mainz), C Teske (Bonn), and M Zimmermann (Hannover).

This project received funding from the European Union's Seventh Framework Program for research, technological development, and demonstration under Grant no. 602030. Additional funding was received:

In Switzerland, from the Swiss Cancer League (KLS-3412-02-2014, KLS-3886-02-2016), the Swiss Cancer Research Foundation (KFS-4157-02-2017), the Bernese Cancer League, and Kinderkrebs Schweiz. The work of the SCCR was supported by the Swiss Pediatric Oncology Group, Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und direktoren, the Swiss Cancer Research, Kinderkrebshilfe Schweiz, Bundesamt für Gesundheit, National Institute for Epidemiology and Cancer Registration, and Celgene.

At the University Hospital of Brno from the Ministry of Education, Youth and Sports of the Czech Republic, under Grant no. 7E13061.

At the University Hospital of Prague from the foundation Národ dětem.

In France, from The Wyeth Foundation, the French National Institute of Cancer (INCa), and the French League against Cancer.

In Germany, from the German Cancer Aid (Grant No. 110298).

The material presented and views expressed here are the responsibility of the authors only. The EU Commission takes no responsibility for any use made of the information set out.

PanCareLIFE (Grant no. 602030) is a collaborative project in the 7th Framework Program of the European Union. Project partners are Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Germany (PD Dr P Kaatsch, Dr D Grabow); Boyne Research Institute, Drogheda, Ireland (Dr J Byrne, Ms H Campbell); Pintail Ltd., Dublin, Ireland (Mr C Clissmann, Dr K O'Brien); Academisch Medisch Centrum bij de Universiteit van Amsterdam, the Netherlands (Prof Dr LCM Kremer); Universität zu Lübeck, Germany (Prof T Langer); Stichting VU-VUMC, Amsterdam, the Netherlands (Dr E van Dulmen-den Broeder, Dr MH van den Berg); Erasmus Universitair Medisch Centrum, Rotterdam, the Netherlands; and Princess Maxima Center for Pediatric Oncology, Utrecht, the Netherlands (Prof Dr MM van den Heuvel-Eibrink); Charité-Universitätsmedizin Berlin, Germany (Prof Dr A Borgmann-Staudt); Westfälische Wilhelms-Universität Münster, Germany (Prof Dr A am Zehnhoff-Dinnesen); Universität Bern, Switzerland (Prof Dr CE Kuehni); Istituto Giannina Gaslini, Genoa, Italy (Dr R Haupt); Fakultni nemocnice Brno, Czech Republic (Dr T Kepak); Centre Hospitalier Universitaire Saint Etienne, St Etienne, France (Dr C Berger); Kraeftens Bekaempelse, Copenhagen, Denmark (Dr JF Winther); Fakultni nemocnice v Motole, Prague, the Czech Republic (Dr J Kruseova); Universitaetsklinikum Bonn, Bonn, Germany (Dr G Calaminus, K Baust); and University Hospital Essen, Essen, Germany (Prof U Dirksen).

Data for this subproject were provided by Academisch Medisch Centrum bij de Universiteit van Amsterdam, the Netherlands (Prof Dr LCM Kremer); Stichting VU-VUMC, Amsterdam, the Netherlands (Dr E van Dulmen-den Broeder, Dr MH van den Berg); Erasmus Medisch Centrum Rotterdam, the Netherlands (Prof Dr MM van den Heuvel-Eibrink); Prinses Máxima Centrum, the Netherlands (Prof Dr MM van den Heuvel-Eibrink, Prof Dr LCM Kremer, Dr E van Dulmen-den Broeder); on behalf of the DCOG LATER Study Center, Universität Bern, Switzerland (Prof CE Kuehni); Fakultni nemocnice Brno, the Czech Republic (Dr T Kepak); Centre Hospitalier Universitaire Saint Etienne, France (Dr C Berger); Fakultni nemocnice v Motole, Prague, the Czech Republic (Dr J Kruseova); and Universitaetsklinikum Bonn, Bonn, Germany (Dr G Calaminus).

Independent ethics advice was provided by Prof Dr NW Paul at the University of Mainz and Prof Dr Lisbeth E Knudsen from the University of Copenhagen.

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## Conflicts of Interest

None declared.

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### Multimedia Appendix 1

Overview of outcome variables, exposures, and confounders for the regression analyses.

[[PDF File \(Adobe PDF File\), 45 KB - resprot\\_v10i1e21851\\_app1.pdf](#) ]

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### Multimedia Appendix 2

Flow diagram of the study sample, from eligible survivors to those included in the health-related quality of life (HRQoL) analyses, and planned subsamples.

[[PDF File \(Adobe PDF File\), 510 KB - resprot\\_v10i1e21851\\_app2.pdf](#) ]

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## Abbreviations

**AT:** as treated

**BCCSS:** British Childhood Cancer Survivor Study

**CCSS:** Childhood Cancer Survivor Study

**CNS:** central nervous system

**DCOG LATER:** Dutch Childhood Oncology Group Survivor Study

**FNM:** Motol Teaching Hospital, Prague, the Czech Republic

**FP7:** European 7th Framework Program

**GCCR:** German Childhood Cancer Registry

**HRQoL:** health-related quality of life

**ICCC-3:** International Classification of Childhood Cancer, 3rd edition

**ITT:** intention to treat

**SCCR:** Swiss Childhood Cancer Registry

**SCCSS:** Swiss Childhood Cancer Survivor Study

**SF-36:** Short Form 36 Health Survey

**VIVE:** First Basic Survey on Life Situation, State of Health, and Quality of Life of Childhood Cancer Survivors in Germany

*Edited by G Eysenbach; submitted 28.06.20; peer-reviewed by O Zolk, M Zafar; comments to author 18.08.20; revised version received 13.10.20; accepted 03.11.20; published 25.01.21.*

*Please cite as:*

*Calaminus G, Baust K, Berger C, Byrne J, Binder H, Casagrande L, Grabow D, Grootenhuis M, Kaatsch P, Kaiser M, Kepak T, Kepáková K, Kremer LCM, Kruseova J, Luks A, Spix C, van den Berg M, van den Heuvel-Eibrink MMM, van Dulmen-den Broeder E, Kuonen R, Sommer G, Kuehni C*

*Health-Related Quality of Life in European Childhood Cancer Survivors: Protocol for a Study Within PanCareLIFE*

*JMIR Res Protoc* 2021;10(1):e21851

URL: <http://www.researchprotocols.org/2021/1/e21851/>

doi: [10.2196/21851](https://doi.org/10.2196/21851)

PMID: [33492237](https://pubmed.ncbi.nlm.nih.gov/33492237/)

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Protocol

# Improving Treatment Adherence and Retention of HIV-Positive Women Through Behavioral Change Interventions Aimed at Their Male Partners: Protocol for a Prospective, Controlled Before-and-After Study

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## Abstract

**Background:** According to the World Health Organization, in 2018, 37.9 million people were living with HIV globally. More than two-thirds were residing in sub-Saharan Africa, where the HIV prevalence in the adult population (aged 15-49 years) was 3.9%. This population included 1.3 million pregnant women, of whom 82% had received antiretroviral therapy (ART) for the prevention of HIV mother-to-child transmission. In these countries, one challenge is an insufficient level of treatment adherence, particularly in HIV-positive pregnant women. Among the causes, the lack of involvement from a male partner is a significant contributor to the problem. This issue has strongly emerged in Malawi, one of the countries with the highest HIV prevalence in the world: 9.2% of its adult population were living with HIV in 2018.

**Objective:** This study aims to assess 3 interventions that are aimed at improving ART adherence and retention among HIV-positive women through engagement with their male partners in 4 Malawian health care centers.

**Methods:** The prospective, controlled before-and-after study is conducted in 3 phases (total duration: 24 months): preintervention, intervention, and postintervention analyses. The number of selected clusters (clinical centers) is limited to 4: one for each intervention, plus a cluster where no intervention is performed (control arm). The interventions are as follows: opening the facility on one Saturday per month only for men, defined as a *special day*; testing peer-to-peer counseling among men, *male champions*; and providing a noneconomic incentive to all women who are accompanied by their partners to the facility, *nudge*. The primary outcome of the study is to evaluate the differences in retention in care and adherence to therapeutic protocols among women; the intermediate outcome is the assessment of differences in male involvement. The level of male involvement in the health of their partners (intermediate outcome) will be evaluated through a dedicated questionnaire administered at baseline and in the postintervention phase. Data will be collected at the clinical centers and stored in 2 electronic databases managed using 2 different types of software.

**Results:** The analysis of data collected in the 4 centers during the preintervention phase is ongoing, as enrollment ended on March 31, 2020. The total number of patients enrolled was 452 (Namandanje: 133; Kapeni: 78; Kapire: 75; and Balaka: 166). Meanwhile, several meetings have been conducted to organize the intervention phase.

**Conclusions:** The study will identify the best intervention that enhances the involvement of male partners in women's health, using an approach that considers a broad spectrum of behaviors. An important aspect is the use of educational tools focused on messages, thereby initiating a reflective discussion of stereotypes and false beliefs related to the idea of masculinity present in the Malawian culture.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/19384

(*JMIR Res Protoc* 2021;10(1):e19384) doi:[10.2196/19384](https://doi.org/10.2196/19384)

## KEYWORDS

retention in care; therapeutic adherence and compliance; men's role; acquired immunodeficiency syndrome; AIDS; HIV; behavior; intervention study; health education; community health education; Malawi; mother-to-child transmission; health-related behavior; social ecology

## Introduction

### Background

According to the World Health Organization, in 2018, 37.9 million people were living with HIV globally [1]. The impact of this disease varies considerably across countries and regions. More than two-thirds of people living with HIV are in sub-Saharan Africa (SSA), where HIV prevalence in the adult population is 3.9%. Globally, there were 1.3 million pregnant women living with HIV in 2018 in the region, of whom 82% had received antiretroviral therapy (ART) for the prevention of HIV mother-to-child transmission (PMTCT).

In 2014, the Joint United Nations Programme on HIV/AIDS launched the 90-90-90 program. According to this ambitious plan, 90% of all people living with HIV would know their HIV status, 90% of all HIV people would receive ART, and 90% of all people receiving ART would have viral suppression by 2020 [2]. In most SSA countries, however, the level of adherence is suboptimal, particularly in HIV-positive pregnant women, among whom the adherence rate varies considerably across different settings, both within and across countries, ranging from 35% to 93.5% [3]. There are several barriers to medication adherence that are often linked to different individual factors (sociodemographic and knowledge base), therapy-related factors (complexity of therapy and side effects), social and economic factors, and health care provider and health system-related factors. Stigma and discrimination at the community level and the fear of disclosure of one's HIV status to their partner are more significant barriers than others [4]. In this scenario, a critical issue is represented by the lack of male partner involvement along the continuum of HIV health care services. This issue represents one of the main reasons for treatment refusal, delayed enrollment, dropout, and low retention of pregnant and breastfeeding women [5-8]. The partner's lack of involvement, on the contrary, is due to cultural, societal, and gender factors, socioeconomic factors, health service barriers, and policy gaps [9]. Barriers operate at different levels: community (gender issues, role on reproductive health, and stigma), health system (health services tailored to women's needs and negative attitude of professionals), interpersonal (discordant couples and disclosure issues), and individual (scarce maternal knowledge of child health and fear of stigma) [9]. Therefore, an important challenge is to attain the support of male partners in promoting the health of their female partners.

This process includes attending clinics, testing for HIV, and treatment adherence.

Studies have demonstrated that many countries have highly gender-specific and women-centered sexual and reproductive health programs and services [10]. Therefore, men see health-seeking in a maternal setting to be a *woman's task* and the antenatal clinics as a space for women, and believe that the activities performed are outside their area of responsibility [11]. They perceive that visiting the antenatal clinic would be *unmanly* and they fear stigmatization by other men [11]. The norms related to masculinity discourage men from acceding to health facilities, in particular, to participate in antenatal care (ANC) [12].

Although the importance of male involvement and potential barriers to male involvement are well known, it is not yet clear which public health interventions are effective for attaining male involvement in the health of their female partners, resulting in positive health outcomes for women. There is currently a lack of high-quality studies evaluating the effect of male involvement on women's health [9]. A 2012 Cochrane review identified only one eligible study pertaining to this issue [13], and a more recent review identified only 12 studies, 6 of which were observational [14]. A limitation of the studies conducted so far on the topic is that they are generally not framed in a theory, model, or framework. Only one of the aforementioned studies designed interventions based on a theoretical model [15]; however, the theory was not considered in the evaluation of results. The use of a theoretical framework allows researchers and health care professionals to be able to design and evaluate interventions by analyzing elements that may favor or decrease the effectiveness of each intervention. This improves the potential for reproducibility of the most effective interventions in different contexts (also known as external validity) [16].

### Design of the Study and Theoretical Framework

In this way, a prospective controlled study is more suitable for the evaluation of promising interventions to improve male involvement and enhance maternal adherence to HIV PMTCT.

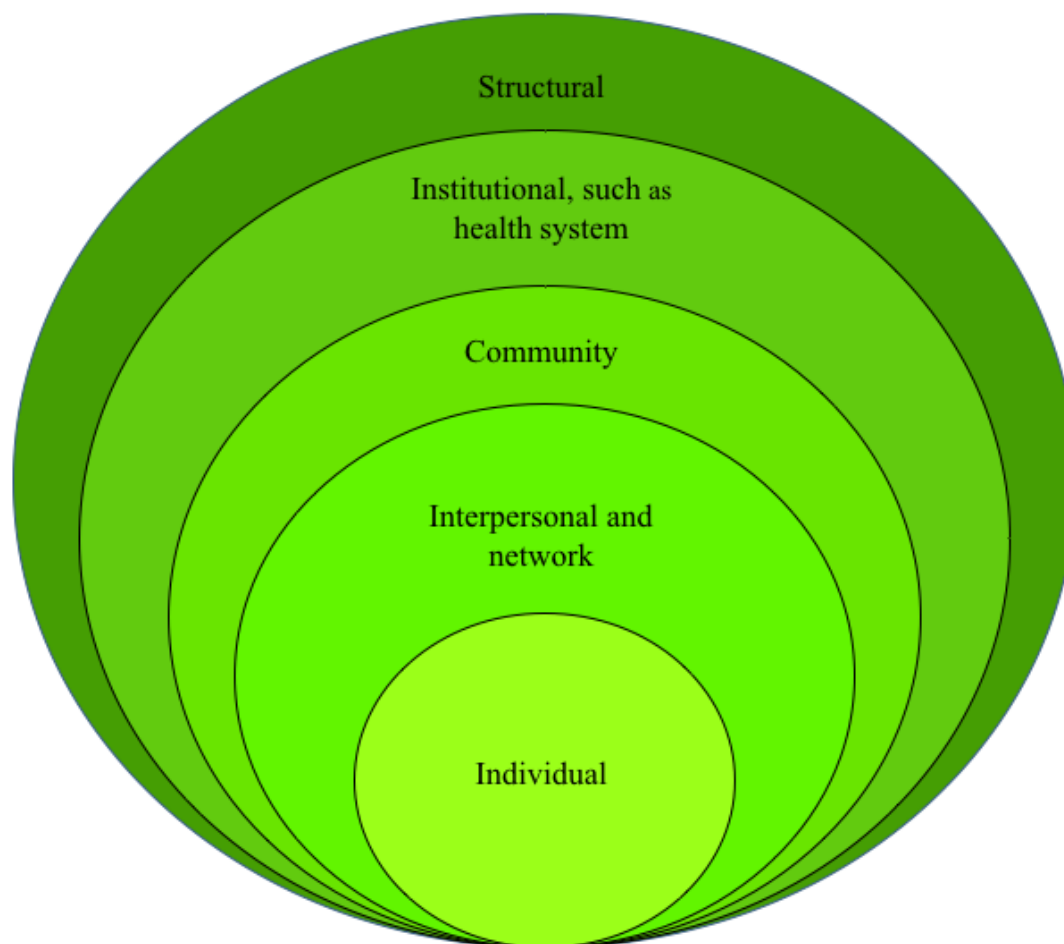
For this study, we adopted a framework based on the ecological model [17] adapted by Kaufman et al [18] to health behaviors in HIV prevention. This model considers not only the PMTCT programs that HIV-positive women are engaged with but also the way they live and their relationship with their families and communities. According to the ecological model of health behavior, these are influenced by someone's living environment,

and this influence is articulated at multiple levels. This model, unlike models such as the Health Belief Model [19], does not focus only on individuals and their choices but tries to intervene on all external causes that support or limit positive individual actions [20-22]. In our study, this model aims to overcome the limitations of various adherence support programs that are exclusively based on health education and awareness-raising activities. In many cases, even though HIV-positive women know the importance of adhering to their ART regimens, external elements are preventing them from complying with their prescriptions. These include the attitude of their partner [23], the stigmatization by their community, and the lack of needed resources, both physical and mental.

According to the ecological model, many factors affect male involvement in women's health care processes at different levels. In this study, we focused on the level presented in Figure 1, namely, individual level, interpersonal and network (eg, family and peers), community, health system (health facility level),

and structural level (eg, access to transportation). These critical issues have strongly emerged in Malawi, one of the countries with the highest prevalence of HIV in the world: 9.2% of the adult population (aged 15-49 years) were living with HIV in 2018, and 59.8% of them were women. In 2018, 1 million Malawians were living with HIV, and 13,000 Malawians died from AIDS-related illnesses in the same year [24]. In July 2011, Malawi became the first country to implement the Option B+ approach, which means that all pregnant women living with HIV are offered antiretroviral treatment for life, irrespective of their CD4 count [25]. Between 2011 and 2018, the proportion of female adults with HIV who were diagnosed ranged from 49% to 94% [26]; the proportion of pregnant women with HIV who were virally suppressed jumped from 2% to 48%. The impact of this program has been huge, with a drastic reduction in HIV mother-to-child transmission (MTCT) rates; however, the percentage of male involvement in MTCT and maternal-child health services is still considerably low, ranging from 3.2% to 23% [27].

**Figure 1.** Effect of multiple integrated component interventions on the social ecological model.



## Aim of the Study

This study aims to evaluate 3 interventions focused on different levels, as described in the ecological model. The primary outcome will be retention and adherence in the care of HIV-positive women, whereas the secondary outcome will be the involvement of male partners in the care of their partners.

## Methods

### Strategy of the Study

The objective of the study is to evaluate 3 different interventions aimed at improving adherence and retention to ART therapy among HIV-positive women through engagement with their life partner. The interventions are (1) testing peer-to-peer



counseling and community-level health education sessions delivered by men, *male champions*; (2) opening the facility once a month, only for men, *special day*; and (3) providing incentive to all women accompanied by their partners at the facility, *nudge* or *incentive*.

The different interventions to be implemented and evaluated in the research plan are designed to assess male involvement at the following levels, as depicted in the model represented in [Figure 1](#). The activities that act on the individual and interpersonal or at the social network level common to past studies are transversal to all 3 interventions. At the individual level, both women and their male partners will receive educational content on the importance of retention and adherence to treatments, but also messages that contradict stereotypes and false myths related to masculinity, health, and gender violence. With regard to the interpersonal or social network level, all interventions will include support activities that are aimed at the family (couples counseling).

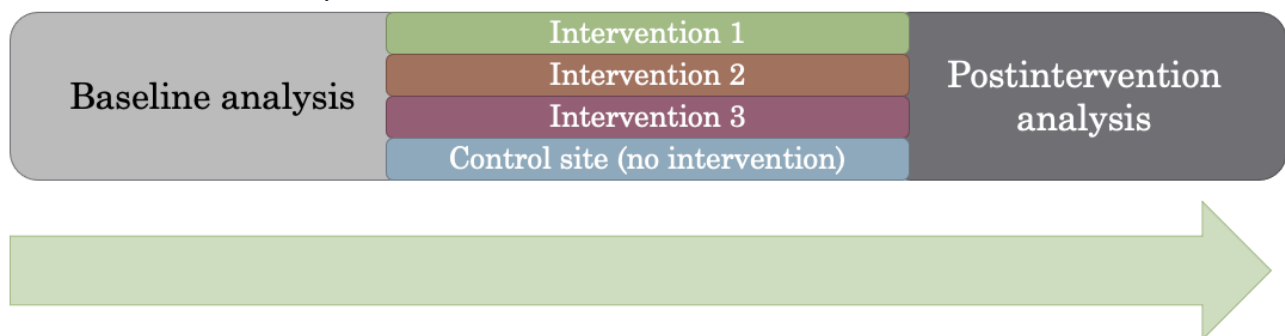
- *Intervention 1 (Male Champions)* will act at the community level, providing educational interventions that are aimed at territorial communities and religious groups.

- *Intervention 2 (Special Day)* will act at the health system level, delivering activities based on health facilities that are aimed at reshaping the clinic as male-friendly.
- *Intervention 3 (Nudge)* will also act at the structural level by providing incentives to support the cost of transportation and other costs that reduce a male partner's ability to access the service.

The study has 3 phases: preintervention (baseline), intervention, and postintervention analyses, as shown in [Figure 2](#).

In the preintervention analysis, the baseline situation of the 3 participating centers will be evaluated. The aim of this phase is to set a starting point to weigh the relative effect of each intervention to be studied. For that purpose, baseline data of each study site will be collected. To evaluate the effect of the interventions, the same indicators will be measured during the pre- and postintervention phases, as described above. The preintervention phase will last 9 months. During this period, data will be collected at each site and included in a database.

**Figure 2.** General structure of the study.



## Setting and Participants

The study was performed in Malawi within the Disease Relief through Excellent and Advanced Means (DREAM) program. DREAM is a health program managed by the Community of Sant'Egidio in 11 African countries [28]. The program delivers a number of health services: HIV care, HIV PMTCT, malnutrition prevention and control, care of noncommunicable diseases, tuberculosis diagnosis and treatment, cervical cancer screening, and treatment of early lesions [29-33]. The DREAM program in Malawi runs 13 health centers and 3 laboratories in collaboration with the Ministry of Health. Currently, the DREAM program in Malawi has cared for over 86,000 patients and assisted over 12,000 HIV-positive pregnant women in the prenatal care and delivery of HIV-uninfected babies. In addition, the DREAM program aims to address health inequalities related to HIV, along with barriers experienced by women in accessing services. For this purpose, an expert client model aimed at improving retention in care and facilitating the inclusion of social aspects in the clinical process was launched [34]. However, activities involving male partners with the goal of improving access of their partners to services have never been tested in this model.

Given the limited resources available for the study and the practical difficulties related to the disadvantaged context in which the study was conducted, sample size calculations and criteria for assigning interventions were based on a pragmatic approach. The number of selected clusters is limited to 4, one for each intervention plus a cluster where no intervention will be performed as a control arm. The number of participants enrolled for data collection is given by the number of patients attending the selected clinical centers during the pre- and postintervention phases. Therefore, the main unit of analysis of the study is the cluster, which is the clinical center. Thus, the interventions will target each health facility.

The following criteria were followed to select the 4 centers included in the intervention:

1. The centers represented the Malawian population. As Malawi is a country where 83% of the population resides in rural or semirural environments [35], rural clinics were selected.
2. Centers that only provided maternal services were excluded because it was not possible to use a male-friendly approach in a center that is designed to accommodate only women.
3. The remaining centers with the highest number of female patients were selected.

The *special day* intervention was assigned to the center of Balaka (Balaka district). At this site, health care staff are available to offer the planned services. The *male champion* intervention was assigned to the Kapire center (Machinga district), where there are patients available to engage themselves as male champions who have sufficient levels of education necessary to perform the task assigned to them and communicate with the researchers. The *nudge* intervention was assigned to the Kapeni center (Blantyre district), where the number of women being treated was consistent with the available budget necessary for the provision of noneconomic incentives.

Although the unit of analysis is the clinical center, and therefore all patients who are referred, the study focuses on the population of adult females and the influence of male partners on the health practices of women. Therefore, data will be collected from this specific population. Eligibility criteria for women included the following: being HIV positive; inclusion in an HIV/AIDS prevention and treatment program; aged 18 years or older; and living at home with a male partner.

There are several possible criteria for defining a partnership relationship. In the Malawian context, the concept of marriage is understood in many different ways depending on local tradition or different religious practices [36]. Furthermore, mobility is quite high and there are situations in which the married partner spends longer periods away from the family or abroad; therefore, there is no possibility of directly influencing his wife's health practices. Hence, in this study, it was decided to consider the man who resides in the same house with the woman as a partner, regardless of religious or legal bonds between the two.

The enrollment of participants will be consecutively based on the order of patient appointments. Recruitment will be entrusted to doctors and clinical officers responsible for the medical visits of women participating in HIV treatment programs, who interact with patients during every visit to the clinical center. All women who met the eligibility criteria and agreed to participate in the study will be enrolled. Recruitment will be conducted before the medical examination: the software used for patient management reports to the clinician whether patients aged less than 18 years are enrolled, allowing the clinician to check entry

criteria and invite eligible participants for study participation with the provision of informed consent.

### Data Collection and Storage

Data will be collected at the clinical centers and will be stored in 2 electronic databases managed through 2 different types of software:

1. Clinical and medical service data are routinely collected through an electronic DREAM program health record software used routinely at the clinical centers named DREAM\_S [37].
2. Data on health behaviors reported by patients who participate in the study will be collected through the software created specifically for the study, also respecting rules for patient privacy and data security.

In the preintervention phase, data will be collected at the medical visit immediately after the enrollment visit to evaluate the partner's acceptance of the invitation to come to the clinical center for testing and counseling in the company of the patient. In the postintervention phase, data will be collected 2 months from enrollment to allow for a wash-out period where the effects of the interventions would be expressed.

### Interventions

There are several strategies and/or interventions to improve male involvement in the PMTCT process described in the literature. These include psychosocial approaches, verbal encouragement, invitation letters, community education, and sensitization. A review performed by Takah et al [38] showed that psychosocial approaches and complex community interventions are more effective, whereas invitation letters are ineffective. Our review of the literature showed that home visits are one of the most effective single interventions, whereas multicomponent approaches could improve male involvement [14]. After a meticulous analysis of the literature on possible interventions, 3 different types of interventions were selected: (1) community sensitization through male champions; (2) special day for a male-friendly clinic; and (3) incentive to attend the clinical center addressing structural barriers. Each intervention will be performed in a selected center (Table 1).

**Table 1.** The interventions.

Centers	Intervention	Ecological model levels	Activities
Kapire	Male Champions	<ul style="list-style-type: none"> <li>Individual</li> <li>Interpersonal or social network</li> <li>Community</li> </ul>	<ul style="list-style-type: none"> <li>Individual counseling for men attending DREAM<sup>a</sup> centers</li> <li>Home care for defaulting male patients</li> <li>Sensitization campaigns in local communities</li> <li>Sensitization campaigns in public spaces (churches, markets, clubs, and bars)</li> </ul>
Balaka	Special Day	<ul style="list-style-type: none"> <li>Individual</li> <li>Interpersonal or social network</li> <li>Health system</li> </ul>	<ul style="list-style-type: none"> <li>Basic health services: <ul style="list-style-type: none"> <li>HIV testing and counseling</li> <li>Blood pressure measurement</li> <li>Counseling regarding cardiovascular disease</li> <li>Blood glucose measurement and counseling for diabetes</li> <li>Nutritional evaluation and counseling</li> </ul> </li> <li>Group educational activities</li> <li>2 educational sessions using the drama technique</li> </ul>
Kapeni	Nudge	<ul style="list-style-type: none"> <li>Individual</li> <li>Interpersonal or social network</li> <li>Structural</li> </ul>	<ul style="list-style-type: none"> <li>First visit <ul style="list-style-type: none"> <li>Woman with partner: <ul style="list-style-type: none"> <li>Food integration is given and an invitation card is delivered. If partners come for the second visit, they receive a second food integration</li> <li>Food integration is not given, but an invitation card is delivered, and if the male partner comes to the second visit, then the family receives a food pack</li> </ul> </li> <li>Woman without a partner: <ul style="list-style-type: none"> <li>Delivery food integration and registration that she has no partner</li> </ul> </li> </ul> </li> <li>Second visit with partner <ul style="list-style-type: none"> <li>If the partner accompanies the woman to the center, the personnel will give a food package and offer couples counseling. The man can take advantage of individual services as educational contents</li> </ul> </li> </ul>

<sup>a</sup>DREAM: Disease Relief through Excellent and Advanced Means.

These strategies will be implemented according to standard clinical practices in Malawi with some modifications based on the international experiences described in the literature.

1. The *male champion* is a figure present in a few settings that conducts home visits with men and couples and follows up with men who did not accompany their partners to ANC visits [39]. Usually, this role is covered by the female expert clients, namely HIV-positive patients working in the organization as volunteers after appropriate training. Some men among patients who are receiving treatment will be identified and trained to cover this role [40]. The intervention called *male champion* aims to change the beliefs and attitudes of men, not intervening directly on individuals but upon entire communities and particularly involving community leaders.
2. The *special day* is a practice that is becoming increasingly common to facilitate access to health facilities by vulnerable groups such as adolescents [41,42]. In this study, we target men. The special day takes place with an extraordinary opening of the clinical center once a month on a pre-festive day (Saturday). During this day, access will be reserved exclusively for men, including those who are not on treatment for HIV. The center will offer free health promotion services to all participants. This intervention

aims to remove the attitude linked to beliefs regarding masculinity, in which the male partners see access to health centers as an activity suitable only for women. The special day aims to make the clinical center more male-friendly and therefore attempts to overcome the social pressure that pushes men to have only sporadic attendance.

3. The intervention based on the use of incentives (*nudge*) [43] to men who follow the prevention and treatment program aims to evaluate whether this action is effective in guiding behavior change toward the test, treatment, involvement, and adherence to therapy approach. The intervention defined as *budget* aims to remove the obstacles of a structural or a material nature, which supports the costs related to transportation to health care facilities and time taken away from work through a noneconomic incentive.

The educational tools developed for these interventions are based on standards adopted in the country for couples counseling on HIV/AIDS. To these standard guidelines, messages were added to initiate a reflective discussion of stereotypes and false beliefs related to the idea of masculinity in the Malawian culture. All staff involved in the delivery of these interventions were provided with a guide (included in [Multimedia Appendix 1](#)) on the contents to be delivered. They also participated in a one-day training of the themes of the project. The guide was developed

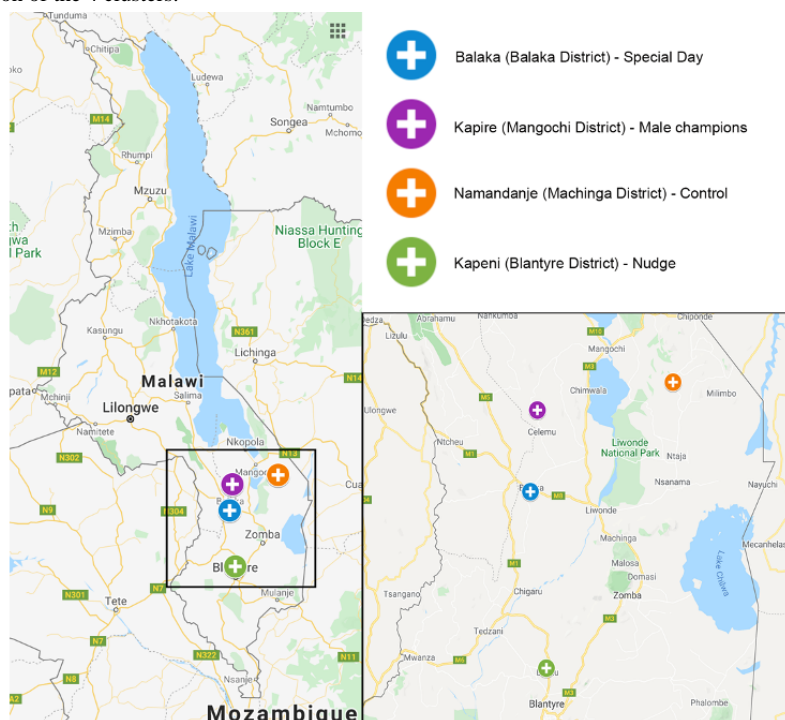
by study investigators and Malawian health care staff. The guide was based on tools developed and applied in other contexts with the purpose of increasing men's access to health care services and to reduce stereotypes and gender-based violence. It was also based on the ecological model [44-49].

The educational content will be delivered using 3 different approaches. The *special day* arm will address the community in the catchment area of the clinical center, but the intervention will take place at the facility level. Through visibility activities such as leaflet distributions or information campaigns with audio messages, men living in the communities surrounding the treatment center will be invited to an extraordinary opening day at the center dedicated only to men. During the special day, the center's clinical staff will offer basic health care services such as HIV testing and counseling, blood pressure measurement and counseling on cardiovascular disease, blood glucose measurement and counseling on diabetes, and nutritional evaluation and counseling. During the morning, group educational activities led by male community health care workers together with the doctors of the center and 2 educational sessions using drama techniques will be conducted. In the *male champions* arm, the intervention will be conducted at the level of regional and religious communities, with group educational sessions and use of the *male champions*. Male champions will be selected from patients receiving treatment for HIV for more than a year at the local DREAM centers. The educational

sessions, based on an interactive approach with questions and answers both from the audience and the male champions, will last between 30 min to an hour. The male champion will be allowed to prolong the intervention if the audience requests it. Meetings will be planned and implemented in communities where at least five patients who receive treatment at DREAM centers reside, including religious communities in those regions. In the *nudge* arm, the intervention will be directed to individuals or to male partners of female patients being treated at DREAM centers. Women who agree to participate in the study will be asked to invite their male partners to the center for a health education session, and male partners who agree to participate will receive an incentive in the form of a food package, approximately worth US \$8. At the second visit, the couple will be given a health education session based on educational materials prepared for the study.

The geographical locations of the 4 centers are shown in Figure 3. The centers are located at a distance that was considered sufficient to avoid geographical contamination. The 2 closest centers, Kapire and Balaka, are located at a distance of about 50 km; therefore, it can be reasonably excluded that patients can participate in both interventions. In any case, patients registered in the DREAM program and their family members are merged into a single database; therefore, the duplication of registration can be excluded.

**Figure 3.** Geographical location of the 4 clusters.



## Outcomes and Statistical Methods

The outcomes will be divided into 2 levels: (1) evaluation of the variations in retention in care and women's adherence to therapeutic protocols (primary outcome) and (2) assessment of the variations in male involvement (intermediate outcome).

Retention in care and adherence to treatment protocols are primary outcomes. Retention in care will be measured as the

cumulative proportion of dropouts from the treatment program at 6 months, 1 year, and 2 years (excluding patients transferred to another center or those who died). Adherence will be measured through the following indicators: (1) the cumulative proportion of medical appointments missed in a month in the center; (2) the cumulative proportion of appointments for drug delivery missed in a month in the center; (3) the cumulative proportion of women who suppressed viral load; and (4) the



cumulative proportion of women with a suppressed viral load that has a rebound in viremia.

To evaluate the level of male involvement in the health of female partners (intermediate outcome), a dedicated questionnaire will be delivered to female partners at baseline (preintervention) and in the postintervention phase. The survey measures the following outcomes related to male involvement: (1) proportion of women accompanied by partners at the facility after receiving an invitation card; (2) proportion of men accepting HIV testing and counseling (if not yet received in the last 6 months); (3) level of partner involvement in the care process measured through a score scale based on health practices reported by the female partners; and (4) level of gender-based violence in the family measured through a score scale based on violent or negative practices reported by female partners.

Some indicators will be collected to monitor the delivery of the intervention and possibly evaluate correlations with the dose of delivery of the 3 interventions, as outlined in [Textbox 1](#).

The primary and secondary indicators of effectiveness are the same for all interventions, hence making it possible to assess the differential impact of the community, health system, and structural-level interventions, particularly with respect to interventions based only on individual and interpersonal levels. These interventions will be compared with the usual services offered at the fourth center.

Data will be presented as mean (SD) for normally distributed data, median with IQR in case of nonnormally distributed variables, or percentage frequencies; within-patient comparisons will be made using an unpaired *t* test and chi-square test, as appropriate, at significance levels of  $P=.04$ . Statistical tests for the comparison of groups include the Mann-Whitney *U* and Kruskal-Wallis *H* tests for continuous variables, whereas the chi-square test will be used for categorical variables. Logistic regression models will be used to compare variables in bivariate and multivariate analyses. Relative risk with 95% CIs will be used to assess the strength of associations. Multivariate survival analysis evaluating retention in care as outcomes will be performed using Cox regression models.

**Textbox 1.** Indicators for each intervention.

<p><b>Male champions (community level)</b></p> <ul style="list-style-type: none"> <li>• Number of meetings in the communities</li> <li>• Duration of meetings</li> <li>• Number of participants in each meeting</li> <li>• Qualitative report of male champions on each meeting (qualitative data)</li> </ul> <p><b>Special day (health-system level)</b></p> <ul style="list-style-type: none"> <li>• Number of men attending the special day</li> <li>• Basic data on men attending the special day:               <ul style="list-style-type: none"> <li>• Employment status</li> <li>• Family status</li> <li>• Level of satisfaction of the intervention</li> <li>• Number of partners of women accessing the health facilities</li> </ul> </li> <li>• Number of men receiving services offered during the special day (HIV test and counseling; blood pressure measurement; blood glucose; nutrition; health talks; drama)</li> </ul> <p><b>Nudge (structural level)</b></p> <ul style="list-style-type: none"> <li>• Number of couples eligible for intervention</li> <li>• Number of incentives and counseling sessions delivered</li> </ul>
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## Results

The enrollment of patients in the preintervention phase started in July 2019 and ended on March 31, 2020. There is an ongoing analysis of preliminary data collected at the 4 centers during the preintervention phase. In total, 452 female participants were enrolled in the preintervention phase, with the following distribution: Namandanje (n=133); Kapeni (n=78); Kapire (n=75); and Balaka (n=166). Several meetings have been performed at the centers to organize the intervention phase. As

of August 1, 2020, the interventions were initiated at the 3 centers and by September 2020 were ongoing.

