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Contents

Protocols

Protocol

Intervention for a Digital, Cognitive, Multi-Domain Alzheimer Risk Velocity Study: Protocol for a Randomized Controlled Trial

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Abstract

Background: In the United States, more than 6 million adults live with Alzheimer disease (AD) that affects 1 out of every 3 older adults. Although there is no cure for AD currently, lifestyle-based interventions aimed at slowing the rate of cognitive decline or delaying the onset of AD have shown promising results. However, most studies primarily focus on older adults (>55 years) and use in-person interventions.

Objective: The aim of this study is to determine the effects of a 2-year digital lifestyle intervention on AD risk among at-risk middle-aged and older adults (45-75 years) compared with a health education control.

Methods: The lifestyle intervention consists of a digitally delivered, personalized health coaching program that directly targets the modifiable risk factors for AD. The primary outcome measure is AD risk as determined by the Australian National University-Alzheimer Disease Risk Index; secondary outcome measures are functional fitness, blood biomarkers (inflammation, glucose, cholesterol, and triglycerides), and cognitive function (Repeatable Battery for the Assessment of Neuropsychological Status and Neurotrack Cognitive Battery). Screening commenced in January 2021 and was completed in June 2021.

Results: Baseline characteristics indicate no difference between the intervention and control groups for AD risk (mean −1.68, SD 7.31; *P*=.90).

Conclusions: The intervention in the Digital, Cognitive, Multi-domain Alzheimer Risk Velocity is uniquely designed to reduce the risk of AD through a web-based health coaching experience that addresses the modifiable lifestyle-based risk factors.

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KEYWORDS

health coaching; Alzheimer risk; digital health; mobile phone

Introduction

Background

Alzheimer disease (AD) is a chronic neurodegenerative disorder characterized by the buildup of neurofibrillary tangles and plaques in the brain and a steady decline in memory and executive function. These cognitive changes eventually lead to physical dependence [1] and ultimately death. Currently, AD is the sixth leading cause of death in the United States, climbing from the 12th position in less than 3 decades [2]; mortality rates of other chronic illnesses such as cardiovascular disease and

stroke have continued to decrease during this same time frame [3]. Although AD was first identified more than 100 years ago, the advances in disease detection, prevention, and treatment have not been as successful as those in other chronic illnesses. Many cases go undetected for up to 20 years, owing to a long prodromal period, fear of diagnosis, and inability to access proper testing [4].

In addition to being a significant contributor to deaths among US adults, AD is a major burden to the health care system. AD accounts for an estimated US $355 billion in annual direct and indirect health care costs [5]. These costs have been rising dramatically, increasing by 38% in the past year alone [2,5]. As the number of older adults is expected to increase by more than 53% within the next 40 years [6], the number of older adults living with AD will also continue to grow and increase the burden on the health care system, as well as individuals with the disease and their caretakers. So far, pharmacological interventions have been ineffective in generating long-term and sustained improvements in cognitive function [7]. The combination of these circumstances has created a critical need for the development and implementation of effective preventative interventions.

AD is a multifactorial disease that involves several mechanisms that contribute to its development and progression. Nonmodifiable risk factors include advanced age, female sex, and presence of the apolipoprotein E4 (APOE4) allele. Such nonmodifiable risk factors are important to consider when assessing an individual's risk for developing AD, but nothing can be done to address these factors. However, some modifiable risk factors (eg, lipids, glucose, inflammatory factors, and multiple lifestyle behaviors) have been identified as possible contributors to the disease [8,9]. These risk factors represent important targets for interventions to reduce the risk for developing dementia.

Many modifiable risk factors for vascular disease are known to concurrently contribute to the development of AD [10]. These risk factors include overweight and obesity, physical inactivity, stress, chronic inflammation, dietary habits, sleep, and blood glucose and lipid levels [11]. Additional risk factors for AD include low cognitive activity and low social engagement [11].

Intervention Strategies

Single-Domain Lifestyle Interventions

The average age of AD diagnosis is 75.5 (SD 9.7) years [12], but current research suggest that subtle changes in cognitive function can begin 20 years before diagnosis [4,5]. This early stage of the disease represents an important time during which interventions targeted at the modifiable risk factors could be the most effective.

Several studies have investigated single-domain lifestyle interventions to lower the risk of dementia and AD [7,9,13]. Three popular interventions include cognitive training [7], dietary changes [9,14], or physical activity [13]. Evidence suggests that strict adoption of a healthy diet significantly reduces AD risk [9,14]; however, there is less effect if adherence is not strictly followed. Computerized cognitive training has gained popularity, and research supports a moderate improvement in cognition among healthy adults after training [7]. In addition, aerobic exercise is a possible intervention for cognitive decline among healthy adults. Researchers found that an aerobic exercise intervention was not better than the control for any cognitive domain; however, this review only selected adults without cognitive decline and did not address the individual risk of cognitive decline or dementia [13]. Although single-domain interventions are effective, combining these interventions may provide an even greater benefit.

Multi-Domain Lifestyle Interventions

Owing to the limited efficacy of the single-domain interventions, researchers have begun to investigate the use of multi-domain lifestyle interventions that target various factors associated with cognitive decline [15]. One of the largest trials is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial [16]. This 2-year longitudinal intervention targeted older adults with increased risk of developing dementia, as determined by the Cardiovascular Risk Factors, and Aging, and Dementia risk score [10,15]. The lifestyle intervention in the study addressed nutrition, exercise, cognitive training, and vascular risk monitoring. At the end of the 2-year intervention, participants in the intervention group showed 25% improvement in cognitive assessment scores compared with the control participants, with the greatest improvements occurring in processing speed and executive function [10,15].

Although these results are promising, not all multi-domain interventions have resulted in cognitive improvements. For instance, prevention of dementia by intensive vascular care [17] and Multi-domain Alzheimer Preventative Trial [18] did not positively affect cognitive decline. Thus, further research is needed to determine the optimal elements to include in a multi-domain lifestyle intervention and the best population to target to maximize the benefits. As such, the Digital, Cognitive, Multi-domain Alzheimer Risk Velocity (DCMARVel) trial will assess the impact of a digital lifestyle intervention targeting the modifiable risk factors for AD in middle-aged to older adults compared with a health education (HE) control. The personalized intervention involves health coaching (HC) to address the lifestyle areas known to be linked to AD risk, such as diet, exercise, sleep, stress, cognitive training, and social interaction.

Purpose

Of the studies on multi-domain lifestyle interventions for reducing AD risk, few have tested middle-aged individuals and few have implemented digital interventions. Using the intervention program earlier in the disease course can maximize its benefits, and using digital technologies rather than relying on face-to-face implementation can greatly increase the reach and scalability of these programs. Therefore, the purpose of the DCMARVel trial is to determine the effects of a 2-year digital, multi-domain lifestyle intervention on AD risk among at-risk middle-aged to older adults (45-75 years). Moreover, the digital and personalized nature of the intervention provides the opportunity to explore the variables that may contribute to the accessibility and subsequent adherence to an AD risk reduction intervention. This paper outlines the study protocol and baseline characteristics of the study population. The main aims of this

study are as follows: (1) to determine the effect of a 2-year digital, multi-domain AD risk reduction intervention on the overall risk of AD in adults at risk of developing the disease; (2) to determine the effect of digital interventions on the rate of cognitive decline; and (3) to determine the effect of digital interventions on the changes in general health outcomes.

Methods

Study Design and Participants

This is a single-site, 2-year randomized controlled trial (RCT). The participants include men and women aged from 45 to 75 years who have risk factors for dementia. Each participant has been informed of the purpose of the intervention and has agreed to be assigned randomly into 1 of the 2 study groups (HC or HE).

To be included in the study, the participants must have at least 2 positive risk factors for AD as determined by the Australian National University-Alzheimer Disease Risk Index (ANU-ADRI) [11] and not more than 1 protective factor (eg, high level of physical activity). Textbox 1 shows the complete list of the inclusion and exclusion criteria. The participants will complete 4 study visits over 2 years: at baseline and 4, 12, and 24 months.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age: 45-75 years
- BMI: 18.5-39.9 kg/m2
- Fluent in English (written and spoken)
- At least 2 of the following risk factors for Alzheimer disease (AD) from Australian National University-Alzheimer Disease Risk Index (ANU-ADRI):
  - High school education or less
  - Overweight or class I or class II obese (BMI 25-39.9 kg/m2)
  - History of diabetes, hypertension, high cholesterol, smoking, or traumatic brain injury
- At most, 1 of the following protective factors for AD from ANU-ADRI:
  - High level of physical activity (as defined by the high International Physical Activity Questionnaire category)
  - High fish consumption (as defined by consumption of fish or seafood that is not fried, for >5-6 times per week)
  - High level of cognitive engagement (as defined by engaging in at least 6 of the following activities several times a week: reading a book, newspaper, or magazine; playing brain games; playing games; writing letters or emails; participating in web-based social network activities; attending a concert, play, or musical; or visiting a library)
- Ability to send and receive SMS text messages
- Own a smartphone with a reliable internet connection and willing to use email
- Ability to participate in light to moderate physical activity
- Willing to be randomized

Exclusion criteria

- Physician diagnosis of the following:
  - Mental health condition (eg, eating disorder, alcohol and substance use, and schizophrenia)
  - Neurologic conditions (eg, epilepsy, stroke, multiple sclerosis, Parkinson disease, brain tumor, or severe traumatic brain injury)
  - Dementia, probable dementia, or mild cognitive impairment
  - Other significant health condition (eg, congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, renal failure, chronic kidney disease, and pulmonary hypertension)
- Recent cardiovascular event or recent treatment for cancer (within the last year), on dialysis, or on active organ transplant list
- Visual problems that prevent viewing screen at a normal distance (eg, legal blindness, detached retina, and occlusive cataracts)
- History of learning disability
- Currently participating in a formal cognitive training coaching program or other lifestyle change program (eg, diabetes prevention program)
- Currently pregnant or planning to become pregnant in the next 2 years
- Not meeting all the inclusion criteria

During the first visit, after eligibility was confirmed and informed consent was obtained, the participants completed a baseline survey. The survey contained questions about demographics (age, race or ethnicity, and education level), contact information, sleep, stress, anxiety, depression, general well-being, and dementia risk. Then, the participants completed a set of cognitive assessments, including the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [19] and the Neurotrack digital assessments. Next, the participants completed a series of physical evaluations, including the Short Physical Performance Battery, 6-minute walk test (6MWT), dual-task, hand grip, and sit-to-stand lower-body power assessment. Finally, biometric data were collected, including body composition: BMI, body fat using dual-energy x-ray absorptiometry, and resting heart rate; blood pressure; fasting blood glucose; lipid panel—total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides; brain-derived neurotrophic factor; interleukin-6; high-sensitivity C-reactive protein; and APOE status. Reassessment will occur after 4, 12, and 24 months and will include the collection of most but not all of the data collected at baseline (Table 1).

Table 1. Summary of measures collected at each study visit.

Category and measurement	Baseline	4 months	12 months	24 months
Informed consent	Yes[a]	No[b]	No	No
Demographics				
Age (years)	Yes	No	No	No
Race	Yes	No	No	No
Education level	Yes	No	No	No
Marital status	Yes	No	No	No
Resting blood pressure (heart rate)	Yes	Yes	Yes	Yes
Supplement and medication list	Yes	Yes	Yes	Yes
Body composition				
Height and weight; BMI	Yes	Yes	Yes	Yes
Body fat (DXA[c])	Yes	Yes	Yes	Yes
Bloodwork				
Lipids (LDL[d], HDL[e], TC[f], and triglycerides)	Yes	Yes	Yes	Yes
Glucose	Yes	Yes	Yes	Yes
BDNF[g]	Yes	Yes	Yes	Yes
hs-CRP[h]	Yes	Yes	Yes	Yes
IL-6[i]	Yes	Yes	Yes	Yes
ANU-ADRI[j]				
Smoking and drinking habits	Yes	Yes	Yes	Yes
Exercise and dietary patterns	Yes	Yes	Yes	Yes
History of diabetes, depression, high cholesterol, and TBI[k]	Yes	Yes	Yes	Yes
Social engagement and cognitive activity	Yes	Yes	Yes	Yes
Fish intake	Yes	Yes	Yes	Yes
Pesticide exposure	Yes	Yes	Yes	Yes
RBANS[l] (total and subscales)				
Immediate memory	Yes	Yes	Yes	Yes
Delayed memory	Yes	Yes	Yes	Yes
Visuospatial and constructional abilities	Yes	Yes	Yes	Yes
Language	Yes	Yes	Yes	Yes
Attention	Yes	Yes	Yes	Yes
Neurotrack digital assessments				
Image pairs	Yes	Yes	Yes	Yes
Symbol match	Yes	Yes	Yes	Yes
Item price	Yes	Yes	Yes	Yes
Arrow match	Yes	Yes	Yes	Yes
Light reaction	Yes	Yes	Yes	Yes
Path points	Yes	Yes	Yes	Yes
Digital choice anxiety survey	Yes	Yes	Yes	Yes
Functional fitness measures				
SPPB[m]	Yes	Yes	Yes	Yes

Category and measurement	Baseline	4 months	12 months	24 months
6MWT[n]	Yes	Yes	Yes	Yes
Dual-task	Yes	Yes	Yes	Yes
Hand grip	Yes	Yes	Yes	Yes
TENDO sit-to-stand	Yes	Yes	Yes	Yes
Behavioral, quality of life, and health care use questions				
Everyday Cognition (E-Cog-12[o])	Yes	Yes	Yes	Yes
Sleep (PSQI[p])	Yes	Yes	Yes	Yes
Stress (PSS[q])	Yes	Yes	Yes	Yes
Well-being (SF-12[r])	Yes	Yes	Yes	Yes
Loneliness (UCLA[s])	Yes	Yes	Yes	Yes
Depression (PHQ-9[t])	Yes	Yes	Yes	Yes
Anxiety (GAD-7[u])	Yes	Yes	Yes	Yes
Health care use (UCSD[v])	Yes	Yes	Yes	Yes
APOE[w] status	Yes	No	No	No

[a]Will be measured.
[b]Will not be measured.
[c]DXA: dual-energy x-ray absorptiometry.
[d]LDL: low-density lipoprotein.
[e]HDL: high-density lipoprotein.
[f]TC: total cholesterol.
[g]BDNF: brain-derived neurotropic factor.
[h]hs-CRP: high-sensitivity C-reactive protein.
[i]IL-6: interleukin 6.
[j]ANU-ADRI: Australian National University-Alzheimer Disease Risk Index.
[k]TBI: traumatic brain injury.
[l]RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.
[m]SPPB: Short Physical Performance Battery.
[n]6MWT: 6-minute walk test.
[o]E-Cog-12: 12-item Everyday Cognition Scale.
[p]PSQI: Pittsburgh Sleep Quality Index.
[q]PSS: Perceived Stress Scale.
[r]SF-12: 12-Item Short Form Health Survey.
[s]UCLA: University of California, Los Angeles, 3-item Loneliness Scale.
[t]PHQ-9: 9-item Patient Health Questionnaire.
[u]GAD-7: General Anxiety Disorder 7-item scale.
[v]UCSD: University of California at San Diego.
[w]APOE: apolipoprotein E.

Cognitive Testing

RBANS Test Battery

The cognitive function of the participants will be assessed using RBANS [19] at all the 4 time points. Details of this test battery are published elsewhere [19,20]. In brief, memory (immediate and delayed), visuospatial and construction, attention, and language will be tested using a digital (iPad) platform. Reliability (r=.81) and validity (r=.59) of the RBANS test battery were previously demonstrated with global cognition scores when tested with community-dwelling older adults [21].

Neurotrack Test Battery

Neurotrack Technologies has developed a digital battery of cognitive assessments measuring attention, associative learning, memory, inhibition, executive function, and processing speed. The Neurotrack assessments were found to be valid (r=.57), reliable (r=.73), and able to discriminate between older adults who are cognitively normal and cognitively impaired [22,23].

Item Price Test

Associative learning and memory will be assessed using the Item Price test. This assessment will consist of a familiarization phase in which the items (eg, various fruits and vegetables) will be presented along with their associated prices. Immediately after the familiarization phase, the participants will be presented with the items and a corresponding price. The participants will be instructed to select *yes* or *no* depending on whether the item price matches the previously viewed amounts. In total, 60 trials will be presented, including 24 targets (images previously paired), 24 foils (images previously present but not paired), and 12 shams (images not presented). Scores will be reported as the accuracy of identifying the correct item based on its price.

Image Pairs Test

Image pairs is an eye-tracking task that measures visual recognition memory and learning [22,23]. The participants will be presented with 110 images, categorized into 4 phases. Phase 1 will be a familiarization phase consisting of 20 images. During phase 2, the participants will be presented with 2 images—1 novel and 1 previously viewed in phase 1. During this phase, the participants will be instructed to focus their gaze on the novel image. Phase 3 will consist of a learning phase in which the participants will be presented with 2 images and will be asked to remember their association with each other as pairs. Phase 4 will consist of 50 trials with 20 targets from phase 3, 20 foils, and 10 sham trials. During this phase, the participants will be instructed to select *yes* or *no* to identify if the presented images were previously viewed together as a pair. This test will measure the participant's ability to learn and identify image pairs. Scores for phase 2 will be reported as the percentage of time spent on gazing at the novel image, and for phase 4, it will be reported as accuracy.

Symbol Match Test

Symbol match is a processing speed and executive functioning task that uses a paired verification or rejection paradigm (forced choice). The participants will be instructed to determine whether 2 symbols are equal or unequal using a legend with 9 number or symbol pairs. The participants will be allotted 2 minutes to complete as many trials as possible. Scores will be determined by the number of correct trials minus the number of incorrect trials.

Arrow Match Test

Arrow Match test is a measure of attention and processing speed. The participants will be shown 5 arrows in the middle of the screen and will be instructed to identify the direction of the middle arrow. The arrow may point in either the same direction or the opposite direction from the other arrows. The participants will be presented with 32 trials, and the scores will be reported as the number of correct responses relative to the time elapsed during all the trials.

Path Points Test

Executive function will be assessed using the Path Points test. Similar to the paper-pencil Trail Making Test Part B [24], the Path Points test is a digital version in which the participants will be instructed to connect a series of alternating numbers and letters from 1-A to 7-G. Scores will be reported as the duration required to complete the 14 responses. Only correct responses will be considered for scoring.

Light Reaction Test

Reaction time and inhibition will be assessed using the Light Reaction test. The participants will be presented with either a positive (green light) or a negative stimulus (red light). The participants will be instructed to press a button if the positive stimulus appears and to refrain from pressing the button if the negative stimulus appears. The average response time for reacting to the positive stimulus (green light) will be recorded.

Physical Function Assessments

Short Physical Performance Battery consists of 3 assessments: standing balance, usual walk time, and chair stand performance. The standing balance score will be compiled from 3 balance tests: standing with feet together, standing in a semitandem position, and standing in a full tandem position. If the participant could stand with their feet together and in the semitandem position for 10 seconds, 1 point will be given for each condition. If the participant stands for 10 seconds in the full tandem position, 2 points will be given, 1 point for 3-9.99 seconds, and 0 points if they do not hold the position for at least 3 seconds. For the assessment of usual walk time, the participants will be instructed to walk at their usual pace for 4 m. Scores will range from 0 to 4 based on the time to completion [25,26]. The chair stand test will be performed in a standard straight-back chair (seat height=0.43 m). The participants will be instructed to sit with both feet on the floor with arms crossed over their chest. The time to complete 5 chair stands will be recorded, with scores ranging from 0 to 4. Each component (balance, walking time, and chair stand) will be summed to generate a composite score; scores <10 indicate physical dysfunction.

Cardiovascular endurance will be assessed using the 6MWT [27,28]. The 6MWT will be performed in a well-lit hallway with cones separated by 25 m. The participants will be instructed to walk as quickly as possible for 6 minutes. The distance covered within the 6 minutes will be recorded. The 6MWT is a valid and reliable estimate of aerobic fitness [28].

Hand grip strength will be assessed using a Takei hand grip dynamometer (Takei Scientific Instruments Co, Ltd). The participants will be properly fit and instructed to squeeze maximally for at least 3 seconds. Verbal encouragement will be provided. Three trials will be completed on each hand with a 60-second rest between trials. Hand grip strength is positively correlated with overall muscle strength and physical mobility [29-31].

Gait speed will be determined using 2 trials: habitual and fast. For the habitual trial, the participants will be instructed to walk 20 m at their habitual or usual walking speed. Immediately after the habitual speed trial, the participants will be instructed to walk as quickly and as safely as possible without running. Two trials will be completed for both conditions and only the middle 10 m gait speed distance will be recorded and used for all the analyses. Gait speed was previously found to be a valid and reliable measure of physical mobility [32] and cognition [33].

Immediately after the gait speed trials, the participants will be instructed to repeat both habitual and fast trials while completing a serial subtraction cognitive task. The participants will be given a randomly generated 3-digit number ranging from 100 to 999 and will be instructed to begin walking immediately upon receiving their number. The participants will walk the entire distance while subtracting 3 from their assigned number aloud. Both, time to cover the 10 m distance and correct and incorrect numbers will be recorded [34-37].

Lower extremity muscular power will be assessed using a power chair stand [38-40]. The participants will be instructed to sit on a chair of standard height (0.43 m) with both feet flat on the floor and arms crossed over their chest. Power (peak and average) and velocity (peak and average) will be measured using TENDO (Tendo Sport). Five trials will be completed, and the average scores will be used for all analyses.

Surveys

ANU-ADRI Tool

ANU-ADRI is an evidence-based 79-item risk assessment tool designed to predict the risk of future AD development. ANU-ADRI collects information on education, BMI, cholesterol, diabetes, history of traumatic brain injury, depression, physical activity, cognitive engagement, social network, fish intake, alcohol consumption, smoking, and pesticide exposure [11]. This valid and reliable tool will be used as the primary inclusion tool and a primary outcome variable in this study. Details of the ANU-ADRI scoring procedures are published elsewhere [11]. Briefly, scores for each subsection will be tallied and a composite risk score will be used for all the analyses. A change of 2 points in the ANU-ADRI score is considered clinically meaningful [41].

Anxiety

Anxiety will be assessed using the General Anxiety Disorder 7-item scale [42]. It is a valid and reliable measure of anxiety among older adults [43]. Scores range from 0 to 21, with higher scores indicating higher anxiety severity [42].

Loneliness

The University of California, Los Angeles, 3-item Loneliness Scale [44] will be used to determine the degree of loneliness among the study population. Scores range from 3 to 9, with higher scores being associated with greater levels of loneliness. Scores above 5 indicate loneliness.

Health-Related Quality of Life

Health-related quality of life will be measured using the 12-Item Short Form Health Survey, which is a valid and reliable measure of health-related quality of life in many study populations [45]. It is composed of 2 subscales: physical health and mental health. Scores range from 12 to 47, with higher scores indicating higher self-reported quality of life.

Perceived Stress

Perceived stress will be assessed using the Perceived Stress Scale [46]. Scores range from 0 to 40, with lower scores indicating lower perceived stress. Scores ranging from 0 to 13 indicate low stress, 14 to 26 indicate moderate stress, and >26 indicate high stress.

Physical Activity

Physical activity will be assessed using the International Physical Activity Questionnaire, which is the physical activity component of the ANU-ADRI. This survey is a valid and reliable self-report tool for quantifying moderate, vigorous, and sedentary behaviors [47]. The International Physical Activity Questionnaire specifically asks about the participant's physical activity performed within the previous 7 days.

Health Care Use

The health care use form of the University of California at San Diego will be used to quantify how frequently the participants have visited their physician or used any form of health care within the previous 3 months. Higher values indicate more health care use during the time frame [48].

Sleep

Sleep quality will be assessed using the Pittsburgh Sleep Quality Index. This 9-item assessment produces a score ranging from 0 to 27, with higher scores indicating poorer sleep. Individuals scoring ≥5 are deemed poor sleepers [49,50].

Depression

Depression will be assessed using 2 surveys. The Patient Health Questionnaire is a 9-item questionnaire with scores ranging from 0 to 27. Higher scores indicate higher levels of depression [51]. The Center for Epidemiological Studies-Depression is a 20-item depression scale. Higher values indicate higher levels of depression, with a score ≥16 indicating individuals at risk for clinical depression. The Center for Epidemiological Studies-Depression is a part of the ANU-ADRI [11].

Everyday Cognition

The 12-item Everyday Cognition scale is a brief questionnaire designed to detect cognitive and functional decline. This scale has been shown to correlate with functional measures and neuropsychological scores in people with normal cognitive function, mild cognitive impairment (MCI), and AD [52].

Blood Biomarkers

Blood sample will be collected at each of the 4 study visits. High-sensitivity C-reactive protein, interleukin-6, and brain-derived neurotrophic factor will be analyzed by a third-party laboratory. Cholesterol (total, HDL, and LDL), triglycerides, and blood glucose levels will be analyzed in whole blood using a Cholestech LDX system (Abbott Laboratories). Whole blood will be collected in a 40 µL capillary tube, immediately transferred into a Cholestech cartridge, and analyzed. Cholestech LDX values are valid and reliable for the assessment of triglycerides, LDL, HDL, and total cholesterol [53]. APOE status will be analyzed at baseline only.

Study Arms

Randomization

Before the recruitment of participants into the intervention, all the study ID numbers were randomly preassigned. A member

of the research team assigned each study ID to a number generated by a random numbers table. As participants (who met all the inclusion criteria and none of the exclusion criteria and signed the informed consent form) were enrolled in the study, they were assigned a study ID number.

HC Intervention

The participants randomly allocated into the HC arm of the study will be assigned a personal health coach to work with for the duration of the study. HC will take place remotely through videoconferences and asynchronous chat messages and focus on helping the participants improve their brain health by working on the following lifestyle domains: nutrition, physical activity, sleep, stress, social engagement, and cognitive activity. HC will communicate with the participants about each of these modifiable risk factors and then tailor their recommendations and communications to the specific lifestyle areas needed for each participant. HC participants will also be provided access to a cognitive health app (Citruslabs), through which they can access cognitive training activities, workout routines, and recipes. HC is different from traditional interventions used in RCTs. Instead of testing a uniform program to fit all the participants, the HC recommendations and communications will be tailored by the coach to fit each participant's unique needs.

The HC will actively reach out to participants 1-2 times per week through asynchronous messages and will provide articles on various lifestyle modifications, such as nutrition information and physical activity, based on the focus for each participant. In addition, the participants will have unlimited access to their coach to ask questions or obtain the coach's recommendations. Meetings with the coach will be scheduled on a monthly basis through videoconference or phone to assess the progress toward the goals, discuss any barriers they have encountered, and strategize personalized ways to attain the goals. The lifestyle domains will be chosen based on a combination of the participant's preferences and the coach's recommendations. For example, if the HC identifies nutrition as the primary source of need for a participant but the participant is not ready to work on that area, the HC will make alternative recommendations to meet the participant where they feel ready to make a change.

The HC intervention is designed to support participants through the recommended lifestyle changes to improve brain health and reduce dementia risk. The topics that will be discussed during the initial intake session include (1) description of the HC process, (2) description of lifestyle domains and how they are related to brain health, (3) gathering information from the participant on which lifestyle domains they seek and are willing to improve, (4) assessing motivation and readiness for change, and (5) assisting the participant for creating a vision for their future, including appropriate goal-setting. Although the monthly follow-up coaching sessions can differ between participants, they will typically include (1) reassessing goals and making appropriate modifications to meet personal health goals and (2) supporting the participant in overcoming the challenges they meet throughout their personal journey.

HE Control

Participants randomly assigned to the HE control group will receive biweekly emails including information on how to change their lifestyle to improve their brain health. To independently evaluate the efficacy of the intervention, the same lifestyle domains will be covered in both arms of the study. These lifestyle domains include physical activity, dietary habits, sleep, stress, social engagement, and cognitive activity. Throughout the duration of the intervention, the participants will only have access to the study staff during their on-site testing sessions. After the intervention, the number of articles opened by the participant will be tallied to determine engagement from the control group.

Participant Recruitment

Participants were recruited in northwest Arkansas using local radio, email, social media advertisements, and word of mouth. The participants who met all the inclusion criteria and none of the exclusion criteria were randomly assigned to one of the groups before any assessments were completed.

The goal sample size for this study is approximately 200 participants. This sample size is considered sufficient to achieve random assortment, which was validated after examining the baseline characteristics of both groups. Cross-sectional, between-group differences in the baseline ANU-ADRI scores will be assessed using analysis of variance (ANOVA). Longitudinal studies following cognitively intact older adults have documented a 0.8 RBANS standard score change (SD 13.8) over a 12-month period [54]. Owing to the younger and wider age range to be recruited, we conservatively estimated a 1.75 standard score change with a comparable SD 10 among the control participants. In a 12-month pilot study of a similar intervention, a 5.8 (SD 7.4) standard score point increase on RBANS (ie, improvement) was found [55]. Assuming no additional improvement owing to a longer intervention, a sample size of 100 participants per group provides 80% power to detect a difference of 3.3 points between the intervention groups on the RBANS total index score (Cohen d=0.33) with an α of .05 and accounting for up to 20% attrition.

Statistical Analyses

Using the results of previous web-based intervention studies designed to reduce AD risk in an RCT design [11,56], a 2-point difference in the ANU-ADRI total score between the groups is expected over time [41]. A longitudinal observational study among adults demonstrated that a 1-point increase in ANU-ADRI score is associated with an 8% increase in the risk for developing MCI or dementia, mediated by brain volume, over the following 12 years [57]. A 2.5-point within-group change was found to be statistically significant in a web intervention [11]. Owing to the population health effects that are possible with a scalable remote intervention, these metrics are clinically and statistically meaningful at the individual and group levels.

Exploratory analyses will be performed on an intent-to-treat basis. One-way ANOVA will be used to compare the groups on functional fitness; biomarker measures; health-related variables; and digital, cognitive assessments at baseline. In

addition, sex differences in baseline characteristics and change scores will be evaluated using a 2×2 (group and sex) ANOVA. Repeated measures ANOVA will be used to determine the differences over time between the groups. APOE status and the presence of homozygous E4 alleles will be used as a dichotomous variable and as a covariate for change in results after the intervention.

Ethics Approval Statement

The study was approved by the University of Arkansas Institutional Review Board. All participants signed an approved consent form in accordance with the ethical standards of Helsinki.

Results

The enrollment funnel for the DCMARVel trial is shown in Figure 1. Enrollment took place between January 2021 and June 2021. The baseline characteristics of the study population are presented in Table 2. A total of 204 adults (n=152, 74.5% women and n=52, 25.5% men) have completed the baseline testing. The participants are aged 45-75 years (mean 61.9, SD 8.3 years).

Figure 1. Participant screening and enrollment funnel.

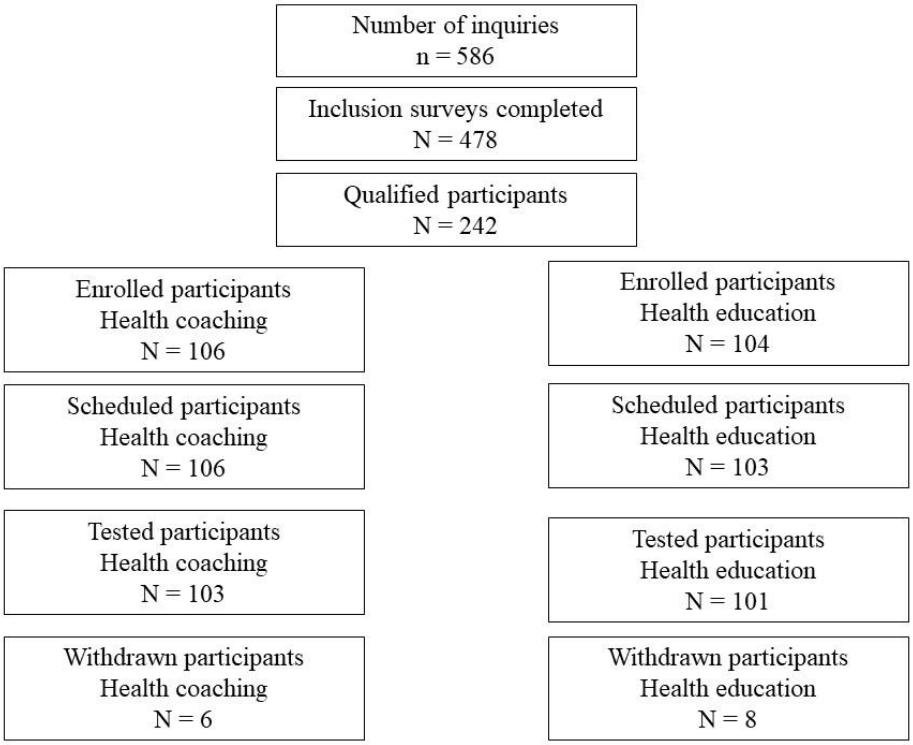

Table 2. Baseline characteristics (N=204).

Variables	Health education (n=101)	Health coaching (n=103)	Total (N=204)	*P* value[a]
Age (years), mean (SD)	61.4 (8.9)	62.4 (7.6)	61.9 (8.3)	.38
Sex (female), n (%)	77 (76.2)	75 (72.8)	152 (74.5)	—[b]
Ethnicity (White), n (%)	98 (97)	100 (97.1)	198 (97.1)	—
ANU-ADRI[c] total, mean (SD)	−1.61 (7.34)	−1.75 (7.32)	−1.68 (7.31)	.90
ANU-ADRI risk, mean (SD)	8.97 (5.91)	8.41 (5.57)	8.68 (5.73)	.48
ANU-ADRI protective, mean (SD)	−10.38 (4.49)	−10.15 (4.60)	−10.26 (4.54)	.72

[a]Obtained from 2-tailed *t* test.

[b]No statistical analysis was performed.

[c]ANU-ADRI: Australian National University-Alzheimer Disease Risk Index.

Discussion

Principal Findings

To our knowledge, this study is the first large-scale 2-year RCT to examine the effect of a digital multi-domain lifestyle intervention on reducing AD risk among a population that includes adults as young as 45 years. Improving the modifiable risk factors for AD has the greatest potential to impact disease development when implemented early and in a targeted manner and effective treatments hinge upon early identification and appropriate lifestyle modification. Although several

single-domain interventions have been implemented with little success, multi-domain interventions have demonstrated greater levels of improvement [8,15,16]. However, many of these interventions have focused on cognitive change among older adults at risk for dementia [8,16]. In addition, the interventions have largely been designed for face-to-face implementation; therefore, greatly reducing the scalability and public health impact of the programs. Thus, this study will focus on impacting multiple lifestyle domains linked to AD risk in a younger population than that studied previously [8,9,17,18].

The HC intervention will address 6 lifestyle domains that have been linked to the development of dementia later in life: diet, exercise, sleep, stress, social engagement, and cognitive activity. In addition to receiving HE material similar to the control group, participants in the intervention arm will work with a health coach to develop and implement changes to the lifestyle areas that they are ready to work on. The tailored nature of the program is designed to maximize the behavior change outcomes.

Dietary habits are an important modifiable risk factor for dementia. The Mediterranean-DASH intervention for neurodegenerative delay (MIND) diet is recommended to participants based on its positive effects on brain health [9,58]. Even moderate adherence to the MIND diet has been linked to better brain health and reduced dementia risk in the long term. In the studies by Morris et al [9,58], participants in the top tertile of the MIND diet scores showed a 53% reduction in the rate of developing AD compared with participants in the lowest tertile and participants in the middle tertile also showed a statistically significant 35% reduction in AD rate compared with those in the first tertile. The diet is also easy to follow because it emphasizes eating more of the recommended foods, such as berries and leafy greens, and less of the unhealthy foods, such as butter and sweets, rather than requiring a strict eating plan. This type of dietary pattern will allow the HC to make substitutions, modifications, and adjustments in the recommendations based on dietary needs and preferences.

Habitual physical inactivity is associated with many chronic health conditions such as type 2 diabetes, cardiovascular disease, and hypertension [59]. More recently, research has suggested that higher cardiorespiratory fitness and physical activity participation have a positive association with cognitive performance [59,60]. Acute exercise has been associated with improved performance in many cognitive paradigms, but the greatest effect has been noted on executive function and reaction time and smaller effects have been noted on memory and processing speed [60,61]. The physical activity recommendations made by the HC will be determined by the participant's current level of exercise and their readiness to do more.

Sleep is an important aspect of both brain health and overall health. Aging is often associated with changes in sleep patterns [62]. The causes of these changes are not well understood, but have been linked to reductions in neurocognitive function [63]. In addition, adults with dementia or AD often experience significant disturbances in sleep quality and sleep patterns [62,63]. Although it is well-recognized that sleep disturbances are common among adults with dementia and AD, identification of sleep disturbances earlier in life may be predictive of future cognitive decline [62]. The HC will work with participants to identify any existing sleep issues and implement strategies to improve the quality and quantity of sleep.

Stress is a multifactorial response to both internal and external stimuli. However, exposure to chronic stress can result in major illnesses and ailments [64,65]. Many studies have linked the exposure to chronic stress with cardiovascular disease [64] and cognitive dysfunction [66]. The specific mechanisms underlying this link have not yet been fully elucidated. However, a potential mechanism includes stress hormones that decrease the glutamate receptor function in the prefrontal cortex [67]. This is important because the prefrontal cortex is responsible for many aspects of executive function, including working memory and inhibition [68]. The participants will work with the HC on personalized strategies to reduce stress based on their individual circumstances and needs.

Loneliness has recently been identified as a positive predictor of dementia among older adults. After a 3-year follow-up, older adults with self-reported feelings of loneliness and living alone showed an approximately 2.5-fold increase in the risk of dementia [69]. A recent meta-analysis supports these results by suggesting that the relative risk of dementia is 25% higher among older adults with feelings of loneliness when compared with those with a greater social network [70]. The HC will work with the participants to assess their level of social engagement or loneliness and make changes as needed.

Low cognitive engagement has previously been linked with increased risk of dementia [71,72]. This particular risk factor has gained significant attention in recent years because it is one of the easiest risk factors to be modified. Cognitive engagement or brain training research has increased significantly over the past few years, but the results have been inconclusive. Bahar-Fuchs et al [73,74] examined changes in global cognition after 8 weeks of cognitive training and found improvements in cognitive function that persisted during a 6-month follow-up period. Edwards et al [75] found that training cognitive processing speed lowered the risk of developing dementia by 29%, whereas memory training and cognitive reasoning reduced dementia risk by 21% [75]. It is likely that sustained participation in cognitively challenging activities, such as learning an instrument or doing crossword puzzles, has a positive impact on brain health in the long term [76-78]. The health coach will work with the participants to identify activities that are of interest to them and encourage regular practice.

Conclusions

The results of this study can produce a novel and highly scalable intervention strategy to reduce the risk of cognitive decline before MCI or AD diagnoses occur. The primary outcome in the DCMARVel trial is AD risk reduction as determined by ANU-ADRI [11]. With the wide range of secondary outcomes (eg, physical, blood biomarkers, and psychosocial), the relative contribution to AD risk reduction can be estimated in addition to changes over time. As the HC program is designed to address multiple factors contributing to vascular disease (eg, physical activity and dietary habits), the intervention is expected to

improve cognitive outcomes over time by significantly reducing AD risk using a digital and scalable format.

Conflicts of Interest

ENM, JMG, and JM are employed by Neurotrack. They receive salary and hold equity in the company.