## Discussion

### Study Strengths

This study aims to assess interventions targeted at enhancing the involvement of males in women antenatal health care in Malawi. Male involvement in prenatal care is still one of the lowest in the world in Malawi, ranging from 3.2% to 23% [27]. There are multiple reasons for the limited role of male partners

in women's health initiatives. Instead of addressing singular factors supposed to directly cause limited male involvement, the approach of our study is based on an ecological model [17]. The decision to base interventions on a theoretical framework is one of the strengths of this study. In fact, a theory-based approach allows us to better understand the reasons for failure or success of an intervention, develop better strategies, and evaluate their external validity [16,50]. In particular, the ecological model was chosen for this study because it considers not only the beneficiaries (HIV-positive women and their partners) and ART adherence as done in other studies [15] but also the social context that can facilitate or hinder the adoption of healthy practices, namely retention in care and adherence to therapy for HIV PMTCT. All the interventions being evaluated act on individual and interpersonal elements, through couple health education. In addition, each intervention addresses other elements such as the health structure, the community, or the structural level linked to transportation costs. This design allows us to understand how the different levels affect behaviors within the target group and, therefore, health outcomes. Another strength of these interventions is the implementation of these activities in a real-life setting, with the use of personnel already active in the center. This is a significant strength of this study, as it provides reproducible information to other sites.

## Limitations

The study design has some limitations. First, the nonrandomized assignment of the interventions based on feasibility criteria could be a possible selection bias. All patients were enrolled in a high-quality program delivered by an international nongovernmental organization, and the results could be different in other settings such as public health facilities. Second, the interventions are designed based on evaluations conducted in different countries and in a potentially different context. This poses the question of their applicability to the Malawian context. Third, the number of studies conducted on male involvement in Malawi is limited and, in many cases, outdated, which do not allow us to have current data at hand on male involvement in Malawi to compare with our ongoing analysis.

If the study is successful in identifying an effective intervention that enhances male involvement and reduces attrition of HIV-positive women in Malawi, then the resulting strategy can be implemented in many other sites in the country as well as in other countries. The results of the study will be shared with local and central health institutions in the country to disseminate our study findings and enhance good practices fostering improved outcomes for families living with HIV.

## Acknowledgments

The study is funded by the Italian Ministry of Foreign Affairs through the Italian Agency for International Cooperation within the *Global Fund 5%* program aimed at providing evidence on how to improve the interventions of the Global Fund against tuberculosis, HIV, and malaria in the countries where the fund operates.

## Conflicts of Interest

None declared.

## Multimedia Appendix 1

Guide on educational contents for staff involved in the project.

[PDF File (Adobe PDF File), 151 KB - [resprot\\_v10i1e19384\\_app1.pdf](#)]

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## Abbreviations

**ANC:** antenatal care  
**ART:** antiretroviral therapy  
**DREAM:** Disease Relief through Excellent and Advanced Means  
**MTCT:** mother-to-child transmission  
**PMTCT:** prevention of mother-to-child transmission  
**SSA:** sub-Saharan Africa

*Edited by G Eysenbach; submitted 15.04.20; peer-reviewed by FC Payton, A Iblasi, C Nweneka; comments to author 21.08.20; revised version received 16.10.20; accepted 26.10.20; published 25.01.21.*

*Please cite as:*

*Orlando S, Palla I, Ciccacci F, Triulzi I, Thole D, Sangaré HM, Marazzi MC, Nielsen-Saines K, Turchetti G, Palombi L  
Improving Treatment Adherence and Retention of HIV-Positive Women Through Behavioral Change Interventions Aimed at Their  
Male Partners: Protocol for a Prospective, Controlled Before-and-After Study  
JMIR Res Protoc 2021;10(1):e19384  
URL: <http://www.researchprotocols.org/2021/1/e19384/>  
doi: [10.2196/19384](https://doi.org/10.2196/19384)  
PMID: [33492232](https://pubmed.ncbi.nlm.nih.gov/33492232/)*

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Protocol

# Development of an Evidence-Based Best Practice Model for Teams Managing Crisis in Dementia: Protocol for a Qualitative Study

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## Abstract

**Background:** Teams working in the community to manage crisis in dementia currently exist, but with widely varying models of practice, it is difficult to determine the effectiveness of such teams.

**Objective:** The aim of this study is to develop a “best practice model” for dementia services managing crisis, as well as a set of resources to help teams implement this model to measure and improve practice delivery. These will be the best practice tool and toolkit to be utilized by teams to improve the effectiveness of crisis teams working with older people with dementia and their caregivers. This paper describes the protocol for a prospective study using qualitative methods to establish an understanding of the current practice to develop a “best practice model.”

**Methods:** Participants (people with dementia, caregivers, staff members, and stakeholders) from a variety of geographical areas, with a broad experience of crisis and noncrisis work, will be purposively selected to participate in qualitative approaches including interviews, focus groups, a consensus workshop, and development and field testing of both the best practice tool and toolkit.

**Results:** Data were collected between October 2016 and August 2018. Thematic analysis will be utilized to establish the current working of teams managing crisis in dementia in order to draw together elements of the best practice.

**Conclusions:** This is the first study to systematically explore the requirements needed to fulfill effective and appropriate home management for people with dementia and their caregivers at the time of mental health crisis, as delivered by teams managing crisis in dementia. This systematic approach to development will support greater acceptability and validity of the best practice tool and toolkit and lay the foundation for a large scale trial with teams managing crisis in dementia across England to investigate

the effects on practice and impact on service provision, as well as the associated experiences of people with dementia and their caregivers.

**International Registered Report Identifier (IRRID):** RR1-10.2196/14781

(*JMIR Res Protoc* 2021;10(1):e14781) doi:[10.2196/14781](https://doi.org/10.2196/14781)

## KEYWORDS

dementia; caregivers; crisis; mental health; home management

## Introduction

### Background

Home-orientated care is a key objective in the UK Dementia Strategy [1] to help people with dementia maintain their independence; however, fluctuations in health and the social needs of people with dementia and/or their caregivers can result in a breakdown of the caring process, making it difficult for the person with dementia to remain at home. This can lead to a crisis where the person with dementia may have to be admitted to an inpatient setting unless skilled management of the situation within the community can be employed. While support from community mental health teams or specialist dementia services exists, waiting times and indirect care pathways can make access difficult [2] at a critical time when the person with dementia may be experiencing an increase in behavioral and psychological symptoms. A specialist rapid access intervention service for people with dementia and caregivers facing crisis could be an effective support mechanism to prevent the breakdown in care at home.

Avoidance of crisis in dementia could reduce unnecessary emergency hospital admissions. An Alzheimer Society report found that one in 10 respondents sought hospital admission for their relative owing to lack of access to community support [3]. Community support for people of working age is well specified, with identified teams (often called crisis resolution teams) in place to avoid hospital admission, but a national survey found that only 16% of these general adult crisis teams accept people with dementia onto their caseload [4]. The availability of teams specific for older people with dementia is limited and variable, with differences in both the remits and names of older adult teams. The same survey identified only 30 standalone dementia or older adult crisis teams nationwide. A subsequent online scoping survey of 62 managers of teams managing crisis in dementia identified wide variations in care pathways and types of services managing crisis in dementia. Such services include dementia intensive support teams, mental health intensive recovery teams, dementia crisis support teams, dementia rapid response teams, and intensive recovery intervention services [5]. This survey further identified variations in how services have developed and in teams' objectives in either preventing events that can lead to a breakdown in care or dealing with the aftermath of care breakdown and preventing hospital admission. Regardless of whether a team has a preventative or management remit, services typically aim for cost saving by maintaining the ability of the person with dementia to stay at home. In many areas, however, services are unavailable and hospital admissions are unavoidable.

A study of nine focus groups found that people with dementia, caregivers, and staff value a coordinated evidenced-based approach to crisis avoidance, one which takes into account increasing dementia symptoms, caregiver inability to continue to provide care, deteriorating physical health of the person with dementia or family caregiver, unsuitability of the home environment, and insufficient community services [6]. With this in mind and drawing on findings from the scoping survey described above [5], research proposed in this protocol, which is part of the Achieving Quality and Effectiveness in Dementia Using Crisis Teams (AQUEDUCT) program funded by the National Institute for Health Research (NIHR) under its Program Grants for Applied Research scheme (RP-PG-0612-20004), will lead to the development of a "best practice model" specific for teams managing crisis in dementia. This is necessary given the current lack of evidence to support, develop, and promote such services.

### Aims

The research described in this protocol aims to explore current practice and to develop an intervention (the best practice tool and toolkit) by addressing the following questions: (1) What is the current practice for a team managing crisis in dementia? (2) What is considered the "best practice" for a team managing crisis in dementia? (3) By which standards should the practice of a team managing crisis in dementia be measured? (4) What does a team managing crisis in dementia require to improve its practice?

## Methods

### AQUEDUCT Research Program

The AQUEDUCT research program is comprised of the following three work packages (WPs): work package 1 (WP1), which concerns the development of the intervention (the best practice tool and toolkit); work package 2 (WP2), which involves a feasibility study for this intervention; and work package 3 (WP3), which involves a full trial of the intervention. This paper describes the protocol for WP1 only.

The research in this WP is informed by the process for promoting service improvement developed by the US evidence-based practice (EBP) program, which has demonstrated effectiveness in supporting high-fidelity implementation of a range of complex interventions and service models [7]. Components of the EBP approach include [8,9] (1) defining a model of best practice with detailed specification; (2) developing a means of assessing adherence to this model; and (3) developing a package of implementation resources to support

service improvement and greater adherence to the “best practice model.”

The intervention to be developed, consisting of the best practice tool and toolkit, will be generated through an iterative understanding of current practice and what is considered to be the best practice in teams managing crisis in dementia. This work will build upon previously conducted research, namely the “Support at Home—Interventions to Enhance Life in Dementia” (SHIELD) program [10]. This previous study developed the home treatment package (HTP), a tool for assessing people with dementia and their caregivers at times of crisis. It incorporates a number of components, including the threshold assessment grid (TAG) risk assessment [11], the Camberwell assessment of needs in the elderly (CANE) [12], a care planning template, a discharge planning template, exemplary case studies, and an advisory protocol. The HTP will be revised in phase 3 of WP1, as described below.

### Sample

Sample sizes to be used in each phase of this research are similar to those considered sufficient to achieve data saturation in previously conducted research on older people and working age crisis management [6,13].

### Inclusion Criteria

For this research, we will consider inclusion of (1) staff members of teams managing crisis in dementia who have been employed by the team managing crisis in dementia for a minimum of 6 months and have been working directly with people with dementia; (2) people with dementia who have a diagnosis or probable diagnosis of dementia, have been discharged from the team managing crisis in dementia within the past 6 months, have the mental capacity to provide informed consent, and have some recollection of the involvement of the team managing crisis in dementia in their care; and (3) caregivers who have cared for people with a diagnosis or probable diagnosis of dementia who received input from the team managing crisis in dementia within the past 6 months.

### Recruitment and Consent

Several different groups of participants will be involved in this research, and they will be recruited in various ways. National Health Service (NHS) Trusts across England will be approached initially by a member of the AQUEDUCT research team who will explain the study to research and development contacts, so that the assessment of the capability and capacity to complete the research can be initiated. NHS Trusts that include appropriate teams will then ascertain capability and capacity for involvement in individual phases of the research (rather than involvement in the protocol as a whole) by discussing the research with team managers. Once the team manager has agreed to their team’s involvement in that phase of the protocol, individual staff members from the widest possible range of roles and bandings will be approached by the manager to discuss participation in the study.

People with dementia, caregivers, and other staff members who work with the teams (stakeholders) will be approached initially by a member of the clinical team and asked if they would be willing to speak with a member of the AQUEDUCT research team. If they are interested in participating, they will then receive a copy of the relevant information sheet. A patient and public involvement (PPI)-approved dementia-friendly participant information sheet will be created by the research team to facilitate understanding of the research for people with dementia. Potential participants will be given up to 3 days to decide whether to participate, after which point, if they indicate to a member of the clinical team that they are happy to participate, the AQUEDUCT research team member will answer any questions and discuss the time and location of the interview or focus group.

For the consensus workshop, participants will be purposively recruited based on their previous contact with a team managing crisis in dementia and their willingness to be recontacted regarding future AQUEDUCT research activity. A personal invitation will be sent to them with all information and details about the workshop. They will be asked to return an expression of interest to indicate their intention to attend, and consent will be taken by members of the AQUEDUCT research team on the day of the workshop itself.

Prior to all research activities, a member of the AQUEDUCT research team will work through the relevant information sheet with the prospective participant, offer an opportunity for further questions, and take written consent. On signing the consent form, all participants will be allocated a unique identification number to ensure their anonymity during analysis and reporting of findings.

### Patient and Public Involvement

The AQUEDUCT program overall will actively engage with people with dementia and caregivers as PPI representatives. The role of PPI will be incorporated into all stages of the research, including advising on study documentation and participant recruitment procedures, assisting in data collection as coresearchers, commenting on the suitability of data analysis, and taking part in the AQUEDUCT Program Steering Group and AQUEDUCT PPI Reference Group. In this way, every stage of the research process will be informed by service user experience and expertise, and the research will adhere to its objectives of benefitting people with dementia, caregivers, and members of the public.

### Phase 1: Mapping Current Practice and Identifying the Best Practice

This is a prospective study using qualitative methods to garner a broad understanding of the necessary elements of service provision for effective crisis management and resolution for people with dementia and their caregivers. The design and three constituent phases of WP1 are illustrated in [Figure 1](#).



**Figure 1.** Design and three constituent phases of work package 1 (WP1).

In the first phase, interviews will be carried out (following purposive sampling) to garner the perspectives of people with dementia, caregivers, staff members of teams managing crisis in dementia, and individuals who work with teams managing crisis in dementia (stakeholders) on current practice and the experience of providing or receiving care. Participants who have accessed, had contact with, or worked in a team managing crisis in dementia are considered eligible for interview. Interviews will map the scope of a service and will document team composition, geographical characteristics and practical operation, links with other services, communication and decision-making, and service evaluation processes. The interviews will result in collection of information concerning clinical processes and procedures, together with information on what works well and what does not work well in order to consider the best practice and possible facilitators of the best practice (see [Multimedia Appendix 1](#) for the interview schedule being used).

Semistructured focus groups will then be carried out with people with dementia, caregivers, staff members of teams managing crisis in dementia, and individuals who work with teams managing crisis in dementia to consider the best practice further and to identify what facilitates the positive working of teams managing crisis in dementia. These groups will ascertain the setup of teams managing crisis in dementia, barriers and facilitators to positive working, and examples of good practice. Data will be analyzed using thematic analysis to develop items for the “best practice model.”

Sixty participants from five teams managing crisis in dementia will be recruited for individual interviews. AQUEDUCT team researchers and PPI coresearchers will then facilitate nine focus groups of four to six participants each.

Incorporating two different stages of qualitative exploration (individual interviews and focus groups) will be the most appropriate methodology to enable understanding of the current practice and identification of the best practice, as it will provide an opportunity to elicit both individual and context-specific characteristics [14]. Through this iterative process, it will be possible to recognize key characteristics in dementia crisis team working in order to increase the validity and richness of the findings.

## Phase 2: Development and Field Testing of the Best Practice Tool

A best practice tool will be created to be used by teams managing crisis in dementia to measure their current practice and the extent to which they fit the “best practice model.” The process of testing the best practice tool will be derived from the CORE study procedure, a NIHR-funded program that developed

a fidelity scale of best practice for working-age crisis resolution teams [15]. The development of the best practice tool detailed in this paper aligns with the development of the CORE Fidelity Scale.

EBP principles [8,9] will be used to draw together evidence gathered during the qualitative phase of this protocol to form a “best practice model” and to develop the first iteration of the best practice tool. A consensus workshop will revise and validate the best practice tool to create the next version. The workshop will involve at least 25 attendees, including PPI representatives, staff and managers of teams managing crisis in dementia, NHS staff from primary and secondary care who interface with teams managing crisis in dementia, senior trust managers, commissioners, and academics.

The revised version of the best practice tool will then be field tested with 12 teams managing crisis in dementia and five older peoples’ community mental health teams that do not have a dedicated dementia crisis response function, to establish face and content validity. Comparing best practice tool scores for these two types of teams will provide construct validity, ensuring that the practice quality of crisis teams, rather than the practice quality of generic mental health teams, is measured by the best practice tool. Each item of the tool will specify various types of evidence that can be inspected to determine whether the team meets the scoring criteria and will be weighted so that the team will receive an overall best practice tool score out of 100.

Each team will take part in a review day during which three reviewers (a member of the AQUEDUCT research team, a PPI member, and a clinician who works with people with dementia) will rate the practice of the team according to the “best practice model.” Evidence will be collected from various sources, including interviews with team members, team managers, staff from other services who work closely with the teams, people with dementia, and caregivers; case note and paperwork reviews; and a visual check of the team base. Reviewers will compile and evaluate all data throughout the day to agree on a best practice tool score. The face and content validity of the best practice tool will be assessed using these data.

The best practice tool will enable identification of “gaps” in the current practice of each team managing crisis in dementia that can be filled by use of the toolkit, the development and implementation of which is outlined below.

## Phase 3: Development and Field Testing of the Best Practice Toolkit

The best practice toolkit will include the HTP developed during the SHIELD study, which has been mentioned above. A briefing will be carried out with two senior staff members of teams

managing crisis in dementia to determine suitability for use and ease of completion of the HTP. The purpose of this is to modify the HTP where required before it is incorporated as an element of the toolkit. The briefing will involve one day of training for the staff members of teams managing crisis in dementia on the purpose and application of the HTP (the latter incorporating case study examples). Thereafter, staff members will draw on their own clinical experience to complete the HTP and provide feedback on the process of doing so to the AQUEDUCT research team.

Additional elements of the best practice toolkit will be determined by drawing on information generated from the qualitative work to identify elements of best practice, considering in particular how teams can best fulfill the criteria laid out in the “best practice model.” The toolkit will promote best practice through the use of templates and documents that can be mapped onto the best practice tool.

Five teams managing crisis in dementia will field test the best practice toolkit. Staff members from these teams managing crisis in dementia will receive online training in the use of the toolkit, and two AQUEDUCT team researchers will then visit these staff in their place of work to discuss their best practice tool score and areas for improvement. The staff members of teams managing crisis in dementia will agree with the AQUEDUCT team researchers about which elements of the toolkit they will implement over a period of 4 weeks, and after this time, they will provide feedback on the suitability of those elements for use in their team. During the 4-week period, an AQUEDUCT team researcher will conduct weekly telephone calls with the team managing crisis in dementia to record usage of the toolkit elements. Following receipt of all feedback from the five teams managing crisis in dementia, the toolkit will be amended for future use in the feasibility study.

### Governance

All information will be treated as confidential, with adherence to the NHS Code of Confidentiality [16], General Data Protection Regulation [17], and Good Clinical Practice guidelines [18]. All insurance and indemnity arrangements will be covered by the study sponsor, Nottinghamshire Healthcare NHS Foundation Trust. Ongoing progress of the research will be monitored by the Program Management Group comprised of the coapplicants who have been awarded the NIHR grant, and a Program Steering Group that will be independent of the sponsor and other interested parties, in association with the chief investigator and program manager, both of whom are consultant clinicians. Overall, this research will benefit from and be guided by experts from the fields of older adult psychiatry, clinical psychology, mental health nursing, social work, and occupational therapy owing to the clinical background and expertise of the coapplicants on the grant, as well as voluntary services for older people, PPI, and research methodology and dissemination.

### Results

Ethical approval was provided by the West Midlands (Black Country) Research Ethics Committee (reference: 16/WM/0273)

on August 4, 2016, and Health Research Authority approval was provided on August 24, 2016. Data collection began in October 2016 and was completed by the end of August 2018.

Interview and focus group data will be analyzed using the six-phase thematic analysis method [19] to establish the current working of teams managing crisis in dementia and to draw together elements of best practice. This analysis process involves researchers (1) becoming familiar with the data, (2) generating initial codes from the data, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) writing up the thematic analysis. Data will be organized using the framework method [20] to assist in comparison of data within themes and across participants. Results will inform items for the evidence-based “best practice model,” and the first version of the best practice tool will be developed using evidence-based practice principles [21]. Feedback data from reviewers, teams, and others who take part in the review days will then be used to evaluate the usability and feasibility of the best practice tool, and the outcome data from this version will be compared between teams managing crisis in dementia and noncrisis teams to ensure that the best practice tool is specific to teams managing crisis in dementia as opposed to generic older adult mental health teams.

### Discussion

This protocol presents extensive qualitative methods and an iterative approach to enable accumulation of in-depth knowledge about the characteristics, processes, and policies of the working of teams managing crisis in dementia. The use of both semistructured interviews and focus groups will mean that decision-making processes and rationales given for ways of working can be explored fully [14] and incorporated into an evidence-based “best practice model.”

Integral to this research is the role of people with dementia and their caregivers, ensuring that their views and experiences will be incorporated. In particular, it is proposed that interviews and focus groups will be carried out with people with dementia, so that this research does not assume what constitutes best practice on their behalf. PPI and research cocreation are built into this protocol to reduce the possibility of this research becoming detached from the working of teams managing crisis in dementia in practice, as experienced by those who receive it.

As this work will make use of participants’ retrospective accounts of the involvement of teams managing crisis in dementia, it is possible that in the case of people with dementia, memory difficulties may lead to gaps in details provided. Caregiver interviews will also be included to compensate for this; however, as general impressions from people with dementia (to include their residual emotions generated by input from teams managing crisis in dementia) are considered crucial to the development of a “best practice model” that takes into account “softer” aspects of care, such information will be collected whenever possible

The research outlined in this protocol will result in the development of a “best practice model” for teams managing crisis in dementia and a best practice tool by which fidelity to

this model can be measured. To date, no such model exists. Additionally, dementia crisis working has been inconsistent and the quality of care delivered has been variable and difficult to measure owing to the lack of quality indicators and lack of standardization across services. This research has the potential to address this current variability in practice. Such variability may be in part due to the variety of team models existing at present, ranging from those that are dementia specific to those serving older people generally (and which thus have a remit for functional disorders) and to those serving adults of all ages who are experiencing a mental health crisis. The “best practice model” will be promoted through the best practice tool and toolkit that will provide teams with a benchmark by which to

measure their practice specific to dementia working and the resources required to improve delivery of their practice, respectively. Ultimately, it is expected that the best practice tool will be suitable for self-completion by the staff of teams managing crisis in dementia who will then be able to identify their own practice areas requiring improvement. This approach will be trialed in a subsequent feasibility study. As the “model of best practice” is based almost exclusively on stakeholder opinion rather than on objective empirical evidence, its validity must be confirmed by establishing the relationship between good model adherence and better outcomes. This will be explored in a future large-scale trial.

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## Acknowledgments

The Achieving Quality and Effectiveness in Dementia Using Crisis Teams (AQUEDUCT) research team acknowledges support from the National Institute for Health Research Clinical Research Network. This research is part of the AQUEDUCT program funded by the National Institute for Health Research (NIHR) under its Program Grants for Applied Research scheme (RP-PG-0612-20004). The views expressed in this paper are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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## Authors' Contributions

All authors have contributed to the drafting of this manuscript and have revised and approved the final version.

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## Conflicts of Interest

None declared.

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## Multimedia Appendix 1

Achieving Quality and Effectiveness in Dementia Using Crisis Teams (AQUEDUCT) work package 1 interview guides. [[DOCX File, 18 KB - resprot\\_v10i1e14781\\_app1.docx](#)]

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## Abbreviations

**AQUEDUCT:** Achieving Quality and Effectiveness in Dementia Using Crisis Teams

**EBP:** evidence-based practice

**HTTP:** home treatment package

**NHS:** National Health Service

**NIHR:** National Institute for Health Research

**PPI:** patient and public involvement

**SHIELD:** Support at Home—Interventions to Enhance Life in Dementia

**WP:** work package



*Edited by G Eysenbach; submitted 22.05.19; peer-reviewed by Q Yuan, K Tingay, K Goniewicz; comments to author 19.07.19; revised version received 01.11.19; accepted 05.11.19; published 27.01.21.*

*Please cite as:*

*Stanyon M, Streater A, Coleston-Shields DM, Yates J, Challis D, Dening T, Hoe J, Lloyd-Evans B, Mitchell S, Moniz-Cook E, Poland F, Prothero D, Orrell M*

*Development of an Evidence-Based Best Practice Model for Teams Managing Crisis in Dementia: Protocol for a Qualitative Study*  
*JMIR Res Protoc* 2021;10(1):e14781

URL: <http://www.researchprotocols.org/2021/1/e14781/>

doi: [10.2196/14781](https://doi.org/10.2196/14781)

PMID: [33502333](https://pubmed.ncbi.nlm.nih.gov/33502333/)

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Protocol

# Metabolic Syndrome Parameters, Determinants, and Biomarkers in Adult Survivors of Childhood Cancer: Protocol for the Dutch Childhood Cancer Survivor Study on Metabolic Syndrome (Dutch LATER METS)

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## Abstract

**Background:** Potential late effects of treatment for childhood cancer include adiposity, insulin resistance, dyslipidemia, and hypertension. These risk factors cluster together as metabolic syndrome and increase the risk for development of diabetes mellitus and cardio- and cerebrovascular disease. Knowledge on risk factors, timely diagnosis, and preventive strategies is of importance to prevent cardio- and cerebrovascular complications and improve quality of life. Currently, no national cohort studies on the prevalence and determinants of metabolic syndrome in childhood cancer survivors, including biomarkers and genetic predisposition, are available.

**Objective:** The objectives of the Dutch LATER METS study are to assess 1) the prevalence and risk factors of metabolic syndrome and its separate components, and 2) the potential diagnostic and predictive value of additional biomarkers for surveillance of metabolic syndrome in the national cohort of adult long-term survivors of childhood cancer.

**Methods:** This is a cross-sectional study based on recruitment of all survivors treated in the Netherlands between 1963 and 2002. Metabolic syndrome will be classified according to the definitions of the third Adult Treatment Panel Report of the National Cholesterol Education Program as well as the Joint Interim Statement and compared to reference data. Dual-energy x-ray absorptiometry scans were performed to assess body composition in more detail. The effect of patient characteristics, previous treatment, and genetic variation on the risk of metabolic syndrome will be assessed. The diagnostic and predictive value of novel biomarkers will be tested.

**Results:** Patient accrual started in 2016 and lasted until April 2020. A total of 2380 survivors from 7 pediatric oncology hospitals have participated. From July 2020, biomarker testing, single nucleotide polymorphism analysis, and data analysis will be performed.

**Conclusions:** The Dutch LATER METS study will provide knowledge on clinical and genetic determinants of metabolic syndrome and the diagnostic value of biomarkers in childhood cancer survivors. The results of this study will be used to optimize surveillance guidelines for metabolic syndrome in survivors based on enhanced risk stratification and screening strategies. This will improve diagnosis of metabolic syndrome and prevent complications.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/21256

(*JMIR Res Protoc* 2021;10(1):e21256) doi:[10.2196/21256](https://doi.org/10.2196/21256)

## KEYWORDS

metabolic syndrome; childhood cancer survivor; Dutch Childhood Cancer Survivor Study; methodology; Dutch LATER METS

## Introduction

Due to increasing survival of patients with childhood cancer, late side effects have become more prominent. Potential late effects include adiposity, insulin resistance, dyslipidemia, and hypertension, which cluster together as metabolic syndrome. Metabolic syndrome is associated with a higher risk of diabetes mellitus, as well as cardio- and cerebrovascular morbidity and mortality later in life [1-3]. The separate components are in themselves risk factors for diabetes and cardiovascular disease but, when coexisting, the components can aggravate each other, leading to an even higher risk of diabetes and cardiovascular disease [4,5].

Studies in childhood cancer survivors have reported a prevalence of metabolic syndrome of over 30% after 25 years follow-up, substantially higher compared to age- and sex-matched controls (odds ratio 1.76) [6,7]. This apparent risk difference for metabolic syndrome further increases the elevated risks for cardiovascular outcomes and endothelial damage from anthracyclines, alkylating agents, and irradiation [8,9]. Consequently, the mortality due to coronary and cerebrovascular disease in long-term survivors is up to 12.7 times higher than in the general population [10-13]. The fact that metabolic syndrome can be subclinical for many years emphasizes the need for timely identification of metabolic syndrome in survivors and early intervention strategies. Lifestyle and diet advice, exercise, and medication may prevent the development of diabetes and cardio- and cerebrovascular disease, improving survival rates and quality of life.

Several underlying conditions have been reported to increase the risk for (components of) metabolic syndrome in survivors: growth hormone deficiency, pancreatic beta cell dysfunction, hypogonadism, hypothyroidism, and altered body composition with increased intra-abdominal fat [14-19]. Hence, an increased risk of metabolic syndrome might be associated with treatment for a brain tumor, treatment with radiotherapy, intensive chemotherapy, nephrectomy, adrenalectomy, or stem cell transplantation [7,16,20-32]. The effects of other potentially harmful treatments, for example corticosteroids, and patient-related factors such as sex, age, body mass index at diagnosis, and lifestyle, are still not clear [3]. Also, heterogeneity in incidence of metabolic syndrome among homogeneously treated survivors suggests a role of genetic susceptibility [33,34]. A few studies using candidate gene approaches [24,35] as well

as one genome-wide association study [36] have identified genetic variants that might be associated with development of metabolic syndrome and its components in survivors. Results based on these studies have not yet been replicated or functionally validated.

Multiple definitions of metabolic syndrome have been developed over the past years. The two most commonly used are those of the third Adult Treatment Panel Report of the National Cholesterol Education Program [37] and the Joint Interim Statement of the International Diabetes Federation; National Heart, Lung, and Blood Institute; and the American Heart Association [38]. Both definitions overlap largely but they differ in waist circumference cut-off point (Table 1). Apart from the 4 components, pro-inflammatory and prothrombotic markers have been reported to be relevant biomarkers of metabolic syndrome, as has hyperuricemia [39,40].

Adequate assessment of metabolic syndrome in survivors using the National Cholesterol Education Program and Joint Interim Statement definitions has specific challenges, particularly after abdominal radiotherapy. It has been shown that body mass index and waist circumference underestimate adiposity due to deformation of spine, muscles, and fat, particularly in past treatment eras when higher radiotherapy doses and larger fields were used [21,41,42]. Similarly, adiposity can be disguised due to sarcopenic obesity after stem cell transplantation [43,44]. Body composition can be more reliably measured by dual-energy x-ray absorptiometry, but this is time consuming and expensive to be implemented for standard follow-up of all survivors. Serum biomarkers may be more cost-effective surrogate markers for metabolic syndrome. In smaller survivor cohorts and in the general population, biomarkers other than triglycerides and high-density lipoprotein cholesterol that have been proposed as predictors of metabolic syndrome include low-density lipoprotein, apolipoprotein-B, leptin, adiponectin, uric acid, and C-reactive protein [39,45-50].

So far, large studies on clinically diagnosed metabolic syndrome in survivors are scarce. Two large multicenter cohort studies with clinically diagnosed metabolic syndrome are the American St. Jude Lifetime (SJLIFE, all types of childhood cancer) [6,7] and the French Leucémies de l'Enfant et l'Adolescent (leukemia) [31,51,52] studies. Other studies have yielded heterogeneous and sometimes conflicting results and can be difficult to compare. This may be due to metabolic syndrome components being analyzed only separately, or due to small patient cohorts,

a questionnaire based or retrospective design, insufficient treatment data (eg, only childhood cancer diagnosis is known, not treatment), and short follow-up (metabolic syndrome risk increases continuously with age, so a follow-up of 10-20 years likely underestimates this) [22,32,53-55]. In addition, comparison of study outcomes can be difficult due to the use of different classifications. Currently, no studies in national cohorts on prevalence and determinants of metabolic syndrome

in childhood cancer survivors, including biomarkers and genetic predisposition to metabolic syndrome, are available.

Here we describe the methodology of the Dutch LATER METS study in the adult cohort of survivors treated between 1963 and 2002. This nationwide study assesses metabolic syndrome prevalence, clinical and genetic risk factors, and the diagnostic and predictive value of additional biomarkers. The results of this study will be used to identify survivors at risk and to optimize surveillance guidelines.

**Table 1.** NCEP-ATP III<sup>a</sup> and JIS<sup>b</sup> classifications of metabolic syndrome, and alternative classification with adiposity measured by dual-energy x-ray absorptiometry scan.

Required for diagnosis (≥3)	Measurement	NCEP-ATP III	JIS	Alternative with dual-energy x-ray absorptiometry scan
Adiposity	Waist circumference (cm)	>102 <sup>c</sup> /88 <sup>d</sup>	≥94 <sup>c</sup> /80 <sup>d,e</sup>	Body fat Z-score >2
Insulin resistance	Fasting glucose (mmol/L)	≥5.5 or treatment	≥5.5 or treatment	≥5.5 or treatment
Dyslipidemia	Triglycerides (mmol/L)	≥1.7 or treatment	≥1.7 or treatment	≥1.7 or treatment
	High-density lipoprotein cholesterol (mmol/L)	<1.0 <sup>c</sup> /1.3 <sup>d</sup> or treatment	<1.0 <sup>c</sup> /1.3 <sup>d</sup> or treatment	<1.0 <sup>c</sup> /1.3 <sup>d</sup> or treatment
Hypertension	Blood pressure (mmHg)	≥130/85 or treatment	≥130/85 or treatment	≥130/85 or treatment

<sup>a</sup>NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III.

<sup>b</sup>JIS = Joint Interim Statement of International Diabetes Federation; National Heart, Lung, and Blood Institute; and the American Heart Association.

<sup>c</sup>Men.

<sup>d</sup>Women.

<sup>e</sup>Cut-off for Caucasian population.

## Methods

### Objectives

The objectives of this study are to assess 1) the prevalence and risk factors (patient characteristics, previous treatment, and genetic variation) of metabolic syndrome and its separate components, compared to reference data, and 2) the potential diagnostic and predictive value of novel biomarkers for surveillance of metabolic syndrome in the national cohort of adult long-term survivors of childhood cancer.

### Study Population and Design

The Dutch LATER METS study is part of the nationwide Dutch LATER study (Figure 1). This study started accrual in all 7 pediatric oncology centers in the Netherlands in 2016, thereby inviting the national cohort of all survivors treated in these hospitals between 1963 and 2002 to participate. Survivors were identified from registries of children with newly diagnosed cancer that are maintained in each of the 7 pediatric oncology centers in the Netherlands. This study merged the available information to create a specific childhood cancer survivors registry containing all registered survivors. Dependent on completeness of the sources in the centers, the starting year varied from 1963 to 1977. The LATER METS study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Center (registered at toetsingonline.nl, NL32117.018.10).

In the Dutch LATER study, data from 15 substudies of late effects were collected, including cardiotoxicity, bone density,

frailty, growth hormone deficiency, renal toxicity, fatigue, and psychological late effects. Individuals who survived at least 5 years after diagnosis of histologically confirmed malignancies (as defined in the 3rd edition of the International Classification of Childhood Cancer [56]) or Langerhans cell histiocytosis, were treated with chemotherapy or radiotherapy, and were between 0 and 17 years of age at diagnosis were invited. Exclusion criteria were treatment for a malignancy in the past year and living abroad.

For all eligible survivors, prior to the visit of the late-effects clinic, sex; date of birth; date of cancer diagnosis; and detailed data on cancer type and treatment, including chemotherapy regimens and doses, radiotherapy fields and (fractionated) dose, stem cell transplantation and corticosteroid treatments, were collected in a pseudonymized, web-based, central database. This includes primary diagnosis as well as, if present, recurrences and subsequent malignancies.

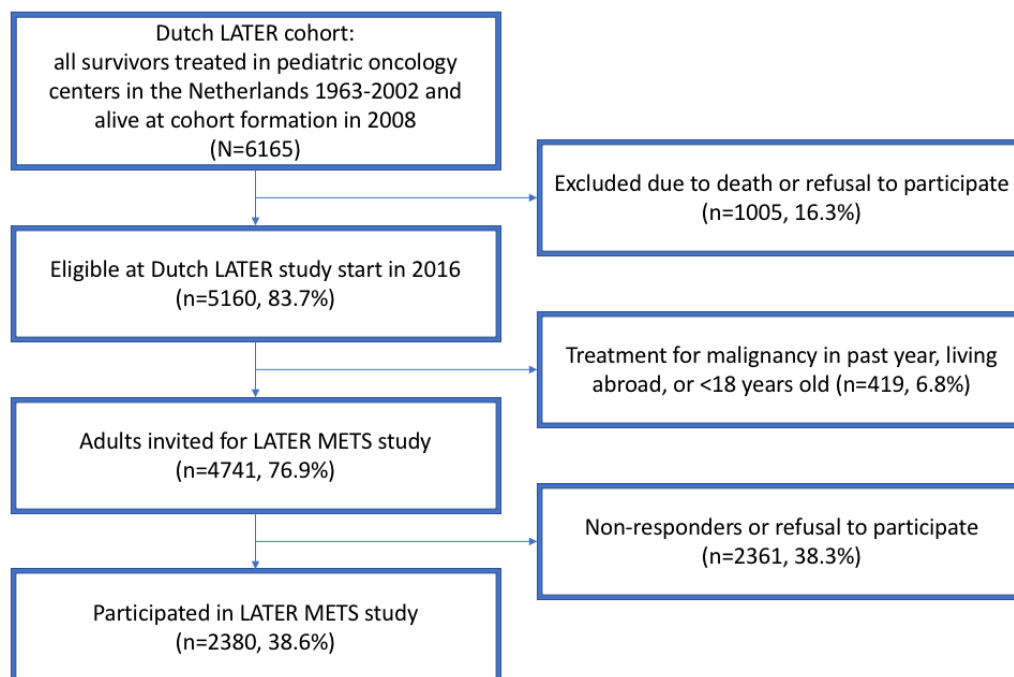
Subsequently, data collection for all studies was combined with the survivors' regular care visit to the late-effects clinic for the majority of survivors. Before the visit, survivors received information about the study, sent by mail by the study personnel. If they agreed to participate, study data was collected by the treating physician or the study personnel.

The entire cohort, at formation in 2008, contained 6165 eligible survivors. By mail, survivors were provided the option to opt-out of future study participation. For the Dutch LATER study, the cohort was frozen in 2016, leaving 5160 subjects eligible. For the LATER METS study, only adults (n=4741) were invited.



Inclusion took place until April 2020. Written informed consent was obtained from all study participants.

**Figure 1.** Overview of the Dutch LATER study cohort and embeddedness of the Dutch LATER METS study cohort within the underlying cohort. Percentages indicate proportion of Dutch LATER cohort (N=6165).



## Reference Population

Normative data from the Dutch Lifelines study cohort will serve as reference population [57]. This is a 3-generation cohort of 167,000 inhabitants (10%) of the north of the Netherlands, from whom, among other data, the following parameters relevant to our study were collected between 2006 and 2013: age, sex, height, weight, waist and hip circumference, blood pressure, comorbidities, medication use, smoking, physical activity, high-density lipoprotein, triglycerides, glucose, apolipoprotein-B, low-density lipoprotein, total cholesterol, uric acid, and high sensitivity C-reactive protein. We aim to use a subset of this reference cohort as controls that have the same age and sex distribution as our study cohort.

## Data Collection

### Data Collected Before Visit of Late-Effects Clinic

An overview of collected variables is presented in Table 2. In addition to the previously mentioned data, the following variables relevant for the Dutch LATER METS study were extracted from the medical records: height and weight at cancer diagnosis and relevant comorbidities.

### Data Collected at Visit of Late-Effects Clinic

Weight was measured without shoes and with light clothing on an electronic scale to the nearest 0.1kg. Height was measured without shoes to the nearest centimeter. Body mass index was calculated from weight and height. Waist circumference was measured in the middle between the lower rib and iliac crest to the nearest centimeter. Hip circumference was measured at the greater trochanter to the nearest centimeter. Waist/hip ratio was calculated. Blood pressure was measured after at least 5 minutes rest with an electronic oscillometric meter (the mean of two measurements).

Survivors completed a general health questionnaire, containing questions about comorbidities, current medication use, smoking and alcohol habits, education level, and family history of diabetes mellitus and cardiovascular disease. They also completed the Short Questionnaire to Assess Health enhancing physical activity [58]. Total body dual-energy x-ray absorptiometry scans (Hologic and Lunar types) were used to assess body composition [41]. These measurements include fat percentage and lean body mass. The 6-minutes walking test was performed in a subset of the survivors (those treated in the Sophia children's hospital/Erasmus Medical Center, Rotterdam) as a measure of functional exercise capacity [59,60].

**Table 2.** Overview of collected variables.

Collection period	Category	Variable	Unit(s) or categories
Collected before visit of late-effects clinic	Childhood cancer type and treatment	Primary childhood cancer diagnosis	ICCC-3 <sup>a</sup> classification
		Treatment protocol	Name and arm
		Chemotherapy, per regimen	TCD <sup>b</sup>
		<b>Radiotherapy field</b>	
		Cranial/craniospinal	TCD, fractions (if applicable)
		Total body	TCD, fractions (if applicable)
		Abdominal	TCD, fractions (if applicable)
		Pancreas involvement	TCD, fractions (if applicable)
		<b>Surgery procedure</b>	
		Autologous stem cell transplantation	Yes / No, conditioning regimen
	Allogeneic stem cell transplantation	Yes / No, conditioning regimen	
	Relapse	Yes / No	
	Patient characteristics	Sex	Male / Female
		Date of birth	Date
		Date of childhood cancer diagnosis	Date
	Medical history	Date of study measurements (follow-up date)	Date
		Height at cancer diagnosis	Centimeter
Weight at cancer diagnosis		Kilogram	
Growth hormone deficiency		Yes / No	
Growth hormone replacement		Yes / No	
Hypothyroidism		Yes / No	
Hypogonadism		Yes / No	
Hypocortisolism with steroid replacement		Yes / No	

Collection period	Category	Variable	Unit(s) or categories	
Collected at visit of late-effects clinic	Physical examination	Height	Centimeter	
		Weight	Kilogram	
		Waist circumference	Centimeter	
		Hip circumference	Centimeter	
		Blood pressure	mmHg	
	General health questionnaire	<b>Does the survivor have or has the survivor experienced</b>		
		High cholesterol	Yes / No, age at diagnosis	
		Hypertension	Yes / No, age at diagnosis	
		Diabetes mellitus	Yes / No, age at diagnosis	
		Myocardial infarction	Yes / No, age at diagnosis	
		Stroke	Yes / No, age at diagnosis	
		Medication use	Type, dose, age at start	
		Smoking status	Yes / Former / No	
		Cardiovascular disease in family	Relative, type of disease, age at diagnosis	
		Questionnaire to Assess Health enhancing physical activity	N/A <sup>c</sup>	N/A
	Dual-energy x-ray absorptiometry scan	Total body fat	Percentage	
		Z-score total body fat	Z-score	
		Lean body mass	Kilogram per m <sup>2</sup>	
		Appendicular lean body mass	Kilogram per m <sup>2</sup>	
	6-minute walking test	N/A	Meter	
	Data determined from stored samples	<b>Serum biomarkers</b>		
		High-density lipoprotein	mmol/L	
		Low-density lipoprotein	mmol/L	
		Total cholesterol	mmol/L	
		Apolipoprotein-B	g/L	
		Glucose	mmol/L	
		Insulin	pmol/L	
Adiponectin		ug/mL		
Leptin		ng/mL		
Uric acid		mmol/L		
High sensitivity C-reactive protein		mg/L		
IL-6 <sup>d</sup>		pg/mL		
hsTNFa <sup>e</sup>		pg/mL		
IL-1 <sup>f</sup>		pg/mL		
IGF-1 <sup>g</sup>		ug/L		
Creatinine		mg/mmol		
Urea		mmol/L		
LH <sup>h</sup>	U/L			
FSH <sup>i</sup>	U/L			
AMH <sup>j</sup>	ug/L			

Collection period	Category	Variable	Unit(s) or categories
		Estradiol	pmol/L
		Testosterone	nmol/L
		DNA from blood/saliva	N/A

<sup>a</sup>ICCC-3: International Classification of Childhood Cancer, edition 3.

<sup>b</sup>TCD: total cumulative dose.

<sup>c</sup>N/A: not applicable.

<sup>d</sup>IL-6: interleukin-6.

<sup>e</sup>hsTNF: high-sensitivity tumor necrosis factor alpha.

<sup>f</sup>IL-1: interleukin-1.

<sup>g</sup>IGF-1: insulin-like growth factor 1.

<sup>h</sup>LH: luteinizing hormone.

<sup>i</sup>FSH: follicle stimulating hormone.

<sup>j</sup>AMH: anti-Müllerian hormone.

### Data Determined From Stored Samples

Venous blood samples were drawn after overnight fasting and stored at -80°C in the biobank. To assess dyslipidemia, a lipid spectrum will be measured, consisting of triglycerides, high-density lipoprotein, low-density lipoprotein, total cholesterol, and apolipoprotein-B. Insulin resistance will be assessed by measuring glucose and insulin. Additionally, adiponectin, leptin, and uric acid will be measured. Inflammatory markers include high sensitivity C-reactive protein, interleukin-6, high sensitivity tumor necrosis factor alpha, and interleukin-1. The following possible confounders will be measured: insulin-like growth factor 1, kidney function (creatinine, urea), sex hormones (luteinizing hormone, follicle stimulating hormone, anti-Müllerian hormone in women, estradiol in women, testosterone in men), thyroid function (thyroid-stimulating hormone, free thyroxine), cortisol.

DNA for analysis of single nucleotide polymorphisms will be isolated from blood or, in survivors who received allogeneic stem cell transplantation, saliva. Saliva was obtained by spitting into a collection tube (Oragene kit) after not drinking or eating for 30 minutes.

### Metabolic Syndrome Definition

Metabolic syndrome will be classified according to definitions by the third Adult Treatment Panel Report of the National Cholesterol Education Program [37] and the Joint Interim Statement of the International Diabetes Federation; National Heart, Lung, and Blood Institute; and the American Heart Association [38] (Table 1). Should these criteria be updated during our analysis, we will strive to take these adjustments into account.

### Risk of Bias

Sex, date of birth, date of cancer diagnosis, and disease and treatment data are also available for nonparticipating survivors. Hence, comparing participating and nonparticipating survivors in order to determine the risk of selection bias is feasible. We will also compare these data between survivors with complete and incomplete data to judge the risk of attrition bias. Neither physician nor study personnel were blinded to the exposures of

the survivors. Objectively measurable outcomes will reduce the risk of bias in this setting.

### Statistical Analysis

#### Prevalence of Metabolic Syndrome

The percentage of subjects with metabolic syndrome and the separate components will be assessed in survivors and in the Lifelines reference cohort according to both aforementioned metabolic syndrome definitions. Both cohorts will be compared by Chi-square (or Fisher exact) test. The relative risk for survivors to develop metabolic syndrome, compared to Lifelines reference data, will be calculated by employing a log-binomial regression model. The agreement between both metabolic syndrome definitions will be investigated with *kappa* statistic, in the whole cohort and stratified by sex.

A total body fat percentage of more than two standard deviations above the mean, as assessed by dual-energy x-ray absorptiometry, will be used as the most reliable marker for adiposity. We will estimate the correlation between waist circumference and fat percentage measured by dual-energy x-ray absorptiometry scan, and we will compare overweight classification with both definitions.

#### Risk Factors

Treatment-related risk factors for occurrence of metabolic syndrome and the separate components will be assessed using multiple uni- and multivariable logistic regression models. Based on literature, an initial model will be built with cranial radiotherapy, abdominal radiotherapy, and alkylating agents (total alkylating dose calculated using cyclophosphamide equivalent dose [61]) as treatment-related independent variables, and age, sex, follow-up time, and smoking as patient-related independent variables. The effect of potential additional risk factors will be assessed by adding them to the initial model, and variables with a *P* value <.20 will be kept in the final model. These potential risk factors include all other chemotherapy agents (type and total cumulative dose), other radiotherapy fields (body location and dose), corticosteroids, education level, family history, physical activity, functional exercise capacity, and comorbidities.



We will also investigate different abdominal radiotherapy fields involved (pancreas, liver), and the influence of stem cell transplantation conditioning regimens. We will also study patient- and treatment-related risk factors for the outcome underdiagnosis of overweight measured by waist circumference.

### **Biomarkers**

Biomarker values will be reported, with reference values from the local laboratory where the samples are measured. This will be compared to Lifelines reference data by Chi-square (or Fisher exact) test. A risk factor analysis of altered biomarker values will be performed similarly to the abovementioned strategy for risk factor analysis of metabolic syndrome occurrence.

The diagnostic and predictive value of the biomarkers to detect metabolic syndrome will be investigated in multiple steps. We will stratify the survivors by metabolic syndrome presence or absence and compare mean or median values with the *t* test or Mann-Whitney U test. We will evaluate sensitivity and specificity and positive and negative predictive value based on the reference values of the local laboratory where the samples are measured. We will compare the area under the curve for a model with metabolic syndrome components and for a model with each biomarker added in order to investigate the additional diagnostic value of the novel biomarkers. We will build multivariable logistic regression models with metabolic syndrome as dependent variable and the biomarker as independent variable. In these models, we will also include metabolic syndrome components as covariates in order to investigate the independent predictive value of the novel biomarkers. We will estimate the metabolic syndrome risk by including the biomarker as categorical as well as continuous variable.

Correlation (Pearson or Spearman) between biomarkers and fat percentage by dual-energy x-ray absorptiometry scan will be used to measure the potential use as surrogate markers for adiposity.

### **Genetic Susceptibility Analysis**

Genotyping will be performed with the Infinium Global Screening Array [62] on DNA isolated from blood or, in post-stem cell transplantation survivors, saliva. Quality control of the genotype data will be performed following a standardized protocol [63] including filtering based on call rate (excluded when <0.975 for either single nucleotide polymorphism or individual call rate), Hardy-Weinberg equilibrium, excess heterozygosity, gender mismatches, and familial relationships. Genetic ancestry will be assessed based on principal component analysis. Imputation will be performed with the Michigan Imputation Server using standard settings [64] with reference panel Haplotype Reference Consortium version r1.1 [65].

The single nucleotide polymorphism analysis will be performed with the RVtests software package [66] using multiple logistic regression models with metabolic syndrome and its separate components as outcomes. The initial analysis will be adjusted for age at follow-up, sex, and genetic ancestry. Then, potentially relevant covariates will be added to the model using forward selection to study whether they influence the single nucleotide polymorphism analysis; if so, they will be kept in the model.

These covariates include: body mass index at follow-up, comorbidities (growth hormone deficiency, hypogonadism, diabetes mellitus, and hypothyroidism), cranial and abdominal radiotherapy, and alkylating agents (cyclophosphamide equivalent dose). We will also perform a time-to-event analysis (with left-censoring) on identified hits in order to get clinically relevant effect estimates.

Quality control of the single nucleotide polymorphism analysis will be performed with the EasyQC package using standard settings [67]. This includes filtering based on minor allele frequency (excluded when <0.05) and imputation quality (excluded when <0.3).

Visualization of the genetic associations and annotation of biological function for the top single nucleotide polymorphisms will be performed with the FUMA platform [68]. Findings will be replicated in available independent international cohorts.

## **Results**

### **Patient Accrual**

Patient accrual started in 2016 and lasted until April 2020. A total of 2380/4741 survivors have participated (participation rate 50.2%). From July 2020, biomarker testing, single nucleotide polymorphism analysis, and data analysis will be performed.

### **Power Calculation**

We performed a power calculation with an expected prevalence of metabolic syndrome in our study cohort of 30%. This percentage is based on results from the SJLIFE cohort, in which the prevalence of clinically diagnosed metabolic syndrome in 1598 survivors, after a mean of 25.6 years since diagnosis, was 31.8% [6]. This is the only large cohort study so far with clinically diagnosed metabolic syndrome in survivors of heterogeneous malignancies with a follow-up time comparable to that of our cohort.

Based on the sample size of 2380 survivors, expected metabolic syndrome prevalence of 30%, power of 80%, and type I error of .05, we will have sufficient power to detect an approximate 3% difference in metabolic syndrome prevalence with the reference cohort. For risk factor analysis among survivors, the minimum detectable difference will depend on in how many survivors the risk factor (eg, treatment regimen) is present. For example, if the risk factor is present in 10%, 25%, or 50% of survivors, a minimum difference of approximately 9%, 7%, or 6%, respectively, can be detected.

A genetic power calculator was used to estimate the relative risk that can be found in the genetic susceptibility analysis for an assumed minor allele frequency of 0.25 [69]. Based on the sample size of 2380, metabolic syndrome population prevalence of 15% [70], a power of 80%, a type I error of  $5 \times 10^{-8}$ , and a case-control ratio of 1:2, the relative risk per high risk allele that can be found is 1.5.

## Discussion

In the current study, we will assess the prevalence and patient- and treatment-related risk factors for metabolic syndrome and its separate components in adult survivors of childhood cancer, as well as the additional diagnostic value of novel biomarkers for surveillance, and the genetic susceptibility to (treatment-related) metabolic syndrome by single nucleotide polymorphism analysis.

A total of 2380 survivors have participated in the study. This corresponds to 38.6% of all survivors (N=6165) in the Dutch LATER cohort, and a participation rate of 50.2% of invited adult survivors (n=4741). The definitive numbers of refusals, nonresponders, deaths or otherwise excluded subjects are not available yet. We will report these in the paper with the results of our study.

Strengths of this study include the availability of a national cohort of survivors, the availability of comprehensive disease

and treatment data, and the clinical assessment of late effects, in addition to questionnaire based endpoints. So far, the role of biomarkers and genetic susceptibility to metabolic syndrome has not been well defined in survivors. We specifically intend to use dual-energy x-ray absorptiometry scans and relevant biomarkers (those with a high independent diagnostic or prognostic value, and a high correlation with fat percentage on dual-energy x-ray absorptiometry scan) to enable identification of survivors at risk for metabolic syndrome, in whom waist circumference measurement is not feasible due to abdominal radiotherapy.

In conclusion, our study will provide knowledge on clinical and genetic determinants of metabolic syndrome and the diagnostic value of biomarkers in adult childhood cancer survivors. The results of this study will be used to optimize surveillance guidelines for metabolic syndrome among survivors, based on enhanced risk stratification and screening strategies. This will improve the diagnosis of metabolic syndrome and prevent complications, thereby improving quality of life.

## Conflicts of Interest

None declared.

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*Edited by G Eysenbach; submitted 09.06.20; peer-reviewed by N Waespe; comments to author 04.07.20; revised version received 18.08.20; accepted 10.11.20; published 27.01.21.*

*Please cite as:*

*Pluimakers V, Fiocco M, van Atteveld J, Hobbelink M, Bresters D, Van Dulmen-den Broeder E, Van der Heiden-van der Loo M, Janssens GO, Kremer L, Loonen J, Louwerens M, Van der Pal H, Ronckers C, Van Santen H, Versluys B, De Vries A, Van den Heuvel-Eibrink M, Neggers S*

*Metabolic Syndrome Parameters, Determinants, and Biomarkers in Adult Survivors of Childhood Cancer: Protocol for the Dutch Childhood Cancer Survivor Study on Metabolic Syndrome (Dutch LATER METS)*

*JMIR Res Protoc 2021;10(1):e21256*

*URL: <https://www.researchprotocols.org/2021/1/e21256>*

*doi: [10.2196/21256](https://doi.org/10.2196/21256)*

*PMID: [32750002](https://pubmed.ncbi.nlm.nih.gov/32750002/)*

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Protocol

# Assessing COVID-19–Related Knowledge, Attitudes, and Practices Among Hispanic Primary Care Patients: Protocol for a Cross-sectional Survey Study

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## Abstract

**Background:** Recent epidemiological data indicate that minority groups, especially Hispanic communities, experience higher rates of infection, hospitalization, and death due to COVID-19. It is important to understand the nature of this health disparity and the socioeconomic or behavioral factors that are placing Hispanic communities and other minority populations at higher risk for morbidity and mortality.

**Objective:** The purpose of this project is to assess current COVID-19–related knowledge, attitudes, and practices (KAP) among a predominantly Hispanic population from Orange County, California, and identify risk factors that may contribute to increased susceptibility and vulnerability to contracting SARS-CoV-2.

**Methods:** Our Orange County–wide community survey consists of quantitative survey questions in four domains: demographic information, COVID-19 knowledge questions, COVID-19 attitude questions, and COVID-19 practices questions. The survey questions are adapted from recent global KAP studies. Participants are being recruited from Amistad Medical Clinic, a private primary health clinic group in Orange County that treats a predominantly Hispanic population. Patients recruited during telehealth visits are surveyed remotely by telephone, and those recruited during in-person clinic visits are surveyed in person. Surveys are conducted by trained members of the study team who are native to the community setting.

**Results:** As of October 12, 2020, we had recruited and enrolled 327 participants. Data collection occurred June 26th to October 30th. Data analysis is ongoing.

**Conclusions:** Very few current COVID-19 studies focus on the perspective and experience of minority populations. Because Hispanic communities are disproportionately affected by COVID-19, it is important to understand the factors that contribute to this disparity and the next steps that should be taken to reduce the COVID-19 burden in this population. We believe that our study model of partnering with a local clinic system that serves our study population can be expanded to other settings to compare COVID-19 KAP and associated factors within different minority communities.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/25265

(*JMIR Res Protoc* 2021;10(1):e25265) doi:[10.2196/25265](https://doi.org/10.2196/25265)

**KEYWORDS**

COVID-19; knowledge; attitude; practices; Hispanic; California; protocol; cross-sectional; survey

## Introduction

The COVID-19 pandemic continues to grow in scale and scope globally, and it represents a major threat to the health and safety of communities worldwide. However, recent epidemiological data indicate that minority populations in the United States, especially Hispanic communities, are disproportionately infected and hospitalized with COVID-19 [1-4]. To develop better public health and preventative measures, it is critical that we collect local data to understand the potential risk factors and perspectives of these populations as they experience the pandemic. This information is necessary to assess existing measures of prevention and create novel, targeted strategies to reduce the burden of COVID-19 on minority populations and control the spread of the virus in all communities [5].

As of October 2020, SARS-CoV-2 has infected more than 7 million people and has resulted in more than 200,000 deaths in the United States [6]. Globally, cases in the United States currently account for over 25% of COVID-19 cases worldwide, and the number of cases is continuing to grow at a concerning rate [7].

This pandemic has highlighted the health disparities that exist in our country, and some of the most apparent inequities are seen among the Hispanic population. In California, Hispanic people comprise only 38.9% of the population; however, they account for 56.1% of COVID-19 cases and 45.6% of COVID-19-related deaths in the state [8]. States across the country report similar case rate disparities, such as Oregon (13% of population vs 39.8% of COVID-19 cases), Washington (13% of population vs 44% of COVID-19 cases) and Utah (14% of population vs 39.4% of COVID-19 cases) [1]. In Chicago, Illinois, COVID-19 cases among Hispanic patients represent almost half of the total cases in the city [9].

Many hypotheses have been proposed for why minority populations and Hispanic communities are disproportionately affected by COVID-19, including limited access to care, increased exposure, and higher prevalence of comorbidities leading to worse outcomes [10,11]. First, it is important to note that Hispanic individuals have the highest uninsured rates of any racial or ethnic group within the United States, creating significant barriers to accessing COVID-19 testing and health care [12]. Additionally, individuals in Hispanic communities are more likely to be employed by public-facing businesses and institutions, including the food service, transportation, and sanitation industries [13]. Because these individuals do not enjoy the privilege of working from home and were required to come into work during stay-at-home orders, they would have been disproportionately exposed to the virus. Living conditions may also play a role in the increased exposure of Hispanic populations to the novel virus; many Hispanic families live in densely populated areas and multigenerational households, which can facilitate person-to-person transmission [10]. Finally, the Hispanic population has an increased burden of comorbidities, including diabetes, hypertension, and heart disease [14]. While these comorbidities do not increase a person's susceptibility to contracting the virus, they lead to worse health care outcomes. In a recent study of the

disproportionate rise in COVID-19 cases among our study population in Orange County, California, researchers at the University of California, Irvine suggested that low income level, household density, lower educational attainment and lower health care coverage are risk factors for COVID-19 infection [15].

While research and epidemiological data have identified COVID-19-related health inequities among minority populations, few efforts have been made to understand how these populations cope with and conceptualize the pandemic. One survey conducted by the Pew Research Center found that Hispanic individuals are more likely to be concerned about COVID-19 compared to the general public. Approximately 65% of Hispanic adults say that the novel virus is a major threat to the health of the US population as a whole, compared with approximately half (47%) of the general public. Additionally, Hispanic adults were more likely to express concern that they would be hospitalized with COVID-19 or spread the virus unknowingly to others [16,17]. These concerns warrant further exploration, especially in the context of a vaccine being released in the coming months. A recent poll conducted by the Associated Press-NORC Center for Public Affairs Research found that only 25% of African Americans and 37% of Hispanic individuals would get a COVID-19 vaccine, compared to 56% of whites [18]. Understanding the attitudes and perspectives of Hispanic communities as they experience the COVID-19 pandemic is equally significant to develop effective, culturally specific public health policies and messaging.

A knowledge, attitudes, and practices (KAP) survey is an ideal tool to understand the risk factors that could predispose Hispanic communities to excess COVID-19 infection and mortality. The data from our survey have yet to be analyzed; however, we believe that understanding these risk factors, as well as the perspectives of this population, will enable public health and clinical institutions to implement effective and culturally relevant interventions to reduce these outcomes. We believe that the methodology of our study to collect KAP and demographic information using a clinic telehealth setup during the COVID-19 pandemic can be an extremely valuable method that can be used to recruit participants in future studies.

## Methods

### Settings and Population

Our quantitative surveys are being conducted at two Amistad Medical Clinic (AMC) health care centers in Orange County, California: AMC Santa Ana and AMC Anaheim. Both clinics are located in predominantly Hispanic areas of Orange County and serve as private primary care clinics for community members. Approximately 90% of the patients served by these clinics identify as Hispanic. The clinics accept California state, federal, and private insurance; therefore, they are accessible to all community members. The AMC centers serve approximately 0.5% of the populations of Santa Ana and Anaheim, respectively.



## Questionnaire

Our survey consists of four question domains with a total of 33 questions, some of which have been adapted from previous COVID-19–related KAP studies [19-21]. The first portion of the survey is focused on sociodemographic data, including age, gender, education, marital status, race, ethnicity, and employment status. We also inquire if the California stay-at-home order has impacted the participant’s employment and whether the participant has ever tested positive for COVID-19. Most importantly, we ask if they were required to leave their home to work during the stay-at-home order, placing them at risk of contracting the disease.

The second portion of the survey is used to measure COVID-19–related knowledge. The knowledge questions are a series of 1 multiple choice question, 1 open-ended question, and 7 “yes” or “no” questions. These questions assess the patients’ understanding about disease symptoms, transmission, spread, and susceptibility.

The third section of the survey is used to measure COVID-19–related attitudes. The attitudes portion of the survey consists of 5 questions that are answered using a 5-point Likert scale and 2 multiple choice questions. This portion of the survey is used to measure participants’ general perceptions about COVID-19 regarding (1) governments’ effectiveness in decreasing disease prevalence; (2) emotions during the pandemic, including anxiety, fear, anger, and optimism; and perceived risk of contracting COVID-19.

The final portion of the survey consists of COVID-19–related practices. The practices questions consist of 2 “yes” or “no” questions and 2 questions using a 5-point Likert scale. Our questions help us discern the steps that our participants are taking to protect themselves and the community from viral spread, and this portion includes questions regarding (1) attending gatherings and entering public spaces; (2) washing hands frequently; (3) wearing masks outside; and (4) interest in and concerns about COVID-19 testing and future vaccines.

Our full questionnaire is provided in [Multimedia Appendix 1](#).

## Recruitment

We have integrated our study within the majority of telehealth appointments in the clinics and in a few in-person appointment systems.

After the patient has completed their telehealth appointment, they are invited to participate in the survey study by their primary care physician, who then documents the patient’s willingness to participate by name, number, and availability on a secure drive. The drive is then accessed by the study interview team, and a member of the team calls the patient within 48 hours of recruitment. The interview team member obtains verbal consent during the telephone call and then proceeds to ask the survey questions.

In-person appointments follow a similar process. After the provider recruits a willing volunteer, a member of the interview team who is present at the clinic obtains verbal consent in person and then proceeds to ask the survey questions.

## Sample Method and Sample Size

Our survey uses a consecutive sampling method. The primary care physicians attempt to recruit each of their patients after their telehealth or in-person appointment. If the patient agrees to participate in the study, they are contacted by the study interview team to undergo the verbal consent process and complete the survey. Our sample size will reflect the number of people who are recruited and surveyed. We aim to interview approximately 400 participants over a span of 3 months.

## Results

The first study patient was enrolled on June 26, 2020, and recruitment and enrollment proceeded until October 30th. As of October 12, 2020, we had recruited and enrolled 327 participants, and we projected that 400 participants would be recruited and enrolled by the end of the recruitment period. We will conduct data analysis after the recruitment period on October 30, 2020.

The study was approved exempt from review by the University of California, San Diego Institutional Review Board on June 22, 2020.

## Discussion

Hispanic and other minority communities are experiencing disproportionately high rates of COVID-19 infection and severe outcomes in the United States. In Orange County, California, Hispanic individuals represent 35% of the population but account for almost half of COVID-19 infections and deaths [22,23]. Therefore, it is important to understand and assess the nature of this increased risk in Hispanic communities to contribute to future disease prevention in the next stages of this pandemic.

The KAP survey format has historically been a useful tool in identifying risk factors that exist within a specific population regarding a highly prevalent disease [24]. In addition, the KAP survey provides insight into the perceptions and stigmas that may be preventing people from seeking health care and following safety guidelines when experiencing a pandemic. Finally, some KAP surveys can also identify behavioral risks that cause a population to be more susceptible to a disease [19,25]. For example, our survey will identify individuals who worked outside of their home during the stay-at-home order because they were considered to work in “essential” industries.

We hope that the hybrid remote/in-person design of our pilot study can be used as a foundation for future COVID-19–related KAP studies. Specifically, we believe that the data from our study will pave the way for future COVID-19–related KAP studies in minority populations. Data from future KAP surveys will be used to create effective, evidence-based public health measures and highlight specific risk factors that affect vulnerable minority communities.

Our method of recruitment and data collection is novel and extremely useful for conducting cross-sectional surveys during the COVID-19 pandemic, where most medical practitioners are relying on telehealth appointments [26]. It is critical that during the pandemic, we are able to safely conduct scientific studies

without compromising the health of the participants and the study team or the accuracy of the data.

Most importantly, we believe that future COVID-19–related KAP studies can partner with local primary care clinics because these clinics have maintained longevity, rapport, and trust with their patients. Therefore, patients are more inclined to be candid when answering surveys, heavily decreasing response bias. Private primary care clinics within minority communities are also agents for public health changes on a local level [27,28]. The clinic staff are typically advocates of their communities and have autonomy over their practices; hence, they can be open

to taking study conclusions and directly implementing them in their patient care routine (ie, increasing COVID-19 education for their patients to prevent future misconceptions).

Our cross-sectional pilot study evaluates the COVID-19–related knowledge, attitudes, and practices of the Hispanic adult population to inform the development of evidence-based COVID-19 prevention policies and public health measures. It is important to partner with local clinics that have existing infrastructures and relationships with their communities to study and ultimately help these vulnerable populations in the era of COVID-19.

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## Authors' Contributions

ZCB and SNM led the writing of the manuscript. ZCB, SNM, and TR led the proposal and protocol development. DO, SS, YL, JK, MM, and AM contributed to the clinical and logistical aspects of protocol development. All authors have approved the final manuscript and agreed to publication.

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## Conflicts of Interest

None declared.

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Multimedia Appendix 1

Study questionnaire.

[PDF File (Adobe PDF File), 90 KB - [resprot\\_v10i1e25265\\_app1.pdf](#) ]

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## Abbreviations

**KAP:** Knowledge, Attitudes, and Practices

**AMC:** Amistad Medical Clinic

*Edited by G Eysenbach; submitted 26.10.20; peer-reviewed by A Khaleghi, MA Bahrami; comments to author 22.11.20; revised version received 15.12.20; accepted 19.12.20; published 27.01.21.*

*Please cite as:*

*Burger ZC, Mehta SN, Ortiz D, Sor S, Kothari J, Lam Y, Meka M, Meka A, Rodwell T*

*Assessing COVID-19-Related Knowledge, Attitudes, and Practices Among Hispanic Primary Care Patients: Protocol for a Cross-sectional Survey Study*

*JMIR Res Protoc 2021;10(1):e25265*

*URL: <http://www.researchprotocols.org/2021/1/e25265/>*

*doi: [10.2196/25265](https://doi.org/10.2196/25265)*

*PMID: [33406051](https://pubmed.ncbi.nlm.nih.gov/33406051/)*

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Corrigenda and Addenda

# Correction: Predictors and Consequences of Veterans Affairs Mental Health Provider Burnout: Protocol for a Mixed Methods Study

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**Related Article:**

Correction of: <https://www.researchprotocols.org/2020/12/e18345/>

(*JMIR Res Protoc* 2021;10(1):e26934) doi:[10.2196/26934](https://doi.org/10.2196/26934)

In “Predictors and Consequences of Veterans Affairs Mental Health Provider Burnout: Protocol for a Mixed Methods Study” (*JMIR Res Protoc* 2020;9(12):e18345) the authors noted one error.

The Multimedia Appendix file attached to the originally published article has been removed, as the file contained some private financial information.

The correction will appear in the online version of the paper on the JMIR Publications website on January 12, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

*Submitted 04.01.21; this is a non-peer-reviewed article; accepted 04.01.21; published 12.01.21.*

*Please cite as:*

*Zivin K, Kononowech J, Boden M, Abraham K, Harrod M, Sripada RK, Kales HC, Garcia HA, Pfeiffer P*

*Correction: Predictors and Consequences of Veterans Affairs Mental Health Provider Burnout: Protocol for a Mixed Methods Study*

*JMIR Res Protoc 2021;10(1):e26934*

*URL: <https://www.researchprotocols.org/2021/1/e26934>*

*doi: [10.2196/26934](https://doi.org/10.2196/26934)*

*PMID: [33434142](https://pubmed.ncbi.nlm.nih.gov/33434142/)*

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Protocol

# Effectiveness of an Electronic Communication Tool on Transitions in Care From the Intensive Care Unit: Protocol for a Cluster-Specific Pre-Post Trial

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## Abstract

**Background:** Transitions in care are vulnerable periods in health care that can expose patients to preventable errors due to incomplete or delayed communication between health care providers. Transitioning critically ill patients from intensive care units (ICUs) to other patient care units (PCUs) is particularly risky, due to the high acuity of the patients and the diversity of health care providers involved in their care. Instituting structured documentation to standardize written communication between health care providers during transitions has been identified as a promising means to reduce communication breakdowns. We developed an evidence-informed, computer-enabled, ICU-specific structured tool—an electronic transfer (e-transfer) tool—to facilitate and standardize the composition of written transfer summaries in the ICUs of one Canadian city. The tool consisted of 10 primary sections with a user interface combination of structured, automated, and free-text fields.

**Objective:** Our overarching goal is to evaluate whether implementation of our e-transfer tool will improve the completeness and timeliness of transfer summaries and streamline communications between health care providers during high-risk transitions.

**Methods:** This study is a cluster-specific pre-post trial, with randomized and staggered implementation of the e-transfer tool in four hospitals in Calgary, Alberta. Hospitals (ie, clusters) were allocated randomly to cross over every 2 months from control (ie, dictation only) to intervention (ie, e-transfer tool). Implementation at each site was facilitated with user education, point-of-care support, and audit and feedback. We will compare transfer summaries randomly sampled over 6 months postimplementation to summaries randomly sampled over 6 months preimplementation. The primary outcome will be a binary composite measure of the timeliness and completeness of transfer summaries. Secondary measures will include overall completeness, timeliness, and

provider ratings of transfer summaries; hospital and ICU lengths of stay; and post-ICU patient outcomes, including ICU readmission, adverse events, cardiac arrest, rapid response team activation, and mortality. We will use descriptive statistics (ie, medians and means) to describe demographic characteristics. The primary outcome will be compared within each hospital pre- and postimplementation using separate logistic regression models for each hospital, with adjustment for patient characteristics.

**Results:** Participating hospitals were cluster randomized to the intervention between July 2018 and January 2019. Preliminary extraction of ICU patient admission lists was completed in September 2019. We anticipate that evaluation data collection will be completed by early 2021, with first results ready for publication in spring or summer 2021.

**Conclusions:** This study will report the impact of implementing an evidence-informed, computer-enabled, ICU-specific structured transfer tool on communication and preventable medical errors among patients transferred from the ICU to other hospital care units.

**Trial Registration:** ClinicalTrials.gov NCT03590002; <https://www.clinicaltrials.gov/ct2/show/NCT03590002>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/18675

(*JMIR Res Protoc* 2021;10(1):e18675) doi:[10.2196/18675](https://doi.org/10.2196/18675)

## KEYWORDS

patient transfers; interprovider communication; transitions in care; electronic charting; clinical documentation; discharge tools; patient discharge summaries; electronic transfer summaries; intensive care unit; electronic tool; ICU; protocol; effective; communication; transfer; patient; transition

## Introduction

### Background

Complete and timely communication between health care providers is integral to seamless transitions in care [1-3]. The transfer of critically ill patients from the intensive care unit (ICU) to another patient care unit (PCU) is a particularly vulnerable period in patient care, due to the high acuity of patients [4-6] as well as the number of health care providers involved and their professional diversity [7-10]. The movement of patients between units requires a high degree of collaboration, with verbal and written communication between health care providers [1-3] as well as patients and families [1,11-13]. Suboptimal communication during transitions can have profound implications for patients, families, and the health care system [14-16], including increased risk of preventable medical errors, adverse events, redundant testing, readmissions, and dissatisfaction with the quality of care [17-24].

An ICU transfer summary is a clinical document that ICU physicians and nurse practitioners (NPs) often prepare to describe a patient's stay in the ICU, including active and resolved health issues and the current care plan. The transfer summary is intended to support verbal communication between transferring and accepting medical teams and should provide sufficient detail to serve as a stand-alone communication [25]. Complete and timely exchanges of patient care information during transitions in care are critical, not only for immediate continuity of care but also for efficient coordination of future care [26,27]. As such, the transfer summary should be easily accessible to inpatient and outpatient health care providers as part of the patient's permanent health care record.