References

1. Mecocci P, Boccardi V. The impact of aging in dementia: it is time to refocus attention on the main risk factor of dementia. Ageing Res Rev 2021 Jan;65:101210 [FREE Full text] [doi: 10.1016/j.arr.2020.101210] [Medline: 33186671]
2. Alzheimer's Association. 2020 Alzheimer's disease facts and figures. Alzheimers Dement 2020 Mar 10:391-460 [FREE Full text] [doi: 10.1002/alz.12068] [Medline: 32157811]
3. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, et al. Decline in cardiovascular mortality: possible causes and implications. Circ Res 2017 Jan 20;120(2):366-380 [FREE Full text] [doi: 10.1161/CIRCRESAHA.116.309115] [Medline: 28104770]
4. Honig LS, Mayeux R. Natural history of Alzheimer's disease. Aging (Milano) 2001 Jun;13(3):171-182. [doi: 10.1007/BF03351476] [Medline: 11442300]
5. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. Alzheimers Dement 2021 Mar;17(3):327-406. [doi: 10.1002/alz.12328] [Medline: 33756057]
6. 2020 profile of older Americans. US Department of Health and Human Services - Administration for Community Living. 2021. URL: https://acl.gov/sites/default/files/Aging%20and%20Disability%20in%20America/2020ProfileOlderAmericans.Final_.pdf [accessed 2021-11-30]
7. Hill NT, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A. Computerized cognitive training in older adults with mild cognitive impairment or dementia: a systematic review and meta-analysis. Am J Psychiatry 2017 Apr 01;174(4):329-340. [doi: 10.1176/appi.ajp.2016.16030360] [Medline: 27838936]
8. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol 2018 Nov 5;14(11):653-666. [doi: 10.1038/s41582-018-0070-3] [Medline: 30291317]
9. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimers Dement 2015 Sep;11(9):1007-1014 [FREE Full text] [doi: 10.1016/j.jalz.2014.11.009] [Medline: 25681666]
10. Kivipelto M, Solomon A, Ahtiluoto S, Ngandu T, Lehtisalo J, Antikainen R, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. Alzheimers Dement 2013 Nov;9(6):657-665. [doi: 10.1016/j.jalz.2012.09.012] [Medline: 23332672]
11. Anstey KJ, Cherbuin N, Herath PM. Development of a new method for assessing global risk of Alzheimer's disease for use in population health approaches to prevention. Prev Sci 2013 Aug;14(4):411-421 [FREE Full text] [doi: 10.1007/s11121-012-0313-2] [Medline: 23319292]
12. Barnes J, Dickerson BC, Frost C, Jiskoot LC, Wolk D, van der Flier WM. Alzheimer's disease first symptoms are age dependent: evidence from the NACC dataset. Alzheimers Dement 2015 Nov;11(11):1349-1357 [FREE Full text] [doi: 10.1016/j.jalz.2014.12.007] [Medline: 25916562]
13. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev 2015 Apr 22;4(4):CD005381. [doi: 10.1002/14651858.CD005381.pub4] [Medline: 25900537]
14. Bartochowski Z, Conway J, Wallach Y, Chakkamparambil B, Alakkassery S, Grossberg GT. Dietary interventions to prevent or delay Alzheimer's disease: what the evidence shows. Curr Nutr Rep 2020 Sep 18;9(3):210-225. [doi: 10.1007/s13668-020-00333-1] [Medline: 32681411]
15. Bott NT, Hall A, Madero EN, Glenn JM, Fuseya N, Gills JL, et al. Face-to-face and digital multidomain lifestyle interventions to enhance cognitive reserve and reduce risk of Alzheimer's disease and related dementias: a review of completed and prospective studies. Nutrients 2019 Sep 19;11(9):2258 [FREE Full text] [doi: 10.3390/nu11092258] [Medline: 31546966]
16. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015 Jun 06;385(9984):2255-2263. [doi: 10.1016/S0140-6736(15)60461-5] [Medline: 25771249]
17. van Charante EP, Richard E, Eurelings LS, van Dalen J, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet 2016 Aug 20;388(10046):797-805. [doi: 10.1016/S0140-6736(16)30950-3] [Medline: 27474376]
18. Rolland Y, Barreto PS, Maltais M, Guyonnet S, Cantet C, Andrieu S, et al. Effect of long-yerm Omega 3 polyunsaturated fatty acid supplementation with or without multidomain lifestyle intervention on muscle strength in older adults: secondary analysis of the Multidomain Alzheimer Preventive Trial (MAPT). Nutrients 2019 Aug 16;11(8):377-389 [FREE Full text] [doi: 10.3390/nu11081931] [Medline: 31426362]

19. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 1998 Jun;20(3):310-319. [doi: 10.1076/jcen.20.3.310.823] [Medline: 9845158]
20. Thaler NS, Hill BD, Duff K, Mold J, Scott JG. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) intraindividual variability in older adults: associations with disease and mortality. J Clin Exp Neuropsychol 2015 Jul 13;37(6):622-629. [doi: 10.1080/13803395.2015.1039962] [Medline: 26168246]
21. Cheng Y, Wu W, Wang J, Feng W, Wu X, Li C. Reliability and validity of the Repeatable Battery for the Assessment of Neuropsychological Status in community-dwelling elderly. Arch Med Sci 2011 Oct;7(5):850-857 [FREE Full text] [doi: 10.5114/aoms.2011.25561] [Medline: 22291831]
22. Gills JL, Bott NT, Madero EN, Glenn JM, Gray M. A short digital eye-tracking assessment predicts cognitive status among adults. Geroscience 2021 Feb 01;43(1):297-308 [FREE Full text] [doi: 10.1007/s11357-020-00254-5] [Medline: 32870437]
23. Gills JL, Glenn JM, Madero EN, Bott NT, Gray M. Validation of a digitally delivered visual paired comparison task: reliability and convergent validity with established cognitive tests. Geroscience 2019 Aug;41(4):441-454 [FREE Full text] [doi: 10.1007/s11357-019-00092-0] [Medline: 31463649]
24. Lezak MD. Neuropsychological Assessment 3rd Ed. New York: Oxford University Press; 1995:1-1026.
25. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000 Apr;55(4):221-231. [doi: 10.1093/gerona/55.4.m221] [Medline: 10811152]
26. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994 Mar;49(2):85-94. [doi: 10.1093/geronj/49.2.m85] [Medline: 8126356]
27. Rikli RE, Jones CJ. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. Gerontologist 2013 Apr 20;53(2):255-267. [doi: 10.1093/geront/gns071] [Medline: 22613940]
28. Rikli R, Jones CJ. Senior Fitness Test Manual. Champaign, IL: Human Kinetics; 2001:1-176.
29. Bohannon RW. Hand-grip dynamometry provides a valid indication of upper extremity strength impairment in home care patients. J Hand Ther 1998 Oct;11(4):258-260. [doi: 10.1016/s0894-1130(98)80021-5]
30. Bohannon RW. Are hand-grip and knee extension strength reflective of a common construct? Percept Mot Skills 2012 Apr 01;114(2):514-518. [doi: 10.2466/03.26.pms.114.2.514-518]
31. Bohannon RW. Muscle strength: clinical and prognostic value of hand-grip dynamometry. Curr Opin Clin Nutr Metab Care 2015 Sep;18(5):465-470. [doi: 10.1097/MCO.0000000000000202] [Medline: 26147527]
32. Cesari M. Role of gait speed in the assessment of older patients. J Am Med Assoc 2011 Jan 05;305(1):93-94. [doi: 10.1001/jama.2010.1970] [Medline: 21205972]
33. Fitzpatrick AL, Buchanan CK, Nahin RL, Dekosky ST, Atkinson HH, Carlson MC, Ginkgo Evaluation of Memory (GEM) Study Investigators. Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. J Gerontol A Biol Sci Med Sci 2007 Nov 01;62(11):1244-1251. [doi: 10.1093/gerona/62.11.1244] [Medline: 18000144]
34. Gray M, Gills J, Glenn J, Vincenzo J, Walter C, Madero E, et al. Cognitive decline negatively impacts physical function. Exp Gerontol 2021 Jan;143:111164 [FREE Full text] [doi: 10.1016/j.exger.2020.111164] [Medline: 33232795]
35. Hausdorff JM, Nelson ME, Kaliton D, Layne JE, Bernstein MJ, Nuernberger A, et al. Etiology and modification of gait instability in older adults: a randomized controlled trial of exercise. J Appl Physiol (1985) 2001 Jun 01;90(6):2117-2129 [FREE Full text] [doi: 10.1152/jappl.2001.90.6.2117] [Medline: 11356774]
36. McCulloch KL, Mercer V, Giuliani C, Marshall S. Development of a clinical measure of dual-task performance in walking: reliability and preliminary validity of the Walking and Remembering Test. J Geriatr Phys Ther 2009;32(1):2-9. [doi: 10.1519/00139143-200932010-00002] [Medline: 19856629]
37. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J Am Geriatr Soc 2012 Nov;60(11):2127-2136 [FREE Full text] [doi: 10.1111/j.1532-5415.2012.04209.x] [Medline: 23110433]
38. Gray M, Paulson S. Developing a measure of muscular power during a functional task for older adults. BMC Geriatr 2014 Dec 30;14(1):145 [FREE Full text] [doi: 10.1186/1471-2318-14-145] [Medline: 25551186]
39. Glenn JM, Gray M, Binns A. Relationship of sit-to-stand lower-body power with functional fitness measures among older adults with and without sarcopenia. J Geriatr Phys Ther 2017;40(1):42-50. [doi: 10.1519/JPT.0000000000000072] [Medline: 26428899]
40. Glenn JM, Gray M, Vincenzo JL, Stone MS. Functional lower-body power: a comparison study between physically inactive, recreationally active, and masters athlete late-middle-aged adults. J Aging Phys Act 2016 Oct;24(4):501-507. [doi: 10.1123/japa.2015-0208] [Medline: 26796422]

41. McMaster M, Kim S, Clare L, Torres S, Cherbuin N, D Este C, et al. Lifestyle risk factors and cognitive outcomes from the multidomain dementia risk reduction randomized controlled trial, Body Brain Life for Cognitive Decline (BBL-CD). J Am Geriatr Soc 2020 Nov;68(11):2629-2637 [FREE Full text] [doi: 10.1111/jgs.16762] [Medline: 32909259]
42. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
43. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 2008 Mar;46(3):266-274. [doi: 10.1097/MLR.0b013e318160d093] [Medline: 18388841]
44. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. Res Aging 2004;26(6):655-672 [FREE Full text] [doi: 10.1177/0164027504268574] [Medline: 18504506]
45. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [doi: 10.1097/00005650-199603000-00003] [Medline: 8628042]
46. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385. [doi: 10.2307/2136404]
47. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
48. Singh JA, Sarkin A, Shieh M, Khanna D, Terkeltaub R, Lee SJ, et al. Health care utilization in patients with gout. Semin Arthritis Rheum 2011 Jun;40(6):501-511 [FREE Full text] [doi: 10.1016/j.semarthrit.2010.07.001] [Medline: 20828793]
49. Beaudreau S, Spira A, Stewart A, Kezirian E, Lui L, Ensrud K, Study of Osteoporotic Fractures. Validation of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in older black and white women. Sleep Med 2012 Jan;13(1):36-42 [FREE Full text] [doi: 10.1016/j.sleep.2011.04.005] [Medline: 22033120]
50. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193-213. [doi: 10.1016/0165-1781(89)90047-4] [Medline: 2748771]
51. Martin A, Rief W, Klaiberg A, Braehler E. Validity of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population. Gen Hosp Psychiatry 2006;28(1):71-77. [doi: 10.1016/j.genhosppsych.2005.07.003] [Medline: 16377369]
52. Tomaszewski Farias S, Mungas D, Harvey DJ, Simmons A, Reed BR, Decarli C. The measurement of everyday cognition: development and validation of a short form of the Everyday Cognition scales. Alzheimers Dement 2011 Nov;7(6):593-601 [FREE Full text] [doi: 10.1016/j.jalz.2011.02.007] [Medline: 22055976]
53. Plüddemann A, Thompson M, Price CP, Wolstenholme J, Heneghan C. Point-of-care testing for the analysis of lipid panels: primary care diagnostic technology update. Br J Gen Pract 2012 Mar;62(596):224-226 [FREE Full text] [doi: 10.3399/bjgp12X630241] [Medline: 22429442]
54. Hammers DB, Suhrie KR, Porter SM, Dixon AM, Duff K. Validation of one-year reliable change in the RBANS for community-dwelling older adults with amnestic mild cognitive impairment. Clin Neuropsychol 2020 Aug 20:1-24. [doi: 10.1080/13854046.2020.1807058] [Medline: 32819188]
55. Kumar S, Tran JL, Moseson H, Tai C, Glenn JM, Madero EN, et al. The impact of the virtual cognitive health program on the cognition and mental health of older adults: pre-post 12-month pilot study. JMIR Aging 2018 Nov 09;1(2):e12031 [FREE Full text] [doi: 10.2196/12031] [Medline: 31518248]
56. Andrews SJ, Eramudugolla R, Velez JI, Cherbuin N, Easteal S, Anstey KJ. Validating the role of the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) and a genetic risk score in progression to cognitive impairment in a population-based cohort of older adults followed for 12 years. Alzheimers Res Ther 2017 Mar 04;9(1):16 [FREE Full text] [doi: 10.1186/s13195-017-0240-3] [Medline: 28259165]
57. Cherbuin N, Shaw ME, Walsh E, Sachdev P, Anstey KJ. Validated Alzheimer's Disease Risk Index (ANU-ADRI) is associated with smaller volumes in the default mode network in the early 60s. Brain Imaging Behav 2019 Feb;13(1):65-74 [FREE Full text] [doi: 10.1007/s11682-017-9789-5] [Medline: 29243120]
58. Morris M, Tangney C, Wang Y, Sacks F, Barnes L, Bennett D, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement 2015 Sep;11(9):1015-1022 [FREE Full text] [doi: 10.1016/j.jalz.2015.04.011] [Medline: 26086182]
59. Lee P. Cognitive function in midlife and beyond: physical and cognitive activity related to episodic memory and executive functions. Int J Aging Hum Dev 2014;79(4):263-278. [doi: 10.1177/0091415015574190] [Medline: 25888534]
60. Huang T, Larsen KT, Ried-Larsen M, Møller NC, Andersen L. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: a review. Scand J Med Sci Sports 2014 Mar 22;24(1):1-10. [doi: 10.1111/sms.12069] [Medline: 23600729]
61. Chang Y, Labban J, Gapin J, Etnier J. The effects of acute exercise on cognitive performance: a meta-analysis. Brain Res 2012 May 09;1453:87-101 [FREE Full text] [doi: 10.1016/j.brainres.2012.02.068] [Medline: 22480735]
62. Yaffe K, Falvey C, Hoang T. Connections between sleep and cognition in older adults. Lancet Neurol 2014 Oct;13(10):1017-1028 [FREE Full text] [doi: 10.1016/s1474-4422(14)70172-3]

63. Kang DW, Lee CU, Lim HK. Role of sleep disturbance in the trajectory of Alzheimer's disease. Clin Psychopharmacol Neurosci 2017 May 31;15(2):89-99 [FREE Full text] [doi: 10.9758/cpn.2017.15.2.89] [Medline: 28449556]
64. Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol 2008 Apr 01;51(13):1237-1246 [FREE Full text] [doi: 10.1016/j.jacc.2007.12.024] [Medline: 18371552]
65. Jood K, Redfors P, Rosengren A, Blomstrand C, Jern C. Self-perceived psychological stress and ischemic stroke: a case-control study. BMC Med 2009 Oct 01;7(1):53 [FREE Full text] [doi: 10.1186/1741-7015-7-53] [Medline: 19796376]
66. McEwen B, Sapolsky R. Stress and cognitive function. Curr Opin Neurobiol 1995 Apr;5(2):205-216 [FREE Full text] [doi: 10.1016/0959-4388(95)80028-x]
67. Yuen E, Wei J, Liu W, Zhong P, Li X, Yan Z. Repeated stress causes cognitive impairment by suppressing glutamate receptor expression and function in prefrontal cortex. Neuron 2012 Mar 08;73(5):962-977 [FREE Full text] [doi: 10.1016/j.neuron.2011.12.033] [Medline: 22405206]
68. Kimberg DY, D'Esposito M, Farah MJ. Cognitive functions in the prefrontal cortex—working memory and executive control. Curr Dir Psychol Sci 2016 Jun 23;6(6):185-192. [doi: 10.1111/1467-8721.ep10772959]
69. Holwerda TJ, Deeg DJH, Beekman ATF, van Tilburg TG, Stek ML, Jonker C, et al. Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL). J Neurol Neurosurg Psychiatry 2014 Mar 10;85(2):135-142. [doi: 10.1136/jnnp-2012-302755] [Medline: 23232034]
70. Lara E, Martín-María N, De la Torre-Luque A, Koyanagi A, Vancampfort D, Izquierdo A, et al. Does loneliness contribute to mild cognitive impairment and dementia? A systematic review and meta-analysis of longitudinal studies. Ageing Res Rev 2019 Jul;52:7-16 [FREE Full text] [doi: 10.1016/j.arr.2019.03.002] [Medline: 30914351]
71. Marioni RE, Proust-Lima C, Amieva H, Brayne C, Matthews FE, Dartigues J, et al. Social activity, cognitive decline and dementia risk: a 20-year prospective cohort study. BMC Public Health 2015 Oct 24;15(1):1089 [FREE Full text] [doi: 10.1186/s12889-015-2426-6] [Medline: 26499254]
72. Marioni RE, van den Hout A, Valenzuela MJ, Brayne C, Matthews FE, MRC Cognitive Function and Ageing Study. Active cognitive lifestyle associates with cognitive recovery and a reduced risk of cognitive decline. J Alzheimers Dis 2012 Jan 12;28(1):223-230. [doi: 10.3233/JAD-2011-110377] [Medline: 21971400]
73. Bahar-Fuchs A, Webb S, Bartsch L, Clare L, Rebok G, Cherbuin N, et al. Tailored and adaptive computerized cognitive training in older adults at risk for dementia: a randomized controlled trial. J Alzheimers Dis 2017 Oct;60(3):889-911. [doi: 10.3233/JAD-170404] [Medline: 28922158]
74. Bahar-Fuchs A, Barendse M, Bloom R, Ravona-Springer R, Heymann A, Dabush H, et al. Computerized cognitive training for older adults at higher dementia risk due to diabetes: findings from a randomized controlled trial. J Gerontol A Biol Sci Med Sci 2020 Mar 09;75(4):747-754 [FREE Full text] [doi: 10.1093/gerona/glz073] [Medline: 30868154]
75. Edwards J, Xu H, Clark D, Guey L, Ross L, Unverzagt F. Speed of processing training results in lower risk of dementia. Alzheimers Dement (N Y) 2017 Nov;3(4):603-611 [FREE Full text] [doi: 10.1016/j.trci.2017.09.002] [Medline: 29201994]
76. Litwin H, Schwartz E, Damri N. Cognitively stimulating leisure activity and subsequent cognitive function: a SHARE-based analysis. Gerontologist 2017 Oct 01;57(5):940-948 [FREE Full text] [doi: 10.1093/geront/gnw084] [Medline: 27117305]
77. Ferreira N, Owen A, Mohan A, Corbett A, Ballard C. Associations between cognitively stimulating leisure activities, cognitive function and age-related cognitive decline. Int J Geriatr Psychiatry 2015 Apr;30(4):422-430. [doi: 10.1002/gps.4155] [Medline: 24989949]
78. Schultz SA, Larson J, Oh J, Koscik R, Dowling MN, Gallagher CL, et al. Participation in cognitively-stimulating activities is associated with brain structure and cognitive function in preclinical Alzheimer's disease. Brain Imaging Behav 2015 Dec;9(4):729-736 [FREE Full text] [doi: 10.1007/s11682-014-9329-5] [Medline: 25358750]

Abbreviations

6MWT: 6-minute walk test
AD: Alzheimer disease
ANOVA: analysis of variance
ANU-ADRI: Australian National University-Alzheimer Disease Risk Index
APOE: apolipoprotein E
DCMARVel: Digital, Cognitive, Multi-domain Alzheimer Risk Velocity
HC: health coaching
HDL: high-density lipoprotein
HE: health education
LDL: low-density lipoprotein
MCI: mild cognitive impairment
MIND: Mediterranean-DASH intervention for neurodegenerative delay
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RCT: randomized controlled trial

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Protocol

Assessing the Efficacy of an Individualized Psychological Flexibility Skills Training Intervention App for Medical Student Burnout and Well-being: Protocol for a Randomized Controlled Trial

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Abstract

Background: Medical student burnout is a prevalent problem with adverse long-term outcomes. Incorporating psychological resource-building interventions into comprehensive burnout prevention approaches during medical training is an identified priority among educators. These interventions could reduce burnout risk by buffering students against nonmodifiable career stressors. However, there is a need for rigorous investigation into optimal intervention targets and methods. Psychological flexibility (PF) is an adaptive behavioral skill set that has demonstrated relationships with medical student burnout and well-being. More broadly, there is evidence that PF mediates burnout and well-being outcomes and may be a protective factor. Efficacy studies assessing the benefits of interventions targeting PF among medical students are needed. Research also supports the need to establish optimal methods for increasing intervention efficacy in the context of individual differences in burnout and PF by using individualized approaches.

Objective: This study aims to assess whether an app-delivered PF intervention (Acceptance and Commitment Training) reduces burnout and improves well-being among medical students. We will examine whether changes in burnout and well-being are mediated by changes in PF. The potential benefits of an individualized version of the app versus those of a nonindividualized version will also be evaluated.

Methods: In this 3-arm, parallel, randomized controlled study, a sample of medical students will be randomly allocated to 1 of 3 intervention arms (individualized, nonindividualized, and waiting list) by using a 1:1:1 allocation ratio. Participants in the individualized and nonindividualized intervention arms will have 5 weeks to access the app, which includes a PF concepts training session (stage 1) and access to short PF skill activities *on demand* (stage 2). Stage 2 will be either individualized to meet participants' identified PF training needs at each log-in or nonindividualized.

Results: Burnout, well-being, and PF will be assessed at baseline and after the intervention. Quantitative analyses will include descriptive and inferential statistics. We hypothesize that the Acceptance and Commitment Training intervention app will be effective in improving burnout and well-being and that changes in these outcomes will be mediated by changes in PF. We further hypothesize that participants in the individualized intervention group will demonstrate greater improvements in burnout and well-being outcomes than those in the nonindividualized group.

Conclusions: The findings of this study could guide the development of burnout prevention and well-being initiatives for medical students. Identifying PF as a mediating process would provide support for the delivery of preventive intervention programs that train individuals to strengthen this psychological resource before burnout symptoms emerge. This would be an important step in addressing and potentially offsetting the significant costs of burnout among medical students and physicians. Demonstrating the superiority of an individualized version of the app over a nonindividualized version would have implications for enhancing intervention precision and efficacy by using scalable interventions.

Trial Registration: Australian New Zealand Clinical Trials Registry ANZCTR 12621000911897; https://www.anzctr.org.au/ACTRN12621000911897.aspx

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KEYWORDS

burnout; psychological; burnout interventions; psychological flexibility; digital intervention; individualized intervention; acceptance and commitment therapy; medical students; well-being; mobile phone

Introduction

A Burnout Epidemic

Burnout is a chronic and pervasive state of work-related stress that substantially disrupts an individual's professional identity and psychological connections to their work [1]. The most widely accepted 3-factor model defines burnout as a psychological crisis that is experienced as a sense of fatigue, overload, and depleted emotional energy and resources (emotional exhaustion); a pattern of withdrawal behaviors; negative, detached attitudes toward others (cynicism); and the perception that one's work performance lacks quality and value (inefficacy) [1,2]. Beyond the experience of burnout itself, affected individuals are at an increased risk of associated psychological difficulties [3-5], poor physical health outcomes [3,5-7], and cognitive impairments [8]. Through its impact on an individual's health and capacity to work [9], burnout adversely affects organizational service delivery and productivity [5,10,11] and places a considerable burden on the economy [12].

Although burnout affects workers across a broad range of professional disciplines, it has become a problem of epidemic proportions within the field of medicine [11]. Prevalence estimates among physicians range between 37.9% [13] and 80.5% [14] compared with rates between 2% and 27.8% reported for the general working population [9,13]. Of particular concern is the increasing frequency of burnout experiences emerging during the early stages of medical training, with a global prevalence of approximately 44.2% among medical students [15]. Physicians and medical students who are affected by burnout experience higher risks of suicide [4,16-18], medical errors, and diminished quality of patient care [4,5,11,19,20].

Study Aims

We aim to assess whether an app-based psychological skills training intervention is effective in reducing burnout and improving well-being among medical students, using research methodologies designed to maximize intervention precision and efficacy for individuals. In the following sections, we outline the background and rationale behind the selection of our intervention model, our methodology, and our research hypotheses.

Calls for Early Intervention: Individual Psychological Resource Training

In response to the burnout crisis among physicians and medical students, there are increasing calls for the early implementation of interventions that facilitate the prevention of burnout and its broader associated outcomes [10,11,21-23]. Determining when and how to intervene most effectively remains an ongoing challenge. It has been proposed that burnout is an adverse psychological response to a pervasive imbalance between demands and individual coping resources, commencing during medical training, and persisting throughout a physician's professional life [24]. Burnout interventions aim to minimize such imbalances, either by modifying external factors known to increase burnout risk at the organizational level or by training individuals to develop protective psychological and behavioral resources [25].

At an organizational level, learning institutions and workplaces may consider how to reduce modifiable external risk factors for burnout [23,26]. Risk factors that can and should be addressed in organizational settings include inadequate resources [27], excessive workloads, a lack of control or autonomy, a lack of reward, organizational unfairness [1], inflexible work schedules [23], bullying, and the mistreatment of students [28,29]. Interventions focused on minimizing organizational risk factors have demonstrated efficacy in reducing burnout among physicians [25]. However, physicians and students face many stressors that are inherent to their work [30], including exposure to distressing or demanding patient relationships, patient illness, death and dying, concerns about litigation, rapidly changing work and knowledge requirements, academic pressures, and

performing highly responsible roles [4,20,24]. In a profession where such unmodifiable risk factors pervade, there is an important place for individual-focused cognitive and behavioral interventions. These interventions focus on enhancing modifiable individual psychological resources and adaptive coping skills [9] to buffer the potential adverse impacts of unmodifiable stressors and demands [9,30,31].

Importantly, although external factors contribute to burnout risk, medical students' behavioral responses to stressors can also play a role [31]. For example, students who transition away from healthy behavior patterns during their medical training are at an increased risk of experiencing burnout [31] as are those who tend not to engage in values-driven behavior [32]. The risk is more than double for students who engage in maladaptive coping repertoires, such as avoidance-based coping (including cognitive, emotional, and behavioral avoidance) [32-35]. Longitudinal evidence suggests that medical students who demonstrate problematic coping patterns are unlikely to spontaneously adopt more effective behavioral repertoires over time [31], and this may have adverse consequences regarding long-term burnout and well-being outcomes [30]. Implementing interventions that promote the development of more adaptive coping repertoires could mitigate behavioral burnout risk factors during the early stages of an individual's medical career [30].

Although organization-level interventions focus on removing contextual risk factors for burnout, individual interventions have the additional benefit of promoting behaviors that facilitate well-being [36,37], which is an identified goal within the medical field [29,38]. Well-being is more than just the absence of ill-health. Rather, it is a state of individual thriving that includes satisfaction with life, the experience of positive affect, engagement in values-aligned activities that promote purpose and vitality, and a sense of social connection that involves valuing and feeling valued by others [39]. It has been proposed that well-being interventions focusing on purposeful and valued living may be more important to individuals than those focusing solely on the removal of stressors [40]. Beyond the baseline goal of staving off burnout, individual interventions can empower medical students and physicians to build skills that facilitate the preservation and cultivation of sustainable well-being during their careers [5,14,41].

In light of these factors, the provision of individual psychological resource-building interventions as early as during undergraduate medical training is receiving growing support [18,20,22,29-31,33,38]. The past 10 years have seen a marked increase in the number of studies investigating such interventions [23]. A recent consensus statement issued by medical educators advocated for initiatives promoting "adaptive responses to stressful situations" as an important component of a broad well-being and burnout prevention plan for medical students in Australia and New Zealand [29]. Similarly, a recent review study identified the need for medical schools to foster training initiatives that ground students in the development of healthy habits, self-awareness skills, and effective mechanisms for coping with stressful experiences [18].

In nonmedical populations, meta-analyses [42,43] and systematic reviews [9,44] demonstrated that cognitive and behavioral interventions can be effective in reducing [9,42,43] and preventing [43,44] work-related stress and burnout. Recent systematic review findings provide support for the potential benefits of such interventions when delivered in medical training settings, however, there remain substantial knowledge gaps regarding the optimal methods for improving medical students' well-being and reducing burnout risk [23]. The identification of the most effective intervention model and methods is constrained by the considerable heterogeneity between intervention approaches and the small number of randomized controlled trials (RCTs) within the existing research [23]. There is a need for further research adopting more "robust and rigorous" research methodologies as well as the use of "systematic and evidence-based" approaches when developing interventions [23].

Our randomized controlled study responds to the need for well-controlled research that can identify effective methods for mitigating the problem of burnout among physicians and medical students, using individual resource-building interventions during early medical training. In line with the identified research needs [23], we developed an app-delivered cognitive behavioral intervention that was grounded in the robust evidence-based psychological flexibility (PF) model. We outline the theoretical relevance of this model regarding these outcomes and this population and the importance of using rigorous mediational and individualized methodological approaches that can improve intervention precision.

PF Model

The Theoretical Model

PF is a model of adaptive behavior that is rigorously grounded in behavioral science [45]. The model is composed of 6 modifiable behavioral flexibility skill sets or *processes* (and corresponding inflexibility processes) [46-48], including present-moment awareness (nonawareness of the present moment), experiential acceptance (experiential avoidance), cognitive defusion (cognitive fusion), self-as-context (self-as-content), contact with values (lack of contact with values), and committed action toward values (inaction) [47,49]. PF reflects the degree to which an individual is able to bring conscious awareness to a broad range of internal and external influences on their behavior and purposefully engage in actions directed toward personally held values and related goals [50]. When faced with challenges and stressors, people with high PF tend to choose adaptive behavioral responses that are driven by their values and facilitate well-being rather than behaviors that are rigidly driven by internal emotional and cognitive experiences [48,51]. PF and its individual processes are associated with a range of psychological health and well-being outcomes [51-53].

The Intervention: Acceptance and Commitment Training

PF processes are modifiable using cognitive behavioral training programs, such as Acceptance and Commitment Training (ACT; referred to as *ACT* in nonclinical settings and *Acceptance and Commitment Therapy* in clinical settings [45]). The benefits of ACT interventions are well established and have been demonstrated in over 600 RCTs [54]. Interventions focus on

facilitating the development of behavioral repertoires that are more flexibly responsive to an individual's present-moment experiences. This is achieved by training individuals to develop greater awareness of the influence of their internal experiences (eg, thoughts and emotions) on their actions, learning to alter their relationships with these internal experiences such that they are more accepting, and developing more flexible values-oriented behavioral repertoires [45].

PF as an Individual Protective Factor and Intervention Target

There is increasing evidence that PF skills can function as protective individual resources regarding burnout and well-being. Recent research has demonstrated associations between individual PF processes and work-related stress [39,41], burnout [55-58], and well-being [39,41,58,59]. PF processes account for unique variance in burnout symptomatology [41,60] and well-being [53]. These demonstrate predictive validity related to long-term workplace mental health [61] and show stronger and more consistent relationships with burnout and work-related well-being than do traditional organizational factors, such as job control and workload [41,56]. Interestingly, PF has also been shown to influence the degree to which employees are able to notice, engage with, and benefit from changes made to organizational burnout risk factors (eg, job control) [61], providing further support for the value of implementing individual interventions in conjunction with organizational interventions. PF skills have been shown to mediate relationships between stressors (eg, COVID-19–related stress) and well-being outcomes [62]. In nonmedical populations, interventions targeting individual components of the PF skill set demonstrate efficacy relating to reducing work-related stress and burnout [63-69], improving well-being [70], and improving coping in response to work-related stressors [63]. ACT interventions that provide training in the full PF skill set have been shown to reduce workplace stress and improve well-being [39].

Relevance of PF to Medical Students and Physicians

PF skills appear to function as important personal resources among medical students and physicians during the early stages of their careers [33]. Among medical students, lower PF is associated with reduced life satisfaction and greater personal distress when seeing others in harm, which may increase burnout risk [33]. Medical students who demonstrate behaviors associated with low PF (eg, avoidance and nonvalues-driven) are at greater risk of burnout. This leads to the suggestion that PF skills training could be of benefit to this population [32,33]. Similarly, burnout risk is higher among resident physicians with low PF [71]. Interventions targeting components of the PF model (eg, present-moment awareness and values) can effectively reduce stress and burnout risk among physicians and medical students [11,23,72]. To the best of our knowledge, no previous intervention studies have been found that have trained medical students or physicians in the full PF skill set.

PF Training and Medical Student Burnout and Well-being

The literature has demonstrated associations between PF and burnout and well-being outcomes and evidence for the relevance of these processes to medical student and physician burnout and well-being. On this basis, we expect that training medical students to develop PF skills will have positive benefits concerning burnout and well-being. Given the absence of intervention studies with this population where all 6 PF processes are trained, we will assess the efficacy of our purpose-developed app-based ACT intervention for medical students. Stage 1 of the intervention will deliver a brief educational module that provides a conceptual explanation of each of the 6 PF processes as well as self-reflection and experiential skill practice activities.

Hypothesis 1 states the following: on the basis of the theoretical background presented, we hypothesize that medical students in the individualized and nonindividualized intervention groups will demonstrate significantly greater improvements in PF, burnout, and well-being outcomes (before and after intervention) compared with those in a waiting-list control group.

PF as a Mechanism of Burnout and Well-being Change

One of the pitfalls of many cognitive behavioral intervention studies is that they deliver training packages that demonstrate efficacy regarding outcomes of interest, without identifying the mechanisms through which these interventions exert their effect [40]. Understanding the processes that underlie an intervention's efficacy can facilitate greater intervention precision [40]. For example, knowing that PF is a mechanism of change for medical student burnout would open up opportunities for the delivery of other interventions that may improve these skills and facilitate the efficient delivery of the intervention *dose* needed to produce meaningful improvements in PF to reduce a particular individual's burnout risk. Demonstrating the efficacy of an intervention through its impact on mediating processes is particularly important when seeking to prevent a distal adverse outcome. This provides opportunities to deliver interventions that strengthen these mediating skill sets among at-risk individuals (eg, medical students) before the emergence of adverse outcomes (eg, burnout).

Expectations of the efficacy of the current ACT intervention regarding burnout and well-being are based on the assumption that the training will help medical students use PF skills as an adaptive coping resource. This assumption is supported by previous mediation studies that demonstrated that ACT interventions influence burnout and well-being outcomes by improving an individual's PF skills [39,58]. PF processes may also mediate longer-term burnout risk as demonstrated in intervention studies where improvements in PF processes reduced the subsequent risk of burnout development [55]. To assess the assumptions of our intervention and improve the rigor of our efficacy assessment, we will explore whether PF is a mechanism of change for any observed burnout and well-being intervention effects.

Hypothesis 2 states the following: on the basis of the theoretical background provided, we hypothesize that changes in burnout and well-being outcomes will be mediated by changes in PF.

Individual Differences and Intervention Precision

There is a high degree of heterogeneity in both the way burnout symptoms develop among individuals over time [36] and individual recovery patterns during and after burnout interventions [9,36,69]. Similarly, although some individuals demonstrate reasonably consistent patterns of high or low PF across all processes, a range of distinct and more complex profiles of flexibility and inflexibility have recently been observed [47,48,53,60]. Each of these unique PF profiles demonstrates different relationships with a range of ill-being and well-being outcomes [47,48,53]. These findings demonstrate that individuals might require different types of interventions that target their individual risk factors to experience improvements in burnout risk and well-being outcomes [36,37,47,69,73]. This poses problems for static interventions that provide the same training for all individuals, as it means that some may not receive the type or amount of training they need, and others may receive more training than necessary [40,69]. Furthermore, interventions that are highly effective for some individuals, but not others, might not be further developed and disseminated because they fail to demonstrate efficacy at the group level [69].

As such, there are increasing calls by leading researchers for the use of individualized intervention methodologies, whereby an intervention is tailored to target the identified needs of each individual [40]. Individualized interventions can be delivered with a higher degree of precision than static interventions, providing the potential for superior efficacy and efficient resource allocation [74]. To address individual-level differences in this study, we will adopt a *treatment utility* methodology that compares an individualized version of the PF skills training app with a nonindividualized version [40]. Stage 1 of the intervention will deliver a static PF training module, and stage 2 will provide access to a library of short PF skills training activities that participants can access *on demand*. Participants receiving the individualized intervention will practice activities from the PF skill set that aligns with their identified needs during each training session, whereas those receiving the nonindividualized intervention will receive nontargeted training from any of the PF skill sets. This approach addresses individual differences in PF at the intervention level, allowing us to compare burnout and well-being outcomes between individualized and nonindividualized groups. A recent study using a similar methodological design demonstrated that an individualized version of a PF intervention was more effective than a nonindividualized version in reducing general psychological distress and improving mental health outcomes [75]. We expect that an individualized intervention will address the problem of individual heterogeneity by delivering more relevant and precisely targeted intervention skills than the nonindividualized version.

Hypothesis 3 states the following: we hypothesize that medical students in the individualized intervention group will demonstrate significantly greater improvements in PF, burnout, and well-being outcomes (before and after intervention) than those in the nonindividualized group.

App-Based Intervention Delivery

Review studies of individual resource-building interventions for medical students highlight the need to explore the efficacy of delivering interventions using nontraditional methods, (eg, smartphone apps) [23]. To the best of our knowledge, there are no published studies assessing the efficacy of smartphone app-based cognitive behavioral interventions for burnout or well-being among medical students or physicians. We adopted this mode of delivery for 5 main reasons. First, app-based platforms facilitate the tailoring of interventions to the needs of each participant, providing opportunities to deliver targeted skills training activities appropriate to the individual's needs in a particular moment [75]. Second, research indicates that medical students tend not to seek support for burnout owing to the perceived stigma related to mental health and beliefs that others will see them as weak or unable to cope with working in the field [24,34]. App-based interventions have the potential to provide greater acceptability to students with these concerns by allowing them to maintain discretion, anonymity, and privacy while engaging in an intervention [34]. Third, the time requirements of participating in well-being programs can also be a barrier to engagement among medical students [76]. App-based formats facilitate the delivery of short training activities and flexible completion options, which may buffer the impact of time-related barriers [34]. Fourth, there is evidence supporting the acceptability and efficacy of web-based PF interventions among university students as well as the capacity for such interventions to promote intervention engagement [75]. Finally, app-based interventions can be favorable to stakeholders because of their scalability, making them accessible to large numbers of individuals [18]. This is particularly important in circumstances where access to health care personnel is limited or where face-to-face interventions are not practical or possible (eg, during a global pandemic).

Methods

Study Setting

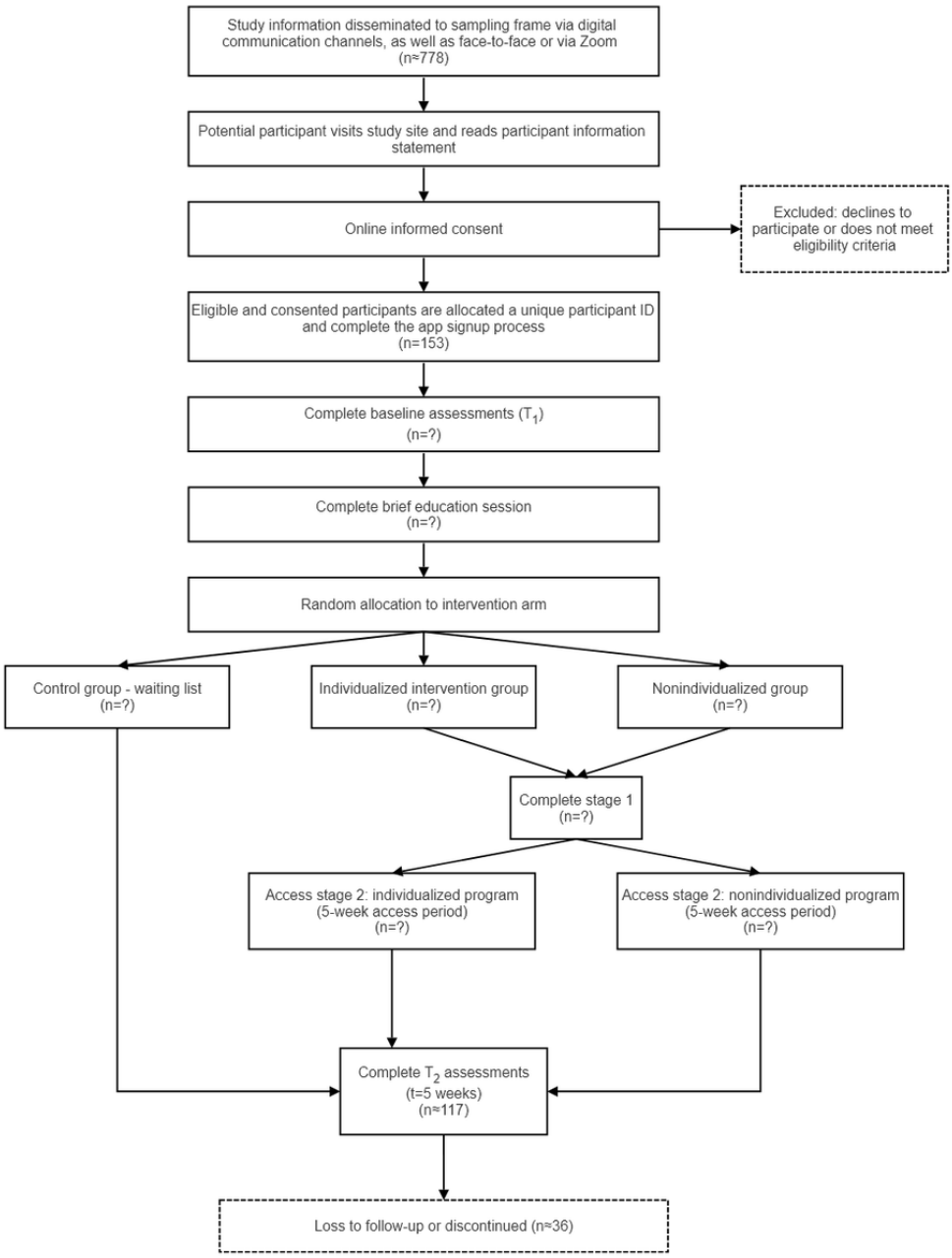
This study will be conducted with the first-, second-, fourth-, and fifth-year undergraduate medical students enrolled in the Joint Medical Program (JMP) at the University of Newcastle and University of New England, Australia, which included 778 enrolled students in June 2021.

Study Design

This study will adopt a 3-arm, parallel, partially blinded (participants), randomized controlled design.

All participants will complete a brief educational session that introduces the potential benefits of PF skills relating to burnout and well-being. Following this, they will be randomized into 1 of the 3 intervention arms using a 1:1:1 allocation ratio. Randomization will be conducted within the app. The three intervention arms are as follows: (1) individualized intervention, (2) nonindividualized intervention, and (3) waiting list. Figure 1 outlines the participants' timeline for this study.

Figure 1. Participant timeline.



Sample Size

We conducted a power analysis to determine an appropriate sample size for a repeated measures multivariate analysis of variance (3 groups; measuring 2 time points [baseline and after the intervention]; high correlation between pre- and postintervention measures, 0.6). The calculation allowed for a small but still clinically meaningful effect size (0.25), given that this is the most conservative approach. For power of 80% and Cronbach α of .05, the total required sample size is 117 (39 per intervention arm). We allow for an attrition rate of up to 30% and set our target recruitment sample size at 153 participants (51 per intervention arm).

Eligibility

Participants will be eligible and included if they are enrolled in the first, second, fourth, or fifth year of the JMP at the University of Newcastle or enrolled in the first, second, fourth, or fifth year of the JMP at the University of New England and have regular access to a reliable internet connection and have regular access to an electronic device that is compatible with app use (smartphone or tablet). Third-year students will not be recruited for this trial, as this cohort was previously invited to participate in a pilot trial of the app intervention.