Standardized transfer protocols that structure documentation are integral for preventing failures in patient care due to incomplete and delayed exchange of information [21,28-30]. However, their value can be limited by the very methods used to produce the document. While quick for the clinician to prepare, traditional methods like dictation or handwritten notes

in the patient chart have been associated with inaccurate, incomplete, and lengthy delays in communication [17,20,31,32], particularly in comparison to transfer summaries prepared using electronic standardized tools [26,33-39]. The advancements of clinical information systems (CISs) and integrated electronic medical records (EMRs) provide a prime opportunity to optimize text-based communication. Structured templates can facilitate completeness of important patient information as well as substantiate and prompt verbal communication between health care providers at the point of care. They can also provide flexibility, permitting physicians to create a "living" document that can be edited over the course of stay and finalized at the point of patient transfer, effectively facilitating clinical workflow in complex settings. Despite the potential for optimizing efficient interprovider communication, the use of standardized tools to prepare ICU transfer summaries has not been widespread, with factors such as usability [39], cost, and workload [40] being barriers to adoption.

### Local Initiative to Standardize Transfer Summaries: The Electronic ICU Transfer Tool

In 2017, we began designing an evidence-informed, computer-enabled, ICU-specific communication tool in the primary, integrated patient care CIS—Sunrise Clinical Manager (Eclipsys Corporation)—used in four acute care hospitals in a single Canadian city. This work was initiated as a quality improvement project to improve upon the conventional system of dictation that physicians and NPs—herein called ICU clinicians—use to prepare medical transfer summaries for ICU patients [41]. To dictate a summary, ICU clinicians use eScription, 2010 release (Nuance Communications), a health information management dictation, speech recognition, and transcription (DST) platform. The clinician verbalizes relevant patient transfer information to create a voice file that is run through speech recognition software to create a text report. The report is then edited by a transcriptionist and sent to the designated ICU clinician for approval before being uploaded for electronic viewing in the CIS as well as to a provincial,

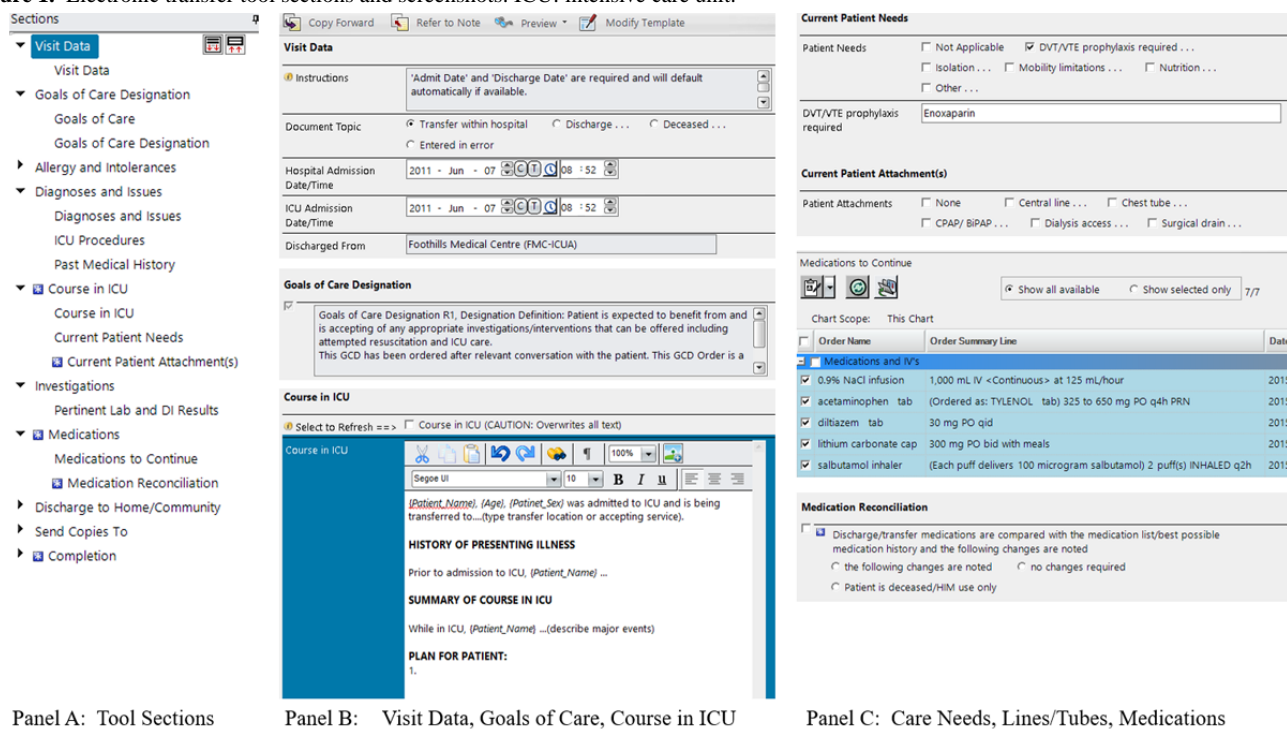


web-based health data repository accessible by community-based physicians (Alberta Netcare).

The content and structure of the ICU electronic transfer (e-transfer) tool was based on a national survey of existing transfer summary tools [42], subsequent consensus-based recommendations of two independent multidisciplinary groups of health care providers [41,43], and a heuristic evaluation [41]. The e-transfer tool consists of 10 overarching document sections: visit data, goals of care, allergy and intolerances, diagnoses and visit issues, course in ICU, investigations,

medications, discharge to home or community, send copies to, and completion. These sections are designed with a user interface combination of structured fields (eg, checkboxes); automated fields, which pull in relevant patient data from other CIS locations; and free-text fields (see Figure 1). The tool permits ICU clinicians to open an ICU summary as a clinical document directly in the patient's EMR and edit the summary over the course of the patient's ICU stay. As with the DST system, the designated ICU clinician must approve transfer summaries. The summaries remain in the CIS and are uploaded to the provincial repository.

**Figure 1.** Electronic transfer tool sections and screenshots. ICU: intensive care unit.



In a small pilot test of the e-transfer tool in one ICU [42], electronic summaries had a significantly greater proportion of essential information fields completed overall (median 87.5%) than those prepared by dictation (median 62.5%) and were available to receiving teams closer to patient release (2.3 versus 45.0 hours). Primary users of the e-transfer tool also responded positively to its use, establishing favorable evidence to scale up implementation across additional municipal hospitals.

## Objective

In this study, we will evaluate the effectiveness of the ICU e-transfer tool for improved completeness and timeliness of transfer summaries and reduced adverse patient outcomes by comparing transfer summaries produced postimplementation to those produced preimplementation.

## Conceptual Framework

We will apply the Donabedian three-pronged model of health care quality (ie, structure, process, and outcome) [44] and the National Health Service Sustainability Model [45] to frame our evaluation of the e-transfer tool. The Donabedian model has been successfully used in multiple contexts to support quality improvement initiatives related to structures (ie, health care context), processes (ie, actions and events in health care), patient

outcomes (ie, effects on health status, quality, knowledge, or behavior), and use of resources [46,47]. Similarly, the National Health Service Sustainability Model has been successfully used to predict the likelihood of sustainability for improvement initiatives [48]. In drawing from each of these models, we will ensure that we identify areas that need strengthening and that we are well positioned for sustainability and continual improvement.

## Methods

### Setting

This evaluation study takes place in four acute care hospitals servicing a single city, Calgary, Alberta, Canada, which has a referral population of approximately 1.7 million. Three of the four hospitals are academic hospitals operating a combined 56 adult medical-surgical ICU beds; the fourth is a nonacademic, community-based hospital operating 10 ICU beds. The annual ICU admission rate across the city approximates 3000 patients. In addition to the CIS hosting the e-transfer tool (ie, Sunrise Clinical Manager), all ICUs also use a dedicated provincial critical care CIS (ie, eCritical MetaVision) and clinical analytics system (ie, eCritical TRACER) that capture key demographic,

clinical, health care service, and outcome data for all ICU patients [49]. ICUs are staffed by multidisciplinary teams; those in academic-based hospitals operate with a clinical fellow and 4 to 10 residents working under the supervision of an attending physician. One ICU has an NP. Critical care resident rotation blocks are 4 weeks in duration. The community-based ICU functions with an attending physician and 4 NPs.

### Study Design

This study uses a cluster-specific pre-post trial design with randomized and staggered implementation of the e-transfer tool across four hospitals.

### E-Transfer Tool Implementation

The e-transfer tool has been sequentially implemented into the four study hospitals at a new site every 2 months. This occurred between July 2018 and January 2019. The study biostatistician (AS), who was not involved with clinical practice in the ICUs, randomized the order of hospitals for implementation. Dictation remained available after implementation, but the ICU e-transfer tool was endorsed as the primary method to prepare ICU transfer summaries; as well, use of the tool was supported with strategies that have been successfully used in previous local initiatives, including in-person and web-based education, point-of-care support, and electronic audit and feedback [50].

### Participants

ICU patients from the four participating hospitals were eligible for inclusion in the study if the patient (1) was admitted to the ICU during the defined pre-post periods; (2) was 18 years of age or older; (3) had an ICU stay equal to, or longer than, 24

hours; and (4) was transferred from the ICU to an in-hospital PCU. Patient admission lists were extracted retrospectively by a data analyst with the critical care CIS repository (ie, eCritical TRACER). As the primary creators of most ICU transfer summaries [42], NPs and residents were invited to participate in a brief survey soliciting their experience creating transfer summaries.

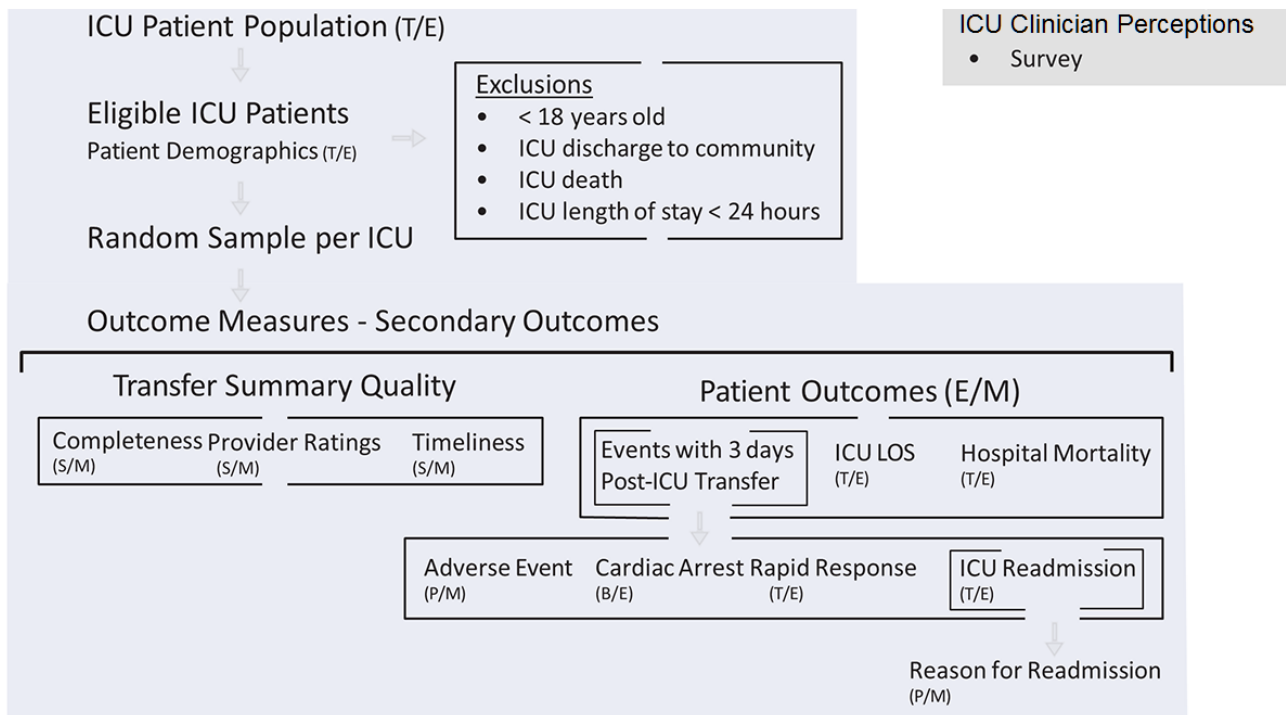
### Data Collection

#### Overview

We set pre- and postimplementation data collection periods to extend for 6 months each, based on the staggered dates when the ICU e-transfer tool was implemented at each hospital. Patients transferred from the ICU prior to the intervention implementation date of their hospital are considered in the preimplementation period, while patients transferred from the ICU on or after the intervention implementation date of their hospital are considered in the postimplementation period.

Data collection involves (1) electronic extraction from provincial system repositories and a local critical care database, (2) manual abstraction from the patient's electronic and paper medical record by trained researchers, and (3) manual rating of sampled transfer summaries by clinicians. Survey data of ICU clinician perspectives was collected pre- and postimplementation of the e-transfer tool. The flow of data collection is shown in [Figure 2](#). Where feasible, we are deidentifying hospital name, dates, and clinician and patient identifiers from clinical documents (eg, transfer summaries and clinician progress notes) secured for manual data abstraction. All data will be encrypted and retained in a secured office.

**Figure 2.** Data collection flow. B: critical care Code Blue database (data source); CIS: clinical information system; E: electronic extraction by CIS analyst (data collection method); ICU: intensive care unit; LOS: length of stay; M: manual extraction by study researcher (data collection method); P: paper chart (ie, medical doctor or nurse practitioner daily progress notes; data source); S: Hospital CIS (ie, Sunrise Clinical Manager; data source); T: critical care CIS analytics (ie, eCritical TRACER; data source).



### Patient Demographics

Patient demographic data includes the following: age; sex; ICU and hospital admission and discharge dates, times, and locations; hospital mortality; comorbidities; ICU interventions (ie, intubation, ventilation, vasoactive medications, and dialysis); and severity of illness measures, including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [51], the Glasgow Coma Scale (GCS) score [52], and the Sequential Organ Failure Assessment (SOFA) score [53].

### Outcome Measures

#### Overview

The primary outcome of interest is a binary composite measure of two conditions: information presence and availability (see Table 1). In the first condition, the presence of four essential information elements in the transfer summary—goals of care

designation, diagnosis, list of active issues on transfer, and medications to continue on transfer—will be assessed and recorded as *yes* or *no*. All four elements must be present to be recorded as *yes*. In the second condition, the availability of the transfer summary to the accepting clinicians at the time of patient transfer from the ICU will be recorded as *yes* or *no*. Transfer summaries that meet these two conditions will be coded as *present*; those that do not will be coded as *absent*.

Secondary outcomes of interest fall into three main domains (see Table 1): (1) transfer summary quality (ie, completeness, timeliness, and clinician ratings), (2) patient outcomes (ie, post-ICU rapid response activation, cardiac arrest, adverse events, and ICU readmission), and (3) clinician perceptions. The rate of use of the e-transfer tool will also be measured by extracting the type of method—dictation or tool—used to prepare the medical summary for each patient transferred from the ICU during the study period.

**Table 1.** Evaluation outcome measures.

Domain and outcome	Outcome description
Primary outcome—binary (present or absent) composite measure of two conditions: information presence and availability (both conditions need to be met)	<p>Presence of four essential information elements:</p> <ul style="list-style-type: none"> <li>• Goals of care</li> <li>• Diagnosis</li> <li>• Problem issues on transfer</li> <li>• Medications to continue on transfer</li> </ul> <p>Completed transfer summary available to patient care unit (PCU) at the time of patient's transfer out of the intensive care unit (ICU)</p>
<b>Transfer summary quality</b>	
Overall completeness: proportion of eight requisite information elements present in transfer summary (%) and presence or absence of each essential information element in transfer summary	<p>Summative score of the presence (score=1) of eight essential information elements—the four elements listed above and the following elements:</p> <ul style="list-style-type: none"> <li>• Patient medical history</li> <li>• Patient supportive needs (ie, venous thromboembolism prophylaxis, isolation, mobility, or nutrition)</li> <li>• Patient attachments (ie, lines and tubes)</li> <li>• Medication reconciliation</li> </ul>
Timeliness: availability of summary relative to the date and time of patient transfer (in hours)	<p>Difference between the following:</p> <ul style="list-style-type: none"> <li>• Date and time transfer summary was transcribed (ie, dictated summaries) or last edited (ie, electronic summaries) and</li> <li>• Date and time of patient transfer from ICU</li> </ul>
Clinician ratings: clinician ratings of perceived general quality of transfer summary (median, IQR)	<p>Rate five criteria on a 7-point Likert scale:</p> <ul style="list-style-type: none"> <li>• Organization</li> <li>• Completeness</li> <li>• Pertinence</li> <li>• Overall satisfaction</li> <li>• Confidence that accepting team will understand patient care plan</li> </ul>
<b>Patient outcomes</b>	
Occurrence of negative patient outcomes within 3 days post-ICU transfer (%)	<p>Patient events occurring within 3 days post-ICU:</p> <ul style="list-style-type: none"> <li>• ICU readmission</li> <li>• Adverse events</li> <li>• Rapid response team activation</li> <li>• Cardiac arrest</li> </ul>
Hospital and ICU total length of stay (in days)	Time between admission and discharge
Mortality (in hours)	Time from ICU transfer to hospital mortality
ICU clinicians' perceptions of their last transfer summary	<p>Rate seven criteria on a 7-point Likert scale:</p> <ul style="list-style-type: none"> <li>• Process: understood process to produce high-quality summary</li> <li>• Workload: manageable to complete within routine ICU workflow</li> <li>• Effectiveness: format able to communicate all relevant information clearly and logically</li> <li>• Revisions: able to revise as new information becomes available</li> <li>• Timely: able to complete at the time of patient transfer from ICU</li> <li>• Satisfaction: produced a high-quality summary</li> <li>• Confident that receiving PCU team will understand the patient care plan</li> <li>• Length of time required to complete last transfer summary, including gathering all relevant information</li> </ul>

## Transfer Summary Quality

### *Completeness of Information*

Trained researchers will manually abstract overall completeness of information in the summary. Completeness will be calculated as the sum of the individual binary scores (1=present; 0=absent) that the researchers will record for eight prospectively identified information elements prioritized as requisite from a list of 63

essential elements identified as important in ICU transfer summaries [43]. The eight information elements are as follows: goals of care designation, patient medical history, diagnosis, ICU active problem list, patient supportive care needs, patient attachments (ie, lines and tubes), active medications, and medication reconciliation. We designed a chart review form in REDCap (Research Electronic Data Capture) [54] (see [Multimedia Appendix 1](#)). As the researchers will need to access



relevant clinical documents in study patients' medical records, they will not be blinded to the study period or hospital.

### **Timeliness of Information**

Timeliness of the summary is defined as the difference in hours between the date and time the patient transferred out of the ICU and the date and time the transfer summary was either transcribed, in the case of dictated documents, or last updated in the CIS, in the case of e-transfer tool documents.

### **Clinician Ratings**

We will recruit ICU and PCU clinicians as volunteers to review and rate the general quality of a subsample of ICU transfer summaries randomly sampled from the larger pool of sampled summaries. Clinicians will use a 7-point scale to assess five criteria adapted from a previous study evaluating a similar tool [39,55]: organization (ie, presentation was logical and clear), completeness (ie, no information gaps or omissions), pertinence (ie, all content was relevant to patient care), overall satisfaction with the quality of the summary, and degree of confidence that the accepting clinician will understand the patient care plan after reading the transfer summary (see Table 1). Clinicians will be blinded to both the study period and hospital.

### **Patient Outcomes**

Incidents of ICU readmissions and rapid response team activations occurring within 3 days of ICU transfer were extracted from the critical care system repository; cardiac events within 3 days of ICU transfer were extracted from the *Code Blue* database maintained within the Department of Critical Care Medicine (see Table 1). Patients who were readmitted to the ICU within 3 days of their first ICU transfer will be further evaluated by a clinician (see Figure 2) to determine if the reason for their readmission was related to a health issue documented in the transfer summary of their first ICU admission; this will be recorded as *yes*, *no*, or *unclear*.

Adverse events within 3 days of ICU transfer will be abstracted using a two-stage manual abstraction process based on the Institute for Healthcare Improvement Global Trigger Tool (GTT) method of chart review [56]. The GTT definition of an adverse event, as described on page 5 of the Institute for Healthcare Improvement white paper [56], is "any unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalization, or that results in death." In Stage 1, two trained researchers will independently review the daily clinician progress notes charted in each patient's paper medical record 3 days post-ICU transfer. Using a list of 19 patient safety indicators, they will identify and record *yes*, *no*, or *unsure* for each incident of a suspected adverse event. The patient safety indicators are based on Southern and colleagues' [57] list of 18 triggers adapted to a Canadian context with newer iterations of health coding data, with the addition of "patient falls." In order to ensure good interrater reliability, Stage 1 reviewers will appraise a small sample of charts, compare results, and resolve any discrepancies before moving forward to evaluate the full sample. In Stage 2, any suspected adverse event recorded as *yes* or *unsure* during Stage 1 will be flagged for review by a third reviewer who will be a clinician. The clinician will review the notes and evaluate

each suspected adverse event to confirm or reject the occurrence of the event using the GTT definition. In cases with a confirmed adverse event, the clinician reviewer will determine if the adverse event was preventable (ie, *yes*, *no*, or *unsure*), as well as designate the severity of the adverse event using the GTT categories of harm [56].

ICU and hospital length of stay will be captured using ICU and hospital admission and discharge dates and times. In-hospital mortality will be captured as the time from ICU discharge to hospital mortality, with censoring at hospital discharge for those who survived hospital.

### **Clinician Perceptions of Practice**

To obtain ICU clinician feedback on preparing transfer summaries (see Table 1), we will analyze survey data collected pre- and postimplementation of the e-transfer tool. Our survey was adapted from a validated survey used to assess physician perceptions using a similar transfer tool [39,55]. We disseminated it via paper and online to ICU NPs and residents. The time between the two dissemination periods was over a year, making response bias unlikely. Participants were asked to rate their experience completing their last transfer summary on seven criteria: process (ie, understood what to include and how to accomplish this), workload (ie, completing was manageable within routine ICU workflow), effectiveness (ie, able to communicate all relevant information clearly and logically), revision (ie, able to easily edit and update the transfer summary with new information), timeliness (ie, able to complete by the time the patient is transferred from ICU), satisfaction (ie, summary was of high quality), and confidence that the accepting medical team will understand the patient care plan. Participants were also asked to estimate how long it took them, in minutes, to complete their last ICU transfer summary.

### **Sample Size Calculations**

Sample size calculations were based on the cluster-specific pre-post study design. Based on our pilot [41,42], we calculated a required sample size of 144 pre- and 144 postimplementation ICU transfer summaries from each hospital to assess our primary outcome. This will be sufficient to detect an absolute difference in our primary outcome of 15% for each hospital with 82% power and an  $\alpha$  value of 5% based on a baseline proportion of 20%; we observed a change in our pilot from 23% to 83%. A random sample of 24 ICU patients per hospital per month, over 6 months pre- and 6 months postimplementation, will facilitate secondary analyses, which accommodate the possibility of secular trends. The study biostatistician (AS) determined the random sample by assigning computer-generated random numbers to the complete list of patients transferred from each ICU within the study period, which was extracted by a data analyst with the critical care analytics system (see Figure 2). The study biostatistician was blinded to the method used to create the summary at the time of randomization.

To collect clinician ratings of the transfer summary quality, we calculated requiring 64 summaries preimplementation (ie, 16 per hospital  $\times$  4 hospitals = 64) and 64 summaries postimplementation (ie, 16 per hospital  $\times$  4 hospitals = 64), which will be sampled from aforementioned summaries, to

detect an absolute difference in means as small as 0.5, assuming an SD of 1, with 80% power and an  $\alpha$  value of 5%. The same patient cases will be used to assess for suspected post-ICU adverse events.

### Data Analysis

Demographic characteristics pre- and postimplementation for each hospital will be described using medians with IQRs, means with SDs, and frequencies with percentages, as appropriate. The primary outcome will be compared within each hospital pre- and postimplementation using separate logistic regression models for each hospital, with adjustment for the following patient characteristics: age, sex, reason for ICU admission, status on ICU admission (ie, Charlson Comorbidity Index, APACHE II, GCS, and SOFA), therapies received while in ICU (ie, ventilation, vasoactive medications, intermittent hemodialysis, and continuous renal replacement therapy), status on transfer (ie, transfer delay time, transfer decision cancellations, and ICU occupancy), and ICU length of stay. Pooled analyses across all four hospitals will use mixed-effects logistic regression models with a fixed effect for intervention and a fixed effect for time in months, in order to model the underlying secular trend. A fixed effect for patient characteristics will also be used, as noted above, and random effects will be used for hospital and hospital by time to account for intracluster and interperiod correlation. In case of poor model fit or convergence issues due to a limited number of clusters, hospital-level analyses will be considered by aggregating the primary outcome over all summaries in each hospital during each month and using linear regression of the aggregated cluster-period proportions of complete and timely summaries with fixed effects for hospital and time in months. Secondary outcomes will be analyzed as described for the primary outcome, using within-hospital and pooled analyses. Wilcoxon rank-sum tests will be used to compare ICU and hospital length of stay, and log-rank tests will be used to compare time from ICU discharge to hospital mortality.

Open-ended comments collected through clinician surveys will be analyzed according to standard practices of qualitative textual analysis.

### Ethical Oversight and Trial Registration

The University of Calgary Conjoint Health Research Ethics Board reviewed this study (No. 17-2317) and granted a waiver of consent to collect retrospective data from relevant sections of patients' paper medical records and EMRs. ICU clinicians who submit a survey will have implied their consent. Operational approvals and a data disclosure agreement was established with the provincial health custodian, Alberta Health

Services. All protocol modifications will be reviewed by our research ethics board before being implemented. The trial was registered at ClinicalTrials.gov (NCT03590002).

## Results

Based on our study design, in fall 2019, the eCritical data analyst completed preliminary extraction of the list of patients transferred from the ICU within the 18-month range: February 12, 2018, to June 30, 2019. We have randomly sampled eligible patients from each ICU, restricting sampling to 6 months before and 6 months after the date the e-transfer tool was implemented in the hospital. Abstraction of primary and secondary outcomes is underway. We anticipate all data to be collected by early 2021, with data cleaning and analyses conducted and first results ready for publication in spring or summer 2021.

## Discussion

### Overview

The ICU e-transfer tool was designed to improve and standardize textual communication between clinicians during transitions in care from the ICU to other PCUs. The number of individuals who experience and recover from critical illness in their lifetime is steadily increasing. The proliferation of life-sustaining technologies has resulted in new challenges with transitions in care of newly vulnerable critically ill patients. We have documented significant gaps in continuity of care for ICU patients, one of the most clinically high-risk groups in the health care system [25,32]. The evidence-informed ICU e-transfer tool that we have developed and will evaluate can potentially optimize care across the health care continuum by mitigating communication errors and adverse events and contributing to improved experiences and outcomes for critically ill patients. Our evaluation will identify how the tool performs, what elements are effective, and what elements are ineffective and need to be refined or eliminated.

### Conclusions

This research will build a foundation for addressing an identified priority gap in patient care by rigorously evaluating a standardized electronic tool that will be adaptable to individual settings and scalable across health care jurisdictions. The study findings will add to the current literature on the effect of computerized tools on reducing communication breaks between the ICU and other PCUs during transitions in care and to ultimately improve patient safety.

## Acknowledgments

JPL and HS conceived of the study. All authors contributed to the study design. AS and MT provided statistical expertise. HS, DK, LWB, and RBM were involved in the implementation of the ICU e-transfer tool. JPL, JP, and RBM prepared the initial manuscript draft. All authors substantively revised the manuscript, and all authors have read and approved the submitted version. This work is supported by the Canadian Frailty Network (grant No. KT2017-15-Grant) and the Canadian Institutes of Health Research (grant No. RN381460-420324). The funders had no role in the study design or in the submission of this manuscript; they will not take part in the collection or analysis of data or in the assessment of outcomes.

## Conflicts of Interest

None declared.

### Multimedia Appendix 1

Intensive care unit (ICU) transfer summary data abstraction form in REDCap (Research Electronic Data Capture).  
[PDF File (Adobe PDF File), 438 KB - [resprot\\_v10i1e18675\\_app1.pdf](#)]

### Multimedia Appendix 2

Grant funding agency peer reviewer comments.  
[PDF File (Adobe PDF File), 167 KB - [resprot\\_v10i1e18675\\_app2.pdf](#)]

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## Abbreviations

- APACHE II:** Acute Physiology and Chronic Health Evaluation II
- CIS:** clinical information system
- DST:** dictation, speech recognition, and transcription
- EMR:** electronic medical record
- e-transfer:** electronic transfer

**GCS:** Glasgow Coma Scale  
**GTT:** Global Trigger Tool  
**ICU:** intensive care unit  
**NP:** nurse practitioner  
**PCU:** patient care unit  
**REDCap:** Research Electronic Data Capture  
**SOFA:** Sequential Organ Failure Assessment

*Edited by G Eysenbach; submitted 18.03.20; peer-reviewed by S Tajalli; comments to author 03.11.20; revised version received 16.11.20; accepted 17.11.20; published 08.01.21.*

*Please cite as:*

*Parsons Leigh J, Brundin-Mather R, Whalen-Browne L, Kashyap D, Sauro K, Soo A, Petersen J, Taljaard M, Stelfox HT  
Effectiveness of an Electronic Communication Tool on Transitions in Care From the Intensive Care Unit: Protocol for a Cluster-Specific  
Pre-Post Trial*

*JMIR Res Protoc 2021;10(1):e18675*

*URL: <https://www.researchprotocols.org/2021/1/e18675>*

*doi: [10.2196/18675](https://doi.org/10.2196/18675)*

*PMID: [33416509](https://pubmed.ncbi.nlm.nih.gov/33416509/)*

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Protocol

# Examining a Digital Health Approach for Advancing Schizophrenia Illness Self-Management and Provider Engagement: Protocol for a Feasibility Trial

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## Abstract

**Background:** In schizophrenia spectrum populations, adherence to treatment is poor, community-based supports are limited, and efforts to foster illness self-management have had limited success. These challenges contribute to frequent, lengthy, and costly hospital readmissions and poor functional outcomes. Digital health strategies, in turn, hold considerable promise in the effort to address these problems.

**Objective:** This feasibility trial will examine a digital health platform called App4Independence (A4i), which was designed to enhance illness self-management and treatment engagement for individuals with schizophrenia.

**Methods:** Feasibility metrics in this single-blind, randomized trial include study recruitment and retention, rate of technology use, safety, and utility in clinical interactions. Other outcome metrics include symptomatology, treatment adherence, patient-provider alliance, and quality of life. In this trial, 160 study participants with schizophrenia spectrum diagnoses will be randomized to either treatment or control conditions, with pretest-posttest outcomes measured over a 6-month period.

**Results:** This study was funded by the Canadian Institutes of Health Research in January 2020 and received Institutional Review Board approval on August 13, 2020. This study plans to begin recruiting in January 2021 and will be completed within 3 years. Data collection is projected to begin in January 2021.

**Conclusions:** This research will provide critical information for the development of this new technology in the larger effort to address a key problem in the schizophrenia field—how to leverage technology to enhance illness self-management and care engagement in resource-limited service contexts.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/24736

(*JMIR Res Protoc* 2021;10(1):e24736) doi:[10.2196/24736](https://doi.org/10.2196/24736)

## KEYWORDS

schizophrenia; psychosis; digital health; mobile health; smartphone

## Introduction

Advancing digital health interventions in schizophrenia is important in the Canadian health care context. Schizophrenia is responsible for 3.8% of the hospital admissions in Canada and accounts for an estimated annual cost of Can \$6.85 billion

annually in health care and lost productivity [1]. The associated challenges include high rates of completed suicide, low quality of life, poor access to nonpharmacological interventions, and pharmacological interventions that have suboptimal effects [2]. Overall, schizophrenia has proven extremely difficult to treat as is evidenced by high relapse and readmission rates [1]. The

most common contributors to relapse in schizophrenia are medication nonadherence, substance use disorders, social isolation, and inadequate supports [3-6].

There has been extensive commentary on the system of care problems for people with schizophrenia. Within these systems, the primary point of engagement—interactions and relationships with health care providers—is challenged. In inpatient units, patients are frequently dissatisfied with custodial approaches to care [7,8], and in outpatient settings, the frequency and nature of contacts with providers are often inadequate. Common concerns include a lack of shared-decision making in treatment, limited support in illness self-management, and insufficient time with providers [5,9,10]. Such suboptimal provider engagement and outpatient support have been directly implicated in treatment adherence rates of 50% or less [11] and poor quality of life [12,13]. In this context, leveraging technology to enhance engagement in outpatient care and to provide support with illness self-management holds considerable promise to (1) ameliorate aspects of schizophrenia that challenge provider contacts (eg, cognition, anxiety) [14,15], (2) facilitate provider access to more detailed information from which to base care decisions, (3) lead to patients feeling more empowered in the care process [16], and (4) lead to enhanced treatment engagement with implications for lower relapse rates [5,10,17]. Furthermore, digital engagement can facilitate more frequent supportive contacts at much less expense than in-person contacts and can offset challenges such as travel time and expense and the stigma of mental illness that can make some individuals reluctant to pursue care in psychiatric services.

To date, evidence for technology-enabled approaches to enhance outcomes for individuals with severe mental illnesses is limited. In particular, feasibility has proven to be a major challenge. In-office technologies require space, infrastructure, and staffing, and have proven difficult to implement due to expenses [18,19]. Web-based approaches are less expensive but have demonstrated high rates of attrition [20]. There are very few mobile apps targeting schizophrenia, in contrast with the large volume of apps for conditions such as anxiety and depression [21]. The reasons for such a gap are unclear, given the observation that over 80% of individuals with schizophrenia and other psychoses routinely use mobile technology and the majority are interested in using technology to assist with illness management [22-25].

A number of pilot studies suggest that schizophrenia-targeted mobile and web-based apps in areas such as cognitive remediation are feasible and do not result in any noted risks [23,26]. Most directly relevant to this proposal is the work of Ben-Zeev and colleagues [27]. Their FOCUS app has features that include daily activity prompts, brief self-assessments, and coping strategy tips. Preliminary investigation of this app indicated no risks associated with its use and sustained use over several months. Another similar digital health approach in this area that has shown feasibility is PRIME, which was developed by Schlosser and colleagues [28]. The core function of PRIME is providing users with access to masters-level clinicians who provide strategy coaching. There is, however, a paucity of trial data. In one of the few examples, the PRIME app described above was recently trialed [29] and demonstrated, compared to treatment-as-usual (TAU), improvement in some social

engagement and depression metrics though no changes in psychosis symptoms, quality of life, or functioning were observed. Systematic reviews [30,31] have highlighted the need for more clinical trials in this area.

In this initial pilot, we focused on the early-stage testing of a digital health tool, App4Independence (A4i), which was performed in 2 steps. Following a preliminary 1-week beta test by 5 individuals to address technical issues, the qualitative and quantitative A4i outcome data from 38 individuals were analyzed, assessing feasibility over a 1-month period [32]. The mean number of interactions with the app per day was 4.21 and, by day 20, a 4% churn rate was observed (rates of individuals who ceased app use). Considering outcomes (noting the lack of a control group), small-to-medium effect changes were observed in several symptom domains: a significant decrease in the depression domain of the Brief Symptom Inventory with a medium effect size ( $ES=0.42$ ) was observed, along with decreases in paranoid ideation ( $ES=0.29$ ), psychoticism ( $ES=0.22$ ), obsessive compulsive symptoms ( $ES=0.38$ ), phobic anxiety ( $ES=0.38$ ), and interpersonal sensitivity ( $ES=0.18$ ) with depression, obsessive compulsive, and paranoid ideation findings being the most robust. Signals of improvement were also seen in medication adherence and ratings of personal recovery, though changes in these areas were limited. Frequency of use did not appear to be related to outcomes, though those who used the app more frequently were more unwell in several symptom areas, including depression. With disagree, neutral, and agree options on satisfaction scale items, the mean average “agree” response was 68% (with agree being positive). Qualitative feedback was primarily positive: “easily reminding me about the next time I need to take my meds;” “(it helps me) redefine my daily thoughts...for people to feel mentally healthy;” and “helps you focus on something when your thoughts are racing.” Critical feedback was largely in the realm of minor enhancements. Only 1 participant noted that the texts made him/her anxious though they also noted that they would “definitely” use A4i in the future, if available.

The trial described in this protocol is the next step in the program of work surrounding A4i—moving on to a feasibility randomized trial. Although this trial is in an early stage, it is one of the most rigorous trials conducted to date of a digital health approach tailored to schizophrenia. This test is needed because (1) this is a rapidly advancing area in which there are multiple calls for better feasibility and effectiveness data, (2) if ultimately effective, A4i will provide a cost-effective approach for a major health care problem, and (3) this study is an important step for the development of A4i, now that we have pilot data for our prototype.

## Methods

### Trial Design

This feasibility study [33,34] will employ a 2-arm, randomized controlled trial design. The design will be single blind as participants will be aware of A4i exposure with the assessor blinded. Measures will be completed by both care providers and persons receiving care, with the latter being adults with



schizophrenia spectrum diagnoses receiving care in a large diverse Canadian city.

This test will determine the following 2 issues:

1. Progression criteria, that is, first, meeting the recruitment target and assessing recruitment rate considerations that may be unique to hospital and community service sites and achieving a representative sample, and second, obtaining outcome data for at least 80% of those recruited. An 80% target would seem indicated, given the retention in the small number of previous studies ranging from 88% (3 months of technology use, PRIME) to 94% (6 months of technology use, FOCUS). Shorter tests have yielded retention closer to 100% (eg, the 1 month pilot of A4i). The third criterion is sustained use of A4i for an average of at least 75% of the weeks in which it was installed (based on a finding of 80% for FOCUS in a 6-month test period), and the fourth criterion is a lack of emergence of significant safety concerns. The fifth criterion is the patient and provider satisfaction with using the provider portal in clinical contacts.
2. Preliminary outcome data in domains hypothesized to be relevant to the likely effects of A4i, including symptomatology, treatment engagement, clinical alliance, and quality of life, as compared with TAU. These data will help to inform and refine A4i treatment target hypotheses and assist with sample size determination and outcome timeframes for effectiveness trials.

## Trial Interventions

The treatment condition is 6 months of participants being provided with A4i. A4i was developed by the Centre for Addiction and Mental Health (CAMH, Academic Health Sciences Centre in Toronto, Canada) and the Canadian digital health company MEMOTEXT. An iterative design and development model [35] was employed to determine the requirements of A4i.

Stage 1: Literature, patent, and commercial market reviews.

Stage 2: Focus groups with patients, family, psychiatrists, and case managers.

Stage 3: An initial test of a beta version by 5 individuals with psychosis for 1 week.

Stage 4: Review of initial test findings and iteration of app design.

Stage 5: Pilot testing by 38 individuals over a 1-month period [32] followed by further iteration. Specific modifications following the pilot study included enhancing the general ease of use of all features, modifications to the auditory hallucination detector to allow accuracy ratings, and modifications to enhance the care provider interface and the quality of the summaries for clinicians.

A4i works on both Android and iPhone platforms, for those with and without data plans (those who rely on Wi-Fi), and is in a testing phase and not yet publicly available. Specific A4i functionality includes (see Figure 1, Figure 2, and a demo [36]) the following:

Figure 1. A4i screenshots.

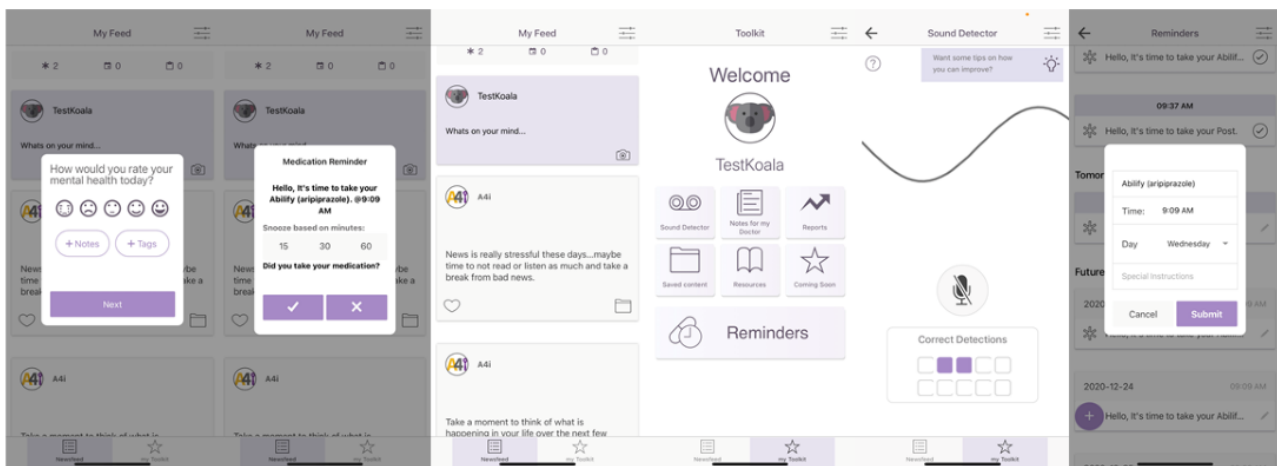
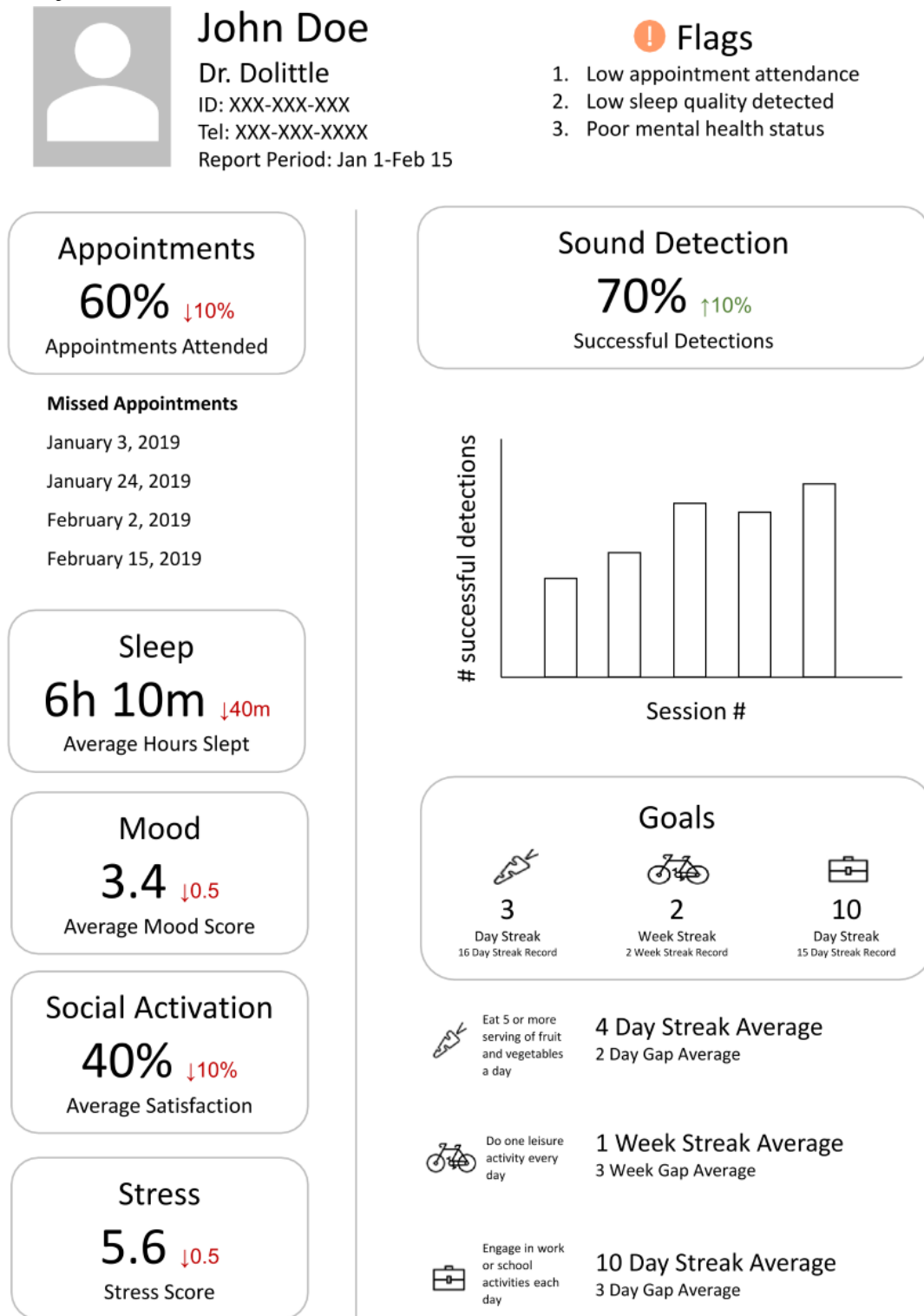


Figure 2. Health care provider's dashboard.



1. Addressing social isolation and cognitive challenges through personalized prompts and the scheduling of activities. These events are entered into a scheduler, with prompts texted through a feed and self-report data collected on attendance (for events) and adherence (for medication reminders).
2. Fostering illness self-management through evidence-informed content that makes suggestions and provides resources relevant to coping with psychosis symptoms, negative symptoms of schizophrenia, cognitive challenges, motivation, and anxiety. The content concentrations are determined by an algorithm built from a short screener completed at the time of upload. This information is also delivered through the feed with the ability to bookmark favorite items into a personal library.
3. The trial intervention includes a peer-peer engagement platform that facilitates strategy/tip sharing between users (anonymous and moderated). This aspect of the platform also functions through the feed.

4. Daily wellness and goal attainment check-ins to highlight mental health trajectories gathered through self-report on rating scales that are prompted daily. This information is graphically summarized for review by the user with goals entered at onboarding and is modifiable.
5. An ambient sound detector with an oscilloscope-type indicator that assists individuals with auditory hallucinations in the effort to separate hallucinations from real sounds with users able to rate and track their responses in terms of success with discernment. Similarly, use and outcome ratings can be reviewed by the user.
6. Passively collected data on phone use as a proxy for sleep and activity levels (generally, when people are awake, they are using and moving their phones) that in the future may prove helpful in developing predictive analytics regarding relapse.
7. A provider dashboard that, with appropriate consent, is provided to the individual's provider prior to their appointment (for this trial, the dashboard was provided via study staff; in future, it will be accessible via electronic medical records). This was co-designed with psychiatrists and patients and generates a summary of day-to-day wellness ratings, responses to reminders, goal progress, sleep detection, self-reported medication adherence, and a "notes for my provider" function (eg, "Please can we discuss my medications making my mouth very dry").

In the treatment condition, A4i will be installed on participant phones for 6 months following screening and baseline assessment completion. Should participants show no interactions with the app in the first 2 weeks or respond to an app prompt regarding A4i utility that there is a problem, they will receive a phone call from a research assistant uninvolved in assessments to coach through and troubleshoot challenges. Both control and experimental condition participants will be receiving standard outpatient care (TAU) for psychosis involving routine (at least monthly) contacts with a care provider. The centralized recruitment process at CAMH facilitates tracking and control over participation in other treatment studies that may confound the findings. For community sites, participants will be asked about their involvement in any other trial (less likely than CAMH) with study implementation adjusted to address potential confounds. Note that those assigned to TAU will be provided with access to A4i after their 6-month evaluation for a period of 6 months if they are interested in this option.

### Randomization and Addressing Bias

A 1:1 blocked randomization, stratified by gender, will be employed to ensure balance in sample size between treatment and control groups and gender representation. Stratification by study site (CAMH vs community agency) will also be undertaken to determine feasibility questions that may differ as a function of same. REDCap (Research Electronic Data Capture) will be employed and will allocate based on the computer-generated randomization list. Allocation concealment will be achieved since the person making the assignment will have no awareness or control over the randomization schedule. Comparison with TAU is single blind as it is not possible for participants to have adequate information to consent without knowing that they are or are not using the technology.

Randomization will be secure as noted above. Statistical analyses will be performed by a biostatistician uninvolved in study operations and kept blind to treatment conditions. During all operational meetings, steps will be taken to ensure that participant identifiers are managed such that the risk of unblinding to assessors is minimized. If unintended unblinding occurs, the event will be documented and arrangements made for a blinded postassessment. Assessors are masters level, with interrater reliability established through mock cases and meeting a minimum of 80%. Finally, participants will be asked to not discuss with the assessor whether they used A4i or not.

### Inclusion/Exclusion Criteria

#### *Inclusion Criteria (Participants With Schizophrenia)*

Participants will be adults, 18 years of age or older, with a chart diagnosis of a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) schizophrenia spectrum illness (schizophrenia, schizoaffective, schizophreniform, delusional disorder, brief psychotic disorder, unspecified) confirmed by a structured diagnostic interview (SCID-5) [37]. All participants will be engaged in outpatient psychiatric treatment. They need to be proficient in English and own and use an Android phone or iPhone.

#### *Exclusion Criteria*

Participants will be excluded if they lack the capacity with no identified substitute decision maker or if they have an intellectual disability.

#### **Criteria (Service Providers)**

Service providers will be psychiatrists and case managers engaged in the care of the participants.

### Measures

For the purposes of this trial, only pretest-posttest (baseline to 6 months) measures will be completed. It is also of note that follow-up data are less relevant for digital health approaches for which ongoing use is anticipated rather than clear end dates as are in the case with other clinical interventions. Measures will be completed virtually or in-person, with an emphasis initially on virtual assessment due to pandemic circumstances.

### Feasibility Indicators

1. Assessment of numbers approached, successfully screened, consented, and numbers assessed at both time points to evaluate recruitment and retention. Additionally, recruitment rates will be compared between CAMH and collaborating community sites.
2. Objective A4i use metrics will be collected, including information on the time, frequency, and nature of use for each participant.
3. An unblinded research assistant will contact treatment arm providers and participants to complete a brief semistructured interview assessing strengths (generally and in clinical interactions) and limitations of A4i and any risks not otherwise reported or observed during study operations. Use of A4i-generated summaries for providers will be assessed both in terms of provider and participant reports of quality in clinical interactions and frequency and duration

of use in a given clinical interaction. Patient satisfaction will also be examined with the 26-item scale used by Ben-Zeev and colleagues [26].

- Safety will be assessed through information gathered via all study-related interactions with significant safety concerns operationalized as one or more critical incidents occurring in which there is evidence of an association between the incident and A4i use. Worsening in one or more outcome areas as compared with TAU would be another domain that would be flagged.

### **Clinical Outcome Metrics**

- Given the observation of improvement in psychiatric symptomatology in pilot testing and the importance of symptom severity for the quality of life and other key outcomes for people with schizophrenia [38], symptom severity is considered the primary outcome. General symptomatology will be assessed using the 53-item, 5-point Likert scale Brief Symptom Inventory [39]. Schizophrenia-specific symptomatology will be assessed with the Positive and Negative Syndrome Scale [40] with negative symptoms assessed with the Scale for the Assessment of Negative Symptoms [41].
- Treatment Engagement was not fulsomely tested in the A4i pilot study due to its short duration, though it is of critical importance to considerations such as rehospitalization [3]. Accordingly, treatment adherence will be measured using (1) the 4-item Brief Adherence Rating Scale [42] with responses obtained by both providers and participants to assess medication adherence, (2) the 5-item, 6-point Likert scale Medical Outcomes Study general adherence scale [43] to capture broader adherence to treatment recommendations (again triangulated with provider responses), and (3) the percentage of scheduled appointments attended through electronic medical record audit at CAMH or provider report at non-CAMH sites. This broader approach to assessing adherence is necessary, as it is a construct that captures both medication regimen adherence and care team engagement.
- Provider-Patient Clinical Alliance will be assessed with STAR (Scale to Assess Relationships) [44]. This 12-item measure employing a 5-point Likert scale has been used extensively in studies of outpatient care for severe mental illness. This measure supports patient and provider versions.
- The Heinrichs-Carpenter Quality of Life Scale, which has 21 items, is well validated for schizophrenia [45] and captures sense of purpose, motivation, emotional, and social interaction, role functioning, and engagement in regular activities.
- Descriptive Measures include core demographics (ethnicity, sexual orientation, age, education, etc, assessed at time 1 and service use history (hospitalization) assessed at both time points and triangulated by providers and participants with schizophrenia. Gender, specifically, will be determined through baseline self-report of female, male, transgender (male-female or female-male), nonbinary, or other. Medication delivery method (injectable vs oral) will be assessed before and after the intervention as this has implications for tracking medication adherence.

### **Sample Size and Recruitment**

We propose to recruit 160 participants, that is, 80 per group. The sample size determination was guided by 2 underlying power considerations driven by our aims. First, we expect to establish the feasibility of the trial by obtaining reliable estimates of feasibility indicators, for example, retention rate and completion rate of key measurements [46]. With 160 participants, we would achieve a small margin of error of 2.8% for an expected retention rate (85%). The margin of error increases to 3.7% for estimating the minimum proposed completion rate of measurement (expected at 80%) with attrition taken into account. Second, while we do not anticipate to have full power to detect treatment effect compared to TAU, given the feasibility test objective of this trial, the proposed sample size will give us a reasonable chance (64%) to detect a small-to-moderate effect ( $ES=0.40$ ). The small-to-moderate effect size is in line with some of the findings in the pilot study, with the caveat that the pilot was an uncontrolled test of outcome. With longer treatment period, we expect to see larger effects as well. The power calculation assumed a level of significance of .05 and accounted for 15% attrition. Recruitment will occur through 2 primary sources. First, recruitment will occur through a centralized CAMH referral process located in the psychosis early intervention service and advertisements and contacts with clinicians in other CAMH schizophrenia services. Across these 2 sets of CAMH services, approximately 3000-4000 patients are annually registered. In the pilot study of 1 month of use (not including an early beta test, recruitment period was September 2017-March 2018), the centralized early psychosis recruitment process was the primary referral route and yielded a rate of 5.5 study completers/month. In the proposed trial, along with this centralized early intervention recruitment process, a greater emphasis will also be placed on recruitment through general schizophrenia services at CAMH. The second major source of recruitment will be community provider sites in Toronto. These 3 sites, all with high rates of contact with the target population, are Canadian Mental Health Association (Toronto), the Schizophrenia Society of Ontario, and Progress Place. At community sites, engagement strategies will include presentations by the principal investigator and research staff, posters, and introductions to clients by providers oriented to A4i. Key differences between the pilot and this trial are the longer duration of A4i use (6 months vs 1 month), which may slow recruitment, and the longer duration of the study which, for some aspects of the strategy, may improve recruitment as providers become better oriented and refer more routinely. Accordingly, it is conservatively estimated that we should be able to obtain a recruitment rate of 7-8 participants per month on average. Recruitment would occur over a period of 21 months.

### **Compliance and Attrition**

Engagement in the use of A4i once uploaded is expected to be good. In our feasibility testing, out of 38 users, 2 (primarily attributed to forgetfulness) could be considered noncompliant with minimal app use over a 1-month period. This is consistent with findings from Ben-Zeev's group [26,27]. To define compliance, the rolling retention and churn rates of app usage were considered with 2 of the 38 users not returning to the app



up to or after 20 days of use. However, it is to be expected that this might be higher over a 6-month period. App features that assist with engagement include the personalization of the peer-to-peer social feed based on the user's intake profile, daily wellness check-ins that are accompanied by motivational content, an escalation of medication and appointment in-app reminders where the reminder will be delivered directly through SMS if no response is provided within an hour of receiving it, and provider engagement about the app. As well, as noted, indication of initial challenges with app use will prompt a call from a research assistant, which might assist with engagement. We experienced no loss to follow up in feasibility testing. This is similar to other studies in this area [27,28] though, again, this will probably be higher over a 6-month period; hence, our attrition estimate of 15%.

### Safety Considerations

None of the published works in the area of digital health approaches for schizophrenia has identified significant user risk. The only potential exception that we found was that a user of FOCUS became "paranoid about his mobile phone and broke it." We have not experienced any incidents of concern in our pilot testing of A4i. However, we have been cognizant of the potential risks. For example, there was an instance of our moderator of the peer-peer strategy network intercepting a post that might be a problem (incoherent content and statement about ceasing medication). Our response was to reach out to the individual to discuss the post and assess the risks (no association with A4i use was indicated) and inform the individual's care provider with participants' consent. Participant privacy is another essential consideration. This risk is mitigated through tricouncil protocols for data safety and storage and MEMOTEXT only having access to phone numbers and provider dashboard data, with that information stored and managed in compliance with provincial and federal data safety and privacy requirements and approved by the CAMH Privacy Officer and Research Legal. Specific protections include the use of duplicate networks and backups, web application programming interfaces, and secure file transfer protocols, where files are encrypted with PGP keys, and only internal personnel may access data from secured locations with 2-level password access and Microsoft Security Best Practices followed regarding password complexity and a 90-day expiration cycle. Further information can be found in the pilot study report [32].

### Data Analysis

The data analysis strategy is as follows:

1. A4i use and satisfaction, along with feasibility metrics, will be examined descriptively with comparisons by gender, age, and study site (CAMH vs community) completed using nonparametric Kruskal Wallis H test (continuous variables) and chi-square analysis (categorical variables) to detect differences.
2. Qualitative data collected from A4i users and providers will be analyzed using qualitative content analysis procedures [47].
3. Descriptive statistics will be used to summarize the data on all participants to understand the unidimensional and multidimensional characteristics of data distribution and

confirm the balance between the 2 groups. To evaluate the treatment effects on the primary and secondary outcomes, we will employ the intent-to-treat approach and use generalized linear models as the primary analytic approach, of which the baseline to 6-month change score will be treated as the response variable and treatment assignment, regardless of compliance, as the primary predictor with the corresponding baseline outcome measure, key demographic variables, and study site being controlled as covariates. The generalized linear model could accommodate potential deviation from normality of the outcome variables. The multiple imputation method [48] will be used to handle missing responses and account for potential bias. Three additional analyses will be conducted in addition to the primary analysis. First, we will conduct a sensitivity analysis by including the number of contacts with the psychiatrist in the model as an additional covariate to be controlled. Second, we will explore the moderation of the treatment effect of baseline symptom severity and key demographic variables by adding their interaction with the treatment assignment in the model. This may provide suggestive evidence of differentiated treatment effects. Third, we will look at the impact of compliance by correlating the change score of the outcomes with the app use for the subjects under the treatment condition. Additionally, if more than 10% of the subjects show no app use, a sensitivity analysis will be conducted with only subjects who used the app at least once. We will complete the analysis upon completion of the postintervention assessments. Given the possible importance of gender (female, male, and nonbinary) and age moderation factors, we will test if they have any effect on the magnitude of change in the outcomes. This will be done by adding an interaction between gender and treatment assignment indicator to the model described above.

## Results

This study was funded by the Canadian Institutes of Health Research in January 2020 and received Institutional Review Board approval on August 13, 2020. The anticipated recruitment start date for this trial is January 2021. However, the global pandemic has caused some delay in the initiation of the trial and may continue to cause delays depending on how the second wave affects the recruitment sites.

## Discussion

This trial is needed now as it will make a significant contribution to the evidence in this emerging area and it is a test of a unique technology. Given the high relapse rates among populations with schizophrenia and the Can \$1000+/day cost of inpatient care, even modest effects of a technology such as A4i are of note, given its relatively low expense and ready access. If successful, technologies such as A4i might reduce the reliance on in-person treatment and augment and enhance the quality of in-person treatment and create access to supports for those who have situational (eg, rural) or other challenges (eg, motivation, self-stigma) that impede access to standard care. At the systems

level, should the promise of early risk detection and mitigation be realized, the reliance upon costly, crisis responses may also be positively affected. However, such business cases will rely upon rigorous lines of investigation of which A4i is one example. Unfortunately, research rigor in digital health is more the exception than the rule at this stage of the field. Such work is essential in the larger effort to ensure that the public and service providers are not misled by unsubstantiated claims of effectiveness. Lastly, this work will bring important information forward to broaden the conversation about measurement-based care in psychiatry. Specifically, platforms such as A4i afford the opportunity to provide more frequent and nuanced assessments of symptomatology and functioning. Such information might prove important in refining medical and behavioral care pathways and algorithms to optimize the outcomes of those with complex conditions such as schizophrenia.

This trial will provide information that will be critical in determining if this technology is ready to move on to an effectiveness trial or if further iterations are needed. With these requirements established, future trials would move on to examine (1) effects observations with larger samples, (2) comparison with a sham condition such as a generic wellness app, and (3) sustainment of use and gains over longer periods. Knowledge exchange activities will include (1) publication in a relevant academic journal, (2) presentation in at least one international conference (eg, Schizophrenia International Research Society Conference) and one eHealth industry conference (BIO), and (3) a webinar advertised through research, practice, and administration networks (eg, Health Quality Ontario, Council of Academic Hospitals of Ontario; Orygen-Australia; RAISE trial network-United States).

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## Acknowledgments

This study was funded by the Canadian Institutes of Health Research (#426889).

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## Authors' Contributions

SK led study design and wrote the manuscript. KM, SA, and AV were involved in study design and assisted with manuscript development. WW designed the statistical and power analysis approaches and assisted with manuscript development.

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## Conflicts of Interest

SK and the Centre for Addiction and Mental Health have a financial interest in A4i technology and the company (A4i) within which the A4i technology was developed.

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## Multimedia Appendix 1

Grant reviews report.

[\[PDF File \(Adobe PDF File\), 854 KB - resprot\\_v10i1e24736\\_app1.pdf\]](#)

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## Abbreviations

**A4i:** App4Independence

**CAMH:** Centre for Addiction and Mental Health

**DSM-5:** Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

**ES:** effect size

**TAU:** treatment-as-usual



*Edited by G Eysenbach; submitted 02.10.20; peer-reviewed by S Doan, E Achtyes; comments to author 24.11.20; revised version received 26.11.20; accepted 01.12.20; published 25.01.21.*

*Please cite as:*

*Kidd S, McKenzie K, Wang W, Agrawal S, Voineskos A*

*Examining a Digital Health Approach for Advancing Schizophrenia Illness Self-Management and Provider Engagement: Protocol for a Feasibility Trial*

*JMIR Res Protoc 2021;10(1):e24736*

*URL: <http://www.researchprotocols.org/2021/1/e24736/>*

*doi: [10.2196/24736](https://doi.org/10.2196/24736)*

*PMID: [33492235](https://pubmed.ncbi.nlm.nih.gov/33492235/)*

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Protocol

# Novel Assessments of Technical and Nontechnical Cardiac Surgery Quality: Protocol for a Mixed Methods Study

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## Abstract

**Background:** Of the 150,000 patients annually undergoing coronary artery bypass grafting, 35% develop complications that increase mortality 5 fold and expenditure by 50%. Differences in patient risk and operative approach explain only 2% of hospital variations in some complications. The intraoperative phase remains understudied as a source of variation, despite its complexity and amenability to improvement.

**Objective:** The objectives of this study are to (1) investigate the relationship between peer assessments of intraoperative technical skills and nontechnical practices with risk-adjusted complication rates and (2) evaluate the feasibility of using computer-based metrics to automate the assessment of important intraoperative technical skills and nontechnical practices.

**Methods:** This multicenter study will use video recording, established peer assessment tools, electronic health record data, registry data, and a high-dimensional computer vision approach to (1) investigate the relationship between peer assessments of surgeon technical skills and variability in risk-adjusted patient adverse events; (2) investigate the relationship between peer assessments of intraoperative team-based nontechnical practices and variability in risk-adjusted patient adverse events; and (3) use quantitative and qualitative methods to explore the feasibility of using objective, data-driven, computer-based assessments to automate the measurement of important intraoperative determinants of risk-adjusted patient adverse events.

**Results:** The project has been funded by the National Heart, Lung and Blood Institute in 2019 (R01HL146619). Preliminary Institutional Review Board review has been completed at the University of Michigan by the Institutional Review Boards of the University of Michigan Medical School.

**Conclusions:** We anticipate that this project will substantially increase our ability to assess determinants of variation in complication rates by specifically studying a surgeon's technical skills and operating room team member nontechnical practices. These findings may provide effective targets for future trials or quality improvement initiatives to enhance the quality and safety of cardiac surgical patient care.

International Registered Report Identifier (IRRID): PRR1-10.2196/22536

(JMIR Res Protoc 2021;10(1):e22536) doi:10.2196/22536

**KEYWORDS**

cardiac surgery; quality; protocol; study; coronary artery bypass grafting surgery; complications; patient risk; variation; intraoperative; improvement

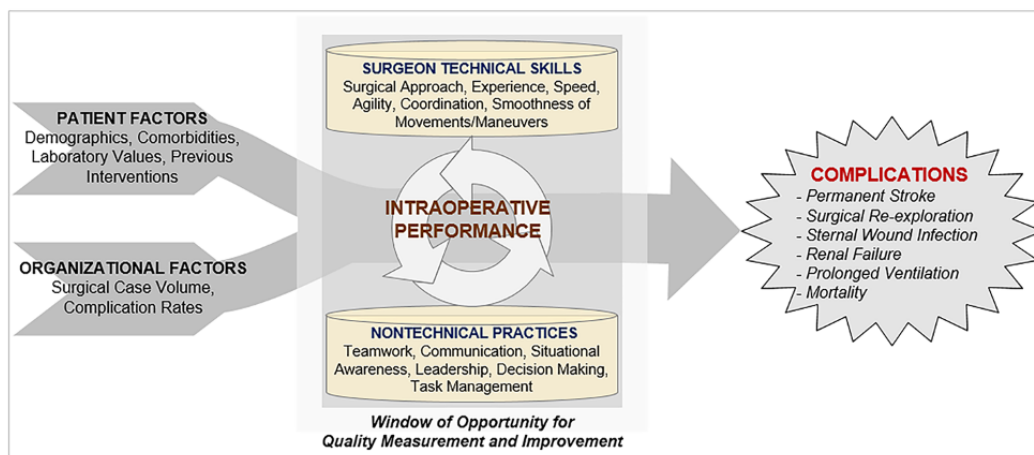
**Introduction**

**The Epidemiology of Cardiac Surgery**

Nearly 150,000 coronary artery bypass grafting (CABG) procedures are performed annually in the United States, and it is a procedure associated with a high rate of major adverse events (35% of patients) that vary by hospital [1]. These adverse

events increase a patient’s risk of mortality 4.7 fold and are associated with more than US \$50,000 in additional health care expenditure per patient [1-4]. While understudied, intraoperative performance (including the surgeon’s technical skills and team-based nontechnical practices) is an important potentially modifiable determinant of operative adverse events (Figure 1) [5,6].

Figure 1. Conceptual model.



**The Role of Technical Skills in Surgical Outcomes**

Prior research has evaluated the association between technical skills (defined as “psychomotor action or related mental faculty acquired through practice and learning pertaining to a particular craft or profession” [7]) and operative outcomes [8]. While taxonomies exist to objectively and reliably assess a surgeon’s technical skills, they are often applied within simulated structured scenarios that may not mimic real-world patient care

(Table 1). In one exception, investigators applied the Objective Structured Assessment of Technical Skill (OSATS) [9] to real operative settings including 10 clinician experts who rated a single 25 to 50-minute video segment of a laparoscopic operation from 20 surgeons [5]. Assessments, linked to data from the last 2 years of each surgeon’s experience, were significantly inversely associated with the surgeon’s adverse events and mortality outcomes. In another study, surgical skills were associated with outcomes from cancer surgery [10].

Table 1. Application of the Objective Structured Assessment of Technical Skills (OSATS) to cardiac surgery.

Domains	Description	Illustrative high-quality cardiac surgical tasks
Respect for tissue	Gentle tissue handling that does not result in tissue injury	Passing a needle through a coronary artery without tearing the tissue
Time and motion	Economy of motion and maximum efficiency	Efficiency of movement for suturing proximal anastomoses
Instrument handling	Fluid use of instruments and absence of awkwardness	Fluidity of motion between the scrub nurse and surgeon (and back)
Flow of operation	Smooth transitions from one part of the operation to another	Smooth transitions from cannulation (venous and aortic) to anastomosis phase
Suture handling	Efficient knot tying using fluid motions of the hands and fingers	Tying an 8-0 or a 7-0 suture (“microsuture”) resulting in secure knots without causing tissue injury
Steadiness	Absence of tremor motions of the hands	Fine motor movement: passing a needle through a coronary artery without tearing the tissue

## The Role of Nontechnical Practices in Surgical Outcomes

Nontechnical practices (“the cognitive, social, and personal resource skills that complement technical skills, and contribute to safe and efficient task performance” [11]) are both individual and team based. While improvement in these practices has been associated with decreases in operative mortality [12], investigations thus far have focused on developing robust validated taxonomies of behavior with corresponding assessment tools customized to the individual team members’ intraoperative care role. Dominant taxonomies [13-15] include Non-Technical Skills for Surgeons (NOTSS), Anesthetists’ Non-Technical Skills (ANTS), Perfusionists Intraoperative Non-Technical Skills (PINTS), and Scrub Practitioners’ List of Intraoperative Non-Technical Skills (SPLINTS). These taxonomies enable assessments of the following four important categories of nontechnical practices: situation awareness, decision making, communication and teamwork, and leadership/task management. Situation awareness [16] is the process of developing and maintaining a dynamic awareness of the operative situation based on gathering and interpreting data from the operative environment. This domain is essential for effective decision-making [17], representing skills for diagnosing a given situation to inform a judgment about appropriate actions. Successful surgery also depends on social skills allowing multiple individuals with task interdependencies and shared goals to communicate and work effectively as a team [18]. Dysfunctional team dynamics, ineffective communication, and ambiguous leadership [19] account for a substantial proportion of operative adverse events [20].

A surgeon’s nontechnical practices, manifesting as diagnostic failure [21] or a breakdown in teamwork and information sharing [22], may contribute to a higher risk of a major adverse event or death. The largest operative study of NOTSS conducted thus far involved 715 surgical procedures and 11,440 assessments [23]. Surgeons’ nontechnical skills were rated as good (score of 4) in 18.8% of responses, acceptable (score of 3) in 49.1%, marginal (score of 2) in 21.9%, and poor (score of 1) in 0.9%. In a video-based study including 82 cardiac surgeons, there was a 129% increased odds (after adjusting for technical skills) of higher patient safety scores with every 1-point increase in the NOTSS score [6].

### Rationale for the Study

This study will evaluate how operative skills and nontechnical practices impact CABG outcomes. Patients undergoing CABG are at risk of harm due in part to the (1) reconstruction of anatomical structures under high magnification, (2) multiple

high-risk phase transitions of care between team members (eg, anesthesiologist and perfusionist), and (3) need for communication and teamwork (eg, instrument handoffs) across many team members.

### Innovation

Our proposed study is novel and innovative for three important reasons. To our knowledge, this study will be the first (1) multicenter intraoperative evaluation of both technical skills and operative team nontechnical practices at scale, (2) study to relate evaluation of intraoperative nontechnical practices with important clinical outcomes, and (3) study to apply a video-understanding platform to high fidelity recorded surgical videos to assess feasibility of automated objective assessments of technical skills and nontechnical practices.

## Methods

### All Aims

Preliminary Institutional Review Board (IRB) review has been completed at the University of Michigan by the Institutional Review Boards of the University of Michigan Medical School. This study will include a single IRB to govern research activities conducted across the collaborating hospitals.

### Study Population

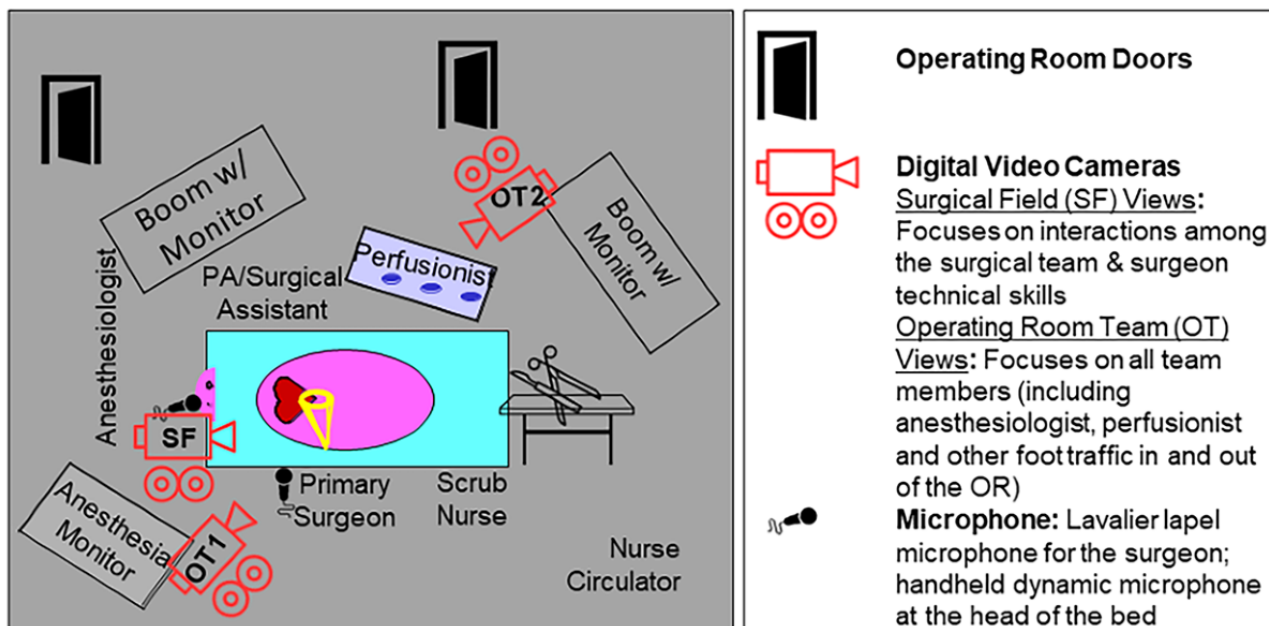
Our population will include adult patients undergoing electively scheduled CABG operations using cardiopulmonary bypass performed by attending surgeons at six hospitals participating in the Multicenter Perioperative Outcomes Group (MPOG) Collaborative, a national physician-led collaborative of academic and community hospitals, and specialty-specific peer assessors. Surgeons who have operated at their hospital for less than 2 years will be excluded.

### Digital Recording

We will record 506 CABG operations at six hospitals. The study coordinator will use a randomization protocol from the Data Coordinating Center (DCC) to select, by week, different cardiac surgical operating rooms for video recording. The coordinator will synchronize the cameras with other operating room data sources (eg, intraoperative record as submitted to MPOG) (Figure 2). Three Canon XC15 cameras will be used, with two focusing on operative team members and one focusing on the surgical team. Beyond maximizing nonobstructed visualization, camera positions have been chosen to maximize capture of team member activities and minimize obstruction of existing workflow.