Recruitment and Enrollment Procedures

Eligible students will be invited to participate in the study via the universities' digital media and communication channels, including internal departmental mailing lists and e-newsletters, blackboard sites, and brief information sessions presented verbally by a researcher who is not connected with the JMP. Participation will be voluntary.

Students who are interested in participating will access the enrollment and consent page using a URL or QR code. The

eligibility, consent, and enrollment processes will be conducted using REDCap (Research Electronic Data Capture; Vanderbilt University). Eligible participants should read the participant information statement on the web. Those who elect to participate will provide their consent via e-consent. Once consented and enrolled, participants will complete a brief demographic questionnaire, following which they will be assigned a unique participant ID and receive instructions for downloading the app. The app will be available for download through the App Store (Apple) and Play Store (Android).

Data Collection Tools and Procedures

Data will be collected at two time points: T_1 (baseline) and T_2 (following the completion of the app-based intervention, commencing 5 weeks after baseline).

Study data will be collected via the app, which will record participant responses to questionnaires as well as app use data. Table 1 shows the administration time points for each outcome measure.

Table 1. Outcome measures and administration time points.

Outcome	Assessment	Baseline (T_1)	After the intervention (T_2)	Every log-in (stage 2)
Demographics	Demographics	✓		
Burnout	Maslach Burnout Inventory–General Survey for Students	✓	✓	
Well-being	Mental Health Continuum–Short Form	✓	✓	
Psychological flexibility and psychological inflexibility	Multidimensional Psychological Flexibility Inventory–Short Form	✓	✓	
Depression, anxiety, and stress	Depression Anxiety and Stress Scale-21	✓	✓	
Current psychological flexibility difficulty	Check-in assessment			✓
Activity acceptability	Like or dislike			✓

Demographic Information

The following demographic information will be collected from the participants: age, gender, university enrollment status, indigenous status, work history, previous history of burnout, current engagement in psychological therapy or other treatment, and self-rating (5-point Likert scale) of current physical health, diet, and self-care behavior.

Primary Outcome: Burnout

We will assess burnout using the 3-factor Maslach Burnout Inventory–General Survey for Students [77]. This 16-item self-report questionnaire assesses the degree to which participants are experiencing each of the following burnout components: *Exhaustion*, stress; *Cynicism*, attitude; and *Academic Inefficacy*, achievement. The Maslach Burnout Inventory scale is valid [2], and the reliability of the Maslach Burnout Inventory–General Survey for Students has been demonstrated among a sample of medical students from the United States [76].

Secondary Outcome: Well-being

Reducing burnout risk via the enhancement of PF processes is the primary goal of the skill development program, however, it is also known that PF tends to improve well-being outcomes. This is an important goal because psychological health is not only reflected by the absence of adverse outcomes but also by the presence of well-being [78]. A secondary goal of the intervention program is to facilitate improved well-being among the participants. We will assess well-being using the Mental Health Continuum–Short Form [78]. This 14-item self-report questionnaire assesses the frequency of well-being experiences during the previous month. The scale has demonstrated validity [78], reliability [75,79], and sensitivity to changes in web-based intervention studies [80].

Process Outcome: PF

We will assess PF and psychological inflexibility (PI) using the Multidimensional PF Inventory–Short Form [47]. This 24-item self-report questionnaire assesses the frequency of each PF and PI experience during the previous 2 weeks. In addition to global PF and PI scores, individual subscale scores can be calculated for each of the 6 PF and 6 PI processes. The scale has demonstrated validity [53] and reliability [81] and is responsive to changes over time [47].

Depression, Anxiety, and Stress

Depressive symptoms, anxiety, stress, and general negative affectivity will be screened as secondary outcomes for two key reasons: (1) for comparison purposes with previous similar studies and (2) to explore whether these factors are related to engagement in the intervention as has been observed in previous studies [82]. We will assess these symptoms using the Depression Anxiety and Stress Scale-21 [83]. This valid and reliable 21-item self-report questionnaire assesses the degree of symptoms of depression, anxiety, and stress during the previous week and a general negative affectivity factor [84].

Engagement Data

We will assess the following behavioral engagement metrics using app use data.

Recruitment

The number of participants who enroll in the study during the recruitment period will be assessed.

Adherence

The proportion of recruited participants who meet adherence requirements, defined as the completion of stage 1 and engagement in at least four skill activities during stage 2 (individualized vs nonindividualized analyses only), will be assessed.

Attrition

We will assess attrition at all stages of the program: enrolled but did not sign-up to use the app, did not complete T_1 assessments, did not complete brief educational module, did not complete stage 1, did not complete adherence requirements for stage 2 (individualized vs nonindividualized analyses only), and did not complete T_2 assessments.

App Engagement Frequency

The frequency of participant engagement with components of the app during stage 2 will be assessed using the following: app log-ins, check-in assessments completed, skill activities completed, and skill activities completed per log-in.

Individual Skill Activity Feedback

Following the completion of each stage 2 skill activity, participants will be asked to indicate whether they *liked* the activity by selecting either a thumbs-up (like) or thumbs-down (dislike) icon.

Intervention

PF Model: ACT Intervention

This study will deliver an ACT PF skills training intervention in written and audio formats via a web-based app. ACT facilitates the development of individual PF skills for nonclinical populations, promoting and facilitating actions that support individual well-being [52,67]. Rather than defining uncomfortable internal experiences (eg, thoughts, emotions, and physical sensations) as *symptoms* that need to be changed or eliminated, ACT focuses on altering the way individuals relate to these internal experiences [46,85] and empowering them to respond in ways that are more adaptive in their own lives [86]. This is accomplished through activities that normalize challenging internal experiences as well as training individuals to strengthen present-moment awareness, recognize the influence of their internal experiences over their actions, learn to alter unworkable responses to these internal experiences, and develop more flexible behavioral repertoires that are consistent with their personally chosen values [45,46,85,86].

ACT is conceptually well defined and links its interventions to the mechanisms through which it purportedly elicits change (ie, the 6 PF processes and their corresponding inflexibility processes) [87]. The components of an ACT intervention include the following: present-moment awareness (mindfulness), cognitive defusion, self-as-context, acceptance, values, and committed action.

Two clinical psychologists (first and second authors: ED and BK) with extensive training and experience with ACT interventions and the PF model designed the app intervention. The piloting of the intervention among a small cohort of medical students at the University of Newcastle indicated high acceptability and usability.

Intervention Stages

All participants will complete a brief introductory session that provides education about burnout, psychological well-being, and PF skills (approximately 10 minutes). Participants will then be randomly allocated to the waiting list, individualized intervention, or nonindividualized intervention arm. Participants who are allocated to the individualized and nonindividualized groups will have access to the 2-stage app for 5 weeks.

Stage 1 (Learn the Concepts) presents a conceptual overview of each PF process and provides a framework through which participants can understand the rationale and potential personal relevance of the skills they will be practicing in stage 2. During stage 1, participants are given opportunities to practice each PF skill set. Depending on whether participants choose to complete these optional skill activities, the completion time for stage 1 is approximately 30 to 60 minutes and can be completed over more than one sitting. The completion of stage 1 will unlock access to stage 2.

During stage 2 (Learn the Behaviors), participants will have access to *on demand* PF skills training. They will be asked to complete a check-in assessment each time they access the app, to assess which PF process they are currently experiencing the most difficulty with. For the individualized intervention arm, a participant's check-in assessment response at each log-in will be used to individualize their intervention. That is, participants will receive access to training in whichever skill they report having the most difficulty with in that moment. Participants will be directed to a dashboard that gives them access to all the available skill activities for their identified PF process (eg, if a participant identifies that they are having difficulty attending to the present moment, they will be presented with the present-moment awareness dashboard). Participants may then select an activity or have the app select a random activity for them from within the targeted PF skill set. This method is similar to one adopted in a recent study assessing a web-based ACT intervention for anxiety and depression [75]. For the nonindividualized intervention arm, check-in assessment responses *will not* be used to select a targeted PF skill set for the participant's training during that session. Rather, participants will be directed to any of the PF process dashboards at random.

Upon the completion of a stage 2 skill activity, participants will be asked if they would like to complete another activity. If they select *yes*, those in the individualized group will return to the dashboard of the PF process identified at check-in and may repeat the aforementioned activity selection process. Participants in the nonindividualized group will be presented with another random activity. Participants may complete as many activities as they choose, but will be asked to complete at least four stage 2 skill activities during their 5-week period of access to the app.

Each of the 6 PF dashboards includes 20 brief (2-7 minutes) experiential skill-building activities, resulting in a total of 120 activities available in stage 2. The inclusion of this number of activities was guided by previous studies, indicating that 28 activities were too few [88] and 136 activities were sufficient

[75]. An example activity for each skill set is provided in Multimedia Appendix 1, along with the activity aims as they relate to the PF processes.

App Engagement

Previous piloting of this intervention by our research team indicated that self-reported acceptability by medical students did not necessarily correspond with regular behavioral engagement with the app. Pilot findings showed high engagement in stage 1 but lower than expected engagement in stage 2. Facilitating ongoing user engagement is a known challenge for developers of app-based mental health interventions [89]. The current version of the intervention incorporates the pilot study participants' feedback and suggestions to enhance engagement for the RCT. This includes ensuring that participants are clear about what to expect throughout the intervention, providing clear indicators of progress and achievement, providing opportunities for personally relevant interactive learning and self-reflection, delivering in-app reminder notifications (push notifications), and delivering information in multiple forms where possible (eg, written and audio) to accommodate individual learning preferences and situational conditions. The app will also encourage engagement through the provision of positive reinforcement when a participant completes certain activities or completes a particular number of activities (eg, an achievement badge acknowledging their commitment and the benefits of practice).

Data Analysis

Descriptive and inferential statistics will be used to describe demographic, outcome, and app engagement data. To assess hypotheses 1 to 3, modeling to examine treatment efficacy with follow-up outcomes will be performed, using mixed models (with appropriate distribution and link function), including a random intercept for participants to account for repeated measures. Descriptive analyses will be performed for use data obtained from the app platform to assess engagement, including engagement frequency and retention and adherence rates.

Institutional Review Board Approval

This research methodology was peer reviewed and approved by the School of Medicine and Public Health at the University of Newcastle, in accordance with the Australian Code for the Responsible Conduct of Research. The study will be conducted according to the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007). Ethics approval was granted by the University of Newcastle Human Research Ethics Committee (approval ID: H-2020-0311) on July 13, 2021, and ratified by the University of New England Human Research Ethics Committee.

Results

Recruitment for this study occurred between August 2021 and September 2021. Data collection for this sample was completed during December 2021. The study results will be available within 12 months of the final data collection date (ie, results are expected to be available by late 2022). The findings will be disseminated to stakeholders by using various methods, including the lead author's doctoral dissertation, peer-reviewed journals, academic conferences, and other verbal and digital communication channels.

Discussion

Overview

The main aim of this study is to assess whether an app-based ACT intervention is effective in reducing burnout and improving well-being among medical students. On the basis of the literature outlined in the *Introduction*, we expect that students in the intervention groups will demonstrate improved burnout and well-being outcomes compared with students in the waiting-list control group. We will also examine whether changes in burnout and well-being are mediated by PF, which is the hypothesized mechanism of change targeted by the intervention. We will further evaluate whether an individualized version of the intervention is more effective than a nonindividualized version. The individualized version focuses on delivering PF skill activities that specifically target individual participants' needs each time they access the app; therefore, we hypothesize that this version will be more effective in improving all outcomes than the nonindividualized version.

This study responds to an identified need for the development of early intervention initiatives that could prevent burnout and improve well-being among medical students by targeting modifiable individual risk factors [20,22,29-31,33,38]. Although there has been an increase in the number of studies assessing such interventions in recent years [23], there is a need for more rigorous approaches that can clarify optimal intervention targets and methods [23,90]. We contribute to existing research by delivering a PF intervention based on sound principles of behavioral science, adopting a robust randomized controlled design, assessing mediators of changes in outcomes, and addressing heterogeneity among individuals by assessing the potential additive benefits of an individualized intervention approach. Our intervention builds on existing research demonstrating the involvement of PF processes as predictors, moderators, and mediators of burnout and well-being outcomes [11,55-58,63-67,69,70,72]. There is evidence that PF is an individual resource of relevance to burnout and well-being among medical students and physicians [23,32,33,71,72]; however, we are unaware of any published RCTs assessing the benefits of training the full PF skill set within this population to date. To the best of our knowledge, this is also the first individualized app-based skills training intervention targeting burnout prevention and well-being among medical students.

Contributions and Theoretical Implications

The demonstration of full or partial support for our hypotheses will provide important information regarding the strategies for improving burnout and well-being during undergraduate medical training. If the ACT intervention demonstrates efficacy regarding burnout and well-being outcomes, this would strengthen the evidence base for PF as a modifiable psychological resource of importance among medical students. It would also be the first study to demonstrate the benefits of providing PF skills training to this group. This finding would also contribute to the growing body of literature supporting the general role of PF skills in maintaining a healthy career

[55-58,63-67,69,70,72]. Furthermore, demonstrating that the intervention exerted its effect on outcomes via its capacity to improve individual PF processes would have important implications for burnout prevention research. If PF is identified as a mediator of burnout and well-being outcomes among medical students, future interventions could specifically target PF skills as a preventive measure. This approach could offset the risk of burnout *before* symptoms emerge and proactively improve well-being. The identification of PF as a mediating process would provide a metric for assessing an individual's potential degree of burnout risk and their responsiveness to a preventive intervention.

The study findings could also have implications for intervention precision. This is important for stakeholders seeking to deliver initiatives as effectively and efficiently as possible, and medical students seeking time-efficient and personally relevant training [76]. Identifying mediators of burnout and well-being outcomes could facilitate the precise delivery of only the training components necessary to generate changes in the mediating processes, allowing for the elimination of extraneous components [37,40]. Findings regarding the potential additive benefits of individualized intervention have further implications for intervention precision. Static interventions experience the problem of delivering the same training components to all participants, without sensitivity to the differences in individual training needs [37,40]. Previous research has demonstrated the benefits of individualized PF interventions over nonindividualized versions regarding other outcomes (eg, depression and anxiety [75]). Replicating these findings for burnout and well-being outcomes would further support the importance of accounting for individual differences when developing interventions and demonstrate an effective method for doing so.

Finally, the delivery of this intervention via an app is a unique approach, and to the best of our knowledge, there are no published RCTs assessing an intervention of this nature with medical students. The demonstration of the efficacy of an app-based intervention for medical student burnout and well-being provides a potential solution to the problem of delivering well-being resources to this group. App-based interventions address a range of challenges by offering accessibility, privacy, time efficiency, precision, and scalability. These findings are important to both organizational stakeholders and medical students seeking strategies for building sustainable work-related well-being.

Limitations

Although the study represents a rigorous and robust contribution to the existing literature, there are potential limitations. This study will assess the outcomes at baseline and following the completion of the intervention. This may not allow sufficient time for burnout or the well-being–related benefits of the intervention to manifest. As such, we intend to conduct subsequent follow-up studies with consenting participants to assess the long-term outcomes. As previously noted, early piloting of the intervention highlighted engagement issues regarding stage 2 of the intervention. Although we believe we have rectified these issues based on feedback from the pilot study, it is possible that participant engagement in stage 2 might be limited. This would hinder our efforts to assess the differences between individualized and nonindividualized versions. Additionally, the problem that we are seeking to address could further hinder engagement in this study, with stressed students potentially being less likely to maintain their participation over time. Early piloting suggests that short intervention components are a positive factor in facilitating intervention engagement among medical students but that time constraints might adversely impact the completion rates of postintervention outcome measures.

We anticipate that the intervention will produce positive outcomes, but there is a risk of the misuse of such findings. As previously noted, interventions empowering students and physicians to build psychological well-being should be incorporated into broader prevention initiatives that take steps to mitigate modifiable external burnout risk factors. However, organizations might overemphasize the role of individual interventions, placing the burden of burnout prevention solely on medical students and physicians. We advocate against the use of this type of training as a stand-alone intervention but rather as a component of a broader strategy that includes organizational-level changes where needed [29].

Conclusions

This study will contribute to the existing literature aiming to elucidate effective methods for improving medical student well-being and preventing burnout and identifying whether PF is a worthy target of future interventions. We offer a unique method of intervention delivery that can deliver individualized skills training with precision, in a way that is acceptable and scalable among medical student populations. This research has the potential to provide a strong foundation upon which to establish preventive resources and interventions for medical students and professionals, which could offset the broader consequences of burnout for individuals, organizations, patients, and the global economy.

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Authors' Contributions

ED wrote the manuscript, designed the study protocol, and created the app. ED and BK wrote the intervention content. NH provided consultation on protocol design, power and data analyses, and app usability. GH led stakeholder engagement and provided consultation on the translation of various aspects of the protocol and intervention in the cohort context. MN and FRW oversaw the project. All authors provided input for the protocol design and reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Aims and example activities for each psychological flexibility skill set.
[DOCX File , 15 KB - resprot_v11i2e32992_app1.docx]

References

1. Leiter MP, Maslach C. Latent burnout profiles: a new approach to understanding the burnout experience. Burnout Res 2016 Dec;3(4):89-100 [FREE Full text] [doi: 10.1016/j.burn.2016.09.001]
2. Maslach C, Jackson SE, Leiter MP. Maslach Burnout Inventory Manual. Sunnyvale, CA: Consulting Psychologists Press; 1996.
3. Kishita N, Shimada H. Effects of acceptance-based coping on task performance and subjective stress. J Behav Ther Exp Psychiatry 2011 Mar;42(1):6-12. [doi: 10.1016/j.jbtep.2010.08.005] [Medline: 21074000]
4. Kumar S. Burnout and doctors: prevalence, prevention and intervention. Healthcare (Basel) 2016 Jun 30;4(3):37 [FREE Full text] [doi: 10.3390/healthcare4030037] [Medline: 27417625]
5. Maslach C, Leiter MP. Understanding the burnout experience: recent research and its implications for psychiatry. World Psychiatry 2016 Jun;15(2):103-111 [FREE Full text] [doi: 10.1002/wps.20311] [Medline: 27265691]
6. Andel R, Crowe M, Hahn EA, Mortimer JA, Pedersen NL, Fratiglioni L, et al. Work-related stress may increase the risk of vascular dementia. J Am Geriatr Soc 2012 Jan 16;60(1):60-67 [FREE Full text] [doi: 10.1111/j.1532-5415.2011.03777.x] [Medline: 22175444]
7. Schnall PL, Landsbergis PA, Baker D. Job strain and cardiovascular disease. Annu Rev Public Health 1994 May;15(1):381-411. [doi: 10.1146/annurev.pu.15.050194.002121] [Medline: 8054091]
8. Deligkaras P, Panagopoulou E, Montgomery AJ, Masoura E. Job burnout and cognitive functioning: a systematic review. Work Stress 2014;28(2):107-123. [doi: 10.1080/02678373.2014.909545]
9. Ahola K, Toppinen-Tanner S, Seppänen J. Interventions to alleviate burnout symptoms and to support return to work among employees with burnout: systematic review and meta-analysis. Burnout Res 2017 Mar;4:1-11 [FREE Full text] [doi: 10.1016/j.burn.2017.02.001]
10. Salvagioni DA, Melanda FN, Mesas AE, González AD, Gabani FL, Andrade SM. Physical, psychological and occupational consequences of job burnout: a systematic review of prospective studies. PLoS One 2017 Oct 4;12(10):e0185781 [FREE Full text] [doi: 10.1371/journal.pone.0185781] [Medline: 28977041]
11. West CP, Dyrbye LN, Erwin PJ, Shanafelt TD. Interventions to prevent and reduce physician burnout: a systematic review and meta-analysis. Lancet 2016 Nov;388(10057):2272-2281. [doi: 10.1016/s0140-6736(16)31279-x]
12. Hassard J, Teoh KR, Visockaite G, Dewe P, Cox T. The cost of work-related stress to society: a systematic review. J Occup Health Psychol 2018 Jan;23(1):1-17. [doi: 10.1037/ocp0000069] [Medline: 28358567]
13. Shanafelt TD, Kaups KL, Nelson H, Satele DV, Sloan JA, Oreskovich MR, et al. An interactive individualized intervention to promote behavioral change to increase personal well-being in US surgeons. Ann Surg 2014 Jan;259(1):82-88 [FREE Full text] [doi: 10.1097/SLA.0b013e3182a58fa4] [Medline: 23979287]
14. Rotenstein LS, Torre M, Ramos MA, Rosales RC, Guille C, Sen S, et al. Prevalence of burnout among physicians: a systematic review. J Am Med Assoc 2018 Sep 18;320(11):1131-1150 [FREE Full text] [doi: 10.1001/jama.2018.12777] [Medline: 30326495]
15. Frajerman A, Morvan Y, Krebs M, Gorwood P, Chaumette B. Burnout in medical students before residency: a systematic review and meta-analysis. Eur Psychiatry 2019 Jan 01;55:36-42. [doi: 10.1016/j.eurpsy.2018.08.006] [Medline: 30384110]
16. Kuhn CM, Flanagan EM. Self-care as a professional imperative: physician burnout, depression, and suicide. Can J Anaesth 2017 Feb;64(2):158-168. [doi: 10.1007/s12630-016-0781-0] [Medline: 27910035]
17. Dyrbye LN, Thomas MR, Massie FS, Power DV, Eacker A, Harper W, et al. Burnout and suicidal ideation among U.S. medical students. Ann Intern Med 2008 Sep 02;149(5):334-341. [doi: 10.7326/0003-4819-149-5-200809020-00008] [Medline: 18765703]
18. Harvey SB, Epstein RM, Glozier N, Petrie K, Strudwick J, Gayed A, et al. Mental illness and suicide among physicians. Lancet 2021 Sep;398(10303):920-930. [doi: 10.1016/s0140-6736(21)01596-8]

19. Shanafelt TD, Boone S, Tan L, Dyrbye LN, Sotile W, Satele D, et al. Burnout and satisfaction with work-life balance among US physicians relative to the general US population. Arch Intern Med 2012 Oct 08;172(18):1377-1385. [doi: 10.1001/archinternmed.2012.3199] [Medline: 22911330]
20. Bugaj T, Cranz A, Junne F, Erschens R, Herzog W, Nikendei C. Psychosocial burden in medical students and specific prevention strategies. Ment Health Prevent 2016 Mar;4(1):24-30. [doi: 10.1016/j.mhp.2015.12.003]
21. Demerouti E. Strategies used by individuals to prevent burnout. Eur J Clin Invest 2015 Oct 02;45(10):1106-1112. [doi: 10.1111/eci.12494] [Medline: 26153110]
22. Costa EF, Santos SA, Santos AT, Melo EV, Andrade TM. Burnout Syndrome and associated factors among medical students: a cross-sectional study. Clinics 2012 Jun 11;67(6):573-579 [FREE Full text] [doi: 10.6061/clinics/2012(06)05]
23. Seo C, Corrado M, Fournier K, Bailey T, Haykal K. Addressing the physician burnout epidemic with resilience curricula in medical education: a systematic review. BMC Med Educ 2021 Feb 01;21(1):80 [FREE Full text] [doi: 10.1186/s12909-021-02495-0] [Medline: 33526019]
24. Fares J, Al Tabosh H, Saadeddin Z, El Mouhayyar C, Aridi H. Stress, burnout and coping strategies in preclinical medical students. N Am J Med Sci 2016 Feb;8(2):75-81 [FREE Full text] [doi: 10.4103/1947-2714.177299] [Medline: 27042604]
25. De Simone S, Vargas M, Servillo G. Organizational strategies to reduce physician burnout: a systematic review and meta-analysis. Aging Clin Exp Res 2021 Apr 09;33(4):883-894. [doi: 10.1007/s40520-019-01368-3] [Medline: 31598914]
26. D'Eon MF, Thompson G, Stacey A, Campoli J, Riou K, Andersen M, et al. The alarming situation of medical student mental health. Can Med Educ J 2021 Jun 23;12(3):176-178 [FREE Full text] [doi: 10.36834/cmej.70693] [Medline: 34249209]
27. Bailey JG, Wong M, Bailey K, Banfield JC, Barry G, Munro A, et al. Pandemic-related factors predicting physician burnout beyond established organizational factors: cross-sectional results from the COPING survey. Psychol Health Med 2021 Oct 14:1-15. [doi: 10.1080/13548506.2021.1990366] [Medline: 34649468]
28. Dyrbye LN, Satele D, West CP. Association of characteristics of the learning environment and us medical student burnout, empathy, and career regret. JAMA Netw Open 2021 Aug 02;4(8):e2119110 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.19110] [Medline: 34369990]
29. Kemp S, Hu W, Bishop J, Forrest K, Hudson JN, Wilson I, et al. Medical student wellbeing - a consensus statement from Australia and New Zealand. BMC Med Educ 2019 Mar 04;19(1):69 [FREE Full text] [doi: 10.1186/s12909-019-1505-2] [Medline: 30832630]
30. Ishak W, Nikravesh R, Lederer S, Perry R, Ogunyemi D, Bernstein C. Burnout in medical students: a systematic review. Clin Teach 2013 Aug;10(4):242-245. [doi: 10.1111/tct.12014] [Medline: 23834570]
31. Voltmer E, Rosta J, Aasland OG, Spahn C. Study-related health and behavior patterns of medical students: a longitudinal study. Medical Teacher 2010 Sep 20;32(10):422-428. [doi: 10.3109/0142159x.2010.496008]
32. Kroska EB, Calarge C, O'Hara MW, Deumic E, Dindo L. Burnout and depression in medical students: relations with avoidance and disengagement. J Context Behav Sci 2017 Oct;6(4):404-408. [doi: 10.1016/j.jcbs.2017.08.003]
33. Palladino CL, Ange B, Richardson DS, Casillas R, Decker M, Gillies RA, et al. Measuring psychological flexibility in medical students and residents: a psychometric analysis. Med Educ Online 2013 Aug 13;18(1):20932 [FREE Full text] [doi: 10.3402/meo.v18i0.20932] [Medline: 23948496]
34. Thompson G, McBride RB, Hosford CC, Halaas G. Resilience among medical students: the role of coping style and social support. Teach Learn Med 2016 Apr 11;28(2):174-182. [doi: 10.1080/10401334.2016.1146611] [Medline: 27064719]
35. Arif NM, Roslan NS, Ismail SB, Nayak RD, Jamian MR, Roshidi AS, et al. Prevalence and associated factors of psychological distress and burnout among medical students: findings from two campuses. Int J Environ Res Public Health 2021 Aug 10;18(16):8446 [FREE Full text] [doi: 10.3390/ijerph18168446] [Medline: 34444193]
36. Mäkikangas A, Kinnunen U. The person-oriented approach to burnout: a systematic review. Burnout Res 2016 Mar;3(1):11-23. [doi: 10.1016/j.burn.2015.12.002]
37. Hofmann SG, Hayes SC. The future of intervention science: process-based therapy. Clin Psychol Sci 2019 Jan 29;7(1):37-50 [FREE Full text] [doi: 10.1177/2167702618772296] [Medline: 30713811]
38. Dunn LB, Iglewicz A, Moutier C. A conceptual model of medical student well-being: promoting resilience and preventing burnout. Acad Psychiatry 2008 Feb 01;32(1):44-53. [doi: 10.1176/appi.ap.32.1.44] [Medline: 18270280]
39. Wersebe H, Lieb R, Meyer AH, Hofer P, Gloster AT. The link between stress, well-being, and psychological flexibility during an Acceptance and Commitment Therapy self-help intervention. Int J Clin Health Psychol 2018 Jan;18(1):60-68 [FREE Full text] [doi: 10.1016/j.ijchp.2017.09.002] [Medline: 30487911]
40. Hayes SC, Hofmann SG, Stanton CE, Carpenter JK, Sanford BT, Curtiss JE, et al. The role of the individual in the coming era of process-based therapy. Behav Res Ther 2019 Jun;117:40-53. [doi: 10.1016/j.brat.2018.10.005] [Medline: 30348451]
41. Puolakanaho A, Tolvanen A, Kinnunen SM, Lappalainen R. Burnout-related ill-being at work: associations between mindfulness and acceptance skills, worksite factors, and experienced well-being in life. J Context Behav Sci 2018 Oct;10:92-102. [doi: 10.1016/j.jcbs.2018.09.003]
42. Maricuţoiu LP, Sava FA, Butta O. The effectiveness of controlled interventions on employees' burnout: a meta-analysis. J Occup Organ Psychol 2014 Dec 16;89(1):1-27. [doi: 10.1111/joop.12099]
43. Ruotsalainen JH, Verbeek JH, Mariné A, Serra C. Preventing occupational stress in healthcare workers. Cochrane Database Syst Rev 2015 Apr 07(4):CD002892 [FREE Full text] [doi: 10.1002/14651858.CD002892.pub5] [Medline: 25847433]

44. Awa WL, Plaumann M, Walter U. Burnout prevention: a review of intervention programs. Patient Educ Couns 2010 Feb;78(2):184-190. [doi: 10.1016/j.pec.2009.04.008] [Medline: 19467822]
45. Moran DJ. ACT for leadership: using acceptance and commitment training to develop crisis-resilient change managers. Int J Behav Consult Ther 2010;6(4):341-355. [doi: 10.1037/h0100915]
46. Hayes SC, Strosahl KD, Wilson KG, Sandoz EK, Craske MG. Acceptance and Commitment Therapy: The Process and Practice of Mindful Change. New York: Guilford Press; 2016.
47. Rolffs JL, Rogge RD, Wilson KG. Disentangling Components of Flexibility via the Hexaflex Model: Development and Validation of the Multidimensional Psychological Flexibility Inventory (MPFI). Assessment 2018 Jun 05;25(4):458-482. [doi: 10.1177/1073191116645905] [Medline: 27152011]
48. Stabbe OK, Rolffs JL, Rogge RD. Flexibly and/or inflexibly embracing life: identifying fundamental approaches to life with latent profile analyses on the dimensions of the Hexaflex model. J Context Behav Sci 2019 Apr;12:106-118. [doi: 10.1016/j.jcbs.2019.03.003]
49. Hayes SC, Pistorello J, Levin ME. Acceptance and Commitment Therapy as a unified model of behavior change. Counsel Psychol 2012 Sep 26;40(7):976-1002. [doi: 10.1177/0011000012460836]
50. Hayes SC, Strosahl KD, Wilson KG. Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change. New York: Guilford Press; 1999.
51. Onwezen MC, van Veldhoven MJ, Biron M. The role of psychological flexibility in the demands–exhaustion–performance relationship. Eur J Work Organ Psychol 2012 Nov 22;23(2):163-176. [doi: 10.1080/1359432x.2012.742242]
52. Biglan A, Hayes SC, Pistorello J. Acceptance and commitment: implications for prevention science. Prev Sci 2008 Sep 9;9(3):139-152 [FREE Full text] [doi: 10.1007/s11121-008-0099-4] [Medline: 18690535]
53. Rogge RD, Daks JS, Dubler BA, Saint KJ. It's all about the process: examining the convergent validity, conceptual coverage, unique predictive validity, and clinical utility of ACT process measures. J Context Behav Sci 2019 Oct;14:90-102. [doi: 10.1016/j.jcbs.2019.10.001]
54. Hayes SC. Acceptance and Commitment Therapy exceeds 600 randomized controlled trials. Association for Contextual Behavioral Science. 2021. URL: https://contextualscience.org/news/acceptance_and_commitment_therapy_exceeds_600_randomized_controlled_trials [accessed 2021-08-04]
55. Lloyd J, Bond FW, Flaxman PE. The value of psychological flexibility: examining psychological mechanisms underpinning a cognitive behavioural therapy intervention for burnout. Work Stress 2013 Apr;27(2):181-199. [doi: 10.1080/02678373.2013.782157]
56. Vilardaga R, Luoma JB, Hayes SC, Pistorello J, Levin ME, Hildebrandt MJ, et al. Burnout among the addiction counseling workforce: the differential roles of mindfulness and values-based processes and work-site factors. J Subst Abuse Treat 2011 Jun;40(4):323-335 [FREE Full text] [doi: 10.1016/j.jsat.2010.11.015] [Medline: 21257281]
57. Veage S, Ciarrochi J, Deane FP, Andresen R, Oades LG, Crowe TP. Value congruence, importance and success and in the workplace: links with well-being and burnout amongst mental health practitioners. J Context Behav Sci 2014 Oct;3(4):258-264. [doi: 10.1016/j.jcbs.2014.06.004]
58. Puolakanaho A, Tolvanen A, Kinnunen SM, Lappalainen R. A psychological flexibility -based intervention for Burnout: a randomized controlled trial. J Context Behav Sci 2020 Jan;15:52-67. [doi: 10.1016/j.jcbs.2019.11.007]
59. Gloster AT, Meyer AH, Lieb R. Psychological flexibility as a malleable public health target: evidence from a representative sample. J Context Behav Sci 2017 Apr;6(2):166-171. [doi: 10.1016/j.jcbs.2017.02.003]
60. Ruiz FJ, Odriozola-González P. The predictive and moderating role of psychological flexibility in the development of job burnout. Univ Psychol 2017 Dec 31;16(4):1-8. [doi: 10.11144/javeriana.upsy16-4.pmrp]
61. Bond FW, Bunce D. The role of acceptance and job control in mental health, job satisfaction, and work performance. J Appl Psychol 2003 Dec;88(6):1057-1067. [doi: 10.1037/0021-9010.88.6.1057] [Medline: 14640816]
62. Arslan G, Allen K. Exploring the association between coronavirus stress, meaning in life, psychological flexibility, and subjective well-being . Psychol Health Med 2021 Jan 25:1-12. [doi: 10.1080/13548506.2021.1876892] [Medline: 33487048]
63. Bond FW, Bunce D. Mediators of change in emotion-focused and problem-focused worksite stress management interventions. J Occupat Health Psychol 2000;5(1):156-163. [doi: 10.1037/1076-8998.5.1.156]
64. Bond FW, Hayes SC, Barnes-Holmes D. Psychological flexibility, ACT, and organizational behavior. J Organ Behav Manag 2006 Nov 07;26(1-2):25-54. [doi: 10.1300/j075v26n01_02]
65. Brinkborg H, Michanek J, Hesser H, Berglund G. Acceptance and Commitment Therapy for the treatment of stress among social workers: a randomized controlled trial. Behav Res Ther 2011 Jun;49(6-7):389-398. [doi: 10.1016/j.brat.2011.03.009] [Medline: 21513917]
66. Flaxman PE, Bond FW. A randomised worksite comparison of Acceptance and Commitment Therapy and stress inoculation training. Behav Res Ther 2010 Aug;48(8):816-820. [doi: 10.1016/j.brat.2010.05.004] [Medline: 20627269]
67. Frögéli E, Djordjevic A, Rudman A, Livheim F, Gustavsson P. A randomized controlled pilot trial of acceptance and commitment training (ACT) for preventing stress-related ill health among future nurses. Anxiety Stress Coping 2016 Apr 07;29(2):202-218. [doi: 10.1080/10615806.2015.1025765] [Medline: 25759942]
68. Ost LG. The efficacy of Acceptance and Commitment Therapy: an updated systematic review and meta-analysis. Behav Res Ther 2014 Oct;61:105-121. [doi: 10.1016/j.brat.2014.07.018] [Medline: 25193001]

69. Kinnunen SM, Puolakanaho A, Tolvanen A, Mäkikangas A, Lappalainen R. Does mindfulness-, acceptance-, and value-based intervention alleviate burnout?—A person-centered approach. Int J Stress Manag 2019 Feb;26(1):89-101. [doi: 10.1037/str0000095]
70. Kinnunen SM, Puolakanaho A, Mäkikangas A, Tolvanen A, Lappalainen R. Does a mindfulness-, acceptance-, and value-based intervention for burnout have long-term effects on different levels of subjective well-being? Int J Stress Manag 2020 Feb;27(1):82-87. [doi: 10.1037/str0000132]
71. Solms L, van Vianen AE, Theeboom T, Koen J, de Pagter AP, de Hoog M. Keep the fire burning: a survey study on the role of personal resources for work engagement and burnout in medical residents and specialists in the Netherlands. BMJ Open 2019 Nov 05;9(11):e031053 [FREE Full text] [doi: 10.1136/bmjopen-2019-031053] [Medline: 31694848]
72. Regehr C, Glancy D, Pitts A, LeBlanc VR. Interventions to reduce the consequences of stress in physicians: a review and meta-analysis. J Nerv Ment Dis 2014 May;202(5):353-359. [doi: 10.1097/NMD.0000000000000130] [Medline: 24727721]
73. Berjot S, Altintas E, Grebot E, Lesage F. Burnout risk profiles among French psychologists. Burnout Res 2017 Dec;7:10-20 [FREE Full text] [doi: 10.1016/j.burn.2017.10.001]
74. Villatte JL, Vilardaga R, Villatte M, Vilardaga JC, Atkins DC, Hayes SC. Acceptance and Commitment Therapy modules: differential impact on treatment processes and outcomes. Behav Res Ther 2016 Feb;77:52-61 [FREE Full text] [doi: 10.1016/j.brat.2015.12.001] [Medline: 26716932]
75. Levin ME, Haeger J, Cruz RA. Tailoring Acceptance and Commitment Therapy skill coaching in the moment through smartphones: results from a randomized controlled trial. Mindfulness 2018 Jul 21;10(4):689-699. [doi: 10.1007/s12671-018-1004-2]
76. Obregon M, Luo J, Shelton J, Blevins T, MacDowell M. Assessment of burnout in medical students using the Maslach Burnout Inventory-Student Survey: a cross-sectional data analysis. BMC Med Educ 2020 Oct 21;20(1):376 [FREE Full text] [doi: 10.1186/s12909-020-02274-3] [Medline: 33087080]
77. Schaufeli WB, Martínez IM, Pinto AM, Salanova M, Bakker AB. Burnout and engagement in university students. J Cross Cult Psychol 2016 Jul 27;33(5):464-481. [doi: 10.1177/0022022102033005003]
78. Keyes CL. Mental illness and/or mental health? Investigating axioms of the complete state model of health. J Consult Clin Psychol 2005 Jun;73(3):539-548. [doi: 10.1037/0022-006X.73.3.539] [Medline: 15982151]
79. Keyes CL. Brief description of the mental health continuum short form (MHC-SF). HSPH Harvard Education. 2009. URL: https://www.hsph.harvard.edu/health-happiness/mental-health-continuum-short-form/ [accessed 2022-01-08]
80. Levin ME, Haeger JA, Pierce BG, Twohig MP. Web-based Acceptance and Commitment Therapy for mental health problems in college students: a randomized controlled trial. Behav Modif 2017 Jan 01;41(1):141-162. [doi: 10.1177/0145445516659645] [Medline: 27440189]
81. Seidler D, Stone B, Clark BE, Koran J, Drake CE. Evaluating the factor structure of the Multidimensional Psychological Flexibility Inventory: an independent replication and extension. J Context Behav Sci 2020 Jul;17:23-31. [doi: 10.1016/j.jcbs.2020.04.007]
82. Perski O, Blandford A, West R, Michie S. Conceptualising engagement with digital behaviour change interventions: a systematic review using principles from critical interpretive synthesis. Transl Behav Med 2016 Dec 13:254-267. [doi: 10.1007/s13142-016-0453-1] [Medline: 27966189]
83. Lovibond SH, Lovibond PF, Psychology Foundation of Australia. Manual for the depression anxiety stress scales. In: Psychology Foundation Monograph. Sydney, N.S.W: Psychology Foundation of Australia; 1995.
84. Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol 2005 Jun;44(Pt 2):227-239. [doi: 10.1348/014466505X29657] [Medline: 16004657]
85. Reeve A, Tickle A, Moghaddam N. Are Acceptance and Commitment Therapy-based interventions effective for reducing burnout in direct-care staff? A systematic review and meta-analysis. Ment Health Rev J 2018 Jul 04;23(3):131-155. [doi: 10.1108/mhrj-11-2017-0052]
86. Larmar S, Wiatrowski S, Lewis-Driver S. Acceptance and Commitment Therapy: an overview of techniques and applications. J Serv Sci Manag 2014;07(03):216-221. [doi: 10.4236/jssm.2014.73019]
87. Stockton D, Kellett S, Berrios R, Sirois F, Wilkinson N, Miles G. Identifying the underlying mechanisms of change during Acceptance and Commitment Therapy (ACT): a systematic review of contemporary mediation studies. Behav Cogn Psychother 2019 May;47(3):332-362. [doi: 10.1017/S1352465818000553] [Medline: 30284528]
88. Levin ME, Haeger J, Pierce B, Cruz RA. Evaluating an adjunctive mobile app to enhance psychological flexibility in Acceptance and Commitment Therapy. Behav Modif 2017 Nov 08;41(6):846-867. [doi: 10.1177/0145445517719661] [Medline: 28689449]
89. Baumel A, Muench F, Edan S, Kane JM. Objective user engagement with mental health apps: systematic search and panel-based usage analysis. J Med Internet Res 2019 Sep 25;21(9):e14567 [FREE Full text] [doi: 10.2196/14567] [Medline: 31573916]
90. Kim E, Mallett R, Hrabok M, Yang YA, Moreau C, Nwachukwu I, et al. Reducing burnout and promoting health and wellness among medical students, residents, and physicians in alberta: protocol for a cross-sectional questionnaire study. JMIR Res Protoc 2020 Apr 17;9(4):e16285 [FREE Full text] [doi: 10.2196/16285] [Medline: 32301742]

Abbreviations

ACT: Acceptance and Commitment Training
JMP: Joint Medical Program
PF: psychological flexibility
PI: psychological inflexibility
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Testing an mHealth System for Individuals With Mild to Moderate Alcohol Use Disorders: Protocol for a Type 1 Hybrid Effectiveness-Implementation Trial

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Abstract

Background: The extent of human interaction needed to achieve effective and cost-effective use of mobile health (mHealth) apps for individuals with mild to moderate alcohol use disorder (AUD) remains largely unexamined. This study seeks to understand how varying levels of human interaction affect the ways in which an mHealth intervention for the prevention and treatment of AUDs works or does not work, for whom, and under what circumstances.

Objective: The primary aim is to detect the effectiveness of an mHealth intervention by assessing differences in self-reported risky drinking patterns and quality of life between participants in three study groups (self-monitored, peer-supported, and clinically integrated). The cost-effectiveness of each approach will also be assessed.

Methods: This hybrid type 1 study is an unblinded patient-level randomized clinical trial testing the effects of using an evidence-based mHealth system on participants' drinking patterns and quality of life. There are two groups of participants for this study: individuals receiving the intervention and health care professionals practicing in the broader health care environment. The intervention is a smartphone app that encourages users to reduce their alcohol consumption within the context of integrative medicine using techniques to build healthy habits. The primary outcomes for quantitative analysis will be participant data on their risky drinking days and quality of life as well as app use from weekly and quarterly surveys. Cost measures include intervention and implementation costs. The cost per participant will be determined for each study arm, with intervention and implementation costs separated within each group. There will also be a qualitative assessment of health care professionals' engagement with the app as well as their thoughts on participant experience with the app.

Results: This protocol was approved by the Health Sciences Minimal Risk Institutional Review Board on November 18, 2019, with subsequent annual reviews. Recruitment began on March 6, 2020, but was suspended on March 13, 2020, due to the COVID-19 pandemic restrictions. Limited recruitment resumed on July 6, 2020. Trial status as of November 17, 2021, is as follows: 357 participants were enrolled in the study for a planned enrollment of 546 participants.

Conclusions: The new knowledge gained from this study could have wide and lasting benefits related to the integration of mHealth systems for individuals with mild to moderate AUDs. The results of this study will guide policy makers and providers toward cost-effective ways to incorporate technology in health care and community settings.

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International Registered Report Identifier (IRRID): DERR1-10.2196/31109

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KEYWORDS

mHealth; mobile health; alcohol use disorder; alcohol reduction; wellness; risky drinking; quality of life; protocol

Introduction

Overview

This paper describes the protocol for a randomized clinical trial testing an evidence-based alcohol use recovery app adapted for use as a prevention and harm-reduction app for individuals with mild to moderate alcohol use disorder (AUD). This was adapted from an app that was shown to be helpful for patients in residential treatment centers. Alcohol misuse, high-risk drinking, and AUD constitute a public health crisis in the United States [1]. This rate of high-risk drinking has substantially increased in recent years, with 1 in 8 adults reporting high-risk drinking in the past year [1]. In the study cited, high-risk drinking was defined as exceeding the recommended drinking limit of 3 in a day for women and men aged ≥65 years or 4 for men aged ≤65 years at least weekly in the past 12 months [2]. Increases in alcohol use in general and high-risk drinking predict an increase in the treatments needed for certain chronic comorbidities [3]. Improving access to effective treatment is critical for a disease as pervasive as AUD, for which few receive treatment.

Background

The use of mobile health (mHealth) apps to improve the self-management of chronic diseases has steadily increased. A growing body of research has begun to show positive outcomes related to mHealth in the management of chronic conditions [4,5], specifically for unhealthy alcohol use [6-8].

This study uses an mHealth app called *Tula*, Sanskrit for *balance*. Tula is based on Addiction-Comprehensive Health Enhancement Support System (A-CHESS), which was one of the first mHealth apps proven effective in a randomized clinical trial of patients recovering from severe AUD [8]. In an earlier study, A-CHESS showed a 57% reduction in risky drinking days among patients using the app with standard of care compared with those who did not use an app when leaving a 90-day residential treatment for AUD. Since then, the platform has been used as an addiction recovery support and relapse prevention with thousands of patients across various settings, including at-risk veterans in upstate New York [9], women in rural Appalachia [10], and drug-court participants in Massachusetts [11]. The intervention was also adapted for specific populations; for instance, a Spanish-language version of the app was developed to test a culturally relevant recovery support service for Hispanic and Latino patients completing residential treatment in the Boston area [12]. The system has been adapted for other substance use disorders, and A-CHESS is currently being tested in a randomized trial of patients with opioid use disorder [13]. In addition, the platform—under the name *Seva*, Sanskrit for *selfless caring*—was used in the first mHealth implementation research trial that aimed to integrate behavioral health treatment into primary care [14]. The original and subsequent versions of A-CHESS have a theoretical basis in self-determination theory, which holds that helping people meet three basic needs—feeling competent, feeling related to others, and feeling internally motivated and not coerced in one's actions—improves their adaptive functioning [15].

To our knowledge, the literature does not address the extent to which human interaction is needed to achieve the most clinically effective and cost-effective benefits of mHealth app use. Addressing these questions is essential for determining the future role of mHealth in reducing drinking and alcohol-related harm. These questions have implications for addressing substance use disorders and other chronic illnesses within health care settings.

Objectives

This study seeks to understand how varying levels of human interaction affect the ways in which an mHealth system works or does not work, for whom, and under what circumstances. This trial tests three different mHealth support models: (1) on their own (a self-monitored, low-touch model) or in conjunction with either (2) peer support from a community organization (a medium-touch model) or (3) clinical support within a primary health care system (a high-touch model). We hypothesize that the differences in level of interaction (*human touch*) within the 3 mHealth support models will demonstrate effectiveness, allowing cost-effectiveness assessment and potential for dissemination in a population (Table 1). The low-touch model is the least costly and easiest to implement because of its low level of required support. However, if active involvement of either peer support specialists or health care staff substantially increases the effectiveness, the additional cost may be a worthwhile investment.

Table 1. The 3-month intervention: 3 study arms.

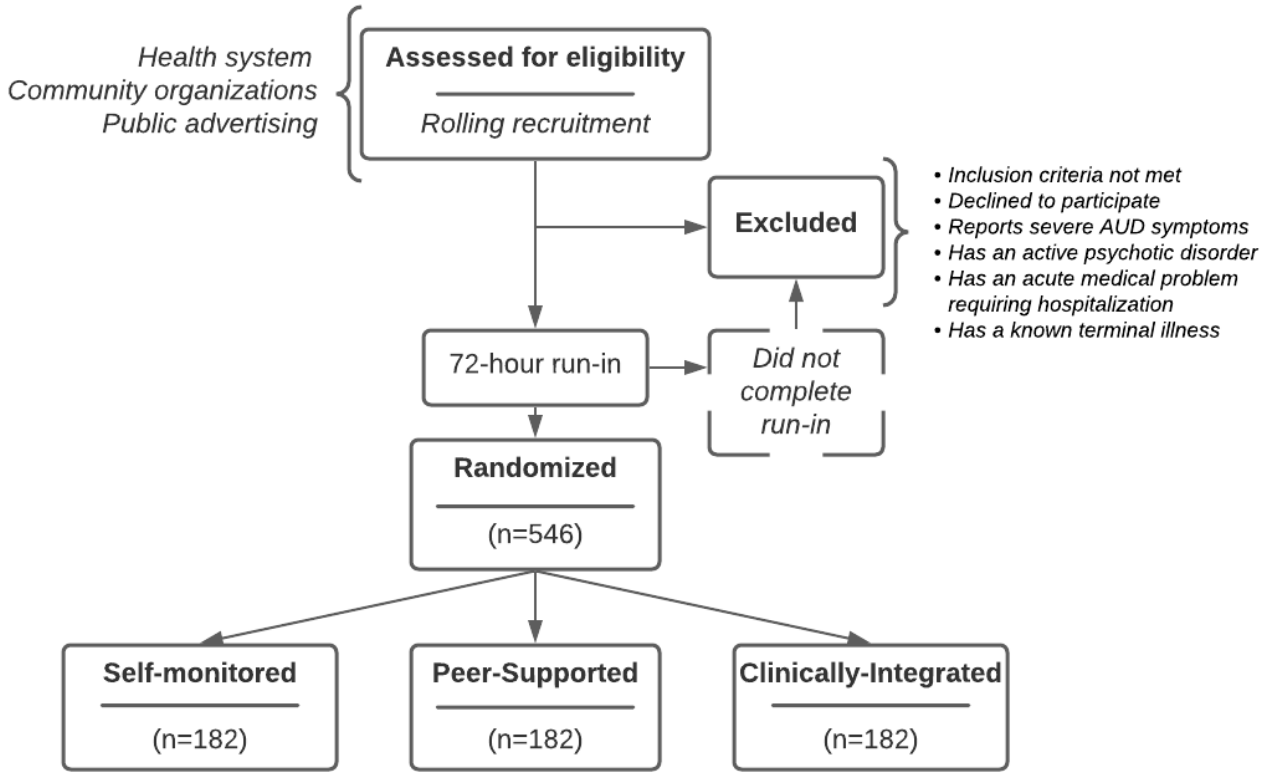
Self-monitored (app only)	Peer-Supported	Clinically integrated
Unguided use of Tula	Tula use supported by a community-based peer support specialist	Tula use supported by the health coach
Study team conducts safety monitoring and technical support	Interpersonal communication and wellness monitoring via the app	Up to three 1:1 health coaching sessions via phone call
No discussion forum	A discussion forum moderated by a peer support specialist	A discussion forum moderated by a health coach
No communication feature with private messaging	The private messaging feature in communication routing to a peer support specialist	The private messaging feature in communication routing to a health coach
No dashboard access	No dashboard access	Health monitoring supported by a clinician dashboard

The primary aim is to detect the effectiveness of the intervention on (1) self-reported risky drinking patterns and (2) quality of life in the three study groups (self-monitored, peer-supported, and clinically integrated). The secondary aims complement the primary aim. First, we will look at the degree to which sex (male or female) and severity of alcohol use moderates the intervention outcomes among Tula users and the degree to which patient competence, relatedness, and autonomous motivation (the 3 tenets of self-determination theory) [15] mediate the intervention effect in the Tula groups. We will also assess the cost-effectiveness of each approach. Finally, we will conduct qualitative assessment interviews to understand clinician and implementer engagement and ways to refine Tula and its associated integration for future implementation and dissemination.

Study Design

The study is an unblinded, patient-level, randomized clinical trial (Figure 1). A hybrid type I design [16] is used to test the effects of an intervention while simultaneously gathering information related to implementation. This hybrid type I trial tests the effects of the use of an evidence-based mHealth system on participants' moderate- to high-risk drinking patterns and quality of life. The study design allows for each of the 3 randomized groups to receive an intervention variant using mHealth support models designed to support the clinical integration of behavioral intervention technologies (BITs), as described by Hermes et al [17]. The study design compares a fully automated BIT with 2 guided BITs, differentiated by graduated levels of external support (as described in detail in the Intervention section).

Figure 1. Study diagram. AUD: alcohol use disorder.



Methods

Participants, Interventions, and Outcomes

Study Setting

Overview

The study setting to recruit participants is the geographic boundaries of a large academic integrated health care system spanning several contiguous counties in a Midwestern state. The study management site is housed within the academic medical center (a university with a medical school and a teaching hospital or health care system) [18]. As an mHealth study, this study is conducted in a fully remote fashion, including partnerships with local community organizations.

Eligibility Criteria

There are two groups of participants for this study: (1) individuals who will receive the intervention and (2) health care professionals practicing in a broader health care environment.

Textbox 1. Patient inclusion and exclusion criteria.

Inclusion criteria

- Aged ≥21 years
- Wants to reduce drinking
- Owns a smartphone and is willing to download and use the Tula app
- Lives within the health system service area
- Meets at least one of the following criteria:
  - Alcohol Use Disorders Identification Test [19] screening score ≥8 or
  - Responds "yes" to at least two questions on the alcohol use disorder (AUD) or the Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) [20] or
  - Reports moderate- to high-risk drinking patterns (as defined by the National Institute on Alcohol Abuse and Alcoholism over the previous week):
    - More than 3 drinks on any single day and more than 7 drinks per week (women)
    - More than 4 drinks on any single day and more than 14 drinks per week (men)

Exclusion criteria

- Reports symptoms consistent with severe AUD during screening (more than 6 of 11 symptoms from DSM-5 criteria; this app does not provide support for severe AUD)
- Has an active psychotic disorder diagnosis
- Has an acute medical problem requiring immediate hospitalization
- Has a known terminal illness

Inclusion and Exclusion Criteria for Health Care Professionals

The selected group of health care professionals will include (1) clinicians who provided information about the study to at least one patient; (2) health care professionals who participated in interviews during the development year preceding the clinical trial; or (3) health care professionals who were involved in the implementation and could provide a health system perspective.

Inclusion and Exclusion Criteria for Participants Receiving the mHealth Intervention

Participants will self-refer to the study; members of the study team will determine eligibility based on self-reported data (Textbox 1) collected via a secure, web-based screening survey.

Other substance use disorders or misuse of other substances will not preclude participants' enrollment in the study. If the following scenarios occur during a participant's study period, the participant will remain enrolled in the study and their circumstances will be documented by the study coordinator:

- The participant is unreachable for follow-up surveys.
- The participant becomes incarcerated. In the case of incarceration, no study data will be collected during the time they are in custody.

Intervention

Overview

Similar to previous and concurrent versions of A-CHESS, Tula operates on smartphones. Tula maintains the core components of A-CHESS but is modified to address the broad spectrum of issues related to alcohol misuse likely to be found in any community in the United States. For example, while the original version of A-CHESS [8] encouraged participants to abstain from using alcohol as a part of their AUD recovery, Tula encourages users to reduce their use of alcohol. One key

adaptation is that Tula adopts the principles of the Whole Health model [18], placing alcohol use reduction within the context of integrative medicine, an adaptation made based on input from partnering health care stakeholders.

Tools and services in Tula (Textbox 2) include self-assessments; goal-setting tools and strategies; techniques for maintaining motivation and building healthy habits; information about drinking and wellness; strategies for reducing drinking and meeting other health goals; audio recordings; and other tools for stress reduction, relaxation, and personal health management.

Textbox 2. Tula content and tools.

Feature and description
• Thought of the Day: daily inspirational quotes intended to motivate and engage participants.
• Whole Health: the Whole Health module provides information and tools to improve the whole health of a person. These topics and tools include the following: What is Whole Health; Circle of Health; Self-Care; Mindful Awareness; Whole Health Resources; and a Personal Health Inventory.
• Motivation: users can record in words and photos their reasons for wanting to work on their drinking and wellness. Other journaling and curation tools to boost motivation include "What Matters to Me," a Gratitude journal, and "Favorites."
• Tracker (the Tracker feature is accessed by all participants but is also monitored by the health coach in the clinically integrated group as part of the health coaching goal-setting): the Tracker tool allows users to set and review goals, track and graph their progress, and record their health and wellness patterns related to their quality of life (such as mood, sleep, social support, etc).
• Communication (communication features are limited in the self-monitored group): users can send and receive private messages with other Tula members and can access in-app discussion forums with other members of their group.
• Information: a content and resource library organized around the Circle of Health's eight domains of self-care—Working Your Body, Sleep and Recharge, Food and Drink, Personal Development, Relationships, Mood and Mindset, Surroundings, and the Power of the Mind.
• Relaxation: information on relaxation techniques, audio recordings for guided meditation, and binaural beats.
• Strategies: tips for reducing drinking, cognitive behavioral therapy, and goal-setting.
• What are you grateful for: a daily prompt to reflect on gratitude.

mHealth Implementation Models

Table 1 outlines the key characteristics of the study arms during the 3-month active intervention period for each patient. All participants had access to the same basic content in Tula. The key differences relate to the level of human touch available by study group assignment.

Self-monitored Group (Low Touch)

Participants will use the app on their own, just as they would any commercially available health app downloaded to their smartphone. There is no access to a discussion forum and private messaging, or the aid of an external care team or social support. Participants may reach out to the study team by email, phone, or from within the app via the "Messages from the Researchers" tool. Communication is only intended for participants to ask questions about the app, about the study, and receive technological support. The study team conducts routine safety monitoring based on participant use data and any communication initiated by the participants to the study team.

Peer-Supported Group (Medium Touch)

Participants have access to social support and access to certified peer support specialists. Peer support specialists are staff members from a community partner outside of the health care system. Newly randomized participants receive a welcome message via the private messaging feature in Tula from peer support specialists. To maintain anonymity, all participants identify themselves using their username. The participants' main interactions are with other members in the same group through discussion forums where they share posts. Peer support specialists moderate and participate in the discussion forums while encouraging the use of Tula (eg, by posting topics in the discussion forum, pointing Tula users to a potentially helpful tip). They have no access to study data and only know the participants through their usernames.

Clinically Integrated Group (High Touch)

Participants have access to a discussion forum specific to this group and have access to a certified health coach. Health coaches, as employees of the health care system, help individuals make lifestyle changes to achieve their goals for health and wellness. Participants can have 3 one-on-one personal health coaching sessions (via phone) during the active 90-day implementation period. Health coaches will provide a structure for participants to achieve their self-identified goals by helping them envision a healthier lifestyle as they reduce their alcohol consumption. Participants can opt to share selected Tula data with the health coach through a dashboard—data on drinking days or drinks per day and other data reported via weekly surveys. These data allow health coaches to provide more responsive support to participants in meeting their goals for alcohol use.

Outcomes

Overview

Table 2 shows the outcomes and the mediators and their measurement. The definition and psychometric properties of each measure are also listed.

Table 2. Outcomes and measures.

Dimension	Measure	Source	Timing (after randomization)
Primary outcomes			
Risky drinking days	Timeline follow back [21,22]	Participant survey	0, 3, 6, 9, and 12 months
Quality of life	PROMIS[a] Global Health [23] and 2 COVID-19 impact items	Participant survey	0, 3, 6, 9, and 12 months
Cost outcomes			
Health care use	Medical services utilization form [24]	Participant survey	0, 6, and 12 months
Implementation costs	COINS[b] [25]	Health care professional interviews	Every 6 months
Mediators			
Relatedness	McTavish Bonding Scale [26]	Participant survey	0, 3, 6, 9, and 12 months
Competence	Perceived Competence Scale	Participant survey	0, 3, 6, 9, and 12 months
Autonomous motivation	TSRQ[c]	Participant survey	0, 3, 6, 9, and 12 months
Tula use (patients)	Number of days used; number of pages viewed	Server log files	Continuous
Other outcomes			
Risk and protection factors	Brief Alcohol Monitor (revised) [27]	Participant survey	Weekly
Tula use (clinicians)	Number of days used	Server log files	Continuous
Patient characteristics	Race, ethnicity, biological sex, and age	Participant survey	0 months

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

[b]COINS: Cost of Implementing New Strategies.

[c]TSRQ: Treatment Self-Regulation Questionnaire.

Primary Outcomes

The primary outcomes include patient-reported risky drinking days and quality of life. Risky drinking days are the number of days on which a participant's drinking in a 2-hour period exceeded 4 standard drinks for men and 3 standard drinks for women, defined using the National Institute on Alcohol Abuse and Alcoholism's definition of a standard drink as 1 containing 14 g of 1 alcohol (12 oz of regular beer, 5 oz of wine, or 1.5 oz of distilled spirits) [2]. Risky drinking days are measured using the patient-reported timeline follow back survey. The timeline follow back survey consistently demonstrates reliability for assessments in recall periods as long as 6 months, test-retest reliability of ≥0.80, and convergent and discriminant validity with other measures; it also correlates with collateral reports and urine toxicology tests [28]. Quality of life will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health scale, a 10-item subjective measure of general health [29]. It includes a 4-item global physical health scale (Cronbach α=.81), a 4-item global mental health scale (Cronbach α=.86), and two additional items—general health and satisfaction with social roles—that can each be scored as a single item. The PROMIS scales were developed using item response theory and capture a greater range of the trait being measured with greater precision than other instruments. At the beginning of the COVID-19 pandemic, we added two 5-point Likert scale items asking about the impact of the COVID-19 pandemic on participants' physical and mental health.

Cost Outcomes

Cost measures include health care use costs and intervention and implementation costs. Health care use will be collected from the self-reported medical services utilization form [24] (6 items). Intervention costs will be determined using Tula time-stamped log files and billing codes logged by the health coach. Implementation costs will be determined through clinic staff interviews at the end of the intervention period using the Cost of Implementing New Strategies model [30]. The cost per participant will be determined for each study arm (self-monitored, peer-supported, and clinically integrated) with intervention and implementation costs separated within each group.

Mediators

Several mediators include the 3 fundamental psychological needs based on the self-determination theory [15] and the Tula use data. Among the 3 core needs specified by self-determination theory, relatedness will be measured using the McTavish 5-item Bonding scale [26], which is highly correlated with other social support scales, has a high reliability of 0.9, and has been found to mediate effects between patients' use of eHealth systems and their coping behaviors [26,31]. Competence will be measured by the perceived competence scale, a 4-item alcohol-addiction focused scale rating confidence in the ability to cope in high-risk situations; reported reliability was above 0.9 [32]. Autonomous motivation will be measured by the modified Treatment Self-Regulation Questionnaire, which uses a 7-point Likert scale to respond to 5 items assessing the degree to which a person's motivation for healthy behavior is

autonomous. Previous tests found good reliability (Cronbach α=.88) and predicted changes in health-related behavior (*P*<.001). Participant use of Tula will be measured by the number of days using Tula and the number of pages viewed. Days of use and pages were found to be associated with a reduction in risky drinking days among AUD participants [8]. Clinician use of Tula will be measured by counting the number of days per month in which clinicians log into the system during the intervention period and the pages viewed.

Participant Timeline

Participants' involvement in the study can be divided into four distinct phases: (1) a pre-enrollment period encompassing screening completion, evaluation by the study team, and downloading the app; (2) an enrollment period consisting of a 2-stage consent process framing a 72-hour run-in period, a phone call with a member of the research team, randomization, and the final confirmation of enrollment; (3) a 3-month active intervention period; and (4) a 9-month follow-up period (Figure 2).

Figure 2. Participant timeline.

The pre-enrollment and enrollment phases, together, may range from approximately 48 hours to 3 weeks, depending on the participant's responsiveness and availability. Once enrolled, a participant will be engaged in the study for 12 months.

Sample Size

This study was designed to detect the differences in the two primary outcomes, Risky Drinking Days and Quality of Life, among the 3 groups. In a previous study [33], after a 6-month web-based intervention study, alcohol users in the internet-based, therapist-led group reported having fewer drinks (Cohen *d*=0.38) and a better quality of life (Cohen *d*=0.44) than those in the internet-based, self-help group. In this protocol, sufficient power (1-β=.80, multiple comparison adjusted Cronbach α=.00833, 2-tailed) to detect a more conservative effect size of Cohen *d*=0.25 in a design with 4 repeated measurements with a first-order autoregressive covariance structure (correlation ρ=0.3) would require approximately 182 participants per group (or a total of 546), assuming 28% attrition. Using prior research [14] to estimate the SD of risky drinking days, the effect of Cohen *d*=0.25 would equate to a difference of approximately 0.24 risky drinking days per week and 1.62 overall quality of life value measured by the PROMIS Global Health instrument.

Recruitment

Participant Recruitment

Recruitment for this study relies on raising its visibility among key groups of stakeholders and tailoring our outreach efforts to be relevant and sensitive to each group's needs and interests. The study's recruitment strategy has centered on three key areas: clinical settings, community-based organizations, and the public media marketplace.

By promoting the study to health care professionals, primary care providers, social workers, emergency departments, and behavioral health specialists operating within the local health systems, we enlisted the help of clinical study champions and aim to provide information and resources they can share with patients who may be eligible for the study. Engaging with local leaders from underrepresented and marginalized communities and working to build or fortify relationships with community-based organizations and partners is critical for promoting the study in a way that invites participation and inclusion of diverse voices, perspectives, and experiences. Finally, the use of targeted digital and print media enables the study team to promote the study broadly but strategically while providing information and materials that enable potential participants to learn about the study in a way that maintains discretion, privacy, and autonomy.

All participants who complete the eligibility screen receive a US $10 incentive, delivered in the form of a digital gift card when the study team notifies them of their eligibility.

Recruitment of Health Care Professionals (After the Intervention)

Upon completion of the study's active intervention and follow-up period, the study team will invite a select group of health care professionals to participate in the interviews. Email invitations will ask if they would like to share their experiences. Details of the study and their participation will be explained, and if they agree to participate in the study, signed informed consent will be collected in person, at the time of the interview, by a member of the study team.

Assignment of Interventions

Randomization

The randomization list was generated using the block randomization procedure in the Power Analysis and Statistical Software (PASS 2020) and stratified for participant-reported biological sex (male or female) and alcohol use severity (mild or moderate) based on Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) scores (eg, mild=DSM-5 score 2-3 and moderate=DSM-5 score 4-6) calculated from participants' responses in the pretest survey (Table 2).

To prepare the randomization tool, the program manager of the study team entered the sequence of randomization assignments for each stratification group into a protected spreadsheet and masked the data. During randomization, a researcher from the study team conducts an active call with the participant, enters the participant's study ID into the next available placement in the randomization sequence, and reveals or unmasks the participant's group assignment. Although on call with the participant, the researcher configures the participant's permissions in the app based on their group assignment and confirms that the participant has access to the version of the app that corresponds to their placement.

Before the randomization call, to limit or avoid interaction between the participants and the study team members responsible for conducting randomization, each stage of the pre-enrollment and enrollment process (screening, eligibility communication, scheduling, and randomization) is led by a different member of the team.

Enrollment

Potential participants will complete a web-based eligibility survey on the research team's website. Eligible participants will receive an invitation to participate with instructions to begin the enrollment process and a link to download the app. They may receive up to 2 email reminders during the 2 weeks following their completed screening.

When participants opened the app, the first of 2 digital informed consent documents appeared. Participants may contact the study team by email or phone with questions or concerns before electronically signing the consent form. If a participant declines to participate (eg, do not consent), reasons for refusal (if provided) will be documented, in keeping with CONSORT (Consolidated Standards for Reporting Trials) standards [32]. The study team will not initiate further contact with the participant.

Once participants consent and submit the digital consent form, they can create a user account initiating a 72-hour run-in period where they complete the baseline survey bundle (10 surveys, 64 questions in total). Participants who do not complete the 72-hour run-in are not randomized; their account is deactivated; they are removed from the study; and the reason for exclusion ("did not complete run-in") is documented accordingly.

Participants completing the 72-hour run-in are invited to schedule a call for the final step in the enrollment process. During the call, a member of the study team reviews the study and first consent form, answers any questions, and completes the randomization process. Once the app permissions have been reconfigured to the appropriate study group, the participant receives a second informed consent to review and sign. The second consent document describes the study activities specific to the participant's group assignment. Both informed consents are stored in the Study Information page in Tula for the participants' records with an option to print a paper copy.

Participants may withdraw their consent at any time throughout the 12-month period after their enrollment, at which time the study team will document their request, deactivate their account, and send a final confirmation. The participant will not receive further communication from the study.

Data Collection, Management, and Analysis

Quantitative Data Collection

The data collected by the Tula system come from multiple sources (Table 2). All surveys are conducted in the Tula app. Participants receive survey notifications from the Tula app on their phones and then complete the survey in the Tula app accordingly.

Baseline and Quarterly Surveys

Weekly Surveys

Tula prompts participants to take weekly surveys administered via the app to track their drinking and quality of life. Participants report their drinking using the 7-day timeline follow back [21,22] survey. A modified version of the Brief Alcohol Monitor [27] survey (10 items) allows participants to track individual risk and protection factors that may influence problematic alcohol use.

Tula Use

Tula use data are collected in time-stamped log files and include when a participant accessed Tula, the services used, duration of service use, pages viewed, messages posted and received, and content of messages. Tula use measures the dose of the intervention received for dose and response analyses.

Health Care Use

Health care use will be collected from the Self-reported Medical Services Utilization Form 61 (6 items; see Table 2 for frequency).

Intervention and Implementation Costs

Intervention costs will be determined using Tula time-stamped log files and billing codes logged by the health coach and peer mentors. Implementation costs will be estimated through health care professional interviews at the end of the intervention period and organized according to the Cost of Implementing New Strategies model [25]. The cost per participant will be determined for each study arm (self-monitored, peer-supported, and clinically integrated) with intervention and implementation costs separated within each group.

Qualitative Data Collection

Interviews will take place once the intervention phase of the study is complete and last 30-60 minutes. Open-ended questions will allow health care professionals to assess their experiences

with Tula and provide feedback on implementation as well as their thoughts on participants' experiences using Tula. Interviews will be conducted in a private location convenient for participants, either in clinician offices or via a secure videoconference call. All interviews will be audio-recorded and transcribed.

Retention or Adherence

Participants who complete their enrollment in the study are eligible for renumeration. Study incentives are built into the first 12 weekly surveys and 4 quarterly follow-up surveys at months 3, 6, 9, and 12. How to earn the incentives (gift cards) and how the incentives will be distributed monthly to participants by digital gift code sent via the message feature in Tula are explained to participants during the final step of enrollment. At the end of the 12-month study period, participants could potentially earn up to US $250 in gift cards.

Data Analysis

Primary Analysis

The analysis assesses the direct treatment effects on participant outcomes over time. We will construct a longitudinal model of the outcome measures at 3, 6, 9, and 12 months after randomization. Variables, stratified by sex and severity of alcohol use, will be included as factors in the model. The baseline values of the outcome will be included as covariates, with a separate model for each primary outcome (risky drinking days and quality of life). This longitudinal analysis is complicated by the dependence on successive observations made on the same individual. Furthermore, as complete control of measurement is not possible, there may be incomplete data from individual participants. Therefore, we will conduct a mixed-model analysis of repeated measures based on the general linear model with the assessment of various covariance structures (compound symmetrical, autoregressive order one, and unstructured). Covariance structure selection is based on the Akaike information criterion and Schwarz Bayesian criterion [23,24]. Pairwise comparisons between treatment groups and specific treatment time contrasts in the mixed model will be conducted to respond to between-group effects and time-based effects.

Descriptive Analyses

The research team will use descriptive statistics for all demographic and clinical variables across all 3 arms. To assess the impact of chance baseline imbalances between arms on intervention effect estimates, variables with noticeable differences will be included as covariates in a sensitivity analysis.

Mediation and Moderation Analysis

To augment the intervention analysis, we will estimate the direct and indirect effects that groups have on the outcomes by mediating variables using the structural equation model method. To test moderation effects, the interaction of the moderators (gender and severity of alcohol use severity) and randomization will be added to the model and estimated separately. We will examine the magnitude and direction of differential intervention effects between levels in these moderators (eg, male vs female).

Cost-effectiveness Analysis

Operational cost will be calculated based on the tenets of engineering economics. This study will use incremental cost-effectiveness ratios to compare the clinically integrated, peer-supported, and self-monitored groups. The incremental cost associated with reductions in drinking days and improvements in quality of life will be calculated over the 12-month intervention period.

Qualitative Data Analysis

Content analysis will describe how Tula use can improve patient outcomes, identify potential improvements in Tula, and identify how qualitative data can supplement the quantitative analysis. A qualitative researcher will construct a coding scheme to assess the ideas of the study to capture references to a concept. The analyses will help the research team refine Tula for future dissemination by determining the individual and organizational conditions necessary to promote effectiveness.

Data Monitoring

All study data collected by the app will be stored in secure password-protected servers. No patient health information will be collected from their electronic medical records, and no data collected by the app will be entered into patients' electronic medical records or affect the legal medical record. All participants are assigned an ID number, and all data will be deidentified before exporting for statistical analyses. Any hard copy–identifying information will be stored in a locked cabinet. When all study activities are complete, audio recordings, participant ID, and other identifiable information will be destroyed; only the deidentified code will remain.

With consultation from the funding agency (National Institute on Alcoholism and Alcohol Abuse) and the institutional review board, this protocol was exempted from requiring a formal data monitoring committee review.

Ethics Approval

This protocol was initially approved by the Health Sciences Minimal Risk Institutional Review Board (2019-0337) with subsequent annual reviews.

Results

This study is currently ongoing. Recruitment began on March 6, 2020, but was suspended on March 13, 2020, due to the COVID-19 pandemic restrictions. Limited recruitment resumed on July 6, 2020. The trial status as of November 17, 2021, is as follows: 357 participants have been enrolled in the study toward a planned enrollment of 546 participants. This study is expected to conclude on September 1st, 2023.

Discussion

Challenges

With the ubiquity of smartphones, the use of mHealth apps to improve the management of chronic diseases, including unhealthy alcohol use, is increasing. However, the extent of human interaction needed to achieve effective and cost-effective benefits of mHealth remains a challenge. The study is designed

to detect differences in the costs and effectiveness of implementing an mHealth intervention using 3 strategies that systematically vary the level of human touch provided to support its use by patients. Such a novel approach to implementing an mHealth system presents several challenges, primarily stemming from disruptions associated with the COVID-19 pandemic. One of the biggest challenges involves outreach and recruitment in communities of color. Creating trust in messaging, which was already a challenge, was doubly impacted by the COVID-19 pandemic as well as by police brutality in African American communities nationwide. Although an mHealth study by design is digital and remote, more challenges arose regarding ways to engage with clinics and community organizations for recruitment, particularly with local leaders from underrepresented and marginalized communities. Finally, with increased reliance on digital technologies caused by the pandemic, there was an unexpected surge in internet bot activities, creating a spike in false screening results that required increased safeguarding and monitoring by the research team.

Lessons Learned

There have been lessons learned, aside from the challenges encountered in executing this protocol. Getting clinician feedback and conducting usability tests of the app with potential participants before recruitment helped create a broader and more user-friendly mHealth intervention and implementation climate. Developing a flexible and adaptive recruitment strategy was also an important lesson learned for a study reliant on participant self-referral, especially when encountering unexpected situations such as the novel COVID-19 pandemic. Another lesson learned has been understanding the varied forms that the stigma of alcohol use presents itself within different communities and cultures. With alcohol misuse, high-risk drinking, and AUD constituting a public health crisis in the United States, testing whether an app such as Tula can benefit patients in a primary health care system is essential in determining the future role of mHealth in reducing drinking and alcohol-related harm. The results of this study may also provide guidance to policy makers and health care decision makers on the most cost-effective ways to incorporate technology in health care settings.

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This protocol was developed in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [34].

Conflicts of Interest

AQ has a shareholder interest in CHESS Health, a public benefit corporation that disseminates technology to the specialty addiction treatment system. The relationship between the author and CHESS Mobile Health is managed the University of Wisconsin–Madison's Conflict of Interest Committee.

References

1. Grant BF, Chou SP, Saha TD, Pickering RP, Kerridge BT, Ruan WJ, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. JAMA Psychiatry 2017;74(9):911-923 [FREE Full text] [doi: 10.1001/jamapsychiatry.2017.2161] [Medline: 28793133]
2. What is a standard drink? National Institute of Alcohol Abuse and Alcoholism. URL: https://www.niaaa.nih.gov/alcohols-effects-health/overview-alcohol-consumption/what-standard-drink [accessed 2021-08-06]
3. Knox J, Hasin DS, Larson FR, Kranzler HR. Prevention, screening, and treatment for heavy drinking and alcohol use disorder. Lancet Psychiatry 2019;6(12):1054-1067 [FREE Full text] [doi: 10.1016/S2215-0366(19)30213-5] [Medline: 31630982]
4. Totten AM, Womack DM, Eden KB, McDonagh MS, Griffin JC, Grusing S, et al. Telehealth: mapping the evidence for patient outcomes from systematic reviews. Rockville: Agency for Healthcare Research and Quality (US); 2016.
5. Lee JA, Choi M, Lee SA, Jiang N. Effective behavioral intervention strategies using mobile health applications for chronic disease management: a systematic review. BMC Med Inform Decis Mak 2018;18(1):12 [FREE Full text] [doi: 10.1186/s12911-018-0591-0] [Medline: 29458358]
6. Song T, Qian S, Yu P. Mobile health interventions for self-control of unhealthy alcohol use: systematic review. JMIR Mhealth Uhealth 2019;7(1):e10899 [FREE Full text] [doi: 10.2196/10899] [Medline: 30694200]
7. Fowler LA, Holt SL, Joshi D. Mobile technology-based interventions for adult users of alcohol: a systematic review of the literature. Addict Behav 2016;62:25-34. [doi: 10.1016/j.addbeh.2016.06.008] [Medline: 27310031]
8. Gustafson DH, McTavish FM, Chih MY, Atwood AK, Johnson RA, Boyle MG, et al. A smartphone application to support recovery from alcoholism: a randomized clinical trial. JAMA Psychiatry 2014;71(5):566-572 [FREE Full text] [doi: 10.1001/jamapsychiatry.2013.4642] [Medline: 24671165]
9. The mPOWER project: results of a pharmacotherapy model integrated with mobile health technology for veterans working through substance use disorders. ChessHealth. 2014. URL: https://www.chess.health/case-studies/the-mpower-project-

results-of-a-pharmacotherapy-model-integrated-with-mobile-health-technology-for-veterans-working-through-substance-use-disorders/ [accessed 2020-01-10]
10. Johnston DC, Mathews WD, Maus A, Gustafson DH. Using smartphones to improve treatment retention among impoverished substance-using Appalachian women: a naturalistic study. Subst Abuse 2019;13:1178221819861377 [FREE Full text] [doi: 10.1177/1178221819861377] [Medline: 31312084]
11. Johnson K, Richards S, Chih MY, Moon TJ, Curtis H, Gustafson DH. A pilot test of a mobile app for drug court participants. Subst Abuse 2016;10:1-7 [FREE Full text] [doi: 10.4137/SART.S33390] [Medline: 26917964]
12. Muroff J, Robinson W, Chassler D, López LM, Gaitan E, Lundgren L, et al. Use of a smartphone recovery tool for Latinos with co-occurring alcohol and other drug disorders and mental disorders. J Dual Diagn 2017;13(4):280-290. [doi: 10.1080/15504263.2017.1348649] [Medline: 28692420]
13. Gustafson Sr DH, Landucci G, McTavish F, Kornfield R, Johnson RA, Mares ML, et al. The effect of bundling medication-assisted treatment for opioid addiction with mHealth: study protocol for a randomized clinical trial. Trials 2016;17(1):592 [FREE Full text] [doi: 10.1186/s13063-016-1726-1] [Medline: 27955689]
14. Quanbeck A, Gustafson DH, Marsch LA, Chih MY, Kornfield R, McTavish F, et al. Implementing a mobile health system to integrate the treatment of addiction into primary care: a hybrid implementation-effectiveness study. J Med Internet Res 2018;20(1):e37 [FREE Full text] [doi: 10.2196/jmir.8928] [Medline: 29382624]
15. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000;55(1):68-78. [doi: 10.1037//0003-066x.55.1.68] [Medline: 11392867]
16. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
17. Hermes ED, Lyon AR, Schueller SM, Glass JE. Measuring the implementation of behavioral intervention technologies: recharacterization of established outcomes. J Med Internet Res 2019;21(1):e11752 [FREE Full text] [doi: 10.2196/11752] [Medline: 30681966]
18. Association of Academic Health Centers. URL: https://www.aahcdc.org/ [accessed 2021-08-06]
19. Volk RJ, Steinbauer JR, Cantor SB, Holzer 3rd CE. The Alcohol Use Disorders Identification Test (AUDIT) as a screen for at-risk drinking in primary care patients of different racial/ethnic backgrounds. Addiction 1997;92(2):197-206. [Medline: 9158231]
20. Alcohol use disorder: a comparison between DSM-IVDSM-5. National Institute on Alcohol Abuse and Alcoholism. Bethesda: National Institutes of Health; 2016. URL: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-use-disorder-comparison-between-dsm [accessed 2021-08-06]
21. Sklar SM, Turner NE. A brief measure for the assessment of coping self-efficacy among alcohol and other drug users. Addiction 1999;94(5):723-729. [doi: 10.1046/j.1360-0443.1999.94572310.x] [Medline: 10563037]
22. Williams GC, Cox EM, Kouides R, Deci EL. Presenting the facts about smoking to adolescents: effects of an autonomy-supportive style. Arch Pediatr Adolesc Med 1999;153(9):959-964. [doi: 10.1001/archpedi.153.9.959] [Medline: 10482213]
23. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974;19(6):716-723. [doi: 10.1109/tac.1974.1100705]
24. Schwarz G. Estimating the dimension of a model. Ann Statist 1978;6(2):461-464. [doi: 10.1214/aos/1176344136]
25. Little RJ, Yau LH. Statistical techniques for analyzing data from prevention trials: treatment of no-shows using Rubin's causal model. Psychol Methods 1998;3(2):147-159. [doi: 10.1037/1082-989x.3.2.147]
26. Namkoong K, DuBenske LL, Shaw BR, Gustafson DH, Hawkins RP, Shah DV, et al. Creating a bond between caregivers online: effect on caregivers' coping strategies. J Health Commun 2012;17(2):125-140 [FREE Full text] [doi: 10.1080/10810730.2011.585687] [Medline: 22004055]
27. Jo B. Statistical power in randomized intervention studies with noncompliance. Psychol Methods 2002;7(2):178-193. [doi: 10.1037/1082-989x.7.2.178] [Medline: 12090409]
28. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. J Consult Clin Psychol 2000;68(1):134-144. [doi: 10.1037//0022-006x.68.1.134] [Medline: 10710848]
29. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res 2009;18(7):873-880. [doi: 10.1007/s11136-009-9496-9] [Medline: 19543809]
30. Saldana L, Chamberlain P, Bradford WD, Campbell M, Landsverk J. The cost of implementing new strategies (COINS): a method for mapping implementation resources using the stages of implementation completion. Child Youth Serv Rev 2014;39:177-182 [FREE Full text] [doi: 10.1016/j.childyouth.2013.10.006] [Medline: 24729650]
31. Gustafson D, Hawkins R, McTavish F, Pingree S, Chen WC, Volrathongchai K, et al. Internet-based interactive support for cancer patients: are integrated systems better? J Commun 2008;58(2):238-257 [FREE Full text] [doi: 10.1111/j.1460-2466.2008.00383.x] [Medline: 21804645]

32. Yoo W, Namkoong K, Choi M, Shah DV, Tsang S, Hong Y, et al. Giving and receiving emotional support online: communication competence as a moderator of psychosocial benefits for women with breast cancer. Comput Human Behav 2014;30:13-22 [FREE Full text] [doi: 10.1016/j.chb.2013.07.024] [Medline: 24058261]
33. Blankers M, Koeter MW, Schippers GM. Internet therapy versus internet self-help versus no treatment for problematic alcohol use: a randomized controlled trial. J Consult Clin Psychol 2011;79(3):330-341. [doi: 10.1037/a0023498] [Medline: 21534652]
34. Moher D, Chan AW. SPIRIT (Standard protocol items: recommendations for interventional trials). In: Moher D, Altman DG, Schulz KF, Simera I, Wager E, editors. Guidelines for reporting health research: a user's manual. Hoboken, NJ: John Wiley & Sons; 2014:56-67.

Abbreviations

A-CHESS: Addiction-Comprehensive Health Enhancement Support System
AUD: alcohol use disorder
BIT: behavioral intervention technology
CONSORT: Consolidated Standards for Reporting Trials
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth edition
mHealth: mobile health
PROMIS: Patient-reported Outcomes Measurement Information System
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Smartphone-Based Self-management Intervention for Individuals With Bipolar Disorder (LiveWell): Empirical and Theoretical Framework, Intervention Design, and Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Bipolar disorder is a severe mental illness with high morbidity and mortality rates. Even with pharmacological treatment, frequent recurrence of episodes, long episode durations, and persistent interepisode symptoms are common and disruptive. Combining psychotherapy with pharmacotherapy improves outcomes; however, many individuals with bipolar disorder do not receive psychotherapy. Mental health technologies can increase access to self-management strategies derived from empirically supported bipolar disorder psychotherapies while also enhancing treatment by delivering real-time assessments, personalized feedback, and provider alerts. In addition, mental health technologies provide a platform for self-report, app use, and behavioral data collection to advance understanding of the longitudinal course of bipolar disorder, which can then be used to support ongoing improvement of treatment.

Objective: A description of the theoretical and empirically supported framework, design, and protocol for a randomized controlled trial (RCT) of LiveWell, a smartphone-based self-management intervention for individuals with bipolar disorder, is provided to facilitate the ability to replicate, improve, implement, and disseminate effective interventions for bipolar disorder. The goal of the trial is to determine the effectiveness of *LiveWell* for reducing relapse risk and symptom burden as well as improving quality of life (QOL) while simultaneously clarifying behavioral targets involved in staying well and better characterizing the course of bipolar disorder and treatment response.

Methods: The study is a single-blind RCT (n=205; 2:3 ratio of usual care vs usual care plus LiveWell). The primary outcome is the time to relapse. Secondary outcomes are percentage time symptomatic, symptom severity, and QOL. Longitudinal changes in target behaviors proposed to mediate the primary and secondary outcomes will also be determined, and their relationships with the outcomes will be assessed. A database of clinical status, symptom severity, real-time self-report, behavioral sensor, app use, and personalized content will be created to better predict treatment response and relapse risk.

Results: Recruitment and screening began in March 2017 and ended in April 2019. Follow-up ended in April 2020. The results of this study are expected to be published in 2022.

Conclusions: This study will examine whether LiveWell reduces relapse risk and symptom burden and improves QOL for individuals with bipolar disorder by increasing access to empirically supported self-management strategies. The role of selected target behaviors (medication adherence, sleep duration, routine, and management of signs and symptoms) in these outcomes will also be examined. Simultaneously, a database will be created to initiate the development of algorithms to personalize and improve treatment for bipolar disorder. In addition, we hope that this description of the theoretical and empirically supported framework, intervention design, and study protocol for the RCT of LiveWell will facilitate the ability to replicate, improve, implement, and disseminate effective interventions for bipolar and other mental health disorders.

Trial Registration: ClinicalTrials.gov NCT03088462; https://www.clinicaltrials.gov/ct2/show/NCT03088462

International Registered Report Identifier (IRRID): DERR1-10.2196/30710

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KEYWORDS

bipolar disorder; self-management; mHealth; eHealth; smartphone; mobile phone; mental health; mobile health

Introduction

Bipolar disorder is a severe mental illness characterized by episodes of mania, hypomania, depression, and mixed states [1,2]. It causes significant impairment in psychosocial functioning and is a leading cause of disability [2,3]. In addition, bipolar disorder doubles all-cause mortality and is associated with a high lifetime risk of suicide [4]. The ongoing suffering produced by this disorder drives a clear need for continuing efforts to develop and increase access to effective treatment.

Pharmacotherapy is the primary treatment for bipolar disorder, but even when pharmacological treatment is initially effective, high rates of episode recurrence, interepisode symptoms, and psychosocial impairment persist [5-9]. Evidence from randomized controlled trials (RCTs) indicates that combining psychotherapy with pharmacotherapy decreases episode recurrence and symptom burden while also improving quality of life (QOL) [10-18]. Treatment guidelines for bipolar disorder recommend providing adjunctive psychotherapy [19-21]. Despite these recommendations and the demonstrated effectiveness of adjunctive psychotherapy, multiple barriers limit access to evidence-based therapy, and only about half of individuals with bipolar disorder receive psychotherapy [22-26].

Smartphones are widely used and accepted for mental health assistance [27-31]. Smartphone-based mental health technologies thus provide a promising means for increasing access to the content of empirically supported psychotherapies for bipolar disorder. In addition, individuals with bipolar disorder in sustained remission report using self-management strategies that overlap significantly with the content of empirically supported psychotherapies, and many people with bipolar disorder are interested in using self-management strategies to stay well [32-35]. These findings suggest that mental health technologies delivering self-management strategies derived from empirically supported psychotherapies may meet user needs and support engagement [36-39]. In addition, mental health technologies provide novel opportunities for improving intervention impact, such as the provision of real-time assessments and adaptive feedback to users as well as status alerts to their mental health providers [40-43]. Furthermore, the use of smartphones allows collection of self-report, app use, and behavioral data that may enhance prediction of longitudinal course and current relapse risk, improve evaluation of treatment response, and provide a better understanding of behavior change processes to facilitate timely and successful intervention delivery [44-46].

Unfortunately, most publicly available smartphone apps for bipolar disorder do not provide information and self-management tools that reflect current practice guidelines [47,48]. However, work is underway to develop and test web- and smartphone-based interventions for bipolar disorder based on empirically supported psychotherapies. These studies consistently demonstrate that individuals use and report high levels of satisfaction with these apps but are less consistent in showing improvement in symptoms and QOL [49-55]. LiveWell, a novel smartphone-based self-management intervention for bipolar disorder, has been developed (NCT02405117) and tested in a single-blind RCT (NCT03088462). As adequate description of interventions is essential to facilitate ongoing efforts to improve and disseminate empirically supported treatments [56-59], the theoretical and empirically supported framework, design, content, mode, and timing of delivery, as well as the evaluation methodology for LiveWell, is described here.

Methods

Overview

The development of LiveWell and its evaluation followed an intervention mapping and person-centered approach [60-62]. This approach used an iterative strategy combining multiple stages of framework and design revisions based on feedback from mental health providers and individuals with bipolar disorder. This intervention development process has previously been described in detail [63-66]. In terms of clinical and recovery needs, the goal of LiveWell is to increase access to empirically supported treatment strategies for bipolar disorder, address the self-management interests of individuals with bipolar disorder, and enhance the utility of these strategies by providing real-time assessment feedback and provider alerts. In terms of research needs, the goal of LiveWell is to provide a self-report, app use, and behavioral data collection platform to enhance

prediction of the longitudinal course and current relapse risk, improve evaluation of treatment response, and provide a better understanding of behavior change processes to facilitate timely and successful intervention delivery. The details of the intervention framework, its practical design, and evaluation methodology are described below.

Intervention Framework

A behavior change framework for use in guiding the creation of content and tools for LiveWell was developed by integrating user feedback with information from empirically supported psychotherapies for bipolar disorder [10-18], health psychology behavior change theories [62,67-85], and chronic disease self-management models [86-92]. The framework proposes that (1) engaging in target behaviors improves clinical and recovery outcomes, (2) behavioral determinants govern the enactment of target behaviors, and (3) exposure to behavior change technique content and tool use alters behavioral determinants (Figure 1 and Table 1). This framework provides a theory-based and empirically supported rationale for including intervention content and tools. It also provides a means to label intervention content in terms of outcomes, targets, and determinants addressed by the behavior change techniques delivered (Tables 2 and 3; Multimedia Appendix 1). This labeling will allow investigation of intervention mechanisms by examining the relationships between changes in outcomes, targets, determinants, and exposure to behavior change technique content and tool use.

Figure 1. Behavior change framework.

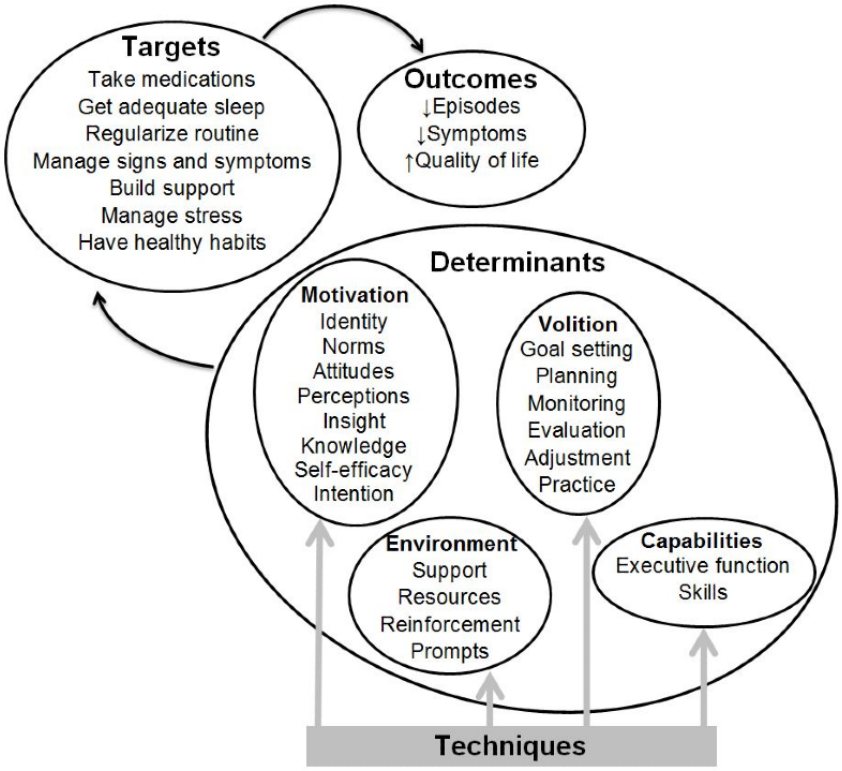


Table 1. Behavior change framework determinant definitions and theories.

Domains and determinants	Definitions	Theories
Motivation		
Identity	• Self-perception of personal characteristics, social roles, and types that form a set of standards guiding behavior	IT[a], TDF[b], TPB[c]
Norms	• Beliefs about whether others would approve or disapprove of a behavior (injunctive) and desire to comply with others (compliance). • Beliefs about whether others engage in a behavior (descriptive) and desire to be like others (identification)	FT[d], IT, TPB
Attitudes	• Beliefs about the tangible costs and benefits (instrumental) or emotional consequences (affective) of engaging in a behavior	HAPA[e], MI[f], SCT[g], TPB
Perceptions	• Beliefs about one's susceptibility to a health condition and the severity of the health condition (risk susceptibility and severity)	HAPA, HBM[h], CDSM[i]
Insight	• Awareness of having a health condition, presence of symptoms and consequences, and need for treatment	CDSM
Knowledge	• Awareness of information necessary to support active participation in management of a health condition	CDSM, COMB[j], HBM, SCT
Self-efficacy	• Beliefs about personal ability to perform a target behavior	GST[k], HAPA, SCT, TPB, TDF
Intention	• Explicit decision to engage in a target behavior to achieve an outcome	GST, HAPA, SCT, TPB, TDF
Volition		
Goal setting	• Identification of a target behavior to engage in to achieve an outcome	CT[l], GST, SCT, SDT[m]
Planning	• Specific plans for engaging in a target behavior (task) or overcoming obstacles to engaging in a target behavior (coping)	CT, CDSM, HAPA
Monitoring	• Maintaining awareness of engagement in a target behavior	CT, CDSM, HAPA
Evaluation	• Detecting degree of alignment between actual behavior and target behavior.	CT, CDSM, HAPA
Adjustment	• On the basis of monitoring and evaluation: acknowledge success and maintain or refocus current goals and plans or understand problems, identify solutions and make changes in current goals and plans	CT, CDSM, HAPA
Practice	• Repetition of an action or its elements to learn or improve a capability	CDSM, SCT
Environment		
Support and obstruction	• Direct informational, emotional, or tangible physical input from others that facilitates or hinders engagement in a behavior	CDSM, COMB, HAPA, SCT, TDF
Resources and constraints	• Physical conditions of a situation that facilitate or hinder engagement in a behavior	CDSM, COMB, HAPA, SCT, TDF
Reinforcement	• Increasing the probability of a behavior by arranging a contingency between the behavior and a consequence that follows the behavior	CT, TDF
Prompts	• Physical or social stimulus that acts as a reminder to engage in a behavior	CT, TDF
Capabilities		
Executive function	• Cognitive capacities such as working memory, inhibitory control, and mental flexibility	COMB, SCT, TDF
Skills	• Abilities acquired or developed through practice	COMB, SCT, TDF

[a]IT: Identity Theory [80,85].
[b]TDF: Theoretical Domain Framework [81,84].
[c]TPB: Theory of Planned Behavior [69].
[d]FT: Focus Theory [93].
[e]HAPA: Health Action Process Approach [76,77].
[f]MI: Motivational Interviewing [74].
[g]SCT: Social Cognitive Theory [68,73].
[h]HBM: Health Belief Model [83].
[i]CDSM: Chronic Disease Self-Management [86-92].
[j]COMB: Capability Opportunity Motivation Behavior [79].
[k]GST: Goal Setting Theory [72,75].
[l]CT: Control Theory [67,71].
[m]SDT: Self-Determination Theory [70,78].

Table 2. Smartphone app content.

Domains, determinants, and techniques	PP[a]
Motivation	40.1
Knowledge	16.1
Information on app use	5.1
Information about a health condition	4.2
Information about treatment of a health condition	4.1
Information about effective self-regulation	1.4
Information about antecedents	1.3
Attitudes and perceptions	14.1
Information about health consequences	9.6
Pros and cons	2.0
Information about social and environmental consequences	1.3
Information about emotional consequences	0.7
Norms	4.8
Social comparison	2.5
Credible source	1.9
Insight	2.4
Guided discovery	2.4
Self-efficacy	1.5
Focus on past success	1.0
Persuasion about capability	0.5
Identity	0.8
Valued self-identity	0.7
Intention	0.5
Elicit commitment	0.5
Volition	35.8
Evaluation	11.4
Feedback on outcome of behavior	7.9
Feedback on behavior	2.5
Discrepancy between current behavior and goal	1.0
Planning	8.3
Coping planning	3.5
Task planning	2.6
Implementation intentions	2.3
Monitoring	5.9
Self-monitoring of outcomes of behavior	4.0
Self-monitoring of behavior	1.9
Adjustment	5.2
Review behavior goals	5.1
Practice	4.1
Behavioral rehearsal	2.9
Graded tasks	1.1
Goal setting	0.9

Domains, determinants, and techniques	PP[a]
Process goal	0.7
Environment	13.0
Support and obstruction	11.0
Social support—feedback	4.1
Social support—treatment	3.7
Restructuring social environment	1.5
Social support—unspecified	0.7
Social support—support group	0.5
Prompts	1.0
Introduce cues	1.0
Resources and constraints	0.8
Restructuring physical environment	0.6
Capabilities	10.1
Skills	10.0
Instruction on how to perform a behavior	3.2
Relaxation training	1.3
Engage in activity	1.2
Reduce negative emotions (stress management)	1.1
Behavioral experiments	0.8
Observing	0.6
Framing and reframing	0.5
Conserving mental resources	0.4
Accepting	0.4
Behavioral substitution	0.4

[a]Percent of smartphone app pages.

Table 3. Coaching scripts content.

Domain, determinant, and behavior change technique	PP[a]
Motivation	49.5
Knowledge	12.1
Information about app use	7.7
Information about a health condition	4.4
Self-efficacy	11.0
Emphasize autonomy	7.4
Affirmation	3.6
Intention	10.4
Agenda mapping	8.7
Summarize the plan	1.4
Elicit commitment	0.3
Attitudes and perceptions	9.4
Desire-ability-reason-need questions	4.8
Elicit-provide-elicit	2.0
Information about health consequences	1.9
Monitoring of emotional consequences	0.4
Information about social and environmental consequences	0.3
Insight	4.5
Guided discovery	4.5
Norms	1.6
Social comparison	1.1
Credible source	0.5
Identity	0.4
Valued self-identity	0.4
Volition	27.9
Planning	14.6
Coping planning	7.2
Task planning	3.7
Consider change options	2.0
Brainstorming	1.5
Implementation intentions	0.3
Adjustment	5.0
Review behavior goal	4.7
Review outcome goal	0.3
Goal setting	3.6
Process goal	2.7
Outcome goal	0.9
Evaluation	2.7
Feedback on behavior	2.4
Discrepancy between current behavior and goal	0.3
Monitoring	2.1
Self-monitoring of behavior	1.8

Domain, determinant, and behavior change technique	PP[a]
Self-monitoring of outcome of behavior	0.3
Environment	22.0
Support and obstruction	18.8
Open-ended questions	5.9
Social support—practical	3.5
Permission to provide information and advice	3.5
Social support—unspecified	3.0
Support change and persistence	2.3
Reflective statements	0.3
Summary statements	0.3
Reinforcement	1.8
Social reward	1.8
Prompts	1.4
Introduce cues	1.4
Capabilities	0.5
Skills	0.5
Conserving mental resources	0.5

[a]Percent of coaching script pages.

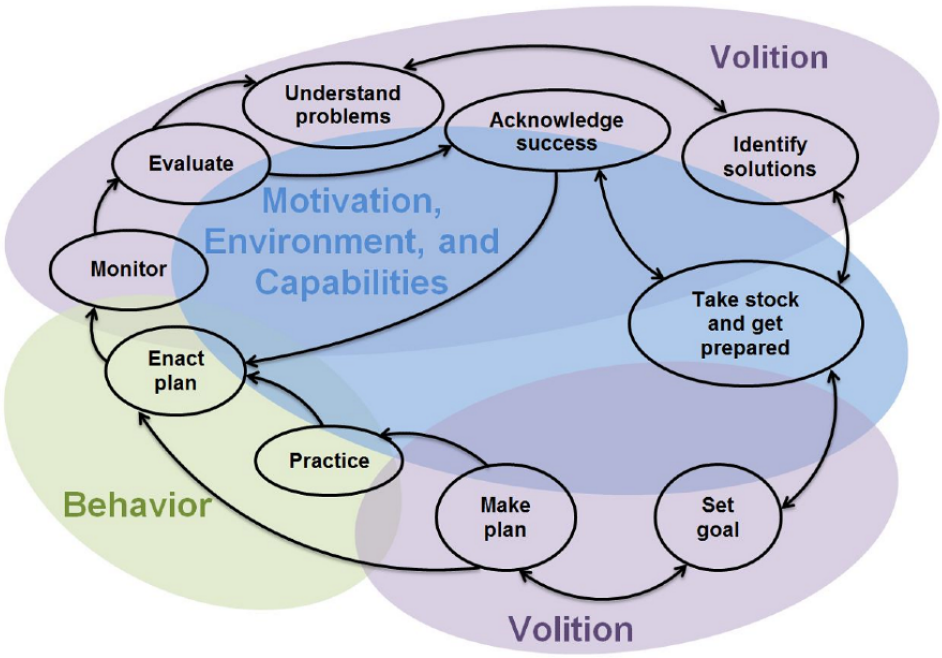
Adjunctive psychotherapy interventions for bipolar disorder typically enroll individuals who are between acute episodes and focus on the prevention of relapse [10-15,18]. Time to episode recurrence was thus selected as the primary clinical outcome (Figure 1) to ensure that the efficacy of LiveWell can be assessed in the context of existing face-to-face studies. As cumulative measures of symptom burden are better predictors of psychosocial functioning than episode recurrence rate [94], percentage time symptomatic and symptom severity were selected as secondary outcomes. QOL was also chosen as a secondary outcome because the absence of symptoms is not synonymous with QOL, and improvement in QOL is highly valued by individuals with bipolar disorder [39,95,96].

Although empirically supported adjunctive therapies for bipolar disorder use diverse approaches, changes in shared behavioral targets may result in the improved outcomes produced by these therapies [5,18,26,33,97,98]. Thus, the LiveWell intervention seeks to improve clinical and recovery outcomes by assisting individuals with managing targets proposed to underlie the impact of existing face-to-face therapies (Figure 1). LiveWell emphasizes the importance of identifying signs and symptoms of relapse, developing plans and monitoring for relapse, and enacting and adjusting plans as needed (managing signs and symptoms) [99,100]. In addition, LiveWell uses a similar process to support taking medications as prescribed [101-105], obtaining adequate sleep duration [106-110], and maintaining regular routines [111-115]. LiveWell also addresses strengthening social support [5,35], managing stressors [33,35], and engaging in healthy habits regarding diet, exercise, and substance use [5,116-118].

Recent studies have proposed that behavioral determinants govern the enactment of target behaviors and that psychosocial interventions produce changes in these determinants via the delivery of behavior change techniques [62,81,82,84,119-124]. Behavior change techniques are replicable and irreducible intervention components that impact behavioral regulation [82]. Taxonomies defining distinct techniques and grouping them into nonoverlapping clusters hypothesized to alter specific behavioral determinants have been developed [82,119-124]. Distinct behavior change techniques can thus be selected and delivered to shift a particular determinant involved in enacting a target behavior (Tables 2 and 3; Multimedia Appendix 1). To align with existing behavior change theories and organize determinants [62,67-85], we grouped determinants and their corresponding techniques into four domains: motivational determinants involved in developing an intention to engage in a behavior, volitional determinants involved in enacting the behavior, environmental determinants and capabilities that impact motivation and volition (Figure 1 and Table 1). Although our behavior change framework is presented as a linear system in which delivery of behavior change techniques alters behavioral determinants to shift target behaviors and improve outcomes (Figure 1), this linear view should be regarded as a simplification. Instead, the behavior change framework should be considered as a continuous and reciprocal system in which multiple wellness outcomes, target behaviors, and behavioral determinants interact continuously and reciprocally to impact the process of health behavior change [87,125]. In terms of providing information about self-management strategies to users, the behavior change framework is therefore recast as an ongoing process that requires assessment of motivation, environment, and capabilities to guide the selection of target

behaviors and creation of plans followed by behavioral enactment and practice accompanied by ongoing reassessment and updating based on monitoring (Figure 2).

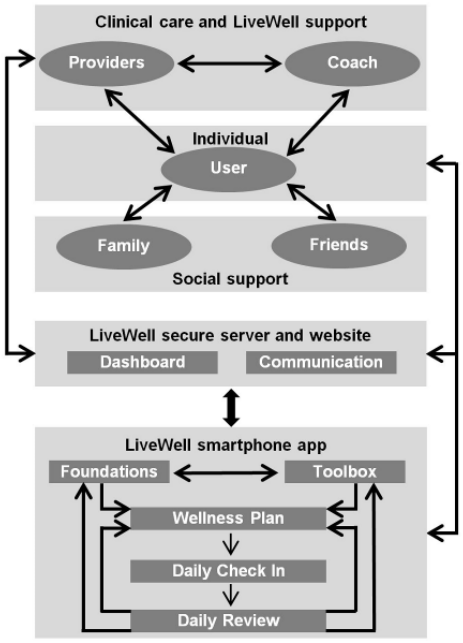
Figure 2. Behavior change process.



Intervention Design

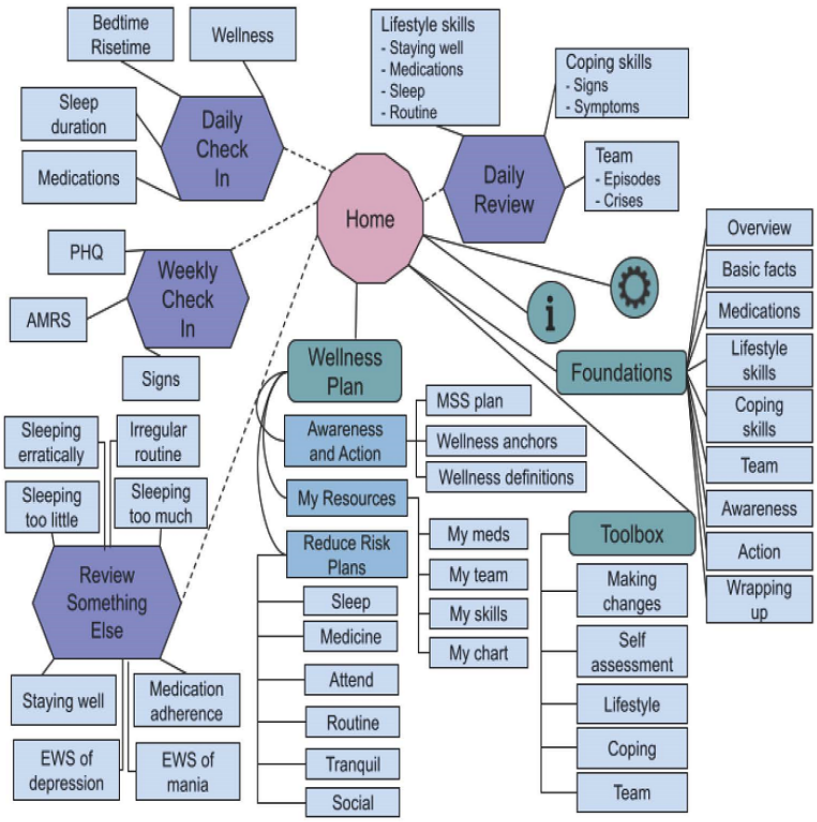
Although the behavior change framework (Figures 1 and 2; Tables 1-3) directs the selection of theory-based and empirically supported strategies for inclusion in LiveWell, it does not address the practical methods for using technology to deliver content and supporting tools [126-129]. Our intervention design thus considers the technical components involved in delivering self-management strategies. In addition, as human support is often a critical feature of effective mental health technology interventions, the design of coaching roles has been addressed [130-136]. As such, the LiveWell intervention has technological and human support components, including a smartphone app, a secure server and a website, and coaching support (Figure 3).

Figure 3. Intervention design: arrows outside gray boxes on left side indicate provider and coach access to dashboard and email communications and on right side user access to the dashboard and smartphone app. Arrows between providers, coach, user, family and friends represent interactions between the user and supports. In the case of the coach, interactions with the user and provider may be prompted by email alerts. Arrows within the app represent the user app workflow. Information in the Foundation lessons and Toolbox is used to develop a personalized Wellness Plan, including daily monitoring using the Daily Check-In. Daily Check-In data are used to provide feedback via the Daily Review. The Daily Review feedback directs the user to relevant app content in their Wellness Plan or the Foundations and Toolbox.



The smartphone app has five main components: Foundations, Toolbox, Wellness Plan, Daily Check-In, and Daily Review (Figures 3 and 4; Multimedia Appendix 2). The Foundations and Toolbox components discuss the rationale for engaging in target behaviors, using self-management techniques, and the role of beliefs, environmental resources, and social support on behavioral engagement (Multimedia Appendix 2). The Foundations and Toolbox also discuss the importance of setting clear and realistic target goals, making detailed plans for accomplishing goals and overcoming obstacles, monitoring target behaviors, evaluating if goals are being met, and making adjustments as needed. In addition, the roles of self-assessment and learning and practicing skills for achieving target goals are discussed. Over 4 weeks, users work through the Foundations and Toolbox components and develop a personalized Wellness Plan that addresses lifestyle skills for reducing risk, coping skills for managing signs and symptoms, and resources for staying well (Figures 3 and 4). As part of the Wellness Plan, users develop a personalized plan for managing signs and symptoms (Awareness and Action) across a range of wellness levels (0 balanced, −1 or +1 daily hassles or uplifts, −2 or +2 prodromal or residual symptoms, −3 or +3 episode, −4 or +4 crisis). Creating this plan includes reviewing past experiences to identify personalized wellness scale anchors. This anchoring process assists users in monitoring and recognizing their current wellness level [35]. The plans also specify personalized actions for each wellness level [65]. In addition, users develop a personalized Reduce Risk plan. The Reduce Risk plan involves setting achievable goals, anticipating obstacles, and specifying clear actions to take for target behaviors, including taking medications as prescribed, obtaining adequate sleep, maintaining regular routines, strengthening and using social support, managing stressors, and engaging in healthy habits regarding diet, exercise, and substance use [65]. This Reduce Risk plan is described by the acronym SMARTS: Sleep, Medicine, Attend (to diet, exercise, and substance use), Routine, Tranquil, Social.

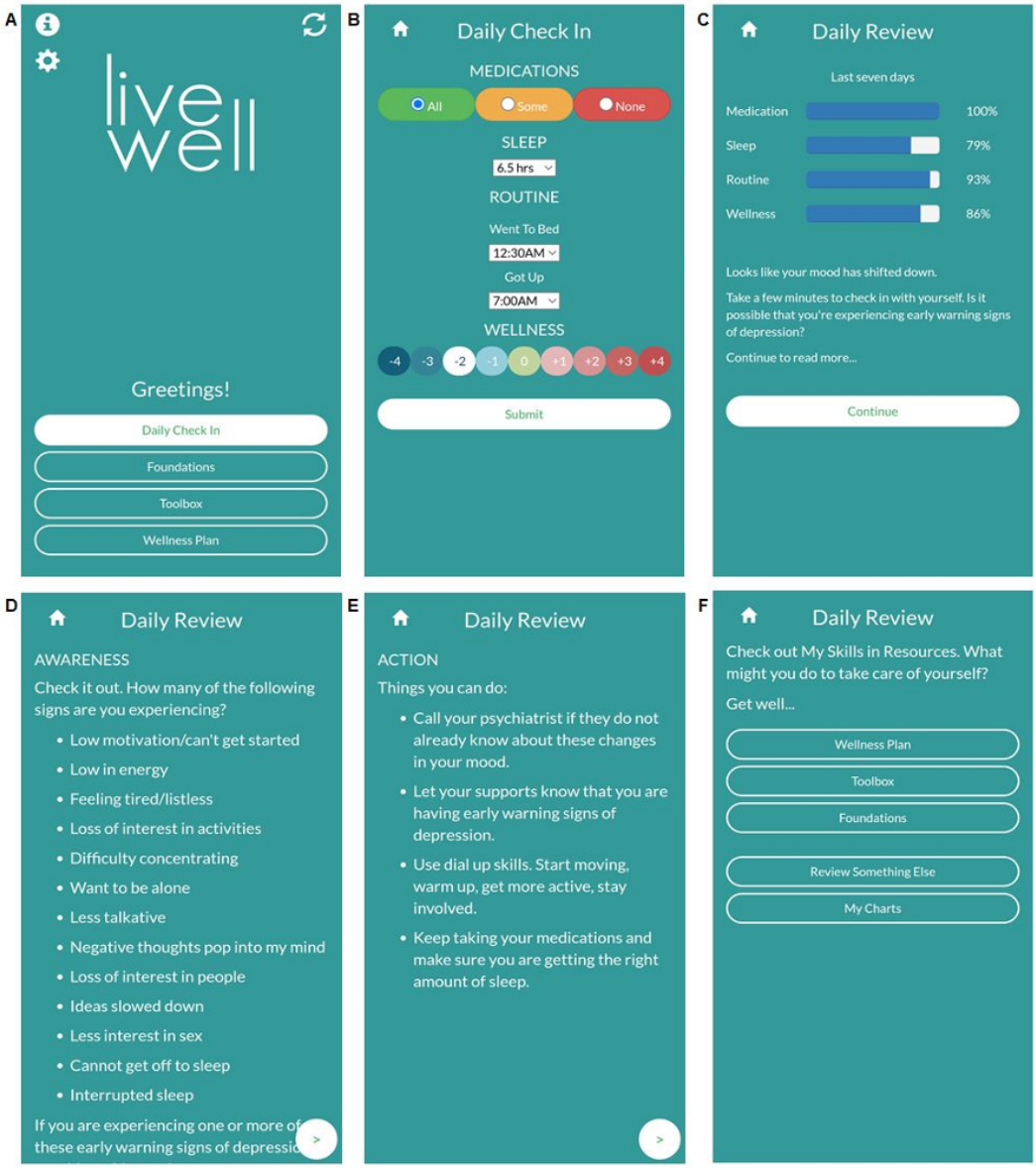
Figure 4. Smartphone App Design: Dashed lines indicate app components available based on timing (Daily and Weekly Check-Ins) or completion of other components (Daily Review, Review Something Else). EWS: early warning signs; MSS: manage signs and symptoms; PHQ: Patient Health Questionnaire 8; AMRS: Altman Mania Rating Scale; i: Instructions; gear symbol: settings.



Monitoring is a major determinant of behavior change [58], an essential strategy for empirically supported bipolar disorder psychotherapies [11,18,97,99], and individuals with bipolar disorder are interested in using self-monitoring tools [32,33]. Thus, the core of the app is a Daily Check-In (Figure 3). The Daily Check-In monitors medication adherence, sleep duration, routine (bedtime and risetime), and wellness level. These targets were selected for daily monitoring because they are consistently addressed in the core content of adjunctive psychotherapy interventions [5,18,26,33,97,98,137] and are readily amenable to goal setting and self-monitoring. Users were asked to check-in daily for 16 weeks. On the basis of data from the Daily Check-In, the Daily Review uses an expert system to provide adaptive, personalized real-time feedback [64]. As described in detail elsewhere [64], the rules linking delivery of feedback and the Daily Check-In data were developed based on existing literature regarding bipolar disorder and psychiatrist feedback from a web-based survey. This feedback reinforces success and directs users to relevant app sections (within Foundations, Toolbox, and Wellness Plan) to assist users with making

adjustments if needed (Figures 3 and 4). If the Daily Check-In data indicate a need for additional clinical support based on the expert system algorithms [64], users receive feedback to contact their psychiatrist, and a message with a link to the psychiatrist's phone number appears. An example of opening the app and completing a Daily Check-In followed by a truncated example of Daily Review feedback is displayed in Figure 5, and a more detailed use case scenario is provided in Multimedia Appendix 3.

Figure 5. Daily Check-In and Daily Review: (A) Upon opening the LiveWell app, user views the home page with Daily Check-In highlighted indicating task to be completed, (B) User completes Daily Check-In with a wellness rating of -2 indicating possible early warning signs of depression, (C) After user submits Daily Check-In data, Daily Review feedback page displays summary of last 7 check-ins. Expert system identifies a possible shift in mood down as priority, (D-E) User continues through Daily Review and receives information about Awareness and Action, F. Last page of Daily Review suggests user check My Skills in Resources in the Wellness Plan. Daily Review feedback truncated here for display.



Users also complete a Weekly Check-In, including the 8-question Patient Health Questionnaire (PHQ-8) [138], Altman Self-Rating Mania Scale (ASRM) [139], and checklists for early warning signs of depression and mania [140-142]. Users receive feedback and a pop-up message if their Weekly Check-In responses indicate the new onset of an episode. For example, if the PHQ-8 score transitions from <10 to ≥10, suggesting the onset of a depressive episode based on the published threshold [138], the pop-up message says, "Looks like you may be entering a depressive episode. Call your psychiatrist to check-in." and contains a link to the psychiatrist's phone number to prompt a call [64]. Overall, the app content encourages users to work with a psychiatrist to come to a mutual understanding of clinical problems and treatment plans and engage in active and sustained collaborative treatment and progress monitoring [63]. The secure server and website aim to support communication with providers by delivering automated email alerts to enrolled providers when additional clinical support may be needed.

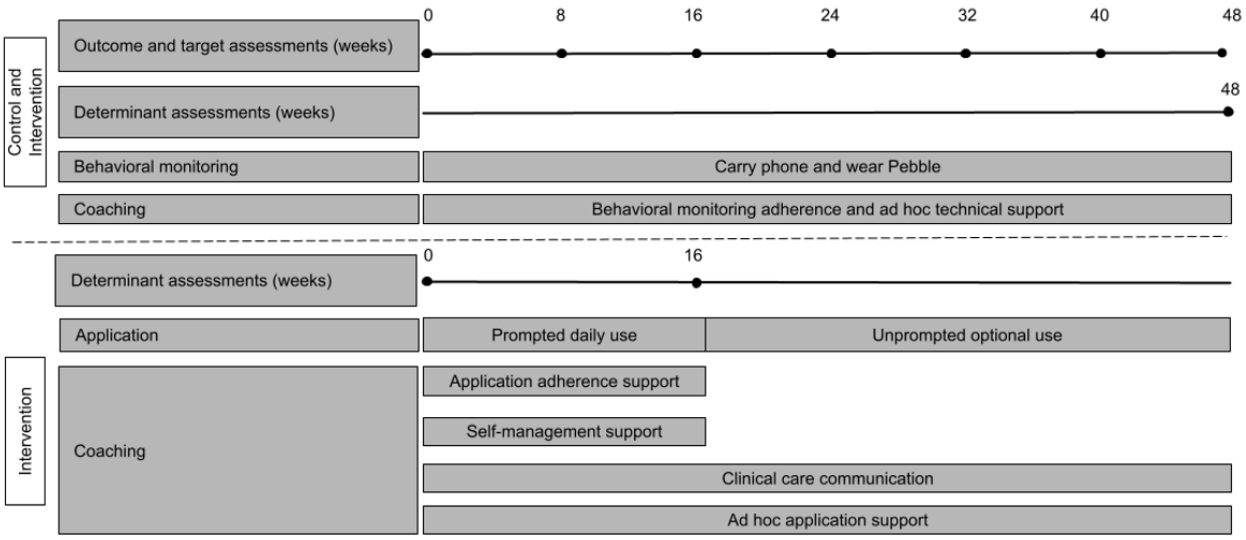
The LiveWell technology was supported by coaches with bachelor's degrees who did not have professional mental health training. The coaches were trained and supervised for their roles. Details of the coach training and supervision are presented

elsewhere [63]. The coach supports app use adherence, self-management, and clinical care communication (Figure 6). The coach uses a supportive accountability model to facilitate app use by working with the user to establish a bond, legitimacy, and accountability [63,135]. The coach provides self-management support using a simplified adaptation of motivational interviewing, which is effective with brief consultations administered by individuals without professional mental health training [63]. The coach also uses a chronic disease self-management model to provide app content guidance that assists the user by setting appropriate target goals, personalizing a Wellness Plan, monitoring target progress, and enacting and adjusting plans based on success or problems [63,86-92,125]. There is a clear division of labor between the technology and the coach to ensure the coach operates within the scope of nonclinical practice. The technology operates as a psychotherapeutic strategy expert and provides status summaries and alerts to the coach, who uses flow sheets and structured scripts to serve as a technology use concierge [63]. In addition, the coach works to support communication and collaboration with the care provider. The coach is prompted via server email alerts to contact providers via telephone when user self-assessments indicate problems with treatment adherence or the presence of early warning signs, worsening, or severe symptoms.

Coaching starts with a structured face-to-face meeting that addresses how using self-management strategies within the app can assist users in managing their wellness (Multimedia Appendix 4). The coach works with the user to review their experiences with normal ups and downs, early warning signs and symptoms, episodes, and related crises. This review leads to developing a personalized 9-point wellness rating scale to facilitate the self-monitoring of signs and symptoms. Next, the coach walks the user through the app and has the user complete a Daily Check-In and Daily Review. The user then sets specific goals for medication adherence, sleep duration, routine bedtime and risetime, and wellness rating range. The coach encourages the user to set parameters known to facilitate health, including maintaining medication adherence, adequate sleep duration, regular bed and wake windows, and "balanced" wellness ratings (expected ups and downs due to routine events) [5,18,26,33,97,98]. The coach wraps up the face-to-face meeting clarifying the coach's role and obtaining a commitment to app use and target goal achievement.

Following the face-to-face meeting, 6 scheduled coaching calls occur during weeks 1-4, 6, and 16 (Figure 6). Before each call, the coach reviews a dashboard summarizing app use and the percentage of days that personalized target goals were met [64]. At each call, the coach uses the summary and a structured script to review progress and guide app use (Multimedia Appendix 4). To provide closure and a time-limited treatment, the sixth and final call wraps up working with the coach as well as the request to check-in daily [143]. The coach reviews with the user what they learned and what future plans may assist the user in living well. The user is encouraged to commit to using the strategies they have found helpful and return to app use as needed. The user is asked if they would like to continue to receive daily notifications on their smartphone as a reminder to check-in (Figure 6). The user is also asked to continue carrying their smartphone whenever they leave home and to wear a Pebble watch all day, every day, to allow ongoing behavioral monitoring for study purposes.

Figure 6. Study timeline.



All coach face-to-face meetings and telephone calls were audiotaped. To assess coach fidelity, 15% of the completed coach face-to-face meetings and 15% of the weekly scheduled call audiotapes were randomly selected for review each month. Coach fidelity was then assessed using an adapted version (Multimedia Appendix 4) of the behavior change counseling index [144] scored by a trained mental health professional (psychologist). Exit questionnaires assessing smartphone app usability and coaching support were delivered at study week 48 through a web survey sent by the coaches to all participants in the intervention arm (Multimedia Appendix 5). In addition, exit interviews were completed by telephone after week 48 for the first 15% of participants exiting the intervention arm (Multimedia Appendix 5). These exit questionnaires and

interviews were completed to obtain user feedback on the intervention to assist with the ongoing development of LiveWell [65].