**Figure 2.** Proposed intraoperative recording configuration. OR: operating room.



Key transitions in phases of patient care are routinely documented within the intraoperative electronic health record of participating MPOG hospitals. These data are validated and mapped to universal MPOG concepts [24]. Digital recordings will be segmented based upon key transitions in phases of care; operative recordings will begin when the patient enters the operating room and end when the patient exits the operating room.

Study data will be transmitted to the DCC, which will conduct audio and video quality checks across hospitals and recordings. Initially, investigators at the DCC will review the entire recording to fine tune the MPOG event timestamping to the exact second. Given the input operative data, a Hidden Markov Model [25,26] or deep learning-based approach [27] will divide the procedure into temporal segments and associate them with the procedural step labels from the operative script. Standardized segments for assessment will only contain critical operative portions (Table 2).

**Table 2.** Illustrative operative phases for video assessments.

Assessment	Critical portions of the operation	Rationale
Technical skills assessment	Performance of distal arterial and venous anastomoses (exposure is completed → last suture is cut after tying) Performance of proximal arterial anastomosis (initial use of electrocautery to isolate the area for anastomosis → last suture is cut after tying)	Video segment would contain technical skills (eg, economy of motion: creation of anastomosis) that are critical for a successful operation.
Nontechnical practices assessment	Preinduction verification (prior to → end of discussion) Preincision timeout (prior to → end of discussion) Prebypass transesophageal echocardiography (TEE) assessment (surgeon request for TEE → completed discussion between the surgeon and anesthesiologist) Preparation and weaning from bypass (surgeon requests the heart to be filled up → protamine finished)	Video segment would contain nontechnical practices (eg, decision making and communication/teamwork: discussion during the verification and timeout, as well as focusing on ensuring a safe weaning from cardiopulmonary bypass).

**Hospital Performance Feedback**

The DCC will provide monthly reports to hospitals, including number of digitally recorded operations, quality of transmitted digital recordings, and adherence to study operational protocols.

**Peer Assessment Module**

We will use a two-stage process for recruiting candidate assessors as follows: (1) we will poll the Michigan Society of

Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC), MPOG, and the Michigan Perfusion Society membership for potential assessors working outside of Michigan or at hospitals not participating in MPOG, and (2) if unable to secure sufficient assessors, we will recruit from the MSTCVS-QC, MPOG, and Michigan Perfusion Society membership.

Assessors, blinded to the hospital and operative team, will provide technical (aim 1) and nontechnical (aim 2) video-based assessments of cardiac surgical operations using a web-based Health Insurance Portability and Accountability Act (HIPAA)-compliant assessment platform.

Each operation will receive at least 12 assessments (three for each provider group), with 20% of assessments rereviewed. Surgeons will assess a surgeon's (1) technical skills (modified OSATS plus cardiac surgery-specific skills) via a validated 5-point behaviorally anchored scale and (2) nontechnical practices using NOTSS [13]. Anesthesiologists will use ANTS [14], scrub nurses will use SPLINTS [15], and perfusionists will use PINTS for nontechnical assessments (all nontechnical taxonomies will use an 8-point ordinal scale). Segments will capture each operation's critical phases. Technical skill assessors will be given one operative field camera angle (Cam Surgical Field [SF]) for their assessment (Figure 2). Given the interdependence of intraoperative team members, nontechnical assessors will be provided alternative camera angles depicting the intraoperative team (Cam Operative Team [OT] #1 and #2). Assessors will receive an Amazon coupon for completed reviews.

We will resubmit 20% of edited segments to the same (test-retest reliability) or other assessors (interrater reliability) using an intraclass correlation coefficient  $\alpha \geq .670$  for good concordance [28].

### ***e-Learning Training Module***

We will use a web-based training and readiness module that will include (1) foundational knowledge of the relevant tool and (2) video examples of correct identification, categorization, and assessment. Assessors will have to reach 70% agreement with gold standard (investigative team) assessments to contribute to the study. A median 70% agreement with reference assessments will serve as a basis for assessor eligibility to conduct real case assessments [29].

### ***Clinical Complications***

We will calculate each surgeon's adverse event rate for the previous 2 years using each hospital's Society of Thoracic Surgeons (STS) data.

### **Aim 1: Investigate the Relationship Between Peer-Rater Assessments of a Surgeon's Technical Skills and Variability in Risk-Adjusted Patient Adverse Events**

#### ***Approach***

We will conduct peer-reviewer assessments of recorded CABG operations at six MPOG hospitals (representing 36 surgeons) to associate technical skills with major adverse events.

Each surgical operation will be divided (using our video segmentation protocol) into prespecified phases containing the most critical operative portions. The DCC will distribute video segments for surgeon assessment via our HIPAA-compliant assessment platform that will provide assessors with a view of the operative field (from Cam SF, Figure 2). Surgeon assessors will provide domain-specific and overall summary judgements

(using a modified OSATS taxonomy). Twenty percent of segments will be resubmitted for review to test assessor reliability. We will associate the average assessments with the adjusted risk of major morbidity and mortality over the prior 2 years for each surgeon.

### ***Measures***

Our primary exposure will be the average summary assessment of each surgeon's technical skills. The primary outcome will be a surgeon's STS composite major morbidity or mortality (ie, permanent stroke, surgical re-exploration, deep sternal wound infection, renal failure, prolonged ventilation, or operative mortality) rate. We will use clinical data from each center to adjust for covariates incorporated within the STS risk prediction models [30,31].

### ***Analytical Plan***

We will use linear mixed effect models to model assessments of surgical procedures where assessors and surgeons are included as random effects. We will quantify variation in peer-assessor assessments of a surgeon's technical skills and use the intraclass correlation coefficient to measure interassessor reliability. We will use predictions of each surgeon's technical skills from the linear mixed effect models as summary measures of a surgeon's technical skills in subsequent analyses. Generalized linear mixed effect models with a logit link will then be used to associate a surgeon's technical skills with our composite outcome. We will model surgeons and hospitals as random effects, accounting for the nesting structure of the data (ie, patients nested within surgeons and hospitals). We will adjust for patient and surgeon factors by including them as fixed effects in the models. The factors of interest are summary measures of a surgeon's technical skills, which are included as surgeon-level explanatory variables. We will consider the overall assessments of a surgeon's technical skills, averaged across three assessors and each domain individually.

### ***Power Analysis***

We use simulations to evaluate statistical power for a two-sided test ( $\alpha=.05$ ). Our analysis will be based on outcomes for approximately 7200 operations over 2 years from 36 surgeons (approximately 100 operations per surgeon) at six hospitals. We estimate having approximately 98% power in detecting an odds ratio of 0.85 per one unit (standardized) increase in a surgeon's technical skills for the rate of adverse events.

### **Aim 2: Investigate the Relationship Between Peer-Rater Assessments of Intraoperative Team-Based Nontechnical Practices and Variability in Risk-Adjusted Patient Adverse Events**

#### ***Approach***

We will leverage each hospital's intraoperative electronic health record system for video segmentation, using in part precomputed, validated, publicly available MPOG phenotypes [24,32]. Segments will be reviewed by at least 12 assessors (three per provider group). We will assess the association between peer assessments of nontechnical practices and surgeon measures of postoperative major morbidity and mortality, adjusted for patient risk factors and surgeon technical skills.

## Measures

Our primary exposure will be the average summary peer assessment of each provider's nontechnical practices. Similar to aim 1, the primary outcome will be the rate of major morbidity or mortality, adjusting for clinical covariates [30,31].

## Analytical Plan

We will use generalized linear mixed effect models with a logit link to associate peer-assessor assessments of nontechnical practices of the surgeon with the surgeon's STS composite score for major morbidity and mortality. Models will be similar to those described in aim 1, although we will include average summary measures of surgeon's nontechnical skills as surgeon-level explanatory variables and hospital-level average summary measures of anesthesiologists, perfusionists, and scrub nurses. Both overall summary measures and individual scale domains will be considered. We will focus primarily on assessing the effects of nontechnical practices on morbidity and mortality rates, while adjusting for patient-level risk factors and a surgeon's technical skills. We will explore the influence of nontechnical practices on the relationship between a surgeon's technical skills and our composite endpoint by including nontechnical practices as an interaction term in models with technical skills.

## Power Analysis

The power analysis is based on approximately 7200 cases across 36 surgeons from six hospitals. As surgeon's nontechnical practices are considered a surgeon-level variable, there will be sufficient power in detecting the same effect sizes as reported in aim 1.

## Aim 3: Explore the Feasibility of Using Objective, Data-Driven, Computer-Based Assessments to Automate the Identification and Tracking of Significant Intraoperative Determinants of Risk-Adjusted Patient Adverse Events

High-dimensional computer-based assessments of digital recordings will be used to recognize and track human activity (computer vision). Computer vision focuses on training computers to derive meaning from visual imagery. Video understanding, a specialty within computer vision, focuses on identifying and tracking objects over time from video and developing mathematical models to train computers to extract the meaning within these moving images. This field may offer unparalleled capabilities for conducting objective peer assessments by automatically identifying and tracking human activity comparable to that of expert human assessors.

## Background

### Surgical Technical Skills

Video understanding may address some of the limitations in traditional mentored or simulation-based approaches for assessing a surgeon's technical skills, including human assessor bias and limited scalability. Prior investigations have documented the reliability of video-based surgical motion analyses for assessing laparoscopic performance as compared to the traditional time-intensive human assessor approach

[33,34]. Azari et al compared expert surgeon's rating assessments to computer-based assessments of technical skills [35]. Computer-based assessments had less variance relative to expert assessors. Sarikaya et al evaluated the feasibility of computer-based methods for technical skill assessment involving 10 surgeons having varying experience with robotic-assisted surgery [36]. This evaluation included acquiring 99 unique videos with 22,467 total frames and the development of a state-of-the-art deep learning-based surgical tool tracking system. The quantitative assessment against gold standard (human annotated) tool tracks found a 90.7% mean average precision over all test videos across all surgeon skill levels.

### Nontechnical Practices

Nontechnical practice assessments have predominantly occurred within simulated environments and relied on trained human observers [37,38]. Investigators have not evaluated whether video understanding could provide an objective alternative for high-fidelity assessments of nontechnical practices in real-world operative environments, generalizable across hospitals with varied operating room layouts and camera configurations. Video understanding may be used to assess features aligned with nontechnical practices without relying on verbal communication [39]. Video understanding requires time-limited human observer involvement to provide labels for training algorithms after which the automated system may be deployed at scale.

### Approach

We will explore the feasibility of using a video-understanding platform to identify important features associated with assessor ratings in recorded operations. To support developing the video-understanding platform, we will conduct interviews and site visits at a subset of low- and high-performing hospitals to enhance the understanding of a hospital's contextual characteristics (eg, culture) and important "usual practices."

### Video Understanding

The video-understanding approach will focus on two specific techniques (ie, visual detection and visual tracking), which will be applied to identify and measure surgeons' technical skills (aim 1) and team-based nontechnical practices (aim 2). We will apply ambiguity reduction across the three time-synchronized video recordings to harmonize (rather than duplicate) *elements* within and across video angles. We will use proven methods for video understanding (eg, boosting [40] and deep learning [41]). We will use boosting for cases of limited data and deep learning for cases of ample data. We will learn detection models to ascertain kinematic features potentially associated with surgical technical skills (eg, path length of the surgeon's suturing and nonsuturing hands) and nontechnical practices (eg, identifying and tracking the gaze direction of team members at critical times of the surgical procedure) based on aims 1 and 2. We will learn these features using the following mutually exclusive data sets containing video segments: (1) training data set (used for training the video-understanding algorithms); (2) computer vision validation data set (used to mitigate risk of overfitting [eg, the video-understanding algorithms]); (3) computer vision testing data set (used for computing the error statistics of the computer vision system to meet human feature annotation); and (4) study set (video segments for peer



assessments). Investigators will observe the raw video from the training data set to provide bounding-box annotations for each feature, within contextual feedback provided by members of the investigative team who work in the operating room. A certain detection model is initialized with a random set of parameters, and then, the training algorithm iteratively refines them based on the model's empirical performance (ability to automatically detect the phenomena bounding boxes) based on the annotations in the training data. The validation set is used during this training process to protect against overtraining and bias. Some technical assessments will require detection in a video frame and tracking of the detected object throughout the video frames ("visual tracking"). For example, to measure the surgeon's economy of motion, we will detect the surgeon's hands at frame  $t$ , track the surgeon's hands at all future frames  $t+k$ , and then compute a trajectory of the centroid of the detected bounding boxes. We will use both classical physics-based tracking models (eg, Lucas-Kanade tracking [42]) and modern deep learning-based methods [43]. We will compute a range of validated kinematic features [35] and quantifiers of economy of motion (eg, path length of the surgeon's suturing and nonsuturing hands, and variance of local change in the trajectory against a linear or smoothed trajectory).

### Qualitative Interviews

Concurrent with developing and testing the video-understanding platform, we will randomly select up to four of the six hospitals (equal representation of low- and high-outlier hospitals) participating in aim 2 for more detailed investigation. We will conduct semistructured interviews with interdisciplinary cardiac surgery operating room team members. To enhance our understanding of technical and nontechnical operating room practices, we will collect data (through interviews with intraoperative team members) concurrent with conducting analyses. We will develop a semistructured interview guide to encourage new and/or unexpected ideas or concepts to surface. For each interview, the interviewer will play back video segments from an operation involving the interviewee and ask the interviewee to describe his/her role within that operative phase. The interviewer will ask questions seeking to better understand team member roles and influences on technical skills and nontechnical practices. We expect the guide will consist of seven to nine open-ended questions with probes. Interviewers will participate in a 3-day training program at the University of Michigan Health Communications Laboratory. Interviews will continue until reaching informational redundancy "saturation" at each hospital. We will (1) conduct 40 to 60-minute interviews in private rooms, (2) digitally record and transcribe transcripts verbatim, (3) compare 10% of transcripts (and correct as needed) against the recordings, and (4) provide interviewees with a gift certificate. We expect that (1) in reviewing the videos, providers will complement peer assessments regarding how and why contextual factors influence performance (technical and nontechnical) and (2) interviewees will validate the video content to maximize our video understanding algorithm's fidelity. Thus, our interview findings will improve our interpretation of the video content to iteratively inform and enhance our video-understanding platform's training.

### Measures

Our primary outcome will be the features derived from the video-understanding platform, which will be compared to a gold standard human identifying the same features. Features, as economy of motion, are derived from the raw output of the video-understanding platform, which naturally performs visual detection and visual tracking. The gold standard uses the analogous "raw output" from humans and the same method for the computation of the derived feature.

### Analytical Plan

We will assess our video-understanding platform's ability to correctly identify and track features within our testing data set. Using the raw video in the testing set, we will provide the necessary bounding-box annotations for each feature, which will be compared to the automatically generated features from the video-understanding system using standard metrics (eg, intersection over union [44] and DICE coefficient [45]). For example, when we compute the economy of motion of the surgeon's hand, we will provide bounding-box annotations of the surgeon's hand. The video-understanding system will use these annotations to learn a mathematical visual detection model capable of producing the detections of the hand on novel video. Thereafter, the economy of motion feature will be derived on the output bounding boxes. We plan a two-phased analysis. First, we will measure agreement and associate each feature with each component of the technical and nontechnical assessments (specific to each operative phase) using Pearson/Spearman correlation coefficients or Kendall tau, depending on data distribution. Second, we will identify the best combination of video-understanding features that are most closely associated with technical and nontechnical score domains (specific to each operative phase). We will use regression (eg, linear, ridge, and deep) to model each domain and technical and nontechnical summary scores as dependent variables, including features from the video-understanding platform as independent variables. We will (1) select features using variable selection and (2) quantify the magnitude of information in peer assessment that can be identified by the computer using generalized R squares.

### Results

The project has been funded by the National Heart, Lung and Blood Institute in 2019 (R01HL146619). Results of aims 1 and 2 will likely yield assessments that identify a wide range of variations in both surgeons' technical skills and nontechnical practices as has already been documented in the literature. Where our study will make an important contribution is in associating these assessments with adverse event rates. The novel contribution of aim 3 will be to associate computer-based assessments with adverse event rates, as a more objective and reliable replacement for human peer assessors, moving us closer to our overall goal of improving outcomes for cardiac surgery patients. We will use the study results to develop data-driven technical skills and nontechnical practice coaching interventions across a subset of hospitals. We plan to undertake our study over a 5-year period (Figure 3).



**Figure 3.** Study timeline.

## Discussion

### Strengths

There is increasing demand from the public and payers to improve health care value (quality divided by expenditures). Despite wide variability in cardiac surgical quality and robust clinical data from the STS for risk adjustment and outcomes ascertainment, only 2% of hospital variability in some outcomes are explainable by currently recorded data elements [46]. Analysis of operative videos may reveal unique opportunities for advancing operative quality improvement beyond that provided through traditional data sources [47].

Our proposed study, leveraging the infrastructure and track record of two established physician-led quality collaboratives integrated with a cutting-edge scalable video-understanding platform, will advance our understanding of how surgical skills and nontechnical practices impact outcomes. Our approach aimed at identifying key modifiable intraoperative determinants of major adverse events may likely be applied to approximately 200,000 additional cardiac surgical procedures involving valve repair or replacement, aortic procedures, and percutaneous cardiac procedures (eg, transcatheter aortic valve replacement) or other high-risk noncardiac surgical specialties (eg, neurosurgery, orthopedics, and head and neck reconstructive surgery).

### Limitations

Although unlikely, there are a few potential challenges with this study.

#### *Aims 1 and 2*

There is a remote possibility that we will not find that the investigated technical skills are associated with adverse events. If needed, we will expand our review of surgical operations to include (1) hospitals with lower operative volume, (2) longer segments for peer rating, (3) an expanded list of operative phases that might distinguish between high- and low-performing surgeons, and (4) high-risk or technically challenging operations. We will consider expanding to other hospitals if (1) hospital variability in adjusted adverse events is less than anticipated or (2) we are unable to amass sufficient digital recordings from our initial six hospitals.

If needed, we will (1) expand our sampling pool of assessors to include providers who have expressed desire to partner on this project but were not selected initially, (2) provide monthly feedback and engagement support to participating assessors, and (3) provide expanded assessor training and calibration.

#### *Aim 3*

Our video-understanding platform may not be completely automated. Alternatively, we will consider a semiautomated platform that relies, for instance, on a human periodically manually annotating the relevant features in the video at a certain segment and then allowing the video-understanding platform to interpolate those annotations.

### Acknowledgments

The authors thank Holly Neilson for her editorial review of this manuscript.

### Conflicts of Interest

DL and FDP receive extramural support from the Agency for Healthcare Research and Quality (AHRQ; R01HS026003) and the National Heart, Lung, and Blood Institute (NHLBI; R01HL146619). FDP is a member of the scientific advisory board of FineHeart, Inc; member of the Data Safety Monitoring Board for Carmat, Inc; member of the Data Safety Monitoring Board for the NHLBI PumpKIN clinical trial; and Chair of The Society of Thoracic Surgeons, Intermacs Task Force. SLK is supported by a Department of Veterans Affairs HSR&D research career scientist award. MRM receives extramural support from the NHLBI (K01HL14170103). AMJ receives extramural support from the NIH through a T32 Research Fellowship (5T32GM103730-07). SJY and RDD receive extramural support from the NHLBI (R01HL126896 and R01HL146619), and National Aeronautics and Space Administration/Translation Research Institute for Space Health. SJY is a member of the Johnson & Johnson Institute Global Education Council. Opinions expressed in this manuscript do not represent those of the NIH, AHRQ, US Department of Health and Human Services, or US Department of Veterans Affairs.

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## Abbreviations

**ANTS:** Anesthetists' Non-Technical Skills

**CABG:** coronary artery bypass grafting

**DCC:** Data Coordinating Center

**HIPAA:** Health Insurance Portability and Accountability Act

**MPOG:** Multicenter Perioperative Outcomes Group

**MSTCVS-QC:** Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative

**NOTSS:** Non-Technical Skills for Surgeons

**OSATS:** Objective Structured Assessment of Technical Skill

**OT:** operative team

**PINTS:** Perfusionists Intraoperative Non-Technical Skills

**SF:** surgical field

**SPLINTS:** Scrub Practitioners' List of Intraoperative Non-Technical Skills

**STS:** Society of Thoracic Surgeons

*Edited by G Eysenbach; submitted 22.07.20; peer-reviewed by C Pugh, MD, PhD, J Li; comments to author 27.08.20; revised version received 03.09.20; accepted 10.11.20; published 08.01.21.*

*Please cite as:*

*Likosky D, Yule SJ, Mathis MR, Dias RD, Corso JJ, Zhang M, Krein SL, Caldwell MD, Louis N, Janda AM, Shah NJ, Pagani FD, Stakich-Alpirez K, Manojlovich MM*

*Novel Assessments of Technical and Nontechnical Cardiac Surgery Quality: Protocol for a Mixed Methods Study*  
*JMIR Res Protoc* 2021;10(1):e22536

URL: <https://www.researchprotocols.org/2021/1/e22536>

doi: [10.2196/22536](https://doi.org/10.2196/22536)

PMID: [33416505](https://pubmed.ncbi.nlm.nih.gov/33416505/)

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Corrigenda and Addenda

# Correction: Effectiveness of Educational Interventions to Increase Knowledge of Evidence-Based Practice Among Nurses and Physiotherapists in Primary Health Care: Protocol for a Systematic Review

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**Related Article:**

Correction of: <https://www.researchprotocols.org/2020/11/e17621>

(*JMIR Res Protoc* 2021;10(1):e27092) doi:[10.2196/27092](https://doi.org/10.2196/27092)

In “Effectiveness of Educational Interventions to Increase Knowledge of Evidence-Based Practice Among Nurses and Physiotherapists in Primary Health Care: Protocol for a Systematic Review” (*J Med Internet Res* 2020;9(11):e17621) four errors were noted.

Affiliation 2, applying to authors Henk Verloo, Pauline Melly, Roger Hilfiker, and Filipa Pereira was incorrectly listed as:

*School of Health Sciences, Haute Ecole Spécialisé  
Suisse Occidentale Valais/Wallis, Sion, Switzerland*

The correct affiliation for these authors is:

*School of Health Sciences, HES-SO Valais-Wallis,  
Sion, Switzerland*

In the originally published manuscript, degree information for author Pauline Melly was listed as "MAS", and degrees for authors Roger Hilfiker and Filipa Pereira were listed as "DPhil". As these degrees have not yet been completed, all have been removed from the corrected manuscript. For author Filipa Pereira, the degree "MSc" has also been added to the corrected manuscript.

The correction will appear in the online version of the paper on the JMIR Publications website on January 15, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

*Submitted 11.01.21; this is a non-peer-reviewed article; accepted 11.01.21; published 15.01.21.*

*Please cite as:*

*Verloo H, Melly P, Hilfiker R, Pereira F*

*Correction: Effectiveness of Educational Interventions to Increase Knowledge of Evidence-Based Practice Among Nurses and Physiotherapists in Primary Health Care: Protocol for a Systematic Review*

*JMIR Res Protoc 2021;10(1):e27092*

*URL: <http://www.researchprotocols.org/2021/1/e27092/>*

*doi: [10.2196/27092](https://doi.org/10.2196/27092)*

*PMID: [33449910](https://pubmed.ncbi.nlm.nih.gov/33449910/)*

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Protocol

# Web-Based Interventions to Promote Healthy Lifestyles for Older Adults: Protocol for a Scoping Review

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## Abstract

**Background:** With the aging of the population and rising rates of chronic diseases, older adults need support if they are to adopt healthy lifestyles. Web-based interventions should be considered for this purpose, since they are easily accessed and can foster healthy lifestyles among older adults. However, the literature on such interventions discusses a variety of components and effects and provides only 2 syntheses of knowledge on web-based interventions with older adults. These studies focus on populations aged 50 years and older, whereas the components and effects of interventions for a population of older adults (ie, 65 years and older) may differ. In addition, these 2 syntheses examined only quantitative studies, although other types of studies (ie, qualitative) are available and could help advance knowledge in this field. A scoping review is therefore relevant in order to explore the extent of the literature on this subject.

**Objective:** The purpose of the study described by this protocol is to explore the extent of the literature (experimental, quasi-experimental, qualitative, systematic reviews, and grey literature) on the components and effects of web-based interventions as a way to promote healthy lifestyles among older adults.

**Methods:** The databases MEDLINE, CINAHL, PsycInfo, Web of Science, Cochrane Database of Systematic Review and Joanna Briggs Library will be searched, in addition to the grey literature using Google Scholar and OpenGrey. Studies will be selected for the review by 2 researchers, working independently. The data will be synthesized based on the conceptualization of web-based interventions (ie, behavior change techniques, dispensation modes, and theories). A thematic analysis will be performed to summarize the components of the interventions studied.

**Results:** The database search will begin in August 2020 and be completed in October 2020.

**Conclusions:** This scoping review should highlight web-based interventions designed to promote healthy lifestyles, as well as their components and effects, among people aged 65 years and older. These results could provide important guidance for intervention developers and designers in identifying the components of web-based interventions relevant to older adults and lead to further studies on this topic.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/23207

(*JMIR Res Protoc* 2021;10(1):e23207) doi:[10.2196/23207](https://doi.org/10.2196/23207)

## KEYWORDS

Aged; web-based intervention; healthy lifestyle; behavioral change; components; effects

## Introduction

The number of older adults worldwide (ie, those aged 65 years and older) is expected to almost double over the next 30 years,

from 12% to 22% [1]. This significant aging of the population will not be without consequences for health care systems. In fact, this phenomenon will lead to an increase in the rate of chronic diseases, considering that the prevalence of these

diseases increases with age and that older adults are seriously affected by them [2,3]. In addition to having beneficial effects on health, healthy lifestyle habits (healthy eating, regular physical activity, smoking abstinence, limiting alcohol consumption, management of stress) could help prevent a significant number of diseases [2] and promote longevity [4]. However, healthy lifestyle adoption is a complex phenomenon, especially in a population of older adults whose behaviors may have been strongly entrenched for many years. Among other things, lack of motivation is one of the greatest barriers to older adults' to adopting a healthy lifestyle [5-7]. This is why they should be able to benefit from interventions aimed at bolstering their motivation to change.

Moreover, with advances in health technologies, web-based is increasingly the preferred method of intervention, even among older adults, for whom internet use has been growing rapidly in recent years [8]. Web-based interventions could be used to support individuals as they adopt healthy lifestyles and would be favorable to older adults [9]. In addition, they constitute an economical and accessible alternative for the health care system [10]. Web-based interventions are all the more relevant in the context of the current global pandemic, since the modes of intervention delivery need to be reconsidered to limit face-to-face contact. The recommendations on social distancing must be followed in order to preserve the population's health, especially among vulnerable older adults. In this context, lifestyle habits can also be disrupted (eg, sedentary behavior, dietary changes) [11], and older adults' access to programs and services that facilitate the adoption of healthy lifestyles (eg, gyms) is limited [12]. As a result, web-based interventions may be a solution to help individuals adopt and maintain healthy lifestyles [12].

However, although the literature documents numerous web-based interventions, their components and effects are diverse, making it difficult to draw conclusions about which components lead to optimal change outcomes for this population. In this regard, Webb et al [13] developed a framework to facilitate investigations of the components of web-based interventions that will optimally influence behavior change. They propose categorizing the various intervention components according to the behavior change techniques (eg, problem solving, barrier identification, information), delivery modes (eg, interaction, feedback, additional modes), and theories (eg, Theory of Planned Behavior, Social Cognitive Theory, Health Belief Model) used [13].

While some authors have published syntheses of the literature focused on web-based interventions designed to promote lifestyle changes in adults [9,13,14], to our knowledge, no synthesis of knowledge has focused on people aged 65 years and older. In fact, there appears to have been only 2 systematic reviews [15,16] conducted on web-based interventions aimed at healthy lifestyle habits for people aged 50 years and older. The primary studies included in these systematic reviews have small sample sizes with an average age of 50 years or older, which means that they do not focus specifically on a population of older adults [15,16]. Although it is difficult to reach a consensus on the specific age threshold used in the literature to define old age, the World Health Organization [2] suggests

defining older adults as persons aged 65 years and older. Because older adults are a heterogeneous group with multiple characteristics, older individuals, such as those aged 65 years and older, may have different needs to be met by these interventions because of the biological (eg, decreased functional capacity, frailty) and psychological changes (eg, changes in roles, social position and priorities) associated with aging [2]. Moreover, older persons should be able to benefit from accessible health services adapted to their needs [17]. Since the components of the interventions as well as their effects could differ for this population, it is essential to explore the literature on this subject.

Finally, these 2 syntheses of the literature [15,16] focus only on quantitative studies, whereas qualitative studies are also available in the literature. Both qualitative and quantitative studies can make relevant contributions on the components and effects of web-based interventions to promote healthy lifestyles among older adults. Qualitative studies could also greatly enrich our knowledge on the impact of these interventions on older adults. A scoping review on this topic is appropriate since, to our knowledge, no study has explored the extent of knowledge on web-based interventions for people aged 65 years and older, including both qualitative and quantitative studies.

Therefore, the purpose of this article is to present the protocol for a scoping review that will explore the extent of the available literature on web-based interventions aimed at promoting healthy lifestyles among people aged 65 years and older.

## Methods

### Overview

This protocol describes the methodology that will be used to conduct a scoping review and the steps that will be followed to ensure its rigor. A scoping review will be conducted based on the framework proposed by Levac et al [18]. This framework was initially developed by Arksey and O'Malley [19] and then refined by Levac et al [18] at the level of its methodological description, which is why it has been chosen. According to Arksey and O'Malley [19], a scoping review may be conducted to determine the scope of the research or to map the available literature on a phenomenon, which is the purpose of this study. The review will follow the 6 steps proposed by Levac et al [18] as presented below.

### Identifying the Research Questions

The research questions were identified following a brief review of the initial literature and discussions with the research team, composed of a doctoral student, a researcher, a research professional, and a librarian. This scoping review will seek to answer the following questions: (1) What web-based interventions are aimed at promoting healthy lifestyles among people aged 65 years and older? (2) What are the components of these interventions (ie, behavior change techniques, delivery modes, and theories used)? and (3) What have been the effects of these interventions as reported in the literature?



## Identifying Relevant Studies

The following databases will be searched: MEDLINE, CINAHL, PsycInfo, Web of Science, Cochrane Database of Systematic Review, and Joanna Briggs Library. These databases were selected for their focus on the field of social and health sciences, which is related to the topic of this study. Grey literature will be searched using the Google Scholar and OpenGrey databases. The reference lists of the identified articles will be checked to ensure that all relevant articles have been included. The authors of primary studies will be contacted if additional information is required.

The search strategy, established with a librarian's assistance, will use keywords and descriptors related to the concepts of older persons (eg, *aged*, *elderly*), lifestyle (eg, *lifestyle*, *exercise*), and web-based interventions (eg, *internet*, *online*). [Multimedia Appendix 1](#) presents an example of such a strategy. Given the broad nature of a scoping review, the criteria for inclusion will be (1) articles published between 1990 and 2020, since the World Wide Web was created in 1989 [20], (2) articles published in French or English, (3) articles related to the goal of the scoping review (ie, to a web-based intervention addressed to a population of older adults) and aimed at promoting healthy lifestyle habits (ie, healthy eating, regular physical activity, smoking abstinence, limiting alcohol consumption, management of stress), and (4) primary studies (eg, experimental, quasi-experimental and qualitative), systematic reviews of any type, and other documents associated with the grey literature (eg, government reports and clinical practice guidelines). The exclusion criteria will be (1) articles in which persons aged 65 years and older are not the population specifically studied, (2) articles in which the web component of the intervention is not predominant (eg, face-to-face interventions complemented by use of a website) because this could mean that the results are not specifically related to the web-based intervention, and (3) articles that do not primarily target healthy lifestyle habits (eg, symptom self-management programs that include physical exercise). Finally, the articles identified will be exported to a data management software program (Covidence, Veritas Health Innovation Ltd) where duplicates will be removed.

## Study Selection

The studies will be selected by 2 independent researchers (ie, the first author, AL, and a research assistant, ML). An initial selection will be made by reading the abstract and title of the article, and then the selected articles will be read in full to retain only those related to the purpose of the study, addressing the research questions, and eligible based on the inclusion and exclusion criteria. In case of disagreement concerning a selection, a third researcher (ie, the second author, VD) will be consulted. As suggested by Levac et al [18], researchers will meet at the beginning, midpoint, and end of the selection process to clarify any difficulties and revise the research strategy. In order to promote transparency, a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) diagram will be used to illustrate the study selection process by presenting the articles excluded and the reasons for their exclusion.

## Charting the Data

Data that include authors, year and location of publication, purpose, type of study, population and sample, method, type of intervention and comparison, and intervention components and effects will be extracted to a table. As suggested by Levac et al [18], data from the first 5 papers will be extracted independently by 2 researchers (ie, the first author, AL, and a research assistant, ML) to ensure consistency. Since the purpose of the review is to explore the breadth of knowledge rather than to assess the rigor of the studies identified, the quality of the studies will not be assessed.

## Collating, Summarizing, and Reporting Results

Data will be collected, synthesized, and reported according to the conceptualization of web-based intervention components proposed by Webb et al [13] (ie, the behavior change techniques employed, the delivery modes and theories used, and the effects of the intervention). A thematic analysis, informed by the method used by Paillé and Mucchielli [21], will be conducted to summarize the data by examining the components and effects of the interventions studied. More specifically, themes and subthemes will be identified from the extracted data, based on the various components of the interventions, and categorized under headings representing the different lifestyle habits targeted by the studies. The themes will then be grouped according to their similarity, divergence, complementarity, or recurrence to form thematic clusters (ie, groups of themes with common characteristics). A narrative summary and descriptive tables will be presented to provide an overview of all the components and effects of the interventions studied [18]. The analysis will first be carried out by one author (AL) and validated by the other author (VD). The PRISMA checklist specific to scoping reviews will be used to ensure that all the key items have been reported and in order to promote study replicability [22].

## Consultation

For this step, a focus group will be organized with stakeholders. Since the interventions in the literature will be aimed at older adults, we will ensure that we have their perspective on this issue by consulting 2 people aged 65 years or older who have a lifestyle habit they need to change. In order to be able to deploy this type of intervention in the community, we will ensure that we have a multidisciplinary group of professionals able to provide support to these people as they adopt healthy lifestyle habits. We will, therefore, consult a department head of a primary health care center and health professionals, (ie, a nurse with expertise in preventive health, a nutritionist, and a physiotherapist). The main purpose of this focus group will be to present the preliminary results to these stakeholders and gather their impressions and any new ideas as a way to enrich the results and guide recommendations for future studies.

## Results

We plan to begin the database search in August 2020 and complete the scoping review in October 2020. Upon completion, recommendations will be provided to facilitate integration of web-based interventions into practice to support older adults in healthy lifestyle habits and on the direction of future studies.

## Discussion

### General

In this paper, we have presented the protocol for a scoping review based on 6 steps [18]. The proposed scoping review protocol is innovative in that, to our knowledge, no knowledge synthesis has been conducted on web-based interventions to promote healthy lifestyle behaviors among people aged 65 years and older, nor on their components, theories, and effects on this population. In fact, only 2 systematic reviews [15,16] have been conducted on this subject, but they include primary studies with an average participant age of 50 years or older, such that the results are not specific to a population of older adults. People aged 65 years and older may have different needs, and experience other impacts from interventions aimed at supporting them as they make changes in their lifestyle habits, particularly because of the biological and psychosocial changes associated with aging. This is why such a focus is necessary. Since older adults are a heterogeneous group of people with multiple characteristics and, within this group, different samples of older adults (eg, 85 versus 65 years of age) could present different results, it is important to be attentive to the effects of interventions by age group. Moreover, the 2 knowledge syntheses reviewed focus solely on the quantitative literature, while other types (ie, qualitative) are available in the literature and could greatly enrich our knowledge on this subject. Since the scoping review allows for the inclusion of different types of studies, use of this method appears justified in order to explore the extent of current knowledge on web-based interventions aimed at promoting healthy lifestyles among people aged 65 years and older. The publication of this scoping review protocol also ensures the rigor and the reproducibility of the review, and facilitates transparency regarding the proposed method, which can guide the conduct of new studies on this subject.

Finally, this scoping review will highlight the various web-based interventions aimed at helping older adults adopt healthy lifestyles, as well as the components and effects on people aged 65 years and older. The protocol for this scoping review proposes a novelty—to gather, synthesize and report the data from the literature reviewed according to a conceptualization of web-based interventions proposed by Webb et al [13]. The goal is to identify intervention components that influence the adoption of healthy lifestyle habits among older adults. This conceptualization appears relevant and innovative for this scoping review, since it will guide the synthesis of knowledge by highlighting the behavior change techniques used, modes of intervention delivery, theories used, and effects of web-based interventions in a population of people aged 65 years and older. To our knowledge, this has never been done before. At the end of this scoping review, a synthesis of these elements will be produced and presented in order to systematically identify the various components and effects of the interventions identified.

The results of this scoping review may help guide the conduct of new studies on web-based interventions with components adapted to people aged 65 years and older, and encourage the integration of these interventions into practice.