Intervention Evaluation

Overview

An RCT to evaluate LiveWell has been carried out, and data analysis is underway for the following: aim (1) to establish the capacity of LiveWell to reduce relapse and symptom burden and improve QOL in bipolar disorder, aim (2) to investigate the impact of LiveWell on proximal behavioral targets and the relationship between changes in these targets and changes in relapse rate and symptom burden, and aim (3) to identify novel behavioral signatures in individuals with bipolar disorder that predict treatment response and relapse. Aim 1 will test the following hypotheses: primary hypothesis—participants in the intervention group will experience (H1) a longer time to relapse relative to treatment as usual (TAU); secondary hypotheses—participants in the intervention group will experience (H2) a lower percentage of time being symptomatic, (H3) lower symptom severity, and (H4) a better QOL relative to TAU. Aim 2 will test the following additional hypotheses: primary hypothesis—participants in the intervention group will experience (H1) larger improvements in proximal behavioral targets (eg, medication adherence) relative to TAU; secondary hypotheses—variation in the proximal behavioral targets will account for substantial variance in the (H2) primary clinical outcome (time to relapse) and secondary clinical outcomes of (H3) percentage time symptomatic and (H4) symptom severity; proximal behavioral targets will mediate the intervention effect on the (H5) primary clinical outcome (time to relapse) and the secondary clinical outcomes of (H6) percentage time symptomatic and (H7) symptom severity; tertiary hypotheses—participants in the intervention group will experience (H8) an increase in performance determinant scores for each target, and at the final time point, will have (H9) higher performance determinant scores for each target relative to TAU. Aim 3 is exploratory and will develop a database of behavioral sensing (intervention and TAU arms) as well as app use and self-assessment (intervention arm only) data. The relationships between these data and clinical status assessment data will be examined with the long-term goal of better predicting current relapse risk, treatment response, and longitudinal course for individuals with bipolar disorder.

Entry Criteria

To facilitate recruitment of eligible participants and minimize exclusions while maximizing safety and study power, the following inclusion and exclusion criteria were used: The inclusion criteria were as follows: (1) adults aged 18 to 65 years, (2) individuals with bipolar disorder type I, and (3) a minimum of one acute episode in the last 2 years. Exclusion criteria were as follows: (1) not receiving psychiatric care, (2) current mood episode, (3) current severe suicidal ideation or a recent serious suicide attempt (last 3 months), (4) current substance use disorder (last 3 months), (5) visual impairments limiting mobile phone use, and (6) inability to speak and read English.

Ethics Approval

The study was reviewed and approved by the Northwestern University Institutional Review Board (STU00202860).

Recruitment, Screening, and Enrollment

The RCT for LiveWell recruited participants from the Chicago and Minneapolis-Saint Paul areas. At both sites, recruitment letters were sent to eligible individuals (bipolar disorder diagnosis, 18-65 years, and consent to contact for research) whose information was available in site-specific research registries or electronic health record data warehouses. The recruitment letters were followed up with phone calls from the study staff. Study recruitment information was also available for both sites at ClinicalTrials.gov, ResearchMatch.org, and WeSearchTogether.org websites. In the Chicago area, individuals were also recruited via mental health and university clinic presentations, flyers, brochures, e-mails to mental-health providers affiliated with Northwestern Medicine, and advertisements (Facebook, Reddit, Craigslist, Google AdWords, Chicago Transit Authority, digital, and print newspapers).

The study team contacted individuals via telephone (research registries) or individuals contacted the study team on the web, by email, or telephone. Individuals then completed a web based or telephone screening consent and completed a brief web-based or telephone-based eligibility screener (Multimedia Appendix 6). Eligible individuals were scheduled for telephone screening using a modified Mini International Neuropsychiatric Interview [145-147] and the National Institute on Drug Abuse Quick Screen followed by the Alcohol Use Disorders Identification Test and National Institute on Drug Abuse-modified assist for additional substance use disorders screening. A suicide attempt screener was also delivered, and demographic information was obtained. If still eligible, individuals attended a face-to-face clinic visit at which written consent was completed, followed by a structured interview with a trained mental health clinician (psychiatrist or psychologist) using an abbreviated and modified version of the Affective Disorders Evaluation and Clinical Monitoring Form [148-150]. Individuals with a confirmed diagnosis at the clinic visit were scheduled for a baseline telephone assessment and enrolled if no exclusion criteria were present at this assessment. Individuals who exhibited a current mood episode or substance use disorder, severe suicidality, or a recent serious suicide attempt at any step during screening were offered the opportunity to repeat the step at a later date and continue the screening process if the exclusion criteria were resolved (Multimedia Appendix 6).

At their initial face-to-face coaching meeting, intervention arm participants were asked if they wanted to allow any of their mental health providers to access a secure password-protected website that summarizes their self-report data (Daily and Weekly Check-Ins). If a participant consented to provider participation, a letter offering participation was mailed to the provider, and the coach contacted the provider by telephone. Providers interested in participating completed a web-based, verbal, or written consent form before receiving access to the website. Providers could opt to receive alerts via email or telephone when participant self-report data indicated reduced medication adherence, increased or decreased sleep duration, or

deterioration in their daily wellness ratings. Providers were not required to opt for alerts to participate in the study. To allow access to the widest range of participants, participants were not required to allow any providers to access the website and providers were not required to consent to access the website or receive alerts for a participant to enroll in the study. However, as part of the written consent to participate in the study, all participants agreed to allow their psychiatrist to be contacted in the event of self-rated crisis situations, including daily wellness ratings of +4 or −4, new onset of depression (PHQ-8 score≥10), new onset of mania (ASRM score≥6), or other indications of emergent clinical problems or mental health deterioration.

Randomization

A biostatistician, blinded to screening and baseline assessment data, conducted computer-generated randomization on a 2:3 ratio (control:intervention) stratified based on clinical status (low risk—asymptomatic recovery; high risk—continued symptomatic, recovering, prodromal, and symptomatic recovery; Tables 4 and 5). Patients were randomized in permuted blocks of 5 at each site. The unbalanced design increases power to investigate effects within the intervention arm with minimal effect on the investigation of outcomes. Participants were stratified because time to relapse is likely to be significantly shorter for the high-risk participants who have not met the time or symptom number criteria for recovery from the last episode or who are recovered but have subsyndromal or prodromal symptoms [9,94,151,152]. Although many prior face-to-face psychotherapy studies restrict participant inclusion to those in asymptomatic recovery [10-15,18], this study includes additional high-risk individuals to increase access to the intervention.

Table 4. Clinical status when in an episode.

DSM 4 episode criteria	Episode entry criteria[a] met?	Number of moderate symptoms of	Impairment	Consecutive days	PSR[b]
Mania	Yes	Mania≥3 if elevated Mania≥4 if only irritable	≥Moderate or hospitalized or psychosis	≥7 or hospitalized	5-6
Depression	Yes	Depression≥5	≥Moderate	≥10 out of 14	5-6
Mixed[c]	Yes, for both mania and depression	Criteria for both mania and depression	≥Moderate	≥7	5-6
Hypomania	Yes	Mania≥3 if elevated Mania≥4 if only irritable	< Moderate and not hospitalized and no psychosis	≥4	3

[a]Entry criteria: mania—moderate severity elevated, expansive, or irritable mood ≥ 7 consecutive days; depression—moderate severity depressed mood or loss of interest/pleasure ≥ 10 out of 14 consecutive days; hypomania—moderate severity elevated, expansive, or irritable mood ≥ 4 consecutive days and < 7 consecutive days. Clinical Monitoring Form symptom severity scale: none=0, mild=0.5, moderate=1, marked=1.5, and severe=2.

[b]PSR: Psychiatric Status Rating score.

[c]Mania with concurrent depression for 1 week. Count depressive symptoms for 5/7 consecutive days instead of 10/14.

Table 5. Clinical status when not in an episode.

Clinical Monitoring Form criteria	Recovered from last acute episode?	Symptom count[a] and impairment	PSR[b]
Continued symptomatic	No	Symptom count>2 or ≥ moderate impairment	3-4
Prodromal	Yes	Symptom count>2 or new[c] or ≥ moderate impairment	2-4
Recovering	No, recovering ≤8 consecutive weeks	Symptom count≤2 and < moderate impairment	1-2
Symptomatic recovery	Yes	Symptom count>0 and ≤2 and < moderate impairment	2
Asymptomatic recovery	Yes	Symptom count=0 and < moderate impairment	<2

[a]Symptom count: sum of symptom severity, if |severity| ≥1 round up, otherwise 0. Clinical Monitoring Form symptom severity scale: none=0, mild=0.5, moderate=1, marked=1.5, and severe=2.

[b]PSR: Psychiatric Status Rating score.

[c]Two new moderate, marked, or severe symptoms developed while in recovery.

Outcome Assessments

The primary outcome, time to relapse, will be measured as the number of weeks to episode onset (depression, mania, hypomania, or mixed) based on the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-4) criteria. The DSM-4 episode criteria were chosen to allow comparison with prior RCTs of face-to-face psychotherapy for bipolar disorder, as these studies primarily used the DSM-4 episode criteria [10-18]. To determine the number of weeks to episode onset, weekly clinical status ratings (Tables 4 and 5) were assessed by timeline follow-back rating of bipolar disorder symptom severity (Multimedia Appendix 7) using a modified Longitudinal Interval Follow-Up Evaluation (LIFE) and Clinical Monitoring Form (CMF) [148,149,153]. The secondary outcomes include the percentage of time symptomatic, symptom severity, and QOL. To determine percentage of time symptomatic, weekly psychiatric status ratings (Table 6) were assessed using the LIFE-CMF to determine the percentage of time symptomatic. A week will be scored as symptomatic if the

psychiatric status rating is greater than one and a half (Table 6). Symptom severity was assessed using the Quick Inventory of Depressive Symptomatology (QIDS)–Clinician Rating and the Young Mania Rating Scale [154-157]. QOL was assessed using the World Health Organization Quality of Life BREF [158].

Table 6. Psychiatric status rating.

Score	Rating	Definition
6	Severe episode	Psychotic symptoms or severe impairment
5	Episode	No psychotic symptoms and no severe impairment
4	Marked symptoms	Symptom count[a] >2 and marked or severe impairment
3	Moderate symptoms	Symptom count >2 or moderate impairment
2	Residual or prodromal symptoms	Symptom count >0 and ≤2. No moderate, marked, or severe impairment
1.5	Mild symptoms	≥One mild symptom. No moderate, marked, or severe symptoms (Symptom count=0). No moderate, marked, or severe impairment
1	No symptoms	No mild, moderate, marked, or severe symptoms. No impairment

[a]Symptom count: Sum of symptom severity, if |severity| ≥1 round up, otherwise 0. Clinical Monitoring Form symptom severity scale: none=0, mild=0.5, moderate=1, marked=1.5, and severe=2.

Target Assessments

The targets selected for assessment were taking medications as prescribed, obtaining adequate sleep duration, maintaining regular routines, and managing signs and symptoms as these targets are readily amenable to monitoring using the Daily Check-In, which is a core feature of LiveWell. Medication adherence was assessed using the Tablet Routine Questionnaire [159-161] and focused on percentage adherence with prescribed psychiatric medications, not including those prescribed as needed. Sleep duration, quality, and excessive sleepiness were assessed using the CMF, QIDS, Pittsburgh Sleep Quality Index, and an additional question to capture excessive sleepiness [162-164]. Sleep duration was primarily considered in this study. Sleep quality and excessive sleepiness will be explored secondarily because interepisode insomnia and hypersomnia are risk factors for relapse [107,163,165,166]. Routine was assessed using a 5-question trait version of the Social Rhythm Metric [167-170] and will be assessed primarily by a frequency score (Multimedia Appendix 7). Finally, the management of residual and prodromal signs and symptoms was assessed using the Symptom Management Scale. This scale was developed from the prodromes coping interview and inventory, which has been used in face-to-face cognitive behavioral therapy for bipolar disorder [99,137,142,171]. The outcome measure will be the total coping score (Multimedia Appendix 7).

Outcome and Target Assessment Delivery

Assessors blinded to the study arm conducted outcome and target assessments by telephone at baseline and then every 8 weeks until study exit at week 48 (Figure 6). Windows for complete assessments were up to 4 weeks after the assessment due date, calculated from the baseline assessment date. To minimize assessment burden and because QOL may vary less rapidly than other outcomes [172], the QOL assessment was delivered only at 0, 24, and 48 weeks. Assessments began by focusing on participants' experiences over the prior 2 weeks. Mood and sleep were assessed using combined mood (CMF, QIDS, and Young Mania Rating Scale) and combined sleep (CMF, QIDS, and Pittsburgh Sleep Quality Index) instruments (Multimedia Appendix 7). The combined instruments streamlined the interviews and reduced the time required to complete the assessments. This was followed by assessment during the prior 2 weeks of routine (Social Rhythm Metric), medication adherence (Tablet Routine Questionnaire), and depending on the week QOL.

Information from the assessment of the prior 2 weeks was then used to anchor the timeline follow-back of weekly depressive and manic symptom severity (LIFE-CMF). In addition to assessing symptom severity, timeline follow-back using the LIFE assessed weekly variations in anxiety, suicidal ideation and attempts, psychotic symptoms, substance use, life events [173], mental health treatment attendance, and psychiatric medication adherence (Multimedia Appendix 7). The Symptom Management Scale was assessed last because it did not focus on experiences during the previous 2 weeks or since the last assessment. Instead, participants were asked to imagine experiencing ongoing or new low-level depressive or manic symptoms and how they might manage them (Multimedia Appendix 7). This approach was used because participant clinical status during the assessment interval may not have required management of prodromal or residual symptoms.

Determinant Assessments

To assess changes in the determinants proposed to govern the enactment of target behaviors, determinant questionnaires were developed for each assessed target (Multimedia Appendix 8). The determinant questionnaires are derived from the question stems of existing medication adherence questionnaires for schizophrenia and bipolar disorder [174,175] and health psychology questionnaires for assessing determinants of physical exercise and other health-related behaviors [76,77,176-183]. The questionnaires measure determinants proposed to underlie the pursuit of LiveWell's four assessed behavioral targets (taking medications as prescribed, obtaining adequate sleep duration, maintaining regular routines, and managing signs and symptoms). The questionnaires were delivered via a web survey sent by the coaches to the participants. For the intervention arm, they were delivered at weeks 0, 16, and 48 (Figure 6). For

participants in the control arm, they were only delivered at week 48 (Figure 6) because the delivery of the determinant questionnaires may serve as an active intervention [76,77,181]. Eventually, the determinant questionnaires may be incorporated into the smartphone app to provide real-time assessment of target change processes to facilitate improved adaptive real-time feedback.

Behavioral Sensing

Participants were offered the option of having the LiveWell app (intervention arm only) and an app for sensor data collection and secure transmission of data (Purple Robot, intervention, and control arms) [184] installed on their smartphone. Alternatively, participants had the option of receiving the apps on a study phone with an unlimited national calling and data plan. Individuals who opted to use their own phone were reimbursed for their plan up to the cost of the study phone plan or their own plan, whichever was less. All participants were provided with a wrist-worn actimeter (Pebble). Participants were asked to (1) use the phone with the apps as their only phone, (2) carry the phone with them whenever they left home, and (3) wear the watch 24 hours a day, 7 days a week except while it was charging.

Assessor Fidelity Assessments

Clinical outcomes and target assessments were performed by assessors with master's degrees in mental health or counseling. Structured interviews can be validly and reliably administered by such personnel [185-189]. Assessors were trained by mental health professionals (a psychiatrist and psychologist) with instruction and practice on audiotaped ratings, followed by observing, role-playing, and observed assessments (≥3 each). All assessment telephone calls were audiotaped. Assessor fidelity focused on using the CMF for assessing status in the prior 2 weeks. Assessment audiotapes were randomly selected each month (15%) for review and scoring by a trained mental health professional (psychologist) to assess the fidelity of CMF scoring for symptom severity (percent match within 0.5), asymptomatic status (percent match), clinical status (percent match), and psychiatric status rating (percent match).

Analysis Overview

As the randomization was stratified by risk group, analyses will examine if an interaction between risk strata and the study arm is present. If no evidence of an interaction is evident, the models will be stratified or adjusted for risk strata. For time to relapse, missing data for participants who dropped out or were lost to follow-up will be censored at their last study visit. Percentage time symptomatic will be calculated based only on the observed time in the study. For longitudinal data (symptom severity, QOL, targets), multiple imputation using Markov Chain Monte Carlo methods will be used to address missing data by creating five unique data sets (SAS procedure PROC MI), and the results will be combined (SAS procedure PROC MIANALYZE) to obtain valid statistical inferences and least square means of the outcomes for each time point data will be calculated.

Aim 1: Primary and Secondary Outcomes Analysis

Time-to-relapse curves will be constructed using the Kaplan-Meier method. Log-rank tests will be used to determine if there is a univariate impact of the study arm while adjusting for risk strata. Cox proportional hazard models will then be fit to adjust for risk strata. Proportional hazards assumptions will be assessed, and the estimated hazard ratio and CIs will be presented. To compare percent time symptomatic, linear regression models will be used to determine if there was an interaction between risk strata and the study arm. If no evidence of interaction is seen, the main effect of arm will be reported and least square means will be estimated while adjusting for risk strata. Generalized linear mixed models for longitudinal data will be used for symptom severity and QOL measures. We will examine the interactive effects of the intervention on time. If no interaction is detected, we will test the independent effects of time as well as the treatment group.

Sample Size Considerations

Under an initial assumption of 200 participants enrolled and randomized at a 2:3 ratio with a control group relapse rate of 0.60, there would be 80% power to detect a hazard ratio of 0.61 assuming a loss to follow-up rate of 12%. The control relapse rate estimate was based on the reported percent relapse at 12 months for control (63%) seven psychosocial interventions for bipolar disorder [190-198]. This would equate to a reduction in relapse rate to 43% in the LiveWell intervention group. This additionally assumes 30 months of accrual, and 12 months follow-up using a log-rank test at a type I error rate of 5% (PASS 2008) [199]. For secondary outcomes, assuming 12% loss to follow-up, a 2-tailed *t* test would have 80% power to detect effect sizes of 0.43, for percent time symptomatic, which would equate to differences in mean time of 14% (45% symptomatic vs 69%, assuming an SD of 32%). While power calculations for generalized linear models do exist, they are quite dependent on assumptions that were speculative at the time of study design. Using multiple linear regression, a sample size of 200, adjusting for one covariate that explains 20% of the variability in outcome, we have 80% power to detect an increase in R-squared of 3%.

Aim 2: Target Analysis

Generalized linear mixed models will be used to examine the effects of time, risk strata, and study arm on longitudinal target and determinant data. We will use the framework of Muller et al [200] to identify the targets that mediate the effect of the intervention on time to relapse, percentage time symptomatic, and symptom severity. To compare the performance determinant scores for each target at the final time point, *t* tests with correction for multiple testing between the two groups will be used.

Aim 3: Behavioral Analysis

For both arms, behavioral sensor data will be collected including activity (Pebble watch and phone accelerometers), location (via the GPS), timing of incoming and outgoing texts, timing and duration of incoming and outgoing telephone calls, and for some phones, ambient light (lux), and sound (power and frequency). Feature variables will be summarized over 1-week windows, to identify behavioral features strongly correlated with depression and mania symptom severity. The relationship between behavioral features and clinical status will then be explored. In addition, for the intervention arm, self-report

assessment and app use data as well as personalized wellness rating anchors and plans, reduce risk plans, sleep duration goals, and routine (bedtime and risetime) goals will be available. These data will be used to explore processes involved in staying well with the aim of improving adaptive delivery of content and tools to decrease relapse risk and symptom burden.

Results

Recruitment and screening began in March 2017 and ended in April 2019. Follow-up ended in April 2020. The results of this study are expected to be published in 2022. Data from this study will be available at the National Institute of Mental Health Data Archive.

Discussion

The primary goal of developing and delivering LiveWell is to increase access to self-management strategies derived from empirically supported bipolar disorder psychotherapies, thereby assisting individuals with bipolar disorder in staying well. It is hoped that this intervention will decrease relapse rates and symptom burden as well as improve QOL. LiveWell seeks to improve these outcomes by helping individuals manage target behaviors proposed to underlie the impact of existing interventions [5,18,26,33,97,98]. Although therapies for bipolar disorder often address the selected targets, there are limited data demonstrating that delivery of these therapies results in target behavior change or that changes in these behaviors mediate outcome changes [5,10-16,97,98,201]. Existing interventions for bipolar disorder have primarily been outcome studies so they have not focused on understanding relapse prevention and other outcome mechanisms. Relative to outcome studies, studies aimed at understanding the mechanisms of change require substantial modification, including measurement of outcomes and multiple proposed mechanisms before, during, and after intervention delivery [202-204]. As existing bipolar disorder interventions do not typically use this approach [5,10-16,97,98,201], our understanding of the mechanisms underlying the improved outcomes resulting from these interventions is limited. Because it is unclear what intervention components are useful for different individuals at different times, our ability to improve these interventions and adapt them for delivery in diverse settings is limited.

As a secondary goal, the LiveWell intervention aims to investigate the relationships between changes in target behaviors and outcomes over time to provide insights into the mechanisms of change. A behavior change framework provides a theory-based and empirically supported rationale for including intervention content and tools and facilitates the investigation of change mechanisms. It proposes that (1) engaging in target behaviors improves clinical and recovery outcomes, (2) behavioral determinants govern the enactment of target behaviors, and (3) exposure to behavior change technique content and tool use alters behavioral determinants. This framework provides a means to label app use and coaching call content in terms of outcomes, targets, and determinants addressed by the behavior change techniques delivered. This labeling will allow a more detailed exploratory investigation of intervention mechanisms by examining the relationships between changes in outcomes, targets, and determinants and exposure to behavior change technique content and tool use.

App use will measure outcomes via the Weekly Check-In (PHQ-8, ASRM) and target behaviors via the Daily Check-In (medication adherence, sleep duration, routine, and management of signs and symptoms) providing a more detailed examination of changes in outcomes and target behaviors over time than can be achieved via our standard telephone-based assessments delivered every 8 weeks. By labeling all pages of the app using the behavior change framework, it will also be possible to investigate how exposure to behavior change techniques relates to changes in determinants and how changes in determinants relate to changes in target behaviors. In addition, the intervention also uses smartphone and watch sensors to collect behavioral data such as activity levels and sleep duration (actimetry), location (GPS), and social interactions (texts and calls). As these behaviors may vary with clinical status, this passively collected behavioral data provides an opportunity to identify behavioral features correlated with clinical status and may improve our ability to determine what content to deliver to different individuals at different times to improve treatment. Overall the goal of the LiveWell intervention is to assist individuals in staying well while also serving as a platform for data collection that provides insights into treatment mechanisms and trajectories to allow iterative development and improvement of the intervention.

Despite the iterative design process used to develop LiveWell [63-66], the intervention design described here continues to have limitations. For instance, time to relapse was chosen as the primary outcome because most face-to-face interventions from which the LiveWell intervention derives focus on relapse prevention for individuals between mood episodes [10-15,18,205]. However, QOL and recovery outcomes (eg, connectedness, hope, and optimism) are highly valued by individuals with bipolar disorder but have not routinely been incorporated as outcomes in existing studies [39,95,96]. As a result, additional work will be needed to measure recovery outcomes, to identify the targets and determinants to address and the change techniques to deliver to facilitate changes in QOL and recovery outcomes. In addition, while the behavioral targets selected for daily monitoring (medication adherence, sleep duration, routine, managing symptoms and signs) are important and readily amenable to monitoring, other important targets have not been strongly emphasized. In particular, during the person-centered design process, building and using supports were strongly endorsed by users as being important for staying well [65,66]. Because of this feedback, coaching support for users was further developed [63]. Additional elements such as an opportunity for participants to engage in peer-to-peer discussion and exchange ideas could be incorporated, as these types of tools have been helpful in other interventions [206,207]. It will also be necessary to integrate assessments of users' social support system strength and support use to assess the impact of the intervention on this target and the impact of changes in social support on outcomes.

Although extensive feedback was received during the development of LiveWell [63-66], most of the feedback was

obtained from individuals with bipolar disorder and less so from providers. Thus, additional work will be required to obtain provider feedback during future efforts to implement and disseminate the LiveWell intervention. Furthermore, to better understand the impact of delivery and use of behavior change technique content and tools on changes in determinants and targets as well as interactions between multiple targets and determinants, a larger number of participants will be required. Hopefully, a structured behavior change framework will facilitate exploring these issues for bipolar disorder and other mental health disorders, thereby allowing data to be synthesized across studies to enhance the ability to improve mental health technologies and their delivery. Thus, we hope that the description of the theoretical and empirically supported framework, design, and protocol for the RCT of LiveWell will facilitate the replication, improvement, implementation, and dissemination of effective interventions for bipolar and other mental health disorders.

Conflicts of Interest

EHG has accepted honoraria from Otsuka Pharmaceuticals. DCM has accepted honoraria and consulting fees from Apple, Inc, Otsuka Pharmaceuticals, Pear Therapeutics, and the One Mind Foundation, royalties from Oxford Press, and has an ownership interest in Adaptive Health, Inc.

Multimedia Appendix 1
LiveWell app and coaching content coding.
[XLSX File (Microsoft Excel File), 622 KB - resprot_v11i2e30710_app1.xlsx]

Multimedia Appendix 2
LiveWell smartphone app content.
[PDF File (Adobe PDF File), 5824 KB - resprot_v11i2e30710_app2.pdf]

Multimedia Appendix 3
LiveWell use case scenario.
[PDF File (Adobe PDF File), 603 KB - resprot_v11i2e30710_app3.pdf]

Multimedia Appendix 4
LiveWell coaching materials.
[PDF File (Adobe PDF File), 3325 KB - resprot_v11i2e30710_app4.pdf]

Multimedia Appendix 5
LiveWell design assessments.
[PDF File (Adobe PDF File), 170 KB - resprot_v11i2e30710_app5.pdf]

Multimedia Appendix 6
LiveWell screening assessments.
[PDF File (Adobe PDF File), 1775 KB - resprot_v11i2e30710_app6.pdf]

Multimedia Appendix 7
LiveWell outcome and target assessments.
[PDF File (Adobe PDF File), 1365 KB - resprot_v11i2e30710_app7.pdf]

Multimedia Appendix 8
LiveWell determinant assessments.
[PDF File (Adobe PDF File), 1423 KB - resprot_v11i2e30710_app8.pdf]

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Washington, DC: American Psychiatric Publishing; 2013.
2. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. Nat Rev Dis Primers 2018 Dec 08;4:18008. [doi: 10.1038/nrdp.2018.8] [Medline: 29516993]
3. Ferrari AJ, Stockings E, Khoo J, Erskine HE, Degenhardt L, Vos T, et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. Bipolar Disord 2016 Aug;18(5):440-450. [doi: 10.1111/bdi.12423] [Medline: 27566286]

4. Hayes JF, Miles J, Walters K, King M, Osborn DP. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr Scand 2015 Jun;131(6):417-425 [FREE Full text] [doi: 10.1111/acps.12408] [Medline: 25735195]
5. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet 2013 May 11;381(9878):1672-1682 [FREE Full text] [doi: 10.1016/S0140-6736(13)60857-0] [Medline: 23663953]
6. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 2014 Oct;1(5):351-359. [doi: 10.1016/s2215-0366(14)70314-1]
7. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005 Dec;62(12):1322-1330. [doi: 10.1001/archpsyc.62.12.1322] [Medline: 16330720]
8. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002 Jun;59(6):530-537. [Medline: 12044195]
9. Judd LL, Schettler PJ, Akiskal HS, Coryell W, Leon AC, Maser JD, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Arch Gen Psychiatry 2008 Apr;65(4):386-394. [doi: 10.1001/archpsyc.65.4.386] [Medline: 18391127]
10. Crowe M, Whitehead L, Wilson L, Carlyle D, O'Brien A, Inder M, et al. Disorder-specific psychosocial interventions for bipolar disorder--a systematic review of the evidence for mental health nursing practice. Int J Nurs Stud 2010 Jul;47(7):896-908. [doi: 10.1016/j.ijnurstu.2010.02.012] [Medline: 20233615]
11. Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. Am J Psychiatry 2008 Nov;165(11):1408-1419 [FREE Full text] [doi: 10.1176/appi.ajp.2008.08040488] [Medline: 18794208]
12. Schöttle D, Huber CG, Bock T, Meyer TD. Psychotherapy for bipolar disorder: a review of the most recent studies. Curr Opin Psychiatry 2011 Nov;24(6):549-555. [doi: 10.1097/YCO.0b013e32834b7c5f] [Medline: 21918448]
13. Lam DH, Burbeck R, Wright K, Pilling S. Psychological therapies in bipolar disorder: the effect of illness history on relapse prevention - a systematic review. Bipolar Disord 2009 Aug;11(5):474-482. [doi: 10.1111/j.1399-5618.2009.00724.x] [Medline: 19624386]
14. Scott J, Colom F, Vieta E. A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders. Int J Neuropsychopharmacol 2007 Feb;10(1):123-129 [FREE Full text] [doi: 10.1017/S1461145706006900] [Medline: 16787554]
15. Bond K, Anderson IM. Psychoeducation for relapse prevention in bipolar disorder: a systematic review of efficacy in randomized controlled trials. Bipolar Disord 2015 Jun;17(4):349-362. [doi: 10.1111/bdi.12287] [Medline: 25594775]
16. Gregory VL. Cognitive-behavioral therapy for depression in bipolar disorder: a meta-analysis. J Evid Based Soc Work 2010 Jul;7(4):269-279. [doi: 10.1080/15433710903176088] [Medline: 20799127]
17. Gregory VL. Cognitive-behavioral therapy for mania: a meta-analysis of randomized controlled trials. Social Work Mental Health 2010 Oct 07;8(6):483-494. [doi: 10.1080/15332981003744388]
18. Miklowitz DJ, Efthimiou O, Furukawa TA, Scott J, McLaren R, Geddes JR, et al. Adjunctive psychotherapy for bipolar disorder: a systematic review and component network meta-analysis. JAMA Psychiatry 2021 Feb 01;78(2):141-150 [FREE Full text] [doi: 10.1001/jamapsychiatry.2020.2993] [Medline: 33052390]
19. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018 Mar;20(2):97-170 [FREE Full text] [doi: 10.1111/bdi.12609] [Medline: 29536616]
20. Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P, et al. The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. Int J Neuropsychopharmacol 2017 Feb 01;20(2):180-195 [FREE Full text] [doi: 10.1093/ijnp/pyw109] [Medline: 27941079]
21. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016 Dec;30(6):495-553 [FREE Full text] [doi: 10.1177/0269881116636545] [Medline: 26979387]
22. Olfson M, Marcus SC, Druss B, Pincus HA. National trends in the use of outpatient psychotherapy. Am J Psychiatry 2002 Nov;159(11):1914-1920. [doi: 10.1176/appi.ajp.159.11.1914] [Medline: 12411228]
23. Busch AB, Ling D, Frank RG, Greenfield SF. Changes in the quality of care for bipolar I disorder during the 1990s. Psychiatr Serv 2007 Jan;58(1):27-33 [FREE Full text] [doi: 10.1176/ps.2007.58.1.27] [Medline: 17215409]
24. Brown JD, Barrett A, Hourihan K, Caffery E, Ireys HT. State variation in the delivery of comprehensive services for Medicaid beneficiaries with schizophrenia and bipolar disorder. Community Ment Health J 2015 Jul;51(5):523-534. [doi: 10.1007/s10597-015-9857-5] [Medline: 25786723]
25. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005 Jun;62(6):629-640. [doi: 10.1001/archpsyc.62.6.629] [Medline: 15939840]

26. Reinares M, Sánchez-Moreno J, Fountoulakis KN. Psychosocial interventions in bipolar disorder: what, for whom, and when. J Affect Disord 2014 Mar;156:46-55. [doi: 10.1016/j.jad.2013.12.017] [Medline: 24439829]
27. Denizard-Thompson NM, Feiereisel KB, Stevens SF, Miller DP, Wofford JL. The digital divide at an urban community health center: implications for quality improvement and health care access. J Community Health 2011 Jun;36(3):456-460. [doi: 10.1007/s10900-010-9327-5] [Medline: 21086028]
28. Proudfoot J, Parker G, Hadzi PD, Manicavasagar V, Adler E, Whitton A. Community attitudes to the appropriation of mobile phones for monitoring and managing depression, anxiety, and stress. J Med Internet Res 2010 Dec;12(5):e64 [FREE Full text] [doi: 10.2196/jmir.1475] [Medline: 21169174]
29. Ben-Zeev D, Davis KE, Kaiser S, Krzsos I, Drake RE. Mobile technologies among people with serious mental illness: opportunities for future services. Adm Policy Ment Health 2013 Jul;40(4):340-343 [FREE Full text] [doi: 10.1007/s10488-012-0424-x] [Medline: 22648635]
30. Torous J, Wisniewski H, Liu G, Keshavan M. Mental health mobile phone app usage, concerns, and benefits among psychiatric outpatients: comparative survey study. JMIR Ment Health 2018 Nov 16;5(4):e11715 [FREE Full text] [doi: 10.2196/11715] [Medline: 30446484]
31. Hollis C, Morriss R, Martin J, Amani S, Cotton R, Denis M, et al. Technological innovations in mental healthcare: harnessing the digital revolution. Br J Psychiatry 2015 Apr;206(4):263-265. [doi: 10.1192/bjp.bp.113.142612] [Medline: 25833865]
32. Michalak EE, Suto MJ, Barnes SJ, Hou S, Lapsley S, Scott MW, et al. Effective self-management strategies for bipolar disorder: a community-engaged Delphi Consensus Consultation study. J Affect Disord 2016 Dec;206:77-86 [FREE Full text] [doi: 10.1016/j.jad.2016.06.057] [Medline: 27466745]
33. Murray G, Suto M, Hole R, Hale S, Amari E, Michalak EE. Self-management strategies used by 'high functioning' individuals with bipolar disorder: from research to clinical practice. Clin Psychol Psychother 2011 Apr;18(2):95-109. [doi: 10.1002/cpp.710] [Medline: 20572206]
34. Janney CA, Bauer MS, Kilbourne AM. Self-management and bipolar disorder--a clinician's guide to the literature 2011-2014. Curr Psychiatry Rep 2014 Sep;16(9):485. [doi: 10.1007/s11920-014-0485-5] [Medline: 25123130]
35. Russell SJ, Browne JL. Staying well with bipolar disorder. Aust N Z J Psychiatry 2005 Mar;39(3):187-193. [doi: 10.1080/j.1440-1614.2005.01542.x] [Medline: 15701069]
36. Nicholas J, Boydell K, Christensen H. Beyond symptom monitoring: consumer needs for bipolar disorder self-management using smartphones. Eur Psychiatry 2017 Jul;44:210-216. [doi: 10.1016/j.eurpsy.2017.05.023] [Medline: 28692910]
37. Daus H, Kislicyn N, Heuer S, Backenstrass M. Disease management apps and technical assistance systems for bipolar disorder: investigating the patients´ point of view. J Affect Disord 2018 Dec 15;229:351-357. [doi: 10.1016/j.jad.2017.12.059] [Medline: 29331693]
38. Murnane EL, Cosley D, Chang P, Guha S, Frank E, Gay G, et al. Self-monitoring practices, attitudes, and needs of individuals with bipolar disorder: implications for the design of technologies to manage mental health. J Am Med Inform Assoc 2016 May;23(3):477-484. [doi: 10.1093/jamia/ocv165] [Medline: 26911822]
39. Todd NJ, Jones SH, Lobban FA. What do service users with bipolar disorder want from a web-based self-management intervention? A qualitative focus group study. Clin Psychol Psychother 2013;20(6):531-543. [doi: 10.1002/cpp.1804] [Medline: 22715161]
40. Mohr DC, Burns MN, Schueller SM, Clarke G, Klinkman M. Behavioral intervention technologies: evidence review and recommendations for future research in mental health. Gen Hosp Psychiatry 2013 Aug;35(4):332-338 [FREE Full text] [doi: 10.1016/j.genhosppsych.2013.03.008] [Medline: 23664503]
41. Clough BA, Casey LM. Technological adjuncts to enhance current psychotherapy practices: a review. Clin Psychol Rev 2011 Apr;31(3):279-292. [doi: 10.1016/j.cpr.2010.12.008] [Medline: 21382535]
42. Lindhiem O, Bennett CB, Rosen D, Silk J. Mobile technology boosts the effectiveness of psychotherapy and behavioral interventions: a meta-analysis. Behav Modif 2015 Nov;39(6):785-804. [doi: 10.1177/0145445515595198] [Medline: 26187164]
43. Areàn PA, Hoa Ly K, Andersson G. Mobile technology for mental health assessment. Dialogues Clin Neurosci 2016 Dec;18(2):163-169 [FREE Full text] [Medline: 27489456]
44. Cornet VP, Holden RJ. Systematic review of smartphone-based passive sensing for health and wellbeing. J Biomed Inform 2018 Jan;77:120-132. [doi: 10.1016/j.jbi.2017.12.008] [Medline: 29248628]
45. Torous J, Staples P, Onnela J. Realizing the potential of mobile mental health: new methods for new data in psychiatry. Curr Psychiatry Rep 2015 Aug;17(8):602. [doi: 10.1007/s11920-015-0602-0] [Medline: 26073363]
46. Trifan A, Oliveira M, Oliveira JL. Passive sensing of health outcomes through smartphones: systematic review of current solutions and possible limitations. JMIR Mhealth Uhealth 2019 Aug 23;7(8):e12649 [FREE Full text] [doi: 10.2196/12649] [Medline: 31444874]
47. Nicholas J, Larsen ME, Proudfoot J, Christensen H. Mobile apps for bipolar disorder: a systematic review of features and content quality. J Med Internet Res 2015;17(8):e198 [FREE Full text] [doi: 10.2196/jmir.4581] [Medline: 26283290]
48. Lagan S, Ramakrishnan A, Lamont E, Ramakrishnan A, Frye M, Torous J. Digital health developments and drawbacks: a review and analysis of top-returned apps for bipolar disorder. Int J Bipolar Disord 2020 Dec 01;8(1):39 [FREE Full text] [doi: 10.1186/s40345-020-00202-4] [Medline: 33259047]

49. Hidalgo-Mazzei D, Mateu A, Reinares M, Matic A, Vieta E, Colom F. Internet-based psychological interventions for bipolar disorder: review of the present and insights into the future. J Affect Disord 2015 Aug 28;188:1-13. [doi: 10.1016/j.jad.2015.08.005] [Medline: 26342885]
50. Depp CA, Ceglowski J, Wang VC, Yaghouti F, Mausbach BT, Thompson WK, et al. Augmenting psychoeducation with a mobile intervention for bipolar disorder: a randomized controlled trial. J Affect Disord 2015 Mar 15;174:23-30. [doi: 10.1016/j.jad.2014.10.053] [Medline: 25479050]
51. Gliddon E, Barnes SJ, Murray G, Michalak EE. Online and mobile technologies for self-management in bipolar disorder: a systematic review. Psychiatr Rehabil J 2017 Sep;40(3):309-319. [doi: 10.1037/prj0000270] [Medline: 28594196]
52. Wenze SJ, Armey MF, Miller IW. Feasibility and acceptability of a mobile intervention to improve treatment adherence in bipolar disorder: a pilot study. Behav Modif 2014 Jul;38(4):497-515 [FREE Full text] [doi: 10.1177/0145445513518421] [Medline: 24402464]
53. Depp CA, Perivoliotis D, Holden J, Dorr J, Granholm EL. Single-session mobile-augmented intervention in serious mental illness: a three-arm randomized controlled trial. Schizophr Bull 2019 Jun 18;45(4):752-762 [FREE Full text] [doi: 10.1093/schbul/sby135] [Medline: 30281086]
54. Enrique A, Duffy D, Lawler K, Richards D, Jones S. An internet-delivered self-management programme for bipolar disorder in mental health services in Ireland: results and learnings from a feasibility trial. Clin Psychol Psychother 2020 Nov;27(6):925-939 [FREE Full text] [doi: 10.1002/cpp.2480] [Medline: 32445611]
55. van der Watt AS, Odendaal W, Louw K, Seedat S. Distant mood monitoring for depressive and bipolar disorders: a systematic review. BMC Psychiatry 2020 Jul 22;20(1):383 [FREE Full text] [doi: 10.1186/s12888-020-02782-y] [Medline: 32698802]
56. Brendryen H, Kraft P, Schaalma H. Looking inside the black box: using intervention mapping to describe the development of the automated smoking cessation intervention 'happy ending'. J Smok Cessat 2012 Feb 21;5(1):29-56. [doi: 10.1375/jsc.5.1.29]
57. Brendryen H, Johansen A, Nesvåg S, Kok G, Duckert F. Constructing a theory- and evidence-based treatment rationale for complex ehealth interventions: development of an online alcohol intervention using an intervention mapping approach. JMIR Res Protoc 2013 Jan;2(1):e6 [FREE Full text] [doi: 10.2196/resprot.2371] [Medline: 23612478]
58. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychol 2008 May;27(3):379-387. [doi: 10.1037/0278-6133.27.3.379] [Medline: 18624603]
59. Spring B. Evidence-based practice in clinical psychology: what it is, why it matters; what you need to know. J Clin Psychol 2007 Jul;63(7):611-631. [doi: 10.1002/jclp.20373] [Medline: 17551934]
60. Yardley L, Morrison L, Bradbury K, Muller I. The person-based approach to intervention development: application to digital health-related behavior change interventions. J Med Internet Res 2015 Jan 30;17(1):e30 [FREE Full text] [doi: 10.2196/jmir.4055] [Medline: 25639757]
61. Yardley L, Spring BJ, Riper H, Morrison LG, Crane DH, Curtis K, et al. Understanding and promoting effective engagement with digital behavior change interventions. Am J Prev Med 2016 Nov;51(5):833-842. [doi: 10.1016/j.amepre.2016.06.015] [Medline: 27745683]
62. Bartholomew LK, Parcel GS, Kok G. Intervention mapping: a process for developing theory- and evidence-based health education programs. Health Educ Behav 1998 Oct;25(5):545-563. [Medline: 9768376]
63. Dopke CA, McBride A, Babington P, Jonathan GK, Michaels T, Ryan C, et al. Development of coaching support for LiveWell: a smartphone-based self-management intervention for bipolar disorder. JMIR Form Res 2021 Mar 24;5(3):e25810 [FREE Full text] [doi: 10.2196/25810] [Medline: 33759798]
64. Goulding ED, Dopke CA, Michaels T, Martin CR, Khiani MA, Garborg C, et al. A smartphone-based self-management intervention for individuals with bipolar disorder (LiveWell): protocol development for an expert system to provide adaptive user feedback. JMIR Form Res 2021;5(12):e32932 [FREE Full text] [doi: 10.2196/32932] [Medline: 34951598]
65. Jonathan GK, Dopke CA, Michaels T, Bank A, Martin CR, Adhikari K, et al. A smartphone-based self-management intervention for bipolar disorder (LiveWell): user-centered development approach. JMIR Ment Health 2021 Apr 12;8(4):e20424 [FREE Full text] [doi: 10.2196/20424] [Medline: 33843607]
66. Jonathan GK, Dopke CA, Michaels T, Martin CR, Ryan C, McBride A, et al. A smartphone-based self-management intervention for individuals with bipolar disorder (LiveWell): qualitative study on user experiences of the behavior change process. JMIR Ment Health 2021 Nov 22;8(11):e32306 [FREE Full text] [doi: 10.2196/32306] [Medline: 34813488]
67. Carver CS, Scheier MF. Control theory: a useful conceptual framework for personality-social, clinical, and health psychology. Psychol Bull 1982 Jul;92(1):111-135. [Medline: 7134324]
68. Zimmerman BJ. A social cognitive view of self-regulated academic learning. J Educ Psychol 1989;81(3):329-339. [doi: 10.1037/0022-0663.81.3.329]
69. Ajzen I. The theory of planned behavior. Org Behav Human Decision Processes 1991 Dec;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-t]
70. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000 Jan;55(1):68-78. [Medline: 11392867]
71. Carver C, Scheier M. Control processes and self-organization as complementary principles underlying behavior. Pers Soc Psychol Rev 2016 Dec 21;6(4):304-315. [doi: 10.1207/S15327957PSPR0604_05]