### Strengths

The studies will be selected systematically and independently by 2 researchers (ie, the first author and a research assistant), and the second author will be consulted in case of disagreement, thus ensuring the reliability of the results. The search strategy involves consulting a large number of databases (n=7) as well as grey literature using Google Scholar, OpenGrey, and a manual search of the references of the articles identified, which reduces the risk of articles being omitted. In addition, the study identification process, including inclusion and exclusion criteria, has been explained in detail to ensure reproducibility. The PRISMA checklist specifically for scoping reviews will be used, which will contribute to the transparency and quality of this study [22].

### Limitations

Although this is not the main objective or a necessary step in a scoping review, the quality of the literature will not be assessed in this review, which may raise concerns about the rigor of the literature and affect the generalizability of the results. We will take this limitation into consideration in our analysis of the results and will still critically analyze the literature reviewed. Otherwise, data will be extracted by 2 researchers only for the first 5 articles, whereas independent 2-researcher extraction of data for the entire sample of literature could have enhanced the reliability of the data by avoiding any misinterpretation or omission of information by the authors. Finally, a language restriction (ie, only studies in English and French) will be imposed, which could affect the exhaustiveness of the set of articles identified.

### Conclusion

The purpose of this scoping review will be to explore the extent of the literature on web-based interventions to promote healthy lifestyles among people aged 65 years and older. Given advancements in the use of technologies in the field of health, web-based may be a preferred method for delivering interventions because of its accessibility, especially for a population of older adults, among whom internet use has been growing rapidly in recent years. Given that web-based interventions have the potential to encourage the adoption of healthy lifestyles and thus promote health, it is relevant to examine the components and effects of these interventions among older adults, whom we know are greatly affected by chronic diseases. The results of this scoping review will inform health professionals and interventions developers about the relevant components and effects of web-based interventions in a population of older adults. Knowing this, we can use web-based interventions to promote healthy lifestyles in this population.

### Conflicts of Interest

None declared.

## Multimedia Appendix 1

Search strategy example.

[\[DOCX File , 19 KB - resprot\\_v10i1e23207\\_app1.docx \]](#)**References**

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## Abbreviations

**PRISMA:** Preferred Reporting Items for Systematic reviews and Meta-Analyses

*Edited by G Eysenbach; submitted 05.08.20; peer-reviewed by T St Quinton, K Champion; comments to author 09.11.20; revised version received 20.11.20; accepted 24.11.20; published 04.01.21.*

*Please cite as:*

*Lavoie A, Dubé V*

*Web-Based Interventions to Promote Healthy Lifestyles for Older Adults: Protocol for a Scoping Review*

*JMIR Res Protoc* 2021;10(1):e23207

*URL:* <https://www.researchprotocols.org/2021/1/e23207>

*doi:* [10.2196/23207](https://doi.org/10.2196/23207)

*PMID:* [33393929](https://pubmed.ncbi.nlm.nih.gov/33393929/)

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Protocol

# Open and Distance Learning Programs for Nursing and Midwifery Education in East Africa: Protocol for a Scoping Review

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## Abstract

**Background:** In the face of growing modernity and the coronavirus disease 2019 (COVID-19) pandemic, open and distance learning (ODL) is considered to play an important role in increasing access to education worldwide. There is a robust evidence base demonstrating its cost effectiveness in comparison with conventional class-based teaching; however, the transition to this new paradigm of learning for nursing and midwifery courses has been difficult in low-income countries. While there are notable efforts to increase internet and education access to health care professionals, not much is known about ODL for nurses and midwives in East African countries.

**Objective:** The objective of this scoping review is to understand whether ODL programs for nursing and midwifery education exist, the drivers of their adoption, their implementation, the topics/courses covered, their acceptability, and their impacts in East African countries.

**Methods:** The scoping review methodology employs the framework developed by Arksey and O'Malley. Using an exploratory approach, a two-stage screening process consisting of a title and abstract scan and a full-text review will be used to determine the eligibility of articles. To be included, articles must report on an existing ODL initiative for nurses and midwives in Uganda, Tanzania, and Kenya. All articles will be independently assessed for eligibility by pairs of reviewers, and all eligible articles will be abstracted and charted in duplicate using a standardized form.

**Results:** Details of ODL for nursing and midwifery education initiatives and study outcomes will be summarized in a table. The extracted data will undergo exploratory descriptive analysis, and the results will be classified into learner and clinical outcomes.

**Conclusions:** Evidence on ODL for nursing and midwifery education will inform the ongoing development and restructuring of health care professional education in East Africa amidst the COVID-19 pandemic.

**International Registered Report Identifier (IRRID):** PRR1-10.2196/17765

(*JMIR Res Protoc* 2021;10(1):e17765) doi:[10.2196/17765](https://doi.org/10.2196/17765)

**KEYWORDS**

open and distance; learning; health care; nurses; midwifery; health; East Africa

## Introduction

In the face of modernity, the coronavirus disease 2019 (COVID-19) pandemic, and increased access to the internet, telecommunication, and related technologies, there is growing interest in open and distance learning (ODL) as a promising entry point to address the challenges of access to educational opportunities worldwide [1-5]. ODL entails a process that facilitates acquisition of knowledge and skills through open and flexible information and instruction mainly by using technology, with all or most of the teaching delivered by an individual who is at a distance from the learner [5,6]. In recent years, ODL has become a foundation for initial training for formal qualifications, in-service training for formal upgrading, and continuing in-service training in particular subjects and topics in many high-income countries and some low-income countries [5,6]. Through ODL, students in one part of the world/country are able to earn educational qualifications from institutions located in other parts of the world/country. Although it may not carry the full package of benefits enjoyed in traditional class-based teaching, a growing body of research continues to provide evidence of the effectiveness of ODL in both high- and low-income countries. Some studies have reported a similar impact between ODL and conventional class-based learning strategies [6,7]; however, a considerable number of studies report ODL as playing a role in increasing student enrollment and performance, and it is mostly preferred by students with work commitments as compared with face-to-face education [8-12].

The world continues to face challenges regarding human resources for health. Concerns of low production from health training institutions and consequently inadequate number of health care workers, as well as gaps in knowledge and skills are large particularly in sub-Saharan Africa [13-16]. The disconnect between the persistent challenge of inadequate and skilled health care workers versus current production under traditional teaching models calls for new teaching strategies for health care profession education to address the challenges regarding human resources for health. The ongoing COVID-19 pandemic has further strained the available human resources for health in Africa, creating a demand for new knowledge and skill sets among health care professionals for personal and patient protection [2,3,17,18]. Likewise, long-standing academic staff shortages in East Africa and recent campus closures due to COVID-19 have caused many universities in the region to consider new teaching delivery methods, with ODL becoming a preferred option [2,3,18]. Backed by the growing and robust evidence of increasing recognition and implementation of ODL across the world [8-12], there is a need for its integration into the formal teaching and learning model within the health care sector. However, transition to this new paradigm of learning for health care professional-related courses in low-income countries, particularly East Africa, remains difficult. The transition from traditional class-based learning to ODL is a challenge, as there are many policy, infrastructural, and structural barriers that training institutions and learners, who are used to face-to-face education, must navigate [19-25]. While efforts to increase internet and education access to health care

workers are evident, not much is known about ODL for nursing and midwifery in East African countries. The objective of this scoping review is to understand whether ODL programs for nursing and midwifery education exist; the drivers of their adoption; their implementation; their acceptability; the topics/courses covered; and their impacts in Tanzania, Kenya, and Uganda.

## Methods

### Design and Framework

Various evidence synthesis approaches were considered for this review; however, the scoping review methodology was seen as the most appropriate, especially since the complex area of ODL in East Africa has not been reviewed comprehensively before. To the best of our knowledge, there has been no prior attempt to establish a baseline of knowledge regarding ODL initiatives for nursing and midwifery education in the study setting. Given this knowledge gap and that literature may be diffuse owing to the multidisciplinary nature of ODL implementation, a scoping review is ideal for taking stock of the volume and nature of the existing literature [26]. The use of a scoping review as a form of exploratory knowledge synthesis allows for the broad exploration of ODL to map key concepts, evidence types, and gaps in research in a defined field and to make use of a wide array of knowledge exhibited through empirical research and anecdotal accounts [26-30].

The scoping review methodology employs the framework developed by Arksey and O'Malley from the Centre for Reviews and Dissemination at the University of York [27]. The framework provides a methodological approach to carry out this type of review, embracing some recent developments [28-30]. Arksey and O'Malley's framework proposes the following five stages that will be followed for this review: (1) identification of the research question to be addressed; (2) identification of studies relevant to the research question; (3) selection of studies to include in the review; (4) charting of information and data within the included studies; and (5) collating, summarizing, and reporting results of the review. An optional sixth stage involves consultation with stakeholders to ensure comprehensive inclusion of all relevant materials [27]. We will use this framework to guide our exploratory scoping review, and where necessary, we will develop more specific procedures to carry out the stages of the review process. The following sections describe the methods that will be followed in our scoping review.

### Identifying the Research Question

Arksey and O'Malley [27] recommended the consideration of all aspects of the research area to generate a breadth of coverage. Drawing on the expertise of our research team, current discussions on teaching and learning in East Africa (Uganda, Tanzania, and Kenya), and an initial scan of the literature, we defined our overriding research question as follows: *What is the extent of published evidence in East Africa relating to the existence of ODL programs for nursing and midwifery education and their drivers, implementation, topics covered, acceptability, and impacts?* The rationale behind this broad question was the lack of harmonized evidence about ODL practices for nursing

and midwifery education in East Africa. By identifying the current educational initiatives, this review seeks to establish a foundational understanding of how ODL programs for nursing and midwifery education, if any, are implemented and glean the critical impact factors and recommendations of these experiences. Based on a combination of informal discussions and a preliminary review of published topics, we developed the following specific questions for our exploratory scoping review: (1) *What ODL interventions exist for nursing and midwifery training programs in East Africa?* (2) *What are the key drivers for adoption of ODL interventions for nursing and midwifery in East Africa?* (3) *What aspects of nursing and midwifery education are taught using the ODL strategy?* (4) *How are the ODL interventions for nursing and midwifery education delivered?* (5) *What are the existing policy and institutional frameworks that guide and promote quality of ODL interventions?* (6) *What is the documented impact of ODL interventions for nursing and midwifery education in East Africa?*

### Stakeholder Consultation

The optional stakeholder consultation phase is meant to be an ongoing interaction throughout the review process [27]. Thus, we feel it is important to initiate contact with stakeholders at the beginning of the review process. Early involvement of stakeholders will allow us to seek guidance regarding our research question, thus ensuring that the results are of broad interest among different stakeholder groups.

Stakeholders of interest represent fellow researchers, instructors, and decision makers involved in nursing and midwifery education in East Africa. Individual stakeholders will be identified through professional networks and contacted via email. We will brief them on our research question and focus areas, as well as approach to searching the literature, and solicit their feedback on our approach. Only their titles and/or positions will be used to ensure anonymity.

### Identifying Relevant Studies

To be comprehensive, Arksey and O'Malley recommended searching several literature sources, including electronic databases, reference lists of relevant literature, key journals (hand searching), existing networks, relevant organizations, and conferences [27]. For our scoping review, we will approach this in multiple steps. First, a search strategy will be co-developed by the research team in collaboration with an experienced librarian targeting different formal and informal health care profession databases that promote African content. The search strategy will consist of subject headings, keywords, and related terms for ODL, nursing, and midwifery education, and all East African countries. The search terms applied in one database will then be translated for use in the other databases. Once relevant material is selected from databases, we will search relevant websites, URLs, and reference lists of key studies to increase our capture of relevant material.

### Electronic Database Searching

We will enlist the services of a library scientist to conduct the electronic database search. The research team will devise a broad list of terms pertinent to ODL in nursing and midwifery

education, including ODL initiatives, ODL implementation, and ODL benefits/impacts. These terms will be combined to create keywords that could be used to search electronic literature databases. Keywords will then be mapped to database thesaurus search terms, where available, and also searched as text word terms in all databases. The goal is to conduct a sensitive rather than specific search of the literature; thus, search terms are kept very broad, resulting in many irrelevant studies being eliminated at the study selection. All literature database searches will be limited to the English language and publication from inception to December 2020.

### Website Searching

Once relevant studies are selected from the literature database search, we will carry out a selective search of relevant websites. Through consultation with our stakeholders and members of the research team and colleagues, we will compile a list of relevant websites in East Africa to search. We will attempt to search websites in a systematic manner, allowing for some variation in search strategies in response to varied website structures. Once hand searching a website's links is complete, we will use the website's search engine to attempt to uncover additional materials. Once again, different types of search engines require different search tactics. For all websites, we will search the terms *open and distance, nursing and midwifery education, nursing education, midwifery education, and East Africa OR Tanzania OR Kenya OR Uganda*. For websites that are not specifically health care focused, we will add the word "health" to the specific term. A log of the website searches will be kept, and links to relevant pages will be saved.

### Other Literature Sources

In an attempt to be as comprehensive as possible in our search, we will also collect literature from reference lists of relevant articles, master's and PhD theses, specific journal issues with related material, technical reports from health care organizations, and suggestions from colleagues.

### Selection of Relevant Studies

A two-stage screening process consisting of a title and abstract scan and a full-text review will be used to determine the eligibility of articles. Both stages will follow the same process, where every article will be independently reviewed in pairs and the results will be documented on the spreadsheet. At the end of each round, the ratings will be compared and resolved by two reviewers or a third reviewer, when consensus is not achieved. Any ambiguities regarding the eligibility of a citation (or article) will be flagged and discussed.

The citations will be assessed for relevance based on a title and abstract scan. To be relevant for full-text review, articles must report on an existing ODL initiative for nurses and midwives in Kenya, Uganda, and Tanzania. The full-text review form will ask reviewers to assess each article using the following questions: *Does the article describe/discuss the ODL initiative/intervention/program for nursing and midwifery education in Tanzania, Kenya, and Uganda?*

This review is inclusive of all types of literature, thus including commentary articles, technical reports, case studies, and

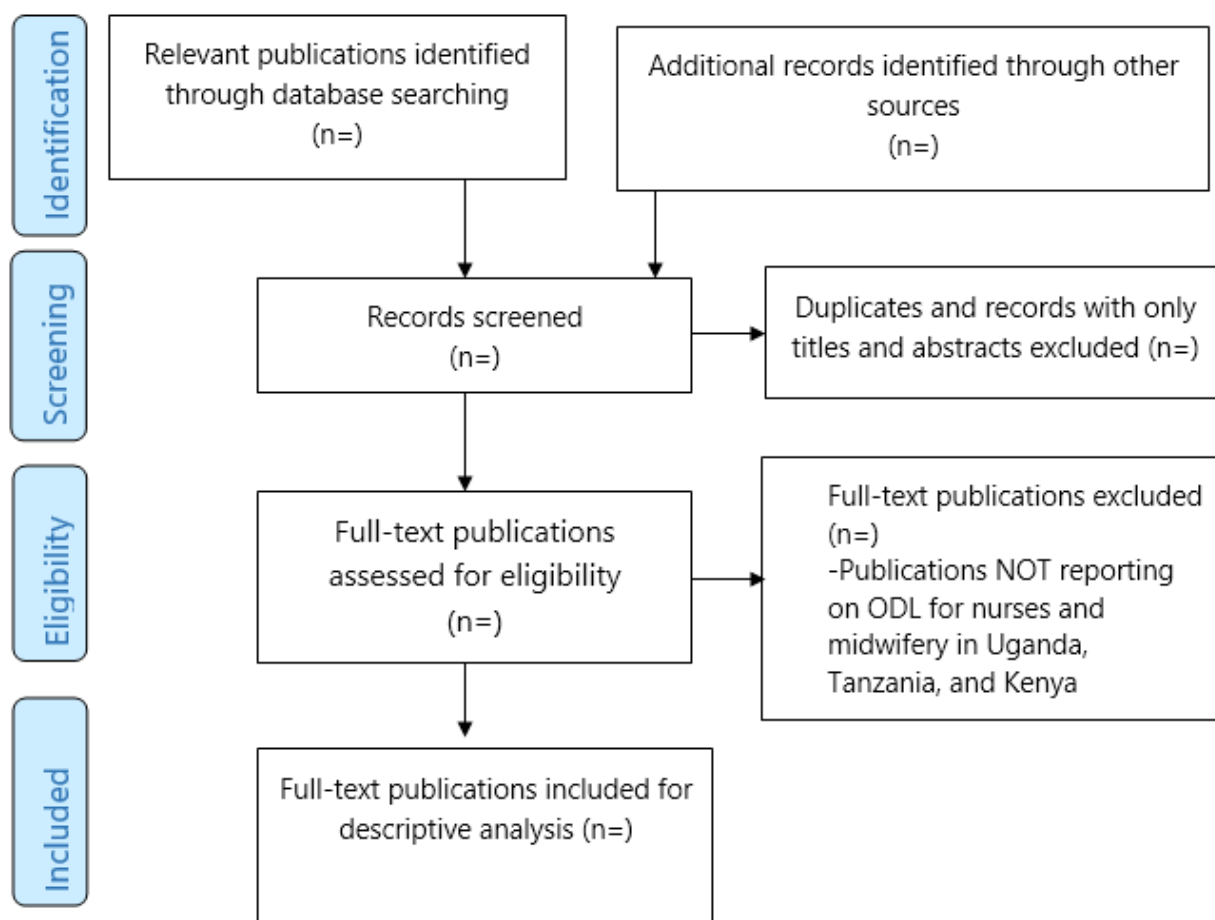
empirical studies employing all types of methodologies (ie, qualitative, quantitative, and mixed methods) and study designs. Viewpoint articles on how ODL education programs should be implemented outside of the context of an existing program will be excluded.

The criteria will be piloted by the reviewers to refine and establish a common understanding of the inclusion criteria. About 10% of the selected citations from a single database will be independently reviewed by four reviewers to establish interrater reliability (IRR). The results of the review will be compared, and the IRR will be calculated. The threshold for IRR is set at an average Cohen kappa of 0.70, indicating substantial agreement [31,32]. The pilot will be run again if the threshold is not met. If met, the remaining articles will be divided and assigned to two sets of pairs for independent review. These adjustments to the inclusion-exclusion process are appropriate, as they provide the team with opportunities to become familiar with the data and to reduce workload [32-34]. Regardless of the IRR outcome, a meeting about the process will be held to compare the results, resolve disagreements, and troubleshoot the challenges that arise during the title-abstract review process.

### Charting of the Data

Arksey and O'Malley indicated that the charting process is multistaged, involving extraction of information from individual articles [27]. A PRISMA chart will be used to summarize the stages of the scoping review and the publications included (Figure 1). However, a detailed standardized charting form will be developed and used to categorize or "chart" the data. The high-level domains for the charting form consist of general citation information, health care profession area, level of reporting, country of origin, and key findings from the included articles; initiative details; and implementation factors. There will be a training session to trial the charting form and ensure there is a common understanding of the categories and how to use the form. The full-text reviewers will be asked if there are any additional variables emerging from the full-text review to consider for charting. The form will be piloted on 5 to 10 articles by the team. A final round of feedback on the form will be solicited prior to the charting process. The charting will also consist of independent charting by the reviewers and validation by the senior investigators. The charters will be encouraged to provide constant feedback on emerging themes not captured in the charting form. The form will be revised as required.

Figure 1. PRISMA flow diagram of the study. ODL: open and distance learning.



### Summation, Collation, and Synthesis

The purpose of this final stage of the scoping review is to provide a structure to the literature uncovered. The extracted

data will first undergo a simple quantitative analysis using descriptive statistics (eg, frequencies) to provide numerical summaries of the education initiatives and article or study characteristics [27]. Multiple articles stemming from a single



ODL initiative will be grouped and treated as a unit of analysis. The data will also undergo a “narrative review” or a descriptive analysis of the contextual or process-oriented data where all data will be thematically analyzed independently by two reviewers to identify emerging themes found within each of the subdomains (ODL availability, implementation, acceptability, and impacts). Focusing on the descriptive nature of the material in the charting phase will allow for the identification of additional categories and themes in the literature. The results will be compared and consolidated by consensus between the two reviewers. The resulting themes will be reviewed by content experts to ensure validity and credibility. The themes will be reported to highlight the similarities, patterns, differences, and outliers found in the literature.

## Results

The results from selected publications will undergo exploratory descriptive analysis and will be classified into learner and clinical outcomes [31-34]. The list of stakeholders consulted, electronic databases, and websites for the search will be tabulated. Details of ODL for nursing and midwifery education initiatives and study outcomes will be summarized in a table. The articles will not be assessed for quality as it is outside the scope of this review; however, details of the included articles (ie, article type and methodology) will be reported using a summary table to provide context for the maturity of the evidence.

## Discussion

The purpose of this review is to gain an understanding of the existence of ODL programs for nursing and midwifery education, the drivers of their adoption, the extent of their

implementation, the courses covered, and their acceptability and impacts. The discussion of the findings will be contextualized based on previous studies and their implications for the ongoing development of ODL initiatives for nursing and midwifery education in East Africa (Uganda, Tanzania, and Kenya) in the face of the COVID-19 pandemic.

This scoping review is not without limitations. The review only focuses on nursing and midwifery education. This means ODL interventions on other aspects of health care professional education will be excluded. However, a snapshot of ODL interventions beyond the nursing and midwifery sphere will be offered to partly overcome this exclusion. The review only focuses on Tanzania, Kenya, and Uganda. While this is driven by the researchers’ institutional affiliation presence, further reviews may extend beyond these countries.

Research ethics approval is not required for this scoping review. This protocol reports a comprehensive, rigorous, and transparent methodology. This review contributes to the advancement of research on this subject and comments on the maturity of the body of literature by identifying gaps in knowledge and research. Through the publication of the results and their dissemination at relevant conferences, the findings of this review could guide the direction of future research and implementation of ODL initiatives for nursing and midwifery by health care institutions in East Africa amidst the COVID-19 pandemic. The results will also be presented at relevant national and international conferences and published in a peer-reviewed journal. The results of this review may inform the design of new initiatives and the policies that support them; moreover, future implementation teams can learn from the experience of others to avoid potential barriers and focus on enablers to increase the chances of success of their ODL programs (existing or new).

## Conflicts of Interest

None declared.

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## Abbreviations

**COVID-19:** coronavirus disease 2019

**IRR:** interrater reliability

**ODL:** open and distance learning

*Edited by G Eysenbach; submitted 10.01.20; peer-reviewed by S Brownie, N Miyoshi, K Cato, A Korchi; comments to author 21.08.20; revised version received 13.10.20; accepted 24.11.20; published 11.01.21.*

*Please cite as:*

*Isangula K, Edwards G, Mwansisya T, Mbekenga C, Pallangyo E, Sarki A, Ndirangu-Mugo E*

*Open and Distance Learning Programs for Nursing and Midwifery Education in East Africa: Protocol for a Scoping Review*  
*JMIR Res Protoc* 2021;10(1):e17765

*URL:* <http://www.researchprotocols.org/2021/1/e17765/>

*doi:* [10.2196/17765](https://doi.org/10.2196/17765)

*PMID:* [33427679](https://pubmed.ncbi.nlm.nih.gov/33427679/)

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Protocol

# Community-Based Physical Activity Interventions for Individuals with Moderate to Severe Traumatic Brain Injury: Scoping Review Protocol

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## Abstract

**Background:** Long-term physical, cognitive, and psychosocial problems resulting from moderate to severe traumatic brain injury (TBI) can prevent individuals from returning to preinjury lifestyles because of significant challenges with employment, leisure, and relationships. While physical activity (PA) is proposed as a cost-effective method to alleviate problems after moderate to severe TBI, there is no review to date that synthesizes the evidence for PA in the community-based context. Further, although sex- and gender-based considerations in research are considered requisite to good science, there is no review on PA and TBI that has included this explicit focus.

**Objective:** The purpose of this review is to map and synthesize the current evidence identified through a systematic search of community-based PA interventions for individuals of all ages with moderate to severe TBI and provide an overview of that evidence by asking the following research questions: (1) what are the characteristics of community-based PA programs for individuals with moderate to severe TBI, (2) what are the reported health-related outcomes and measurement tools used to evaluate them, and (3) what considerations have been given to sex and/or gender?

**Methods:** Searches will be conducted of six academic databases for peer-reviewed articles. Two reviewers will independently screen the articles for inclusion and extract data for the analysis. The extracted data will be coded according to the Consensus on Exercise Reporting Template checklist and the Template for Intervention Description and Replication checklist to provide sufficient detail for replication.

**Results:** The abstract screening was completed by two reviewers and the extracted data were analyzed. A qualitative synthesis and description of community-based PA interventions for individuals with moderate to severe TBI will be provided.

**Conclusions:** This scoping review will generate new knowledge from published and publicly available literature. Dissemination of the results will include activities related to knowledge transfer for community-based PA after moderate to severe TBI for future research and practice. Evidence-based recommendations, future directions, potential limitations, use of online/digital components, and the possible need for a systematic review will be discussed as well.

**International Registered Report Identifier (IRRID):** DERR1-10.2196/24689

(*JMIR Res Protoc* 2021;10(1):e24689) doi:[10.2196/24689](https://doi.org/10.2196/24689)



**KEYWORDS**

traumatic brain injury; community; physical activity; exercise; sex; gender

## Introduction

### Background

Traumatic brain injury (TBI) is a leading cause of long-term disability around the world [1], and the physical, cognitive, and psychosocial consequences resulting from moderate to severe cases of TBI frequently lead to a significant reduction in employment, interpersonal relationships, and leisure activities after injury [2]. Moderate to severe TBI is considered to be a “chronic disease process” because of the progressive nature of associated problems that result in high economic, personal, and social costs that extend over a lifetime [3]. Further evidence of this chronic disease process is demonstrated through a risk of social failure with higher rates of unemployment [4], homelessness [5], and incarceration [6]. The abundance of long-term social and health problems after moderate to severe TBI therefore emphasize a need for interventions to address management in the chronic recovery time period (eg, >2 years postinjury), when individuals typically live in the community setting and may no longer be supported by health professionals.

### Physical Activity (PA) After TBI

PA is recommended as a nonstigmatizing approach to improve recovery after TBI [7], and positive PA habits are shown to positively influence community integration, mood, and quality of life [8]. In this context, PA is shown to reduce depressive symptoms [9] and positively affect cognitive functioning [10] after TBI, especially in the chronic phases of recovery [11]. In addition, and relevant to the chronic recovery time period, a Cochrane review about cardiorespiratory training demonstrated that PA positively affects fitness after TBI and is acceptable for individuals to perform without adverse events [12].

That same Cochrane review reported that although cardiorespiratory training is effective at increasing cardiorespiratory fitness for adults with moderate to severe TBI, the clinical value of including fitness training after injury for the improvement of secondary health-related outcomes could not be assessed because of a lack of available data [12]. A number of studies in that review were excluded based on the types of interventions (nonrandomized control trials), as well as the necessity for interventions to focus specifically on cardiorespiratory fitness according to frequency, intensity, time, and type of training. Thus, it is plausible that other modalities of PA intervention (ie, walking, Qigong, circuit training) that do not specifically target cardiorespiratory fitness may have contributed to the enhancement of other health-related outcomes, but they were not included. Since then, more recent PA studies for adults with moderate to severe TBI have reported promising health improvements with weight management [13], mood, social participation, and recovery after TBI [14,15], as well as independent exercise performed in community fitness centers with minimal guidance [16].

In addition, identifying sex- and gender-based considerations may be relevant to the use of PA for health-related outcomes

among adults with moderate to severe TBI. For example, men and women with TBI may experience exercise differently based on varying recovery outcomes, social behaviors, and motivation to participate in community-based physical therapy [17,18]. This information was lacking from the Cochrane review cited above. Thus, providing a qualitative description and synthesis of the characteristics of PA interventions, their reported health-related outcomes, and the measurement tools used to evaluate them, as well as considerations provided for sex and/or gender, is warranted.

### Objectives

The purpose of this review is to map and synthesize the current evidence identified through a systematic search of community-based PA interventions for individuals with moderate to severe TBI and provide an overview of that evidence by asking the following research questions: (1) what are the characteristics of community-based PA programs for individuals with moderate to severe TBI?; (2) what are the reported health-related outcomes and measurement tools used to evaluate them?; and (3) what considerations have been given to sex and/or gender? For the purposes of this review, definitions of “PA,” “intervention,” and “community-based” are provided below. A relevant and timely summary of these findings may assist researchers and community-based organizations (ie, fitness centers, TBI and/or disability associations) with the design and implementation of PA programs for individuals with moderate to severe TBI, as well as the appropriate outcome measurement tools for their evaluation.

## Methods

### Identifying Relevant Studies

This protocol was prepared according to the checklist of PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols Extension for Scoping Reviews [19]; [Multimedia Appendix 1](#)), as well as the step-by-step guidelines of Arksey and O'Malley [20], with enhancements provided by Levac et al [21].

### Search Strategy

Searches will be limited to human studies written in English or French because of the language proficiency of the research team and the scope of this review. Searches will be developed and conducted by an information specialist at University Health Network (UHN)–Toronto Rehabilitation Institute with consultation and feedback from the research team, who have extensive content and methodological expertise in the area of rehabilitation and TBI. A detailed description of the search strategy for this scoping review is provided in [Multimedia Appendix 2](#).

### Databases

Searches will be conducted in MEDLINE(R) (in Ovid, including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Ovid MEDLINE[R] Daily), Embase (in Ovid,

including Embase Classic), Cochrane Central Register of Controlled Trials (in Ovid, CENTRAL), CINAHL (EBSCOhost), SportDISCUS (EBSCOhost), and PeDRO.

## Selection Criteria

### *Types of Participants*

Studies including people of any age, sex, or gender with moderate to severe TBI living in the community will be included. Moderate to severe TBI includes nonpenetrating head injuries caused by external forces that are assessed to be between 3 and 12 on the Glasgow Coma Scale to reflect individuals who live with the greatest number of TBI-related impairments [22]. Penetrating head injuries or anoxic brain injuries (ie, caused by stroke) will be excluded.

### *Types of Studies*

All studies of community-based PA interventions will be included. No restrictions will be placed on the type of study design or methods used. The full-text article or report of the study must be included; therefore, reports of research only available in abstract form will be excluded. Reviews will not be included. However, review references will be carefully hand-searched by the lead reviewer (EQ) to ensure that relevant studies about community-based PA programs are identified. Gray literature, including theses/dissertations, conference proceedings, policies, reports, protocols, and book reviews will be excluded in order to reflect high-quality empirical research about PA interventions that focus on health-related outcomes.

### *Types of PA*

Studies that include any type of PA intervention provided in a community setting—including home-based, community center-based, gym-based, outdoor-based, and park- and recreation center-based interventions—will be included. Leisure interventions that do not include PA, exercise, or sport will be excluded (eg, arts and crafts, music). For the purposes of this review, the operational definition of PA is any bodily movement produced by skeletal muscles that results in energy expenditure and positively correlates with physical fitness. The operational definition of exercise is PA that is planned, structured, and repetitive, with an objective to improve or maintain physical fitness components. Finally, the operational definition of sport is further defined as being a form of leisure-time PA [23]. For the purposes of this review, fitness is defined as the state of being in good health, intervention is defined as the action or process of intervening for the purpose of improving health, and community-based is defined as an intervention provided in the community rather than in hospitals or institutions [24].

### *Types of Outcomes*

The World Health Organization's International Classification of Functioning, Disability, and Health (ICF) [25] will be used to establish the criteria for health-related outcomes relating to body functions and structures, activities, participation, and environmental factors. Reported perceptions about the quality of PA interventions (ie, implementation and adherence), as well as the barriers, facilitators, and environmental factors (eg, setting and accessibility) related to intervention delivery, will be included as well.

## Screening

Electronic search results will be downloaded into EndNote X9 [26] and Covidence [27] software. EndNote is a management software that will facilitate backup reference information for each one of the identified studies. Covidence is a web-based software platform that streamlines the production of systematic/scoping reviews and will assist with the removal of duplicates and the screening process. Two of the authors (EQ and CA) will independently screen all titles and abstracts for eligibility according to the inclusion/exclusion criteria. To support the iterative process suggested by Levac et al [21], the reviewers will meet at the beginning, midpoint, and final stages of the abstract review process. Discrepancies will be resolved by mutual discussion with a third senior author (AC). For studies with insufficient information in the title and abstract, the full text will be retrieved to make a decision. A full-text review will be carried out for studies marked for possible inclusion. During full-text review, if both EQ and CA determine a study does not meet the criteria, it will be excluded. Any disagreements at this stage will be resolved through discussions with AC. The reasons for excluding a full-text study will be documented.

## Data Extraction

A Microsoft Excel data extraction form developed by the authors will be used to extract data about the PA intervention characteristics, health-related outcomes, and measurement tools, as well as any relevant information about sex- and gender-based considerations. Data about the intervention characteristics will be categorized according to the 16 items of the Consensus on Exercise Reporting Template (CERT) checklist [28] and the 12 items of the Template for Intervention Description and Replication (TIDieR) checklist [29]. This information will include characteristics such as the type of equipment used, whether the intervention was individual- or group-based, a description of progressions, home-based components, nonexercise components, adverse events, and setting. Additional information about the authors and study design, as well as participants' gender, age, ethnicity, injury severity, key conclusions, and any digital/online components, will be recorded. Two authors (EQ and CA) will independently extract data from the first 5 to 10 included studies using the charting form and will meet with the senior author (AC) to determine if the approach is consistent with the research question.

## Data Analysis

Descriptive data on intervention characteristics, health-related outcomes, evaluation tools, and sex- and gender-based considerations will be extracted for a summary analysis and organized according to the respective ICF domains. Similarly, qualitative data on intervention experiences, evaluations, and barriers and facilitators to PA participation will be extracted for a qualitative summary analysis. Intervention characteristics about feasibility and acceptability will also be extracted to provide a synthesis (ie, summary matrix) of best practices for the use of PA in the community after moderate to severe TBI with regard to frequency, intensity, time, and type of PA according to sex and/or gender. Where possible, explicit details of any subgroup considerations based on PA types, contexts, time points, and participant demographics (ie, age, sex/gender,

ethnicity, and injury severity) will be included. The findings about the characteristics of community-based PA interventions that improve health-related outcomes for individuals with moderate to severe TBI, as well as respective evidence-based recommendations, will be presented in relation to future research and practice.

## Results

Progress to date includes searches that were conducted on January 10, 2019, and updated on November 22, 2019, and October 23, 2020. Search strategies included the use of text words and subject headings (eg, Medical Subject Headings [MeSH], Emtree) related to TBI, exercise, and community settings. The search strategy was first developed in MEDLINE and subsequently translated to other databases. As of November 2020, abstract screening was completed and the extracted data were analyzed.

## Discussion

### Principal Findings

The aim of this review is to map and synthesize the evidence about community-based PA interventions for adults with moderate to severe TBI, their respective health-related outcomes, and any sex- and gender-based considerations. The results of this review are expected to inform a practical summary matrix of common types of PA interventions (eg, fitness, leisure-time PA, sport) and their health-related outcomes, as well as the feasibility of running them in the community under the current circumstances with COVID-19 and the necessity for digital/online components that respect physical distancing guidelines. In addition, given the relatively new and emerging understanding about the effect of sex and gender on recovery from TBI, the study will provide a novel review of sex- and gender-based considerations for PA after TBI. The findings from this review are expected to be published and disseminated through academic journals and conferences. It is anticipated that the findings will be relevant and useful for researchers and community organizations for the development, implementation,

and evaluation of PA interventions that are designed to assist with the management of TBI-related sequelae in the community.

### Limitations

The main limitation of this review is related to publication bias, as it will exclude gray literature, such as theses/dissertations, conference proceedings, policies, reports, protocols, and book reviews. Thus, it is possible that omitting gray literature may affect the results of this review. A second limitation is related to the potentially wide range of PA intervention types and reported health-related outcomes leading to heterogeneity of studies to summarize. However, this review will still maintain an accurate and qualitative summary of the use of PA to improve health-related outcomes after moderate to severe TBI. Finally, only English- and French-language studies will be considered because of the language proficiency of the research team, so relevant data published in other languages may not be included.

### Comparisons with Prior Work

Consultation with stakeholders may provide opportunities for further insight and enhance knowledge transfer [30]. Therefore, in order to further disseminate the practical use of these findings, and as part of a larger grant that supports the exploration, development, and evaluation of a community-based PA program for adults with TBI, a consultation will be carried out with a multidisciplinary team of researchers and community organization representatives from both the fitness industry and the TBI community. The purpose of the consultation will be to share the summary of results from the review to generate future directions associated with the project and specific opportunities for knowledge transfer with experts in the field.

### Conclusion

This scoping review will generate new knowledge from published and publicly available literature. Research ethics board approval is therefore unnecessary. Dissemination of the results will include activities related to knowledge transfer for community-based PA after moderate to severe TBI for future research and practice. For example, evidence-based recommendations, future directions, potential limitations, and the possible need for conducting a systematic review will be discussed.

## Acknowledgments

We would like to acknowledge the support of Jessica Babineau, Information Specialist with the UHN Library and Information Services at Toronto Rehab's University Centre.

This work is indirectly supported by a Social Sciences and Humanities Research Council (SSHRC) Insight Grant #504363, which also provides salary support to the lead author, EQ.

This research was undertaken, in part, thanks to funding from the Canada Research Chairs Program.

## Authors' Contributions

All authors were involved in the design of the protocol, review of the manuscript, approval of the final product, and all steps of the review. More specifically, EQ, BS, CA, and AC contributed to the planning, conduct, and reporting of this scoping review. EQ drafted this manuscript. BS and AC were involved with revisions. In addition, EQ, BS, CA, and AC approved the final version and are accountable for all aspects of the work.