72. Locke EA, Latham GP. Building a practically useful theory of goal setting and task motivation. A 35-year odyssey. Am Psychol 2002 Sep;57(9):705-717. [doi: 10.1037//0003-066x.57.9.705] [Medline: 12237980]
73. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004 Apr;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
74. Markland D, Ryan R, Tobin V, Rollnick S. Motivational interviewing and self–determination theory. J Soc Clin Psychol 2005 Sep 21;24(6):811-831. [doi: 10.1521/jscp.2005.24.6.811] [Medline: 5637250]
75. Latham GP, Locke EA. New developments in and directions for goal-setting research. European Psychol 2007 Jan;12(4):290-300. [doi: 10.1027/1016-9040.12.4.290]
76. Schwarzer R. Modeling health behavior change: how to predict and modify the adoption and maintenance of health behaviors. Applied Psychol 2008 Jan;57(1):1-29. [doi: 10.1111/j.1464-0597.2007.00325.x]
77. Schwarzer R, Lippke S, Luszczynska A. Mechanisms of health behavior change in persons with chronic illness or disability: the Health Action Process Approach (HAPA). Rehabil Psychol 2011 Aug;56(3):161-170. [doi: 10.1037/a0024509] [Medline: 21767036]
78. Su Y, Reeve J. A meta-analysis of the effectiveness of intervention programs designed to support autonomy. Educ Psychol Rev 2010 Sep 25;23(1):159-188. [doi: 10.1007/s10648-010-9142-7]
79. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011;6:42 [FREE Full text] [doi: 10.1186/1748-5908-6-42] [Medline: 21513547]
80. Ries F, Hein V, Pihu M, Armenta JM. Self-identity as a component of the Theory of Planned Behaviour in predicting physical activity. Eur Physical Educ Rev 2012 Oct 02;18(3):322-334. [doi: 10.1177/1356336x12450792]
81. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci 2012 Apr 24;7:37 [FREE Full text] [doi: 10.1186/1748-5908-7-37] [Medline: 22530986]
82. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
83. Jones CJ, Smith H, Llewellyn C. Evaluating the effectiveness of health belief model interventions in improving adherence: a systematic review. Health Psychol Rev 2014;8(3):253-269. [doi: 10.1080/17437199.2013.802623] [Medline: 25053213]
84. Cane J, Richardson M, Johnston M, Ladha R, Michie S. From lists of behaviour change techniques (BCTs) to structured hierarchies: comparison of two methods of developing a hierarchy of BCTs. Br J Health Psychol 2015 Feb;20(1):130-150. [doi: 10.1111/bjhp.12102] [Medline: 24815766]
85. Berkman ET, Livingston JL, Kahn LE. Finding the “self” in self-regulation: the identity-value model. Psychol Inquiry 2017 Aug 18;28(2-3):77-98. [doi: 10.1080/1047840x.2017.1323463]
86. Von Korff M, Gruman J, Schaefer J, Curry SJ, Wagner EH. Collaborative management of chronic illness. Ann Intern Med 1997 Dec 15;127(12):1097-1102. [doi: 10.7326/0003-4819-127-12-199712150-00008] [Medline: 9412313]
87. Clark NM, Gong M, Kaciroti N. A model of self-regulation for control of chronic disease. Health Educ Behav 2001 Dec;28(6):769-782. [doi: 10.1177/109019810102800608] [Medline: 11720277]
88. Miller WR, Lasiter S, Bartlett Ellis R, Buelow JM. Chronic disease self-management: a hybrid concept analysis. Nurs Outlook 2015;63(2):154-161. [doi: 10.1016/j.outlook.2014.07.005] [Medline: 25241136]
89. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. Milbank Q 1996;74(4):511-544. [Medline: 8941260]
90. Lorig KR, Sobel DS, Stewart AL, Brown BW, Bandura A, Ritter P, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. Med Care 1999 Jan;37(1):5-14. [doi: 10.1097/00005650-199901000-00003] [Medline: 10413387]
91. Salyers MP, Godfrey JL, McGuire AB, Gearhart T, Rollins AL, Boyle C. Implementing the illness management and recovery program for consumers with severe mental illness. Psychiatr Serv 2009 Apr;60(4):483-490. [doi: 10.1176/appi.ps.60.4.483] [Medline: 19339323]
92. Salyers MP, Godfrey JL, Mueser KT, Labriola S. Measuring illness management outcomes: a psychometric study of clinician and consumer rating scales for illness self management and recovery. Community Ment Health J 2007 Oct;43(5):459-480. [doi: 10.1007/s10597-007-9087-6] [Medline: 17514504]
93. Jacobson RP, Mortensen CR, Cialdini RB. Bodies obliged and unbound: differentiated response tendencies for injunctive and descriptive social norms. J Pers Soc Psychol 2011 Mar;100(3):433-448. [doi: 10.1037/a0021470] [Medline: 21171790]
94. Gitlin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995 Nov;152(11):1635-1640. [doi: 10.1176/ajp.152.11.1635] [Medline: 7485627]
95. Leitan ND, Michalak EE, Berk L, Berk M, Murray G. Optimizing delivery of recovery-oriented online self-management strategies for bipolar disorder: a review. Bipolar Disord 2015 Mar;17(2):115-127. [doi: 10.1111/bdi.12258] [Medline: 25238632]
96. Michalak EE, Yatham LN, Lam RW. Quality of life in bipolar disorder: a review of the literature. Health Qual Life Outcomes 2005 Nov 15;3:72 [FREE Full text] [doi: 10.1186/1477-7525-3-72] [Medline: 16288650]

97. Miklowitz DJ, Goodwin GM, Bauer MS, Geddes JR. Common and specific elements of psychosocial treatments for bipolar disorder: a survey of clinicians participating in randomized trials. J Psychiatr Pract 2008 Mar;14(2):77-85 [FREE Full text] [doi: 10.1097/01.pra.0000314314.94791.c9] [Medline: 18360193]
98. Miklowitz DJ, Scott J. Psychosocial treatments for bipolar disorder: cost-effectiveness, mediating mechanisms, and future directions. Bipolar Disord 2009 Jun;11 Suppl 2:110-122. [doi: 10.1111/j.1399-5618.2009.00715.x] [Medline: 19538690]
99. Lam D, Wong G. Prodromes, coping strategies and psychological interventions in bipolar disorders. Clin Psychol Rev 2005 Dec;25(8):1028-1042. [doi: 10.1016/j.cpr.2005.06.005] [Medline: 16125292]
100. Morriss RK, Faizal MA, Jones AP, Williamson PR, Bolton C, McCarthy JP. Interventions for helping people recognise early signs of recurrence in bipolar disorder. Cochrane Database Syst Rev 2007 Jan 24(1):CD004854 [FREE Full text] [doi: 10.1002/14651858.CD004854.pub2] [Medline: 17253526]
101. Colom F, Vieta E, Tacchi MJ, Sánchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. Bipolar Disord 2005;7 Suppl 5:24-31. [doi: 10.1111/j.1399-5618.2005.00248.x] [Medline: 16225557]
102. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatr Scand 2002 Mar;105(3):164-172. [doi: 10.1034/j.1600-0447.2002.1r084.x] [Medline: 11939969]
103. Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. Am J Psychiatry 2002 Nov;159(11):1927-1929. [doi: 10.1176/appi.ajp.159.11.1927] [Medline: 12411230]
104. Adams J, Scott J. Predicting medication adherence in severe mental disorders. Acta Psychiatr Scand 2000 Feb;101(2):119-124. [doi: 10.1034/j.1600-0447.2000.90061.x] [Medline: 10706011]
105. Scott J. Predicting medication non-adherence in severe affective disorders. Acta Neuropsychiatr 2000 Sep;12(3):128-130. [doi: 10.1017/S0924270800035584] [Medline: 26975270]
106. Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatry 2008 Jul;165(7):820-829. [doi: 10.1176/appi.ajp.2008.08010098] [Medline: 18519522]
107. Gruber J, Miklowitz DJ, Harvey AG, Frank E, Kupfer D, Thase ME, et al. Sleep matters: sleep functioning and course of illness in bipolar disorder. J Affect Disord 2011 Nov;134(1-3):416-420 [FREE Full text] [doi: 10.1016/j.jad.2011.05.016] [Medline: 21683450]
108. Bauer M, Grof P, Rasgon N, Bschor T, Glenn T, Whybrow PC. Temporal relation between sleep and mood in patients with bipolar disorder. Bipolar Disord 2006 Apr;8(2):160-167. [doi: 10.1111/j.1399-5618.2006.00294.x] [Medline: 16542186]
109. Bauer M, Juckel G, Correll CU, Leopold K, Pfennig A. Diagnosis and treatment in the early illness phase of bipolar disorders. Eur Arch Psychiatry Clin Neurosci 2008 Nov;258 Suppl 5:50-54. [doi: 10.1007/s00406-008-5009-z] [Medline: 18985295]
110. Jackson A, Cavanagh J, Scott J. A systematic review of manic and depressive prodromes. J Affect Disord 2003 May;74(3):209-217. [Medline: 12738039]
111. Jones SH. Circadian rhythms, multilevel models of emotion and bipolar disorder--an initial step towards integration? Clin Psychol Rev 2001 Nov;21(8):1193-1209. [doi: 10.1016/s0272-7358(01)00111-8] [Medline: 11702512]
112. Johnson SL. Life events in bipolar disorder: towards more specific models. Clin Psychol Rev 2005 Dec;25(8):1008-1027 [FREE Full text] [doi: 10.1016/j.cpr.2005.06.004] [Medline: 16129530]
113. Ehlers CL, Frank E, Kupfer DJ. Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. Arch Gen Psychiatry 1988 Oct;45(10):948-952. [doi: 10.1001/archpsyc.1988.01800340076012] [Medline: 3048226]
114. Frank E. Interpersonal and social rhythm therapy: a means of improving depression and preventing relapse in bipolar disorder. J Clin Psychol 2007 May;63(5):463-473. [doi: 10.1002/jclp.20371] [Medline: 17417811]
115. Murray G, Harvey A. Circadian rhythms and sleep in bipolar disorder. Bipolar Disord 2010 Aug;12(5):459-472. [doi: 10.1111/j.1399-5618.2010.00843.x] [Medline: 20712747]
116. Suto M, Murray G, Hale S, Amari E, Michalak EE. What works for people with bipolar disorder? Tips from the experts. J Affect Disord 2010 Jul;124(1-2):76-84. [doi: 10.1016/j.jad.2009.11.004] [Medline: 19969370]
117. Lopresti AL, Jacka FN. Diet and bipolar disorder: a review of its relationship and potential therapeutic mechanisms of action. J Altern Complement Med 2015 Dec;21(12):733-739. [doi: 10.1089/acm.2015.0125] [Medline: 26348597]
118. Bauer IE, Gálvez JF, Hamilton JE, Balanzá-Martínez V, Zunta-Soares GB, Soares JC, et al. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. J Psychiatr Res 2016 Mar;74:1-7 [FREE Full text] [doi: 10.1016/j.jpsychires.2015.12.006] [Medline: 26724541]
119. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: a meta-regression. Health Psychol 2009 Nov;28(6):690-701. [doi: 10.1037/a0016136] [Medline: 19916637]
120. Michie S, Johnston M, Francis J, Hardeman W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. Applied Psychol Int Rev 2008 Oct;57(4):660-680. [doi: 10.1111/j.1464-0597.2008.00341.x]
121. Michie S, Webb TL, Sniehotta FF. The importance of making explicit links between theoretical constructs and behaviour change techniques. Addiction 2010 Nov;105(11):1897-1898. [doi: 10.1111/j.1360-0443.2010.03161.x] [Medline: 21064254]
122. Kwasnicka D, Dombrowski SU, White M, Sniehotta F. Theoretical explanations for maintenance of behaviour change: a systematic review of behaviour theories. Health Psychol Rev 2016 Sep;10(3):277-296 [FREE Full text] [doi: 10.1080/17437199.2016.1151372] [Medline: 26854092]

123. Sheeran P, Klein WM, Rothman AJ. Health behavior change: moving from observation to intervention. Annu Rev Psychol 2017 Jan 03;68:573-600. [doi: 10.1146/annurev-psych-010416-044007] [Medline: 27618942]
124. Hardcastle SJ, Fortier M, Blake N, Hagger MS. Identifying content-based and relational techniques to change behaviour in motivational interviewing. Health Psychol Rev 2017 Mar;11(1):1-16. [doi: 10.1080/17437199.2016.1190659] [Medline: 27189713]
125. Clark NM. Management of chronic disease by patients. Annu Rev Public Health 2003;24:289-313. [doi: 10.1146/annurev.publhealth.24.100901.141021] [Medline: 12415147]
126. Mohr DC, Schueller SM, Montague E, Burns MN, Rashidi P. The behavioral intervention technology model: an integrated conceptual and technological framework for eHealth and mHealth interventions. J Med Internet Res 2014 Jun;16(6):e146 [FREE Full text] [doi: 10.2196/jmir.3077] [Medline: 24905070]
127. Oinas-Kukkonen H. Behavior change support systems: a research model and agenda. In: Ploug T, Hasle P, Oinas-Kukkonen H, editors. Persuasive Technology. Berlin, Heidelberg: Springer; 2010.
128. Oinas-Kukkonen H, Harjumaa M. A systematic framework for designing and evaluating persuasive systems. In: Persuasive Technology. Berlin, Heidelberg: Springer; 2008.
129. Ritterband LM, Thorndike FP, Cox DJ, Kovatchev BP, Gonder-Frederick LA. A behavior change model for internet interventions. Ann Behav Med 2009 Aug;38(1):18-27 [FREE Full text] [doi: 10.1007/s12160-009-9133-4] [Medline: 19802647]
130. Mohr DC, Vella L, Hart S, Heckman T, Simon G. The effect of telephone-administered psychotherapy on symptoms of depression and attrition: a meta-analysis. Clin Psychol (New York) 2008;15(3):243-253 [FREE Full text] [doi: 10.1111/j.1468-2850.2008.00134.x] [Medline: 21369344]
131. Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. Cogn Behav Ther 2009;38(4):196-205. [doi: 10.1080/16506070903318960] [Medline: 20183695]
132. Baumeister H, Reichler L, Munzinger M, Lin J. The impact of guidance on Internet-based mental health interventions — A systematic review. Internet Interventions 2014 Oct;1(4):205-215. [doi: 10.1016/j.invent.2014.08.003]
133. Spek V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med 2006 Nov 20;37(03):319. [doi: 10.1017/s0033291706008944]
134. Schueller SM, Tomasino KN, Mohr DC. Integrating human support into behavioral intervention technologies: the efficiency model of support. Clin Psychol Sci Practice 2017 Mar;24(1):27-45. [doi: 10.1037/h0101740]
135. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res 2011;13(1):e30 [FREE Full text] [doi: 10.2196/jmir.1602] [Medline: 21393123]
136. Mohr DC, Duffecy J, Ho J, Kwasny M, Cai X, Burns MN, et al. A randomized controlled trial evaluating a manualized TeleCoaching protocol for improving adherence to a web-based intervention for the treatment of depression. PLoS One 2013 Aug;8(8):e70086 [FREE Full text] [doi: 10.1371/journal.pone.0070086] [Medline: 23990896]
137. Lam DH, Bright J, Jones S, Hayward P, Schuck N, Chisholm D, et al. Cognitive therapy for bipolar illness—a pilot study of relapse prevention. Cognit Ther Res 2000;24(5):503-520. [doi: 10.1023/A:1005557911051]
138. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009 Apr;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
139. Altman EG, Hedeker D, Peterson JL, Davis JM. The Altman self-rating mania scale. Biol Psychiatry 1997 Nov 15;42(10):948-955. [doi: 10.1016/S0006-3223(96)00548-3] [Medline: 9359982]
140. Goossens PJ, Kupka RW, Beentjes TA, van Achterberg T. Recognising prodromes of manic or depressive recurrence in outpatients with bipolar disorder: a cross-sectional study. Int J Nurs Stud 2010 Oct;47(10):1201-1207. [doi: 10.1016/j.ijnurstu.2010.01.010] [Medline: 20189172]
141. Keitner GI, Solomon DA, Ryan CE, Miller IW, Mallinger A, Kupfer DJ, et al. Prodromal and residual symptoms in bipolar I disorder. Comprehensive Psychiatry 1996 Sep;37(5):362-367. [doi: 10.1016/s0010-440x(96)90018-8]
142. Wong G, Lam D. The development and validation of the coping inventory for prodromes of mania. J Affect Disord 1999 Apr;53(1):57-65. [doi: 10.1016/s0165-0327(98)00096-2] [Medline: 10363667]
143. Ly KH, Janni E, Wrede R, Sedem M, Donker T, Carlbring P, et al. Experiences of a guided smartphone-based behavioral activation therapy for depression: a qualitative study. Internet Interventions 2015 Mar;2(1):60-68. [doi: 10.1016/j.invent.2014.12.002]
144. Lane C, Huws-Thomas M, Hood K, Rollnick S, Edwards K, Robling M. Measuring adaptations of motivational interviewing: the development and validation of the behavior change counseling index (BECCI). Patient Educ Couns 2005 Feb;56(2):166-173. [doi: 10.1016/j.pec.2004.01.003] [Medline: 15653245]
145. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33;quiz 34. [Medline: 9881538]
146. Gaynes BN, DeVeaugh-Geiss J, Weir S, Gu H, MacPherson C, Schulberg HC, et al. Feasibility and diagnostic validity of the M-3 checklist: a brief, self-rated screen for depressive, bipolar, anxiety, and post-traumatic stress disorders in primary care. Ann Fam Med 2010 Apr;8(2):160-169 [FREE Full text] [doi: 10.1370/afm.1092] [Medline: 20212303]

147. Sheehan D, Lecrubier Y, Harnett Sheehan K, Janavs J, Weiller E, Keskiner A, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. European Psychiatry 1997;12(5):232-241. [doi: 10.1016/s0924-9338(97)83297-x]
148. Sachs GS, Guille C, McMurrich SL. A clinical monitoring form for mood disorders. Bipolar Disord 2002 Oct;4(5):323-327. [doi: 10.1034/j.1399-5618.2002.01195.x] [Medline: 12479665]
149. Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2003 Jun 01;53(11):1028-1042. [doi: 10.1016/s0006-3223(03)00165-3] [Medline: 12788248]
150. Sachs GS. Use of clonazepam for bipolar affective disorder. J Clin Psychiatry 1990 May;51 Suppl:31-4; discussion 50. [Medline: 1970815]
151. De Dios C, Ezquiaga E, Agud JL, Vieta E, Soler B, García-López A. Subthreshold symptoms and time to relapse/recurrence in a community cohort of bipolar disorder outpatients. J Affect Disord 2012 Dec 20;143(1-3):160-165. [doi: 10.1016/j.jad.2012.05.047] [Medline: 22925351]
152. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006 Feb;163(2):217-224. [doi: 10.1176/appi.ajp.163.2.217] [Medline: 16449474]
153. Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, et al. The Longitudinal Interval Follow-up Evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987 Jun;44(6):540-548. [doi: 10.1001/archpsyc.1987.01800180050009] [Medline: 3579500]
154. Rush AJ, Bernstein IH, Trivedi MH, Carmody TJ, Wisniewski S, Mundt JC, et al. An evaluation of the quick inventory of depressive symptomatology and the hamilton rating scale for depression: a sequenced treatment alternatives to relieve depression trial report. Biol Psychiatry 2006 Mar 15;59(6):493-501 [FREE Full text] [doi: 10.1016/j.biopsych.2005.08.022] [Medline: 16199008]
155. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med 2004 Jan;34(1):73-82. [doi: 10.1017/s0033291703001107] [Medline: 14971628]
156. Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord 2009 Aug;11(5):453-473. [doi: 10.1111/j.1399-5618.2009.00726.x] [Medline: 19624385]
157. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978 Nov;133:429-435. [Medline: 728692]
158. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment.. Psychol Med 1998 May;28(3):551-558. [doi: 10.1017/s0033291798006667] [Medline: 9626712]
159. Depp CA, Lebowitz BD, Patterson TL, Lacro JP, Jeste DV. Medication adherence skills training for middle-aged and elderly adults with bipolar disorder: development and pilot study. Bipolar Disord 2007 Sep;9(6):636-645. [doi: 10.1111/j.1399-5618.2007.00397.x] [Medline: 17845279]
160. Sajatovic M, Ignacio RV, West JA, Cassidy KA, Safavi R, Kilbourne AM, et al. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. Compr Psychiatry 2009;50(2):100-107 [FREE Full text] [doi: 10.1016/j.comppsych.2008.06.008] [Medline: 19216885]
161. Sajatovic M, Levin J, Tatsuoka C, Micula-Gondek W, Fuentes-Casiano E, Bialko CS, et al. Six-month outcomes of customized adherence enhancement (CAE) therapy in bipolar disorder. Bipolar Disord 2012 May;14(3):291-300 [FREE Full text] [doi: 10.1111/j.1399-5618.2012.01010.x] [Medline: 22548902]
162. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193-213. [Medline: 2748771]
163. Kaplan KA, McGlinchey EL, Soehner A, Gershon A, Talbot LS, Eidelman P, et al. Hypersomnia subtypes, sleep and relapse in bipolar disorder. Psychol Med 2015 Jun;45(8):1751-1763 [FREE Full text] [doi: 10.1017/S0033291714002918] [Medline: 25515854]
164. Ng TH, Chung K, Ho FY, Yeung W, Yung K, Lam T. Sleep-wake disturbance in interepisode bipolar disorder and high-risk individuals: a systematic review and meta-analysis. Sleep Med Rev 2015 Apr;20:46-58. [doi: 10.1016/j.smrv.2014.06.006] [Medline: 25060968]
165. Gruber J, Harvey AG, Wang PW, Brooks JO, Thase ME, Sachs GS, et al. Sleep functioning in relation to mood, function, and quality of life at entry to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Affect Disord 2009 Apr;114(1-3):41-49 [FREE Full text] [doi: 10.1016/j.jad.2008.06.028] [Medline: 18707765]
166. Kaplan KA, Gruber J, Eidelman P, Talbot LS, Harvey AG. Hypersomnia in inter-episode bipolar disorder: does it have prognostic significance? J Affect Disord 2011 Aug;132(3):438-444 [FREE Full text] [doi: 10.1016/j.jad.2011.03.013] [Medline: 21489637]

167. Boland EM, Bender RE, Alloy LB, Conner BT, Labelle DR, Abramson LY. Life events and social rhythms in bipolar spectrum disorders: an examination of social rhythm sensitivity. J Affect Disord 2012 Aug;139(3):264-272 [FREE Full text] [doi: 10.1016/j.jad.2012.01.038] [Medline: 22381951]
168. Shen GH, Alloy LB, Abramson LY, Sylvia LG. Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals. Bipolar Disord 2008 Jun;10(4):520-529 [FREE Full text] [doi: 10.1111/j.1399-5618.2008.00583.x] [Medline: 18452448]
169. Monk TH, Kupfer DJ, Frank E, Ritenour AM. The Social Rhythm Metric (SRM): measuring daily social rhythms over 12 weeks. Psychiatry Res 1991 Feb;36(2):195-207. [doi: 10.1016/0165-1781(91)90131-8] [Medline: 2017534]
170. Monk TH, Flaherty JF, Frank E, Hoskinson K, Kupfer DJ. The Social Rhythm Metric. An instrument to quantify the daily rhythms of life. J Nerv Ment Dis 1990 Feb;178(2):120-126. [doi: 10.1097/00005053-199002000-00007] [Medline: 2299336]
171. Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 2003 Feb;60(2):145-152. [doi: 10.1001/archpsyc.60.2.145] [Medline: 12578431]
172. Orley J, Saxena S, Herrman H. Quality of life and mental illness. Reflections from the perspective of the WHOQOL. Br J Psychiatry 1998 Apr;172:291-293. [doi: 10.1192/bjp.172.4.291] [Medline: 9715330]
173. Paykel ES. The interview for recent life events. Psychol Med 1997 Mar;27(2):301-310. [Medline: 9089823]
174. Harvey NS. The development and descriptive use of the Lithium Attitudes Questionnaire. J Affect Disord 1991 Aug;22(4):211-219. [doi: 10.1016/0165-0327(91)90067-3] [Medline: 1939930]
175. Weiden P, Rapkin B, Mott T, Zygmunt A, Goldman D, Horvitz-Lennon M, et al. Rating of medication influences (ROMI) scale in schizophrenia. Schizophr Bull 1994;20(2):297-310. [doi: 10.1093/schbul/20.2.297] [Medline: 7916162]
176. Arbour-Nicitopoulos KP, Duncan M, Remington G, Cairney J, Faulkner GE. Development and reliability testing of a health action process approach inventory for physical activity participation among individuals with schizophrenia. Front Psychiatry 2014 Jun;5:68 [FREE Full text] [doi: 10.3389/fpsyt.2014.00068] [Medline: 24959152]
177. Krämer LV, Helmes AW, Seelig H, Fuchs R, Bengel J. Correlates of reduced exercise behaviour in depression: the role of motivational and volitional deficits. Psychol Health 2014;29(10):1206-1225. [doi: 10.1080/08870446.2014.918978] [Medline: 24785393]
178. Ghisi GL, Grace SL, Thomas S, Oh P. Behavior determinants among cardiac rehabilitation patients receiving educational interventions: an application of the health action process approach. Patient Educ Couns 2015 May;98(5):612-621. [doi: 10.1016/j.pec.2015.01.006] [Medline: 25638305]
179. Luszczynska A, Schwarzer R. Planning and self-efficacy in the adoption and maintenance of breast self-examination: a longitudinal study on self-regulatory cognitions. Psychol Health 2003 Jan;18(1):93-108. [doi: 10.1080/0887044021000019358]
180. Reyes Fernández B, Fleig L, Godinho CA, Montenegro Montenegro E, Knoll N, Schwarzer R. Action control bridges the planning-behaviour gap: a longitudinal study on physical exercise in young adults. Psychol Health 2015;30(8):911-923. [doi: 10.1080/08870446.2015.1006222] [Medline: 25587901]
181. Schwarzer R. Models of health behaviour change: intention as mediator or stage as moderator? Psychol Health 2008;23(3):259-263. [doi: 10.1080/08870440801889476] [Medline: 25160477]
182. Schwarzer R, Renner B. Social-cognitive predictors of health behavior: action self-efficacy and coping self-efficacy. Health Psychol 2000 Sep;19(5):487-495. [Medline: 11007157]
183. Sniehotta FF, Scholz U, Schwarzer R. Bridging the intention–behaviour gap: planning, self-efficacy, and action control in the adoption and maintenance of physical exercise. Psychol Health 2005 Apr;20(2):143-160. [doi: 10.1080/08870440512331317670]
184. Schueller SM, Begale M, Penedo FJ, Mohr DC. Purple: a modular system for developing and deploying behavioral intervention technologies. J Med Internet Res 2014;16(7):e181 [FREE Full text] [doi: 10.2196/jmir.3376] [Medline: 25079298]
185. Morriss R, Leese M, Chatwin J, Baldwin D, THREAD Study Group. Inter-rater reliability of the Hamilton Depression Rating Scale as a diagnostic and outcome measure of depression in primary care. J Affect Disord 2008 Dec;111(2-3):204-213. [doi: 10.1016/j.jad.2008.02.013] [Medline: 18374987]
186. Mohr DC, Carmody T, Erickson L, Jin L, Leader J. Telephone-administered cognitive behavioral therapy for veterans served by community-based outpatient clinics. J Consult Clin Psychol 2011 Apr;79(2):261-265. [doi: 10.1037/a0022395] [Medline: 21299274]
187. Mohr DC, Hart SL, Julian L, Catledge C, Honos-Webb L, Vella L, et al. Telephone-administered psychotherapy for depression. Arch Gen Psychiatry 2005 Sep;62(9):1007-1014. [doi: 10.1001/archpsyc.62.9.1007] [Medline: 16143732]
188. Mohr DC, Ho J, Duffecy J, Reifler D, Sokol L, Burns MN, et al. Effect of telephone-administered vs face-to-face cognitive behavioral therapy on adherence to therapy and depression outcomes among primary care patients: a randomized trial. JAMA 2012 Jun 06;307(21):2278-2285 [FREE Full text] [doi: 10.1001/jama.2012.5588] [Medline: 22706833]
189. Carroll JK, Yancey AK, Spring B, Figueroa-Moseley C, Mohr DC, Mustian KM, et al. What are successful recruitment and retention strategies for underserved populations? Examining physical activity interventions in primary care and community settings. Behav. Med. Pract. Policy Res 2011 Apr 12;1(2):234-251. [doi: 10.1007/s13142-011-0034-2]

190. Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 2003 Apr;60(4):402-407. [doi: 10.1001/archpsyc.60.4.402] [Medline: 12695318]
191. Colom F, Vieta E, Reinares M, Martínez-Arán A, Torrent C, Goikolea JM, et al. Psychoeducation efficacy in bipolar disorders: beyond compliance enhancement. J Clin Psychiatry 2003 Sep;64(9):1101-1105. [doi: 10.4088/jcp.v64n0917] [Medline: 14628987]
192. Gomes B, Abreu L, Brietzke E, Caetano S, Kleinman A, Nery F, et al. A Randomized Controlled Trial of Cognitive Behavioral Group Therapy for Bipolar Disorder. Psychother Psychosom 2011;80(3):144-150. [doi: 10.1159/000320738]
193. Miklowitz DJ, Simoneau TL, George EL, Richards JA, Kalbag A, Sachs-Ericsson N, et al. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biological Psychiatry 2000 Sep;48(6):582-592. [doi: 10.1016/s0006-3223(00)00931-8]
194. Rea MM, Tompson MC, Miklowitz DJ, Goldstein MJ, Hwang S, Mintz J. Family-focused treatment versus individual treatment for bipolar disorder: results of a randomized clinical trial. J Consult Clin Psychol 2003 Jun;71(3):482-492. [doi: 10.1037/0022-006x.71.3.482] [Medline: 12795572]
195. Reinares M, Colom F, Sánchez-Moreno J, Torrent C, Martínez-Arán A, Comes M, et al. Impact of caregiver group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial. Bipolar Disord 2008 Jun;10(4):511-519. [doi: 10.1111/j.1399-5618.2008.00588.x] [Medline: 18452447]
196. Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, et al. Cognitive-behavioural therapy for bipolar disorder. Br J Psychiatry 2006 May;188:488-489. [doi: 10.1192/bjp.188.5.488] [Medline: 16648539]
197. Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. Br J Psychiatry 2006 Apr;188:313-320. [doi: 10.1192/bjp.188.4.313] [Medline: 16582056]
198. Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A Randomized Study of Family-Focused Psychoeducation and Pharmacotherapy in the Outpatient Management of Bipolar Disorder. Arch Gen Psychiatry 2003 Sep 01;60(9):904-912. [doi: 10.1001/archpsyc.60.9.904]
199. Hintze J. Power Analysis and Sample Size (PASS). Kaysville, UT: NCSS Dr. Jerry L. Hintze; 2008.
200. Muller D, Judd CM, Yzerbyt VY. When moderation is mediated and mediation is moderated. J Pers Soc Psychol 2005 Dec;89(6):852-863. [doi: 10.1037/0022-3514.89.6.852] [Medline: 16393020]
201. Beynon S, Soares-Weiser K, Woolacott N, Duffy S, Geddes JR. Psychosocial interventions for the prevention of relapse in bipolar disorder: systematic review of controlled trials. Br J Psychiatry 2008 Jan;192(1):5-11. [doi: 10.1192/bjp.bp.107.037887] [Medline: 18174500]
202. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol 2007;3:1-27. [doi: 10.1146/annurev.clinpsy.3.022806.091432] [Medline: 17716046]
203. Kazdin AE, Nock MK. Delineating mechanisms of change in child and adolescent therapy: methodological issues and research recommendations. J Child Psychol Psychiatry 2003 Nov;44(8):1116-1129. [doi: 10.1111/1469-7610.00195] [Medline: 14626454]
204. Nock MK. Conceptual and design essentials for evaluating mechanisms of change. Alcohol Clin Exp Res 2007 Oct;31(10 Suppl):4s-12s. [doi: 10.1111/j.1530-0277.2007.00488.x] [Medline: 17880341]
205. Murray G, Leitan ND, Thomas N, Michalak EE, Johnson SL, Jones S, et al. Towards recovery-oriented psychosocial interventions for bipolar disorder: quality of life outcomes, stage-sensitive treatments, and mindfulness mechanisms. Clin Psychol Rev 2017 Mar;52:148-163. [doi: 10.1016/j.cpr.2017.01.002] [Medline: 28129636]
206. Aschbrenner KA, Naslund JA, Shevenell M, Kinney E, Bartels SJ. A pilot study of a peer-group lifestyle intervention enhanced with mHealth technology and social media for adults with serious mental illness. J Nerv Ment Dis 2016;204(6):483-486. [doi: 10.1097/nmd.0000000000000530]
207. Waring ME, Jake-Schoffman DE, Holovatska MM, Mejia C, Williams JC, Pagoto SL. Social media and obesity in adults: a review of recent research and future directions. Curr Diab Rep 2018 Apr 18;18(6):34-39. [doi: 10.1007/s11892-018-1001-9] [Medline: 29671135]

Abbreviations

ASRM: Altman Self-Rating Mania Scale
CMF: Clinical Monitoring Form
PHQ-8: 8-question Patient Health Questionnaire
QIDS: Quick Inventory of Depressive Symptomatology
QOL: quality of life
RCT: randomized controlled trial
TAU: treatment as usual

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Protocol

Evaluation of an Experimental Web-based Educational Module on Opioid-related Occupational Safety Among Police Officers: Protocol for a Randomized Pragmatic Trial to Minimize Barriers to Overdose Response

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Abstract

Background: As drug-related morbidity and mortality continue to surge, police officers are on the front lines of the North American overdose (OD) crisis. Drug law enforcement shapes health risks among people who use drugs (PWUD), while also impacting the occupational health and wellness of officers. Effective interventions to align law enforcement practices with public health and occupational safety goals remain underresearched.

Objective: The Opioids and Police Safety Study (OPS) aims to shift police practices relating to PWUD. It adapts and evaluates the relative effectiveness of a curriculum that bundles content on public health promotion with occupational risk reduction (ORR) to supplement a web-based OD response and naloxone training platform (GetNaloxoneNow.org, or GNN). This novel approach has the potential to improve public health and occupational safety practices, including using naloxone to reverse ODs, referring PWUD to treatment and other supportive services, and avoiding syringe confiscation.

Methods: This longitudinal study uses a randomized pragmatic trial design. A sample of 300 active-duty police officers from select counties in Pennsylvania, Vermont, and New Hampshire with high OD fatality rates will be randomized (n=150 each) to either the experimental arm (GNN + OPS) or the control arm (GNN + COVID-19 ORR). A pre- and posttraining survey will be administered to all 300 officers, after which they will be administered quarterly surveys for 12 months. A subsample of police officers will also be qualitatively followed in a simultaneous embedded mixed-methods approach. Research ethics approval was obtained from the New York University Institutional Review Board.

Results: Results will provide an understanding of the experiences, knowledge, and perceptions of this sample of law enforcement personnel. Generalized linear models will be used to analyze differences in key behavioral outcomes between the participants in each of the 2 study arms and across multiple time points (anticipated minimum effect size to be detected, d=0.50). Findings will be disseminated widely, and the training products will be available nationally once the study is completed.

Conclusions: The OPS is the first study to longitudinally assess the impact of a web-based opioid-related ORR intervention for law enforcement in the U.S. Our randomized pragmatic clinical trial aims to remove barriers to life-saving police engagement with PWUD/people who inject drugs by focusing both on the safety of law enforcement and evidence-based and best practices

for working with persons at risk of an opioid OD. Our simultaneous embedded mixed-methods approach will provide empirical evaluation of the diffusion of the naloxone-based response among law enforcement.

Trial Registration: ClinicalTrail.gov NCT05008523; https://clinicaltrials.gov/show/NCT05008523

International Registered Report Identifier (IRRID): DERR1-10.2196/33451

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KEYWORDS

occupational health; law enforcement; police/education; naloxone; opioid overdose prevention and response training; online education; opioids; occupational risk

Introduction

Background

Accidental opioid-involved overdose (OD) mortalities in the U.S. have escalated at an alarming pace, with 81,000 OD deaths recorded in 2019-2020, the highest number ever recorded in a 12-month period. Deaths due to synthetic opioids, primarily illicitly manufactured fentanyl, increased by 38.4%. OD deaths have continued to accelerate as a result of disruptions caused by the pandemic [1,2]. According to provisional data for 2020 from the Centers for Disease Control and Prevention (CDC), US drug OD deaths increased by almost 30% to a record 93,331 deaths during the pandemic year of 2020 [3], with the highest number of deaths occurring amongst those aged 35-44 years [4]. Interventions involving OD response training, including use of the opioid antagonist naloxone, have been a critical part of the national response to the crisis. Several Food and Drug Administration (FDA)-approved products (eg, Narcan Nasal Spray) have made the administration of naloxone easier for laypeople and professional first responders by reducing the risk of needle stick injuries (NSIs) [5-11]. Recent large-scale strategies to address the opioid crisis have invoked a greater role for law enforcement, including being trained in OD response and naloxone administration. For example, researchers [12-14], health advocacy organizations, and government agencies, including the US Department of Justice [15], emphasize the need to implement programs that address the role of law enforcement in shaping health risks among people who use drugs (PWUD) [16-18].

Despite the widely perceived benefits of engaging law enforcement in OD response, considerable barriers limit the uptake of policing practices that could further public health goals [19,20]. Past research has demonstrated that police officers experience an elevated risk of NSIs emanating from routine contact with people who inject drugs (PWID), which, in turn, can lead to infectious disease acquisition. Although the risk of acquiring HIV from NSIs is low [21,22], the perceived risk is high. Concern about NSIs and broader risks related to infectious disease exposure contribute to already elevated levels of stress and burnout among the police. For instance, Strathdee et al [13] noted that of 803 officers working in Tijuana, Mexico, 666 (83%) felt that NSIs carry a level of risk analogous to a gunshot wound. Additionally, widespread sensational and misleading information in news media about incidental fentanyl exposure may reduce the likelihood an officer would intervene in an OD situation [23,24].

Good Samaritan laws providing legal immunity to OD responders who administer naloxone vary across US states. However, these laws are often not well understood, including by police officers. For example, police officers are not always aware of their protection from liability and the protection offered to bystanders [25]. Finally, persistent accounts of police unions filing “unfair labor complaints” because officers have been told to carry naloxone can be an additional barrier, even for police officers who want to carry the life-saving medication [26].

The choices that the police make also have serious implications for the relative harm and safety of the PWID whom they confront. Several studies indicate that policing strategies related to arrests for drug possession and decisions made therein about the confiscation of syringes can influence where, with whom, when, and how PWID consume drugs [27-33]. This aggravates the drug use risk environment by pushing use further to the social and geographical margins (eg, back alleys and shooting galleries). In these settings, risky consumption practices, such as syringe sharing and rushed injection, are more likely, while ODs are less likely to be witnessed [34-37]. Law enforcement may also serve as a barrier to the uptake of syringe exchange services or drug treatment, as the police have frequently been observed to obstruct the transport of syringes, harass treatment program patients, interfere in program operations, and aggressively surveil these programs, which deters people who use opioids (PWUO) from accessing them [38-44]. Racial gradients in police encounters among PWID also suggest that policing practices can be a structural driver in injection-related risk and disease acquisition [45]. Stigma against PWUO and PWID has also been common in press reports citing police chiefs and sheriffs for refusing to allow their officers to carry and administer naloxone [46,47]. A recent survey revealed that some police officers, particularly those who responded to the most OD emergencies, expressed negative attitudes about naloxone administration, drug treatment, and their role in handling drug-related OD emergencies [48].

Despite the barriers described, engaging law enforcement in opioid OD prevention and response initiatives is critical to minimizing some of the secondary harms related to commonplace policing practices [49-51]. Although some overdose education and naloxone distribution (OEND) training initiatives with law enforcement have had mixed results [48,52,53], police education programs, including our own online curricula [54,55], have shown promise in precipitating procedural and attitudinal changes related to substance use. Previous research using the Safety and Health Integration in the Enforcement of Laws on Drugs (SHIELD) model developed

by another member of our team (author LB) demonstrated that police officers are especially receptive to education on working with at-risk groups when bundled with occupational safety messages that highlight their own risk of acquiring HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) from a needle stick and other harms [14,22,30,56]. Police education programs also can address pervasive misconceptions about addiction, and medication for the treatment of opioid use disorder (OUD), as well as the efficacy of harm reduction programming [57] and accurate information about the risks of fentanyl exposure [57,58]. Finally, police education can disseminate promising policing protocols to divert and deflect PWUD to lifesaving health and supportive services in lieu of arrest. Reducing the confrontational nature and frequency of contact with law enforcement is especially salient in the context of racial disparities in US drug law enforcement, although the footprint of the police's role in treatment and other service navigation remains controversial [18,59].

Despite the promise of police education programs to reduce risky—and encourage protective—behavior, no previous study has longitudinally assessed the impact of such an intervention in the U.S. The Opioids and Police Safety Study (OPS) closes this gap with a focus on Pennsylvania (PA), Vermont (VT), and New Hampshire (NH)—3 states with some of the highest rates of OD in the U.S. (PA, 39.9/100,000; VT, 22.8/100,000; and NH, 31.1/100,000) [60,61]. Since the early years of the current opioid crisis in the U.S., PA, VT, and NH have experienced OD mortality at rates far exceeding national averages and those rates continue to rise alarmingly [62,63].

Delivering easily accessible web-based educational interventions to overcome barriers to OD response among law enforcement is particularly important in rural areas and states experiencing the highest opioid-related mortality rates. The study team has demonstrated the effectiveness of their online computer-assisted instructional course on GetNaloxoneNow.org (GNN) [54,55], which promotes learning by presenting information that requires active responding to queries or situational scenarios [64,65]. Use of feedback and remediation functions as a computer-based coach, allowing users to evaluate progress [66]. All 50 states have utilized the module, either formally when approved by state officials or informally when individuals within the state take it on their own. Accordingly, the protocol leverages existing capacity within the states while investigating potential differences between major metropolitan areas and more rural and geographically isolated areas.

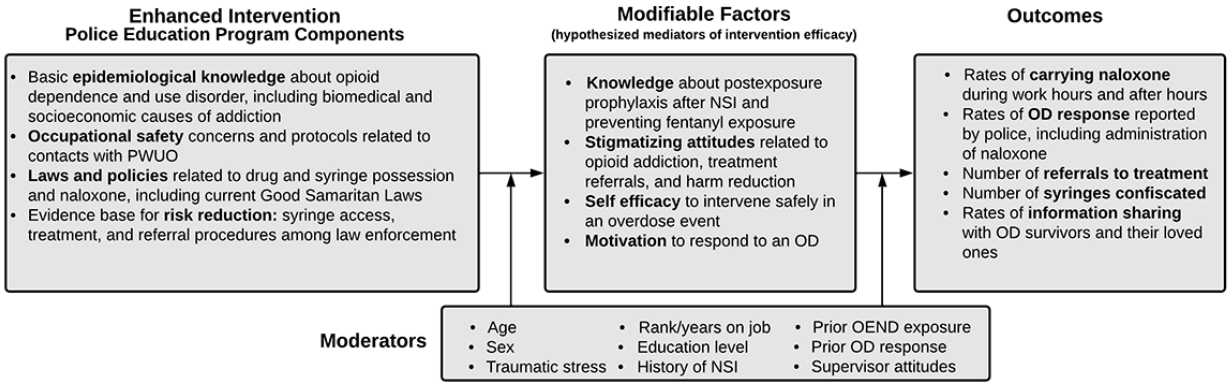
Using a mixed methods design, organized around a pragmatic trial design, this study will achieve the following objectives: (1) adapt a web-based occupational risk reduction (ORR) curriculum to add to a web-based OD response and naloxone training platform, the GNN First Responder Training; (2) describe naloxone use patterns, OD response experiences, and attitudes related to illicit opioid use among a sample (N=300) of police officers in PA, VT, and NH, trained via the GNN platform; (3) evaluate the relative effectiveness of GNN + ORR compared with GNN + COVID-19 (with respect to the rates of carrying naloxone while on/off duty, rates of OD response in which naloxone is/is not administered, number of referrals to treatment, number of syringes confiscated, and rates of information sharing with OD survivors and others), as well as analyze mediators and moderators of efficacy; and (4) document the range of psychosocial mechanisms underlying participant OD response engagement postintervention.

Accordingly, our hypotheses include the following: Officers enrolled in the experimental arm will carry naloxone both while on duty and while off duty at greater rates than officers in the control arm of the study. In addition, officers in the experimental arm will also have higher rates of OD response in which naloxone is administered, a lower rate of confiscating syringes, and a higher rate of information sharing with OD survivors and others.

Conceptual Framework

The study is guided by an integrated conceptual framework comprising risk environment theory (RET) and the elaboration likelihood model of persuasion (ELM). Together, these models are ideally suited to identifying and contextualizing the barriers to and facilitators of OD response (see Figure 1) and presenting strong arguments *in terms of police safety* about the value in promoting risk reduction practices and treatment among PWID [67].

Figure 1. Overarching conceptual model. NSI: needle stick injury; OD: overdose; OEND: overdose education and naloxone distribution; PWUO: people who use opioids.



RET defines a risk environment as "the space, whether social or physical, in which a variety of factors exogenous to the individual interact to increase vulnerability" [68]. RET specifically guides our understanding of how policing practices at the "micro" environment or community level have direct influences over the behavior, perceptions, and health outcomes of PWUO and of PWID. These practices may also increase occupational health risks for police officers. Similarly, "meso" level policy and legal statutes influence the attitudes and practices of police officers, as do "macro" level forces, such as the US war on drugs via the criminalization of drug use and the arrest and incarceration of drug users who suffer from addiction [26,69,70].

The *ELM* guides the adaptation of the ORR curricula. This model emphasizes the importance of intrinsic motivation in modifying attitudes or shaping behavior through interventions grounded in persuasion and argumentation. Guided by this theory, the ORR intervention will seek to appeal to law enforcement personnel through appeals to their own self-protection, while also highlighting the agency and utility of the police in combating the opioid crisis. These approaches take the form of strong arguments within the ELM, as they are far more likely to create favorable thoughts than what might be considered weak arguments [71,72] grounded in moral assertions about the value of PWID to society, the importance of compassionate community policing, or the disease model of addiction, for example. Within the ELM, the influence carried by an argument is also dependent upon the extent of personal involvement that the audience assumes with regard to the topic [72,73]. The proposed ORR intervention will therefore feature the voices and experiences of active police personnel and will highlight the ways in which policing practices more aligned with public health agendas are fundamentally safer for the police and the communities they serve.

Methods

Study Design

The protocol proposed here is a pragmatic trial design [74,75]. Pragmatic trials, unlike more conventional randomized controlled trials, are ideally suited to scenarios in which it is inefficient or unethical to isolate intervention components and compare their efficacy in an explanatory trial involving a placebo control [76].

Intervention

The GNN First Responder Training (both experimental and control; 45 minutes) (1) explains why first responders need education and tools to reverse opioid ODs, (2) teaches and demonstrates (using animated scenarios, graphic sequences, and narration provided by professional voice actors) how to effectively respond to an opioid OD in accordance with the American Heart Association, and (3) describes barriers to calling 911 and the purpose and content of Good Samaritan laws. A detailed question-and-answer session and a posttest reinforce learning.

The OPS (experimental only; 50 minutes) provides web-based ORR training for police in 49 slides, including 8 filmed videos (police officers, physicians, syringe service program staff, and a person in recovery). The training is delivered online, with secure access only for enrolled study participants.

- Module 1 (NSIs): Teaches occupational NSI risk reduction and prevention of bloodborne disease, such as HIV, HBV, and HCV, and provides a protocol for what to do if stuck with a needle. Proper search techniques, confiscation, and the importance of clear communications are emphasized by a police officer, who also shares their own experience with an NSI and demonstrates the proper technique for preventing NSIs during a search in videos created for the training.
- Module 2 (Overdose scene safety): Addresses fentanyl potency, common myths about the risk of fentanyl exposure, how to protect oneself from accidental exposure, and what to do if an officer is exposed. A video developed for the US Customs and Border Protections is utilized in this section and clearly addresses the elevated concern law enforcement officers feel about fentanyl exposure, while simultaneously addressing the best practices in the case of suspected fentanyl exposure.
- Module 3 (Workplace wellness, stress, burnout, and compassion fatigue): Describes the mental and emotional impact of being on the front lines of the opioid crisis and how to recognize trauma and secondary trauma and provides resources for those who may be struggling. This module also presents alternatives to arrest strategies, the importance of evidence-based medication to treat OUD, and the utility of harm reduction programs in reducing recidivism and police burden.

The *COVID-19 and Police Safety Training* (control only) takes approximately 25 minutes to complete and includes 22 slides, also narrated by a professional voice narrator.

Recruitment and Enrollment

Total Number of Study Participants

- Pilot: In total, 10 officers will participate in 1 of 3 hour-long online (Zoom) focus groups after viewing presentations of the content and length of the intervention and survey measures (45-minute presentations) and will provide feedback on the measures.
- Full study: In total, 300 police officers from PA, VT, and NH will be enrolled and subsequently randomized (n=150 officers in each study arm) to take either the COVID-19 control or the OPS experimental training. Both groups will then be invited to fill out quarterly online surveys over 12 months. In addition, 40 (13.3%) of the 300 enrolled police officers will also be invited to participate in 1-hour qualitative interviews during the year-long follow-up period. Prior to the administration of these longer interviews, a subset of 20 (6.7%) enrolled police officers will take a short (15-minute) qualitative interview to help us better address recruitment challenges. A subset of 20 officers will also receive incentives for successful referrals of their peers (ie, referrals that result in study enrollment).

Recruitment Protocol

Recruitment will focus on precincts in select PA, VT, and NH counties with high OD mortality rates. Those precincts agreeing to participate will be sent a package containing the recruiting flyers that will note the principal foci of the intervention as well as the incentives and time frame. The flyer displays the URL for the OPS secure data collection portal hosting the assessment instruments. Each participating station will also be provided with refillable cash cards supplied by the controlled trial (CT) Payer. A distinct identification number displayed on each CT card will be used by each study participant to enroll in the study and enable them to receive incentives. Although recruitment efforts initially focused on PA counties only, and included some in-person recruitment efforts, due to the COVID-19 pandemic, recruitment shifted to remote only and expanded to VT and NH as well.

Study Randomization

It should be noted that to avoid contamination resulting from having participants within the same precinct participating in different conditions, all members of the same participating precinct will be assigned to the same arm. Therefore, half of the precincts will be randomly assigned to the control arm and the other half to the experimental arm. Assignments are made at the initiation of online enrollment.

Follow-up

Participants will be asked to enter responses for the quarterly web-based survey at their earliest convenience after receiving an email reminder. Once they enter their unique identification code on a secure website that hosts the quarterly survey, participants will read questions that prompt them to enter multiple-choice responses from their keyboard or phone keypad. All questionnaires will be computerized such that participants in all study conditions can complete them using any mobile device (phone or computer) with an internet connection. Participants will complete the quarterly follow-up survey online using a unique login ID and password. Delivering surveys via a computer ensures that questionnaire administration is more consistent and accurate, data processing is eliminated, and the lag time between the data collection and data analyses phases is reduced.

Measures

Baseline Data

The survey instrument is outlined in Table 1. This instrument will also assess critical demographic and psychosocial factors that could potentially moderate the intervention efficacy (ie, prior experiences with opioid-related OD, experiences with naloxone, and length of time serving as police officers). Once participants log in to the portal for the first time, complete the informed consent sections, complete their baseline survey, and complete the assigned training modules, their cash cards will be automatically credited with US $75.

Table 1. Measures for baseline and follow-up online survey instruments.

Measure	Description
Outcomes	
Behavioral outcomes in policing procedure	• Days in the past 30 days during which participants had naloxone available and carried during work • Days in the past 30 days during which participants had naloxone available and carried outside of work hours • Days in the past 30 days during which participants responded to an OD[a] event, attempted to intervene, or administered naloxone • Referrals to evidence-based or other drug treatment or social services made during the past 30 days • Number of episodes involving syringe confiscation in the past 30 days with/without a proper technique • Number of episodes involving drug confiscation with/without a proper technique
Hypothesized mediators of intervention efficacy	
Knowledge related to NSIs[b] and treatment	• Participant familiarity with the proper technique for dealing with contaminated injection equipment • Participant awareness of postexposure prophylaxis (PEP) and its uses • Participant awareness of the risk of fentanyl exposure and the proper technique for dealing with synthetic opioids
Knowledge about illicit fentanyl and analogues	• Participant familiarity with fentanyl-class substances, including more recent analogues and their potency • Participant familiarity with the best practices related to policing PWUO[c] and PWID[d] who may be carrying heroin contaminated with fentanyl-class substances (best practices derived from the Centers for Disease Control and Prevention [CDC] and Drug Enforcement Agency [DEA] curricula)
Opioid-related OD knowledge	• Questions related to the ability to recognize and respond to an opioid-related OD, with/without naloxone adapted from the Opioid Overdose Knowledge Scale (OOKS) [77]
Willingness to intervene in opioid OD	• Questions related to willingness, confidence, and preparedness to intervene in an opioid-related OD, adapted from the Opioid Overdose Attitudes Scale (OOAS) [77]
Stigma	• Perceived mental health–related stigma, adapted from addiction/OUD[e] [78] and the OOAS [77]
Motivation	• Autonomous motivation to intervene in an opioid OD; motivation to refer PWID/PWUO to treatment—both adapted from the Situational Motivation Scale [79]
Potential moderators of intervention efficacy	
Background variables	• Age and sex, adapted from the National Survey on Drug Use and Health (NSDUH) [80] • Law enforcement rank and years on the job • Perceived attitudes/expectations of peers, the chief, and other supervisors
Traumatic stress	• Traumatic stress symptomatology short form checklist (Posttraumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [PCL-5]) [81,82]
Prior OD and naloxone exposure history	• Prior instances of witnessing an opioid-related OD • Prior instances of responding to an opioid-related OD • Prior uses of naloxone to reverse an opioid-related OD
Past NSIs and synthetic opioid exposure	• Prior incidence of an NSI or feared contact with contaminated sharp or other injection equipment • Prior incidence of fentanyl exposure or feared contamination with synthetic opioids

[a]OD: overdose.

[b]NSI: needle stick injury.

[c]PWUO: people who use opioids.

[d]PWID: people who inject drugs.

[e]OUD: opioid use disorder

Quarterly Follow-up Surveys

The study's web portal will automatically generate an email notification 90 days after the completion of the first, baseline survey, informing the participant that they are eligible to access their next short online survey and receive the US $40 transfer to their cash card. Upon completion of each survey, each participant's next notifications will be automatically scheduled to be sent 90 days later.

Short Qualitative Interviews

Short (15-minute) qualitative interviews will be administered via phone or Zoom to a subsample of 20 (6.7%) of 300 study participants during times that are convenient to the participants, once. Interviews will be recorded using a handheld digital

recording device, and US $25 will be transferred to their cash card upon completion of the interview.

In-depth Qualitative Interviews

In-depth interviews will be administered via phone or Zoom to a subsample of 30 (10%) of 300 study participants during times that are convenient to the participants, once or twice during the 1-year follow-up period. Interviews will be recorded using a handheld digital recording device and will last roughly 1 hour, and US $50 will be transferred to their cash card upon completion of the interview.

Ethics Approval

The study was approved by the New York University Institutional Review Board (IRB-FY2019-3315). The study was registered on ClinicalTrials.gov (NCT05008523) and approved on June 21, 2021. Enrollment began on January 22, 2021, prior to the approval date due to technical difficulties we experienced with the clinical trial registration website. Delays due to the COVID-19 pandemic and the national spotlight on policing practices in the U.S. posed numerous challenges to recruitment, including minimal enrollment prior to the approval of our clinical trial on ClinicalTrial.gov. To address these challenges, we added 2 sites (VT and NH) after commencing enrollment. Additional changes to our methodology—all of which were approved by the New York University Institutional Review Board (Washington Square Campus)—included the addition of a short qualitative interview (15 minutes) with a subset of approximately 20 (6.7%) of the 300 study participants to better understand and address recruitment challenges and the addition of referral incentives for study participants. There were no changes to our attitudinal and behavioral outcome measures once enrollment commenced in January 2021.

Analysis

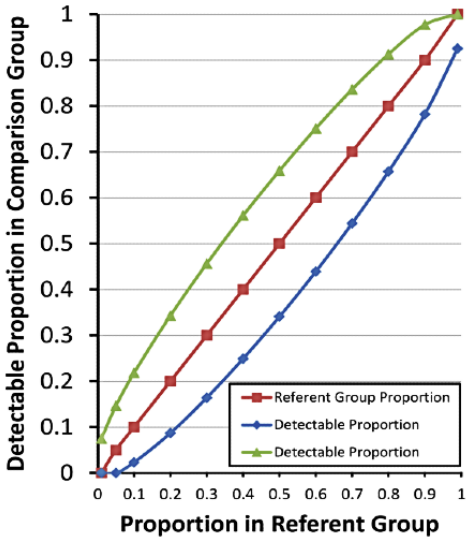
Baseline Data

Descriptive analyses will describe the sample on each of the aforementioned constructs to provide an understanding of the experiences, knowledge, and perceptions of this sample of law enforcement personnel. A series of bivariate analyses will also be used to examine how different demographic and psychosocial factors correlate with attitudes toward substance use and different degrees of OD knowledge. These analyses will build upon the team's previous research, allowing us to carefully examine how preparedness to intervene in an OD emergency might relate to different sociodemographic and experiential factors. The results of these initial analyses will help inform subsequent analyses. Following the randomization of the sample into 1 of the 2 study arms, differences on each key construct at baseline and between the 2 study conditions/groups will be assessed to determine whether there are any statistically significant differences that must be accounted for in subsequent analyses. This will also help the study team identify which constructs produce greater variance in this sample.

Analysis of Intervention Efficacy Over Time

Generalized linear mixed models will be used to analyze behavioral outcomes indicated in Table 1 and Figure 2. Overall tests of the time effect, group effect, and group-by-time interaction will be followed by contrasts of the groups at a particular point in the follow-up period (analogous to independent-sample *t* tests) and contrasts of 2 of the 5 assessment points within 1 group (analogous to paired *t* tests) to determine when the groups were different and when significant changes occurred within each group. Data from the monthly follow-up assessments will be used to assess the extent to which initial behavior changes are sustained over time. In particular, differences in behavioral outcomes between each subsequent monthly time point and baseline will be highlighted. Depending on distributions of risk behaviors, we will consider binary, Poisson, zero-inflated Poisson, negative binomial, and 2-part models.

Figure 2. Statistically significant differences in proportions of participants achieving study endpoints between intervention and control arms.



Confounding Covariates

Randomization will create groups that are balanced in all characteristics, but meaningful imbalance among arms may occur by chance. Consequently, we will use multivariate analyses for each study endpoint to assess and control for confounding covariates. Baseline demographic factors and psychosocial parameters found or hypothesized in previous research to be associated with each study endpoint will be examined as possible confounders by entering each one individually, together with group assignment (study arm), into a logistic regression model. Factors changing the effect estimate for group assignment by 10% or more will be considered confounders and retained in a final multivariate model.

Mediation and Moderation Analyses

One of our primary analysis goals is to determine whether there are statistically significant differences in our key study outcomes (eg, are there significant differences in behavioral outcomes in policing procedures?) between our control and experimental groups. Our proposed set of analyses here will seek to evaluate these differences. All psychosocial parameters hypothesized to have a potentially mediating or moderating impact on intervention effectiveness (see Figure 3 and Table 2) will be measured at baseline and monthly follow-ups to determine whether changes in these parameters during the intervention affect the likelihood of achieving study endpoints. To evaluate effects of the intervention on key study outcome variables, while considering the potential mediating effects of psychosocial variables, we will conduct a series of path analyses using Mplus modeling software (Muthén & Muthén) [83], which accommodates categorical and continuous observed and latent variables [84] Using robust mean- and variance-adjusted weighted least squares (WLSMV) estimation, models will be fit that include paths from the intervention condition to potential mediators as well as paths from the mediators to the study endpoint. Mediated (ie, indirect) effects will be estimated by multiplying the coefficients for component direct effects (eg, the direct effect of the intervention on treatment self-efficacy × the direct effect of treatment self-efficacy on initiating treatment). Bootstrapping methods will be used to derive interval estimates of the mediated effects. Bootstrapping approaches to indirect effect inferences [85] take a random sample from the data with replacement numerous times (eg, 50,000 times) and use the variability in the statistic from sample to sample to construct an interval estimate [86]. Such estimates will provide useful insight into which aspects of our intervention are responsible for its effects, by allowing us to assess whether and how changes in mediators accounted for observed differences in outcomes.

Table 2 summarizes the main contributions of the proposed study, both to practical efforts to remediate the opioid crisis and to a broader scientific understanding of naloxone programs and educational interventions targeting law enforcement personnel.

Figure 3. Interrelationship of study aims. GNN: GetNaloxoneNow.org; OD: overdose; OEND: overdose education and naloxone distribution; ORR: occupational risk reduction.

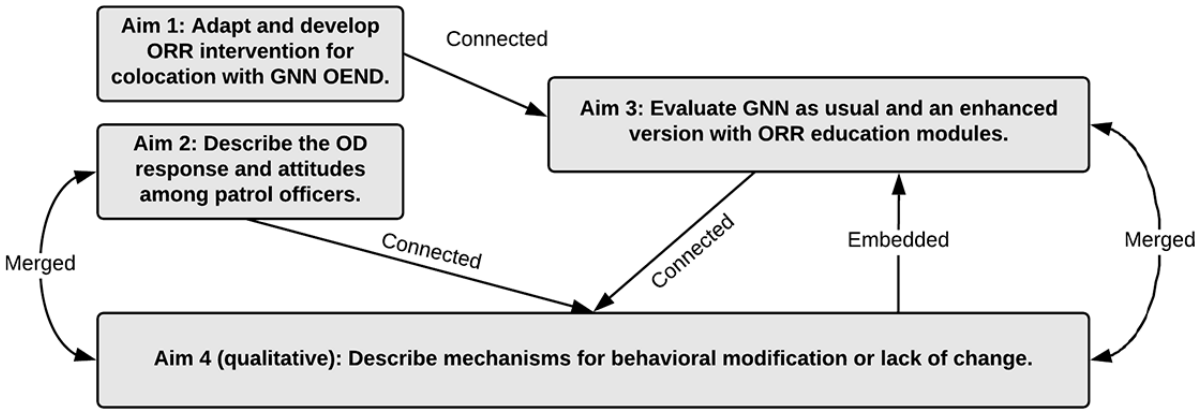


Table 2. Study implications and impacts.

Gaps in extant research	Policy/intervention implications of findings
Studies on law enforcement interventions with naloxone in OD[a] events are sparse and limited to pre- and posttests of knowledge and attitudes.	Study findings from baseline data will provide important indicators of police engagement with the topic of opioid-related OD in terms of policing behaviors and personal attitudes.
Studies on police officers' willingness to intervene in an opioid-related OD, in relation to their attitudes toward opioid misusers, are also sparse and understudied.	Baseline findings will provide a knowledge base regarding key obstacles to and facilitators of the willingness and preparedness of the police to administer naloxone and related risk reduction practices.
The relationship of first-hand OD experiences with attitudes toward PWUO[b]/PWID[c] is unstudied.	Baseline findings will establish potential correlations between background experiences with OD and current attitudes.
Current easily accessed OEND[d] interventions for law enforcement do not include modules related to ORR[e] during engagement with PWUO.	This study will be the first to prospectively examine the impact of ORR training to align law enforcement with public health goals in relation to the opioid OD crisis.
Training of law enforcement personnel does not commonly engage issues of stigma related to PWUO/PWID.	The study will assess the potential for behavioral and attitudinal modification to result from an emphasis on police safety and strong argumentation about how treatment (and referrals to treatment) and risk reduction practices protect the police.
Training tends to be limited to knowledge and confidence to intervene and is not aimed at increasing the willingness to intervene or greater engagement.	Study findings will provide empirical evidence to warrant scale-up of police education programs to cover ORR and best-practice engagement with PWUO and PWID.
ORR training protocols for law enforcement are not colocated with OEND.	Findings and enhanced ORR/OEND training curricula will be disseminated directly to law enforcement and public health professionals allowing for rapid implementation of new training protocols and curricula.
Psychosocial mechanisms underlying changes in OD knowledge and the willingness to intervene, as well as changes in stigmatizing attitudes toward opioid misusers, are not well understood.	Longitudinal (12-month) follow-ups posttraining will provide an evidence base for changes in knowledge, the willingness to intervene, and stigmatizing attitudes toward opioid misusers.
Police attitudes and practices related to PWUO/PWID are likely grounded in personal experience, such that the same event (eg, witnessing or intervening in an opioid OD emergency with or without naloxone) may compel changes in attitudes and behavior in some officers and not in others.	Qualitative research will aid in the interpretation of study findings, leading to greater specificity in terms of the psychosocial processes involved and, therefore, greater utility to law enforcement officers who frequently come in contact with opioid-dependent populations during and after OD events.
The experiences and perceptions of law enforcement personnel are not well represented in the scientific literature on OD in the current opioid crisis.	Dissemination of experiences and perceptions of law enforcement personnel will support policy and protocol changes in respect to OD-related experiences among law enforcement.

[a]OD: overdose.

[b]PWUO: people who use opioids.

[c]PWID: people who inject drugs.

[d]OEND: overdose education and naloxone distribution.

[e]ORR: occupational risk reduction.

Sample Size and Power Considerations

Using standard methods [87] for computing power calculations, with α=.05, and with the reasonable goal of detecting a medium effect size (*d*=0.50), we utilized G*Power (version 3.1) and determined that a randomized trial comparing 2 study arms with 150 (50%) participants in each arm will have more than 80% power that will subsequently allow us to detect statistically significant differences outcomes between our 2 groups. This proposed sample size will allow us to reasonably achieve our study aims.

Missing Data

In line with other research collecting online survey data, we anticipate that there may be some missing data among our survey data, but that falls within reasonable expectations for studies with this kind of study design. To address the possibility of some missing data in our analyses, we will use group mean imputation, a common estimation method utilized in survey data [88].

Analysis of Qualitative Interview Data

Transcribed audio-recorded interviews (N=60) will be analyzed following Lewis et al's [89] 5-step framework analysis approach [90]. A priori qualitative constructs include the first experience with OD, personal experience with OD, naloxone knowledge, naloxone training, experience with OD and naloxone, naloxone costs and benefits, dual-role challenges, other kinds of challenges, attitudes toward PWUD and stigma, concerns about health risks, personal values and institutional environment, the opioid crisis, and COVID-19.

Mixed Methods Synthesis

As depicted in Figure 3, the study will join qualitative and quantitative data sources at a number of key intersections throughout. Mixed methods studies in public health conventionally focus on multiple (and potentially interacting)

determinants of health-related outcomes by locating points of articulation between different theoretical and methodological approaches [91-98]. Our mixed methods strategy has multiple "points of interface" [99] designed to yield a dialogue between data sources [100]. The National Institutes of Health (NIH) Best Practices for Mixed Methods Research [101] distinguishes 3 primary mechanisms for integration: merging, connecting, and embedding.

Results

Expected Outcomes

The OPS will be the first study to longitudinally assess the impact of a web-based opioid-related ORR intervention for law enforcement in the U.S. Findings from our randomized pragmatic clinical trial will provide evidence as to whether our experimental training actually removes barriers to life-saving police engagement with PWUO/PWID by focusing both on the safety of law enforcement and on evidence-based and best practices for working with persons at risk of an opioid OD. In sum, we expect our simultaneous embedded mixed methods approach will provide empirical evaluation of the diffusion of a naloxone-based response among law enforcement.

Expected Timeline

Despite the fact that COVID-19-related precautions and the national spotlight on policing practices hindered study participation, we expected our baseline data collection to be complete (with a sample of 300 police officers) by the end of 2021, with a 1-year follow-up for each study participant, ending in December 2022.

Discussion

Summary

OD deaths are currently the largest cause of accidental deaths in the U.S., and opioid-related OD deaths constitute the overwhelming majority of these deaths. To address the epidemic, a knowledge base for effective law enforcement interventions is both necessary and urgent. This proposed study is designed to provide a knowledge base regarding key obstacles to and facilitators of the willingness and preparedness of the police to administer naloxone and the related risk reduction practices, and evaluate the efficacy of a web-based opioid-related occupational safety and risk reduction curriculum.

Strengths and Limitations

The OPS is the first study to longitudinally assess the impact of an opioid-related ORR intervention for law enforcement in the U.S.

Our randomized pragmatic clinical trial aims to remove barriers to life-saving police engagement with PWUO/PWID by focusing both on the safety of law enforcement and evidence-based and best practices for working with persons at risk of an opioid OD.

Our simultaneous embedded mixed methods approach will provide empirical evaluation of the diffusion of the naloxone-based response among law enforcement.

However, COVID-19-related precautions and the national spotlight on policing practices may hinder study participation.

Conclusion

Findings from this study will be applied to the development and implementation of effective interventions for police officers aimed at harmonizing law enforcement practices with public health goals. Study products (training curricula) will also be disseminated nationally.

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Authors' Contributions

JS and LE jointly conceived the study; JS provided the conceptual framework; SR and LB developed the statistical analysis; LB, JS, and LE (with support from the entire team) provided educational content; BA provided expertise in relation to policing and police training; and JS, LE, ASB, LB, SR, and ND wrote the protocol.

Conflicts of Interest

The Opioids and Police Safety Study (OPS) training, along with the COVID-19 training, will be disseminated free of charge once the study is complete. There will also be no charge for certificates of completion. New York University (NYU) will own the copyright for the OPS and COVID-19 training programs. The training programs will be housed at GetNaloxoneNow.org (GNN), an entity developed and owned by the first author and principal investigator (PI), JS. Currently, JS houses the first responder training, along with a training for laypeople—the bystander training—on GetNaloxoneNow.org for free as well. A US $10 donation is requested in exchange for a certificate of completion in order to defray costs for keeping the training modules up to date. Theoretically, the study could lead to additional GNN users, which could, potentially, increase the financial value of these computer-based training programs. The study could also benefit due to the potential for enhanced licensure to other users, although licensure to other users never has been initiated nor is planned. JS is the founder and owner of GetNaloxoneNow.org, where the training modules are housed and where they will become available (at no cost) at the conclusion of the study.

References

1. Press Release: Overdose Deaths Accelerating During COVID-19. Centers for Disease Control and Prevention (CDC). 2020. URL: https://www.cdc.gov/media/releases/2020/p1218-overdose-deaths-covid-19.html, [accessed 2021-12-01]
2. Friedman J, Beletsky L, Schriger DL. Overdose-related cardiac arrests observed by emergency medical services during the US COVID-19 epidemic. JAMA Psychiatry 2021 May 01;78(5):562-564 [FREE Full text] [doi: 10.1001/jamapsychiatry.2020.4218] [Medline: 33270086]
3. Vital Statistics Rapid Release: Provision Drug Overdose Death Counts. Centers for Disease Control and Prevention (CDC). 2021. URL: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm [accessed 2021-12-01]
4. Drug Overdoses Killed A Record Number Of Americans in 2020, Jumping by Nearly 30%. National Public Radio (WNYC). 2021. URL: https://www.npr.org/2021/07/14/1016029270/drug-overdoses-killed-a-record-number-of-americans-in-2020-jumping-by-nearly-30 [accessed 2021-12-01]
5. Volpe DA, McMahon Tobin GA, Mellon RD, Katki AG, Parker RJ, Colatsky T, et al. Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol 2011 Apr;59(3):385-390. [doi: 10.1016/j.yrtph.2010.12.007] [Medline: 21215785]
6. Lewis C, Vo H, Fishman M. Intranasal naloxone and related strategies for opioid overdose intervention by nonmedical personnel: a review. SAR 2017 Oct;Volume 8:79-95. [doi: 10.2147/sar.s101700]
7. U.S. Food and Drug Administration Approves Kaleo's EVZIO™ for the Emergency Treatment of Opioid Overdose. Public Radio Newswire. 2014. URL: https://www.prnewswire.com/news-releases/us-food-and-drug-administration-approves-kaleos-evzio-for-the-emergency-treatment-of-opioid-overdose-253743961.html [accessed 2021-12-01]
8. Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. J Emerg Med 2005 Oct;29(3):265-271. [doi: 10.1016/j.jemermed.2005.03.007] [Medline: 16183444]
9. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction 2016 Jul 30;111(7):1177-1187 [FREE Full text] [doi: 10.1111/add.13326] [Medline: 27028542]
10. Jones JD, Roux P, Stancliff S, Matthews W, Comer SD. Brief overdose education can significantly increase accurate recognition of opioid overdose among heroin users. Int J Drug Policy 2014 Jan;25(1):166-170 [FREE Full text] [doi: 10.1016/j.drugpo.2013.05.006] [Medline: 23773683]
11. Ashrafioun L, Gamble S, Herrmann M, Baciewicz G. Evaluation of knowledge and confidence following opioid overdose prevention training: a comparison of types of training participants and naloxone administration methods. Subst Abus 2016 Oct 29;37(1):76-81. [doi: 10.1080/08897077.2015.1110550] [Medline: 26514071]
12. Arredondo J, Strathdee SA, Cepeda J, Abramovitz D, Artamonova I, Clairgue E, et al. Measuring improvement in knowledge of drug policy reforms following a police education program in Tijuana, Mexico. Harm Reduct J 2017 Nov 08;14(1):72 [FREE Full text] [doi: 10.1186/s12954-017-0198-2] [Medline: 29117858]
13. Strathdee SA, Arredondo J, Rocha T, Abramovitz D, Rolon ML, Patiño Mandujano E, et al. A police education programme to integrate occupational safety and HIV prevention: protocol for a modified stepped-wedge study design with parallel prospective cohorts to assess behavioural outcomes. BMJ Open 2015 Aug 10;5(8):e008958 [FREE Full text] [doi: 10.1136/bmjopen-2015-008958] [Medline: 26260350]
14. Cepeda JA, Beletsky L, Sawyer A, Serio-Chapman C, Smelyanskaya M, Han J, et al. Occupational safety in the age of the opioid crisis: needle stick injury among Baltimore police. J Urban Health 2017 Feb 19;94(1):100-103 [FREE Full text] [doi: 10.1007/s11524-016-0115-0] [Medline: 28105586]
15. Attorney General Loretta Lynch. Memorandum for Heads of Department Components. Department of Justice. 2016. URL: https://www.justice.gov/opa/file/891366/download [accessed 2021-12-01]

16. Police Executive Research Forum. The Unprecedented Opioid Epidemic: As Overdoses Become a Leading Cause of Death, Police, Sheriffs, and Health Agencies Must Step up Their Response. Washington DC: Police Executive Research Forum; 2017.
17. Baker P, Beletsky L, Avalos L, Venegas C, Rivera C, Strathdee SA, et al. Policing practices and risk of HIV infection among people who inject drugs. Epidemiol Rev 2020 Jan 31;42(1):27-40 [FREE Full text] [doi: 10.1093/epirev/mxaa010] [Medline: 33184637]
18. Park JN, Rouhani S, Beletsky L, Vincent L, Saloner B, Sherman SG. Situating the continuum of overdose risk in the social determinants of health: a new conceptual framework. Milbank Q 2020 Sep 18;98(3):700-746 [FREE Full text] [doi: 10.1111/1468-0009.12470] [Medline: 32808709]
19. Del Pozo B, Beletsky L, Goulka J, Kleinig J. Beyond decriminalization: ending the war on drugs requires recasting police discretion through the lens of a public health ethic. Am J Bioeth 2021 Apr 07;21(4):41-44. [doi: 10.1080/15265161.2021.1891339] [Medline: 33825640]
20. Goulka J, Del Pozo B, Beletsky L. From public safety to public health: re-envisioning the goals and methods of policing. J Community Saf Well Being 2021 Mar 19;6(1):22-27 [FREE Full text] [doi: 10.35502/jcswb.184] [Medline: 34660886]
21. Gerberding JL. Management of occupational exposures to blood-borne viruses. N Engl J Med 1995 Feb 16;332(7):444-451. [doi: 10.1056/nejm199502163320707]
22. Mittal ML, Beletsky L, Patiño E, Abramovitz D, Rocha T, Arredondo J, et al. Prevalence and correlates of needle-stick injuries among active duty police officers in Tijuana, Mexico. J Int AIDS Soc 2016 Jul 18;19:20874. [doi: 10.7448/ias.19.4.20874]
23. McDaniels AK, Butler E. Butler, Deputy, Two EMS Providers Treated for Overdose Symptoms Responding to Call. 2017. URL: http://www.baltimoresun.com/health/bs-md-harford-opioid-exposure-20170523-story.html [accessed 2021-12-01]
24. Beletsky L, Davis CS. Today's fentanyl crisis: Prohibition's Iron Law, revisited. Int J Drug Policy 2017 Aug;46:156-159. [doi: 10.1016/j.drugpo.2017.05.050] [Medline: 28735773]
25. Banta-Green CJ, Beletsky L, Schoeppe JA, Coffin PO, Kuszler PC. Police officers' and paramedics' experiences with overdose and their knowledge and opinions of Washington State's drug overdose-naloxone-Good Samaritan law. J Urban Health 2013 Dec 31;90(6):1102-1111 [FREE Full text] [doi: 10.1007/s11524-013-9814-y] [Medline: 23900788]
26. Associated Press. Police Union Files Complaint against Carrying Naloxone. 2017. URL: https://www.seattletimes.com/news/police-union-files-complaint-against-carrying-naloxone/ [accessed 2021-12-01]
27. Bluthenthal R, Lorvick J, Kral A, Erringer E, Kahn J. Collateral damage in the war on drugs: HIV risk behaviors among injection drug users. Int J Drug Policy 1999 Feb;10(1):25-38. [doi: 10.1016/s0955-3959(98)00076-0]
28. Shannon K, Rusch M, Shoveller J, Alexson D, Gibson K, Tyndall M, Maka Project Partnership. Mapping violence and policing as an environmental-structural barrier to health service and syringe availability among substance-using women in street-level sex work. Int J Drug Policy 2008 Apr;19(2):140-147. [doi: 10.1016/j.drugpo.2007.11.024] [Medline: 18207725]
29. Pollini R, Brouwer KC, Lozada RM, Ramos R, Cruz MF, Magis-Rodriguez C, et al. Syringe possession arrests are associated with receptive syringe sharing in two Mexico-US border cities. Addiction 2008 Jan;103(1):101-108 [FREE Full text] [doi: 10.1111/j.1360-0443.2007.02051.x] [Medline: 18028520]
30. Strathdee SA, Lozada R, Martinez G, Vera A, Rusch M, Nguyen L, et al. Social and structural factors associated with HIV infection among female sex workers who inject drugs in the Mexico-US border region. PLoS One 2011 Apr 25;6(4):e19048 [FREE Full text] [doi: 10.1371/journal.pone.0019048] [Medline: 21541349]
31. Beletsky L, Lozada R, Gaines T, Abramovitz D, Staines H, Vera A, et al. Syringe confiscation as an HIV risk factor: the public health implications of arbitrary policing in Tijuana and Ciudad Juarez, Mexico. J Urban Health 2013 Apr 18;90(2):284-298 [FREE Full text] [doi: 10.1007/s11524-012-9741-3] [Medline: 22806453]
32. Hammett TM, Bartlett NA, Chen Y, Ngu D, Cuong DD, Phuong NM, et al. Law enforcement influences on HIV prevention for injection drug users: observations from a cross-border project in China and Vietnam. Int J Drug Policy 2005 Aug;16(4):235-245. [doi: 10.1016/j.drugpo.2005.05.009]
33. Small W, Kerr T, Charette J, Schechter MT, Spittal PM. Impacts of intensified police activity on injection drug users: evidence from an ethnographic investigation. Int J Drug Policy 2006 Mar;17(2):85-95. [doi: 10.1016/j.drugpo.2005.12.005]
34. Strathdee SA, Fraga WD, Case P, Firestone M, Brouwer KC, Perez SG, et al. "Vivo para consumirla y la consumo para vivir" ["I live to inject and inject to live"]: high-risk injection behaviors in Tijuana, Mexico. J Urban Health 2005 Sep 01;82(3 Suppl 4):iv58-iv73 [FREE Full text] [doi: 10.1093/jurban/jti108] [Medline: 16107441]
35. Rhodes T, Mikhailova L, Sarang A, Lowndes CM, Rylkov A, Khutorskoy M, et al. Situational factors influencing drug injecting, risk reduction and syringe exchange in Togliatti City, Russian Federation: a qualitative study of micro risk environment. Soc Sci Med 2003 Jul;57(1):39-54. [doi: 10.1016/s0277-9536(02)00521-x]
36. Cooper HL, Des Jarlais DC, Tempalski B, Bossak BH, Ross Z, Friedman SR. Drug-related arrest rates and spatial access to syringe exchange programs in New York City health districts: combined effects on the risk of injection-related infections among injectors. Health Place 2012 Mar;18(2):218-228 [FREE Full text] [doi: 10.1016/j.healthplace.2011.09.005] [Medline