## Conflicts of Interest

None declared.

### Multimedia Appendix 1

PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. [[DOCX File , 24 KB - resprot\\_v10i1e24689\\_app1.docx](#)]

### Multimedia Appendix 2

Search strategy.

[[DOCX File , 19 KB - resprot\\_v10i1e24689\\_app2.docx](#)]

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## Abbreviations

**CERT:** Consensus on Exercise Reporting Template

**ICF:** International Classification of Functioning, Disability, and Health

**MeSH:** Medical Subject Headings

**PA:** physical activity

**PRISMA-ScR:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

**TBI:** traumatic brain injury

**TIDieR:** Template for Intervention Description and Replication

**UHN:** University Health Network

*Edited by G Eysenbach; submitted 01.10.20; peer-reviewed by A Samuel, R Lystad; comments to author 13.11.20; revised version received 25.11.20; accepted 01.12.20; published 13.01.21.*

*Please cite as:*

Quilico E, Swaine B, Alarie C, Colantonio A

*Community-Based Physical Activity Interventions for Individuals with Moderate to Severe Traumatic Brain Injury: Scoping Review Protocol*

*JMIR Res Protoc* 2021;10(1):e24689

URL: <http://www.researchprotocols.org/2021/1/e24689/>

doi: [10.2196/24689](https://doi.org/10.2196/24689)

PMID: [33439145](https://pubmed.ncbi.nlm.nih.gov/33439145/)

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Viewpoint

# Research Priorities to End the Adolescent HIV Epidemic in the United States: Viewpoint

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## Abstract

Youth represent 21% of new HIV diagnoses in the United States. Gay, bisexual, and transgender (GBT) youth, particularly those from communities of color, and youth who are homeless, incarcerated, in institutional settings, or engaging in transactional sex are most greatly impacted. Compared with adults, youth have lower levels of HIV serostatus awareness, uptake of antiretroviral therapy (ART), and adherence. Widespread availability of ART has revolutionized prevention and treatment for both youth at high risk for HIV acquisition and youth living with HIV, increasing the need to integrate behavioral interventions with biomedical strategies. The investigators of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) completed a research prioritization process in 2019, focusing on research gaps to be addressed to effectively control HIV spread among American youth. The investigators prioritized research in the following areas: (1) innovative interventions for youth to increase screening, uptake, engagement, and retention in HIV prevention (eg, pre-exposure prophylaxis) and treatment services; (2) structural changes in health systems to facilitate routine delivery of HIV services; (3) biomedical strategies to increase ART impact, prevent HIV transmission, and cure HIV; (4) mobile technologies to reduce implementation costs and increase acceptability of HIV interventions; and (5) data-informed policies to reduce HIV-related disparities and increase support and services for GBT youth and youth living with HIV. ATN's research priorities provide a roadmap for addressing the HIV epidemic among youth. To reach this goal, researchers, policy makers, and health care providers must work together to develop, test, and disseminate novel biobehavioral interventions for youth.

(*JMIR Res Protoc* 2021;10(1):e22279) doi:[10.2196/22279](https://doi.org/10.2196/22279)

**KEYWORDS**

HIV/AIDS; adolescents

## Introduction

### The HIV Epidemic in the United States

HIV infections among adolescents and young adults aged 13 to 24 years have more than doubled in the last 15 years, and these individuals represented 21% of the epidemic population (approximately 7100 infected youth) in the United States in 2018 [1-3]. Gay, bisexual, and transgender (GBT) youth represented up to 70% of new infections among youth in 2017. Among GBT youth, 37% were Black youth and 29% were Hispanic/Latino youth in terms of race/ethnicity, whereas 28% were White youth [3]. HIV also disproportionately impacts other marginalized youth, including those who are homeless, those who are incarcerated, those placed in foster care or other types of institutions, and those who engage in transactional sex [4-18]. Furthermore, there are geographic disparities in new HIV diagnoses. As reflected in the Ending the HIV Epidemic Initiative, southern states accounted for 52% of new HIV diagnoses in 2017 [19]. To stop HIV among adolescents, it is essential to routinely engage youth at the highest risk for HIV in prevention strategies and to achieve and sustain viral suppression in all youth living with HIV.

### HIV Prevention and Treatment Continua

There are sequenced steps, referred to as the HIV treatment continuum and the HIV prevention continuum, that provide a metric for monitoring success toward ending the HIV epidemic. The first step in the HIV treatment continuum is to identify youth living with undiagnosed HIV infection. To achieve this, youth at high risk for HIV acquisition need to be tested for HIV every 3 months. However, 60% of youth living with HIV remain undiagnosed, and this is the highest rate in any age group [2]. Once diagnosed, the next steps are to ensure that youth living with HIV are linked to care, receive antiretroviral therapy (ART), and are regularly monitored so they can achieve viral suppression. ART, which is more effective and easier to take than before, improves quality of life and reduces early mortality. Furthermore, when youth achieve viral suppression, the risk of HIV transmission is reduced [9,10]. Impressively, about two-thirds (68%) of youth living with HIV are linked to care within 1 month of their diagnosis [13]. Among youth in care, 98% were prescribed antiretroviral therapy and 89% achieved viral suppression at 1 year [13]. However, less than half (34%-44%) of youth living with HIV are retained in HIV care for a year or more, and viral suppression among youth living with HIV is only about 16% at 5 years after diagnosis (compared with 58% among adults) [14,15], indicating that linkage to care is insufficient to achieve and sustain viral suppression [20].

Similar to the HIV treatment continuum, the HIV prevention continuum involves several key steps [21]. These include (1) access to health care; (2) regular HIV testing for youth at high

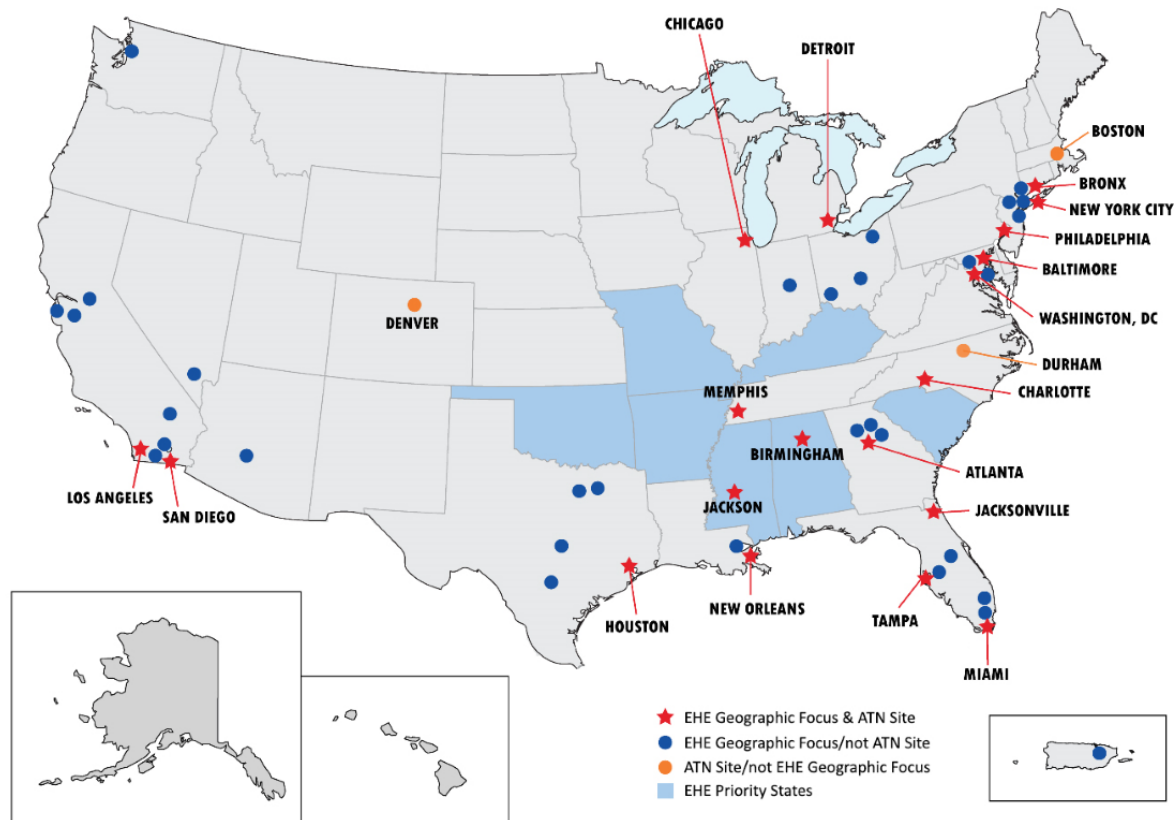
risk, especially among GBT youth; (3) adoption of prevention strategies, such as condom use, pre-exposure prophylaxis (PrEP), and postexposure prophylaxis (PEP) for one time acute exposure; and (4) retention and adherence to these prevention strategies over time. Many youth, especially GBT youth, have limited access to health care. Approximately one in three GBT youth between 12 and 17 years of age do not receive preventive care, and one in three do not seek or receive care within a year of symptom onset for a health problem [16,18,22]. Youth who need PrEP are those least aware of and least likely to use PrEP [17,18]. Despite the demonstration of PrEP acceptability among GBT youth [23], PrEP utilization estimated from 2017 national data was only 9.4% among young men who have sex with men (MSM) compared with 19.9% among all MSM [24]. Although the proportion of health care providers prescribing PrEP in the United States has risen to 24%, differences in PrEP use between racial/ethnic groups remain, with a use percentage of 26% among eligible Black MSM versus 42% among White MSM [25]. Moreover, once initiated, PrEP adherence has been found to be suboptimal among young MSM, even when paired with tailored behavioral interventions [23,26].

In light of the suboptimal utilization of the treatment and prevention continua, the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) identified research gaps and defined five priority areas to guide its research agenda. The ATN is the only domestic research network (established in 2001) focused on youth at high risk for HIV and youth living with HIV (age 12-24 years). In this paper, we outline ATN's research agenda for reducing new HIV infections among youth in the United States.

## Overview of the ATN

The ATN is a collaborative National Institutes of Health (NIH)-supported research network with the goal of reducing the number of HIV infections among youth by (1) increasing the number of youth who know their HIV status; (2) developing, testing, and scaling up sustained use of biobehavioral approaches (condoms, PrEP, and PEP) among youth at high risk for HIV; and (3) increasing the number of youth living with HIV who achieve and sustain viral suppression. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development provides the primary financial support for this network; additional resources are provided by the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute on Minority Health and Health Disparities. As shown in Figure 1, ATN sites are located in heavily impacted areas, many of which were identified in the Ending the HIV Epidemic: A Plan for America (EHE) initiative [27]. These sites reflect the concentration and the distribution of youth living with HIV nationally.



**Figure 1.** Map of Adolescent Medicine Trials Network for HIV/AIDS Interventions study sites and Ending the HIV Epidemic geographic areas.

First established in 2001, the ATN is in its fourth project period. Currently, the ATN is comprised of three thematically focused peer-reviewed Research Program Grants (U19) (Scale It Up, CARES, and iTech), a Coordinating Center (U24), a number of independent and cross-network research protocols managed by the U24, a Diversity Scholars Program, and several cross-network working groups. The ATN facilitates the sharing of ideas, data, scientific expertise, and specialized resources, such as equipment, services, and clinical facilities. Although all ATN protocols address one or more steps in the HIV treatment and/or prevention continua, they are addressed through the thematic lens of their managing U19. Thus, research projects are complementary and act synergistically to achieve the network's goals (a list of currently funded ATN projects can be found on the ATN website) [28]. A brief summary of each U19 is provided below.

ATN Scale It Up includes six studies specifically focused on implementation science and the process of improving self-management among youth [29]. This multisite U19 identifies and builds on efficacious and effective interventions to improve self-management among youth at high risk for HIV infection and youth living with HIV. One of its goals is to develop, test, and disseminate new methods for implementation and analysis with strong theoretical foundations, such as tailored motivational interviewing to help adolescent medicine providers advance the movement of their patients across the treatment and care continua. To attain this goal across all the interventions being tested in Scale It Up, researchers are assessing how youth self-management varies over time, is improved by interventions, and mediates intervention effects.

CARES is focused on identifying and leveraging novel community-based settings to act as gateways where youth at high risk and youth living with HIV can be engaged in HIV prevention and treatment [30]. Youth recruited into one of CARES' three studies complete a behavioral assessment and are tested for sexually transmitted infections (STIs) every 4 months. Both seronegative youth and youth living with HIV enrolled in the studies receive a stepped care model of increasingly intensive interventions, which include text messaging and mobile self-assessment, peer support through social media groups, and interpersonal coaching. This stepped care model has been successfully used with other chronic diseases [31-33], and CARES is evaluating the model's efficacy for HIV prevention and treatment.

iTech aims to lower the burden of HIV infection by developing and evaluating innovative interdisciplinary research on technology-based interventions across the HIV prevention and care continua for youth at high risk or youth living with HIV [34]. Each of iTech's 11 research projects includes the use of technological innovations (eg, apps/mobile websites, videoconferencing/telehealth, and home-based HIV/STI testing) to advance the field. The iTech objectives are discussed in more detail under the Technology section below.

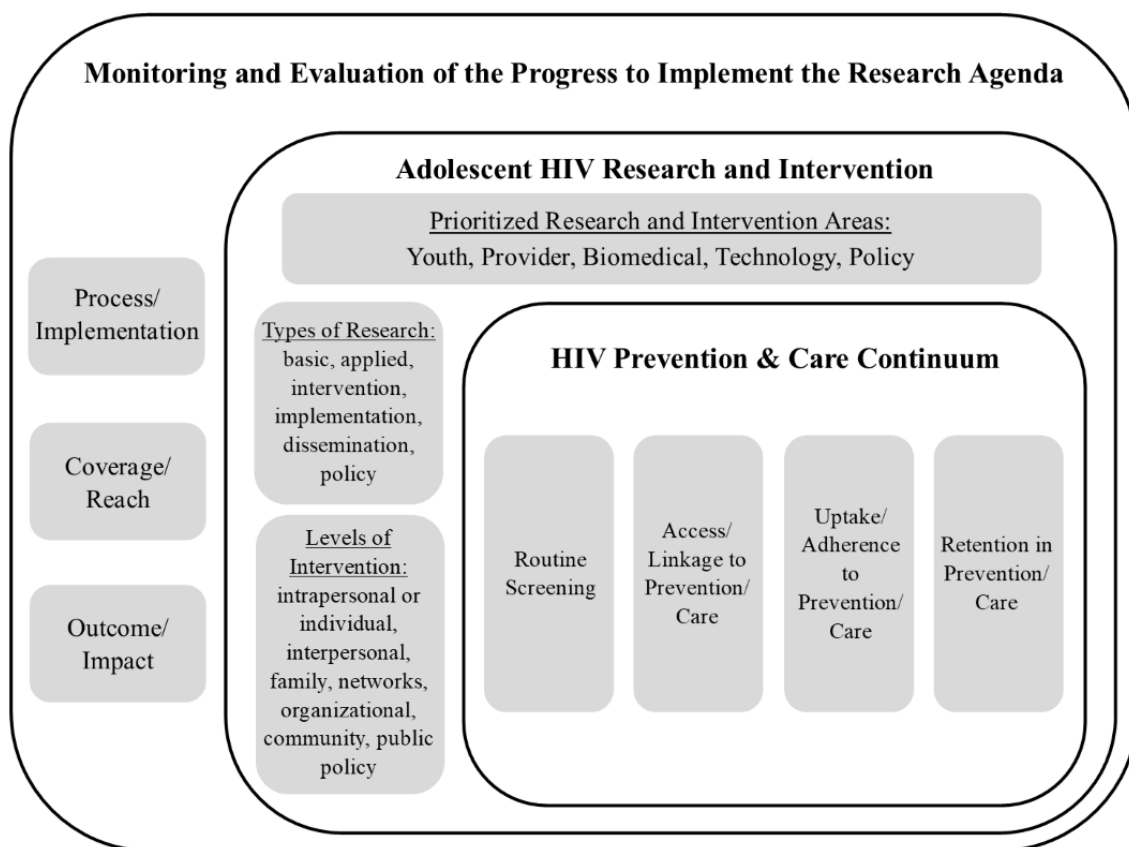
The Coordinating Center provides support, coordination, and operational infrastructure to the three ATN research programs and provides expertise in project management, data management, and statistics to the ATN [35]. The Coordinating Center manages multiple network studies, collaborating with principal investigators and project sites at health care organizations and universities around the country.

## Development of the ATN Research Priorities

The Executive Committee (EC), the leadership and governing body of the ATN, is comprised of representatives from each U19, the Coordinating Center, participating National Institutes of Health, selected scientific experts, and community youth representatives. The EC identifies emergent scientific priorities, defines the research agenda, and fosters collaboration with other HIV research networks and investigators. To begin the research prioritization process, the EC held a series of conference calls, workshops, presentations, and meetings. Furthermore, the EC

surveyed ATN investigators and consulted with scientific experts outside of the EC to identify the key research issues, priorities, and knowledge gaps regarding the adolescent HIV/AIDS epidemic in the country. The EC completed the research prioritization process in 2019 and identified the following five priority research areas: (1) innovative strategies to engage youth in HIV treatment and prevention, (2) health systems and provider interventions, (3) biomedical interventions, (4) technology, and (5) data-informed policies. A nested model (Figure 2) was also created to illustrate the complex set of factors that need to be considered in attempting to implement and evaluate the newly developed research plan.

**Figure 2.** A nested model of the research needed to defeat the rising HIV epidemic among adolescents and young adults in the United States. This model includes the primary targeted outcomes to achieve reductions in HIV among youth at high risk and viral suppression among youth living with HIV.



At the core of the nested model lies the continua of care elements for both HIV prevention and HIV treatment, since these are the focal points for ATN’s research and intervention work. At the next level are our prioritized research areas that could be applied to all of the factors within the continua of care. Also included in this level are descriptions of the various types of research that could be conducted in order to explore prioritized research areas (ie, basic, applied, intervention, implementation, dissemination, and policy) and the levels at which ATN’s research and interventions could be focused (ie, intrapersonal or individual, interpersonal, family, networks, organizational, community, and public policy).

The outermost level demonstrates the need to continually monitor and evaluate the research agenda to assess its utility and to offer insights for needed adjustments. We suggest that such monitoring and evaluation should occur at three different levels in order to ensure maximum benefit to adolescents, including process/implementation, coverage/reach, and outcome/impact.

Three principles emerged that guided our thinking as we developed the research priorities. First, the recognition that segmenting by serostatus was no longer salient since the approaches (eg, sustained health care engagement and ART

adherence for PrEP or treatment as prevention) needed to promote movement along the HIV treatment continuum for youth living with HIV and the HIV prevention continuum for youth at risk are similar. Second, at each step on these continua, youth often confront multiple barriers to care that may stem from personal and interpersonal issues, societal/community norms, structural factors, and challenges with the health care system. Furthermore, the salience of these barriers varies by geography, context, and sociocultural contexts. Third, there are concurrent developmental processes unfolding during adolescence. Youth are most likely to first initiate risky behaviors that lead to HIV acquisition or transmission during adolescence, including sexual activity without a condom, and alcohol and drug use [36-38]. Adolescence is also the period of onset of many lifelong mental health challenges, particularly among sexual, gender, racial, and ethnic minority youth [39]. These developmental trajectories offer opportunities for interventions, such as comprehensive sex and substance abuse prevention, and age-appropriate and culturally sensitive HIV-prevention programs [40]. The developmental processes are more complicated for GBT youth, who face additional challenges stemming from their marginalized and stigmatized sexual orientation [41-44]. For instance, unlike their heterosexual peers, GBT youth must decide who, when, how, where, and what to disclose regarding their sexual orientation and/or their HIV status [45,46].

## ATN's Priority Research Areas

### Overview

In this section, we describe each research priority area and highlight some of ATN's efforts to address them. It is important to note that the ATN regularly reviews these research priorities to ensure that they continue to be responsive to scientific advances, changes in the epidemic of HIV, and emerging needs in the youth we serve.

### Innovative Strategies to Engage Youth in HIV Treatment and Prevention

Engaging youth in interventions to increase their uptake, adherence, and retention with HIV treatment and prevention services poses great challenges but remains a critical research priority. It has long been known that community agencies and venues where youth congregate are fruitful settings for engaging youth [47,48]. Providing safe and affirming spaces where youth can receive culturally congruent support and services can promote engagement of HIV prevention and treatment services [49]. The importance of using text messages and social media platforms and apps for engaging and retaining youth is increasing [50-54]. Recent community mobilization programs, focused on addressing structural-level factors to improve HIV testing and prevention, yielded mixed results [55-57].

Leveraging and expanding this knowledge, ATN investigators have launched innovative studies that are examining social media-based strategies for engaging, recruiting, and retaining youth in research studies and testing technology-based interventions. For example, one current ATN project focuses on helping youth living with HIV secure jobs through vocational

training to overcome socioeconomic barriers to health care [58]. ATN studies are focusing on how to more effectively reach youth with adaptations or novel delivery strategies of evidence-based interventions that are lower cost, more attractive, and more accessible, while having a greater impact on decreasing HIV transmission and acquisition, and increasing engagement and adherence to therapeutic and preventive interventions.

Implementation science research is one of the most important approaches for optimizing interventions and maximizing their impact on youth at high risk for HIV acquisition and youth living with HIV. The ATN employs innovative methods, such as implementation-effectiveness hybrids, to address effectiveness and implementation along the same timeline [59]. The portfolio of current ATN studies also includes interventions that were designed with dissemination in mind. They can be scaled rapidly, reduce the need to precisely replicate a manualized intervention, and focus on each youth's personal risks, tailoring the work to address the variability that occurs across and between communities [60,61]. The studies also build on evidence-based interventions systematically assembled and disseminated by the Centers for Disease Control and Prevention (CDC), Substance Abuse and Mental Health Services Administration (SAMHSA), and Health Resources and Services Administration (HRSA) to identify the most robust intervention components for wider utilization and scale-up.

### Health Systems and Provider Interventions

Although researchers have identified that adolescents prefer medical care that is local, integrated, quick, confidential, nonprejudicial, hassle-free, and inexpensive [62,63], this type of care is yet to become widely available. Lesbian, gay, bisexual, transgender, and queer (LGBTQ) youth face particular challenges in accessing and receiving culturally affirming health care services, as health care providers and others with whom youth interact in care settings may hold stigmatizing views of LGBTQ youth [64-66]. Such forms of stigma perpetuated by health care providers and others in clinical settings have been shown to be barriers to seeking health care, especially among transgender young people [67-69]. These challenges may be exacerbated for LGBTQ youth of color, as racism is a form of intersectional stigma that negatively impacts access to health care, especially for Black LGBTQ youth [65,70,71]. Clinical providers can play a pivotal role in promoting change within their organization, reducing stigma, and increasing youths' engagement and progression through the HIV prevention and care continua. Health system and provider interventions can promote changes in practice as well as in care settings. For example, training medical, clerical, and administrative staff to be culturally responsive to GBT youth clients successfully transformed policies and protocols of a set of health care agencies [72]. Providing feedback on the perceived quality of a clinic's care and services can also improve the quality of care and the services provided. For example, a current ATN project in iTech sends "mystery shoppers," adolescent consumer advocates, to visit existing HIV testing sites to evaluate their HIV counseling and testing services according to a number of youth-focused dimensions. Testing sites receive informational reports that they can use to improve service delivery [73].

Despite the efficacy of PrEP and PEP in reducing HIV acquisition, some providers are reticent to prescribe these medications to youth because they are concerned about risk compensation (ie, adjusting one's behavior according to the perceived level of risk), nonadherence, and ART toxicities [74,75]. Other providers have expressed concerns regarding prescribing PrEP and ART to substance users [76]. Clearly, provider-based interventions to promote PrEP and PEP are needed. Although several approaches for scaling up PrEP and PEP in youth have been developed [77,78], they are yet to be widely disseminated and some are yet to be rigorously evaluated. For instance, public health jurisdictions, such as the New York City Health Department, are using academic detailing, a strategy typically used by pharmaceutical companies that engages providers in their work setting, to efficiently educate providers about PrEP [79,80]. Interventions to help providers to deliver culturally affirming care to GBT youth are also needed. Although there are many text and web resources to promote the use of PrEP among primary care providers, the efficacy of these programs to improve practice and services for youth has not been fully evaluated [81–83]. TMI, one of the studies in Scale it Up, addresses this need.

### Biomedical Interventions

PrEP, PEP, and treatment as prevention have become important biomedical interventions that can either protect youth from becoming infected or ensure longer life and higher quality of life for youth living with HIV [9,84,85]. The first trials of PrEP (tenofovir plus emtricitabine) in 15- to 21-year-old youth at high risk for HIV infection, conducted by the ATN, demonstrated that PrEP offered high levels of protection for youth who were adherent and did not identify safety concerns [26,86,87]. Concerns related to long-term adherence to daily oral therapy has led researchers to examine the efficacy of long-acting antiretroviral agents, particularly injectable formulations of ART, which are currently being evaluated in phase III studies with adults, and broadly neutralizing antibodies, which are currently in phase IIb testing [88–90]. To help ensure that these novel formulations are approved for youth, the ATN is collaborating with the HIV Prevention Trials Network (HPTN) to examine the acceptability, tolerability, and adherence to injectable cabotegravir in youth. Because of its experience navigating the ethical, legal, and regulatory issues associated with the participation of youth in trials of biomedical interventions, the ATN has and will continue to play a pivotal role in advancing biomedical prevention efforts for youth [91,92].

HIV vaccine research and the development of immune-based and topical microbicide-based therapies are other promising biomedical interventions [93–97]. Basic and clinical scientists have made major developments in knowledge about HIV reservoirs and interventions for an HIV cure, although attempts to achieve a cure have been unsuccessful to date [98,99]. One of the studies in the CARES U19 focuses on treatment of acutely infected youth, comparing their viral reservoirs over time to those of youth with established infections who were treatment naive. This project will provide important data on developmentally linked immunological processes associated with early and sustained viral suppression. Additionally, there

has been an improved understanding of the role of the mucosal microbiome, semen exposure, and STIs in the risk of HIV acquisition and transmission [100]. The most futuristic approaches are studies of gene editing, which look to either eliminate the *CCR5* gene or mutate the HIV virus successively so that it is no longer robust and easily transferable [101]. When these interventions are ready for testing, the ATN is well positioned to initiate trials of these biomedical studies in collaboration with researchers conducting trials with adults.

### Technology

Technology use is ubiquitous among adolescents; thus, its power and reach can be harnessed for interventions targeting each stage of the prevention and care continua. Technology offers unique opportunities to recruit, engage, and retain adolescents in research through provision of tailored messages, inclusion of game-based elements, and delivery of personalized theory-based intervention components and health content [102]. Given that more than 96% of youth aged 18 to 29 years in the United States have smartphones and regularly use the internet for a variety of activities, interventions delivered through the internet and mobile phones are highly acceptable to youth [103,104]. Although the costs for initial start-up and development of technology-based interventions are high, once developed, the associated costs of adaptation and dissemination are more moderate. It is not surprising that the number of researchers developing and testing internet- and app-based HIV interventions is rapidly increasing. Unfortunately, these efforts are not well coordinated, and there is a proliferation of similar apps or websites that fail to make novel contributions or address unanswered questions [105,106].

Each ATN U19 program (iTech, CARES, and Scale it Up) is developing and evaluating innovative technology-based interventions across the HIV prevention and care continua. iTech focuses on the evaluation of technologically oriented and youth-oriented interventions, with each project utilizing mobile technologies, including apps, mobile-optimized websites, and online video counseling. The apps within iTech are tailored to the population addressed (eg, seronegative youth and youth living with HIV), the targeted health outcome (eg, PrEP uptake or adherence, engagement with health care, and viral suppression), and the technology platform utilized. iTech will foster the identification of the specific features across apps that are most used and most useful for specific populations. Using a harmonized set of technology-focused metrics and paradata for evaluation and cost-effectiveness analyses, iTech represents a coordinated effort that will allow for more impactful technology-based interventions. For example, one of its projects is a three-arm, randomized, controlled trial that is testing the efficacy of P3 (Prepared, Protected, emPowered), a novel, theory-based mobile app to promote PrEP adherence through social networking and gamification. This app utilizes game mechanics (rewards and unlocking app features) and social networking/peer support to also improve retention in PrEP clinical care and PrEP persistence among GBT youth [107].

In contrast, CARES adopted low-cost, scalable, device-agnostic platforms that are utilized across all subpopulations and outcomes, with a focus on personalizing risk messages within



platforms. Personalized messaging will be the same regardless of the delivery format (text message, phone call, and video chat). CARES interventions combine text messages and peer-support chat rooms with more traditional counseling methods. The CARES approach focuses on messages and probes, which address the following core functions of behavioral change: establish a framework for change, convey necessary information, build self-management skills, address barriers, and provide tools and support. Scale It Up is conducting an effectiveness trial,

called SMART, of an intervention comparing text messaging and cell phone support to improve HIV medication adherence among youth living with HIV. Youth are recruited and enrolled online, using social media and app-based approaches. Across all ATN projects, the opportunity to provide a tailored suite of technology-based tools is a useful and innovative way to engage youth at high risk or youth living with HIV to improve HIV-related prevention and treatment outcomes (Table 1).

**Table 1.** Technology-based tools utilized in ATN studies.

Name of the study	Brief description of technology-based tools	Associated theories	Targeted outcomes	Research program
YouThrive	Web app including peer support via social networking, daily tips for living with HIV, self-monitoring tools, and goal setting/tracking	Information, motivation, and behavioral skills model	Viral suppression	iTech
Get Connected	Web app with content tailored to demographic characteristics, HIV/STI <sup>a</sup> risk behaviors, and sociocultural contexts of individual participants	Integrated behavior model and self-determination theory	Uptake of HIV prevention services, PrEP <sup>b</sup> awareness, and willingness	iTech
LYNX	Mobile app including personalized HIV risk scores, HIV/STI testing, and prevention information	Information, motivation, and behavioral skills model	HIV/STI testing and PrEP uptake	iTech
My Choices	Mobile app including tools for tracking HIV risk, HIV/STI testing, and prevention information	Social cognitive theory	HIV/STI testing and PrEP uptake	iTech
P3	Mobile app utilizing game mechanics and social networking features P3+ includes provision of in-app adherence coaching	Social cognitive theory and Fogg behavioral model	PrEP adherence, retention in PrEP care, and PrEP persistence	iTech
SMART	Comparison of text messaging-based and cell phone-based adherence support	Supportive accountability model	Viral suppression and adherence self-management	Scale It Up
TMI	Automatic feedback reports to providers to improve motivational interviewing competency	Modeling, rehearsal (verbal/behavioral), and feedback strategies	Motivational interviewing competency	Scale It Up
Stepped Care for Youth	Stepped care intervention utilizing text messaging and monitoring, peer support via online social networks, and e-coaching	N/A <sup>c</sup>	Viral suppression	CARES
Engaging Seronegative Youth	Text messaging and monitoring, peer support via online social networks, and e-coaching	N/A	HIV/STI testing, PrEP uptake, and adherence	CARES
Triggered Escalating Real-time Adherence (TERA)	Electronic dose monitoring, adherence monitoring via text messaging, and e-coaching as needed	Therapeutic drug monitoring	ART adherence and viral suppression	Coordinating Center
ePrEP	Mobile app-based home care system for PrEP prescription and care	Anderson behavioral model adapted to HIV care	PrEP adherence, retention in PrEP care, and PrEP persistence	iTech
TechStep	Stepped care intervention utilizing text messaging, a web app, and e-coaching	Information, motivation, and behavioral skills model	PrEP uptake and reduction of HIV risk behaviors	iTech

<sup>a</sup>STI: sexually transmitted infection.

<sup>b</sup>PrEP: pre-exposure prophylaxis.

<sup>c</sup>N/A: not applicable.

## Data-Informed Policies

Actionable policies are optimally derived from and shaped by data. Fortunately, many of the recent state and federal policy

shifts in the United States reflect the belief that youth should be empowered to advocate and take individual responsibility for their health. Some of these shifts include expanding minors' authority to consent to health care, including care related to

sexual activity and STIs, HIV testing and treatment, and the constitutional right to privacy regarding a minor's decision to obtain contraceptives [108].

Most states today have a policy requiring some form of HIV education. Federally funded school-based HIV prevention programs typically do not address issues related to GBT youth and thus are not relevant for these youth [109,110]. For instance, many state-supported abstinence-only programs exclude discussions of same-gender sexuality (eg, State Abstinence Education Grant Program). Furthermore, the efficacy of such programs to reduce STI incidence and HIV prevalence has not been established since the majority of evaluations were not powered to detect changes in biological outcomes. A recent meta-analysis of school-based interventions reported that only one of seven programs reduced STI incidence and none decreased HIV incidence [111]. Thus, rigorous evaluation of multilevel school-based programs is being considered as a future ATN research priority.

Evidence on the relationship between school climate and hate crimes should be used to inform and create policies to monitor the increase and levy consequences for discriminatory acts against marginalized groups such as GBT youth. Similarly, policies to create safe spaces for GBT youth and monitor the success of engaging GBT youth and other youth at high risk for HIV acquisition should also be enacted [112]. There is evidence that in jurisdictions with more affirming LGBTQ school climates, these youth reported fewer days of episodic drinking and fewer drinking days at school [113]. The ATN is gathering and disseminating data to policy makers, public health officials, and other officials to make informed decisions and implement efficacious HIV prevention and treatment models for US youth. The Community-Engaged Dissemination and Implementation Research (CEDI) Workgroup is working in collaboration with ATN members to translate their evidence-based research findings for dissemination and implementation in clinic and community settings, and to inform policy and advocacy for delivery of care. Another example is the work being conducted by the ATN Modeling Core, which is developing a detailed health policy mathematical model to monitor and evaluate HIV in adolescents and young adults. The Modeling Core is using a novel approach to microsimulation modeling of HIV disease progression, patterns of care, and treatment outcomes, and applying innovative statistical methods to populate the model with data about patterns of health care, HIV viral load trajectories, and ART derived from completed ATN studies and

other national studies. This model will be used to evaluate the potential clinical and economic impacts of ATN intervention trials to support medication adherence, retention in care, and improved clinical outcomes for youth living with HIV and inform decision makers [114,115].

### Responsiveness to Emerging Needs

While the current ATN agenda focuses on community and provider interventions that are acceptable to youth and scalable at the national level, the network's structure is nimble enough to allow for additional high-priority studies generated internally within the network and/or in collaboration with other networks, agencies, and outside investigators. The EHE identified several focus and geographical areas where ATN investigators and research programs can contribute [27]. Taking the EHE focus areas into consideration, the network solicited research studies in 2019 that included a focus on (1) conducting assessments that use an implementation science framework, (2) expanding ongoing efforts in EHE geographic areas to reach underserved youth, or (3) building connections with health departments and other community-based partners in EHE geographic areas.

New projects resulting from this allow the network to increase its youth research portfolio in focused EHE geographic areas where ATN is currently not represented and to contribute to efforts to end the HIV epidemic. The ATN will continue to regularly review its priorities and launch new studies in response to changing needs, scientific advances, and epidemiological shifts in HIV incidence.

### Conclusions

This paper describes the top five research priority areas guiding ATN's efforts to address the domestic HIV epidemic in youth. Monitoring implementation and progress from current ATN projects requires ongoing monitoring of the indicators of coverage and outcomes as youth progress through the HIV prevention and care continua, and targeting efforts in areas most heavily impacted such as EHE hotspots. Addressing the research agenda and key priority areas for youth at high risk for HIV infection and youth living with HIV also necessitates ongoing collaborations between academic research institutions, health care providers, community-based organizations, impacted communities, and youth in the United States, as well as scientific leadership and expertise on state-of-the-art HIV prevention and care research for adolescents through the ATN.

### Acknowledgments

This report was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Institute on Minority Health and Health Disparities, and the Adolescent Medicine Trials Network for HIV/AIDS Interventions Executive Committee. The comments and views of the authors do not necessarily represent the views of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

### Conflicts of Interest

ACS receives support from a Gilead FOCUS grant. The other authors have no conflicts to declare.

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## Abbreviations

**ATN:** Adolescent Medicine Trials Network for HIV/AIDS Interventions

**ART:** antiretroviral therapy

**EC:** Executive Committee

**EHE:** Ending the HIV Epidemic: A Plan for America

**GBT:** gay, bisexual, and transgender

**LGBTQ:** lesbian, gay, bisexual, transgender, and queer

**MSM:** men who have sex with men

**NIH:** National Institutes of Health

**PAW:** Policy and Advocacy Workgroup

**PEP:** postexposure prophylaxis

**PrEP:** pre-exposure prophylaxis

**STI:** sexually transmitted infection

*Edited by G Eysenbach; submitted 07.07.20; peer-reviewed by C Lelutiu-Weinberger, K Madkins; comments to author 20.08.20; revised version received 30.09.20; accepted 30.09.20; published 04.01.21.*

*Please cite as:*

*Fernandez MI, Harper GW, Hightow-Weidman LB, Kapogiannis BG, Mayer KH, Parsons JT, Rotheram-Borus MJ, Seña AC, Sullivan PS*

*Research Priorities to End the Adolescent HIV Epidemic in the United States: Viewpoint*

*JMIR Res Protoc* 2021;10(1):e22279

URL: <https://www.researchprotocols.org/2021/1/e22279>

doi: [10.2196/22279](https://doi.org/10.2196/22279)

PMID: [33393918](https://pubmed.ncbi.nlm.nih.gov/33393918/)

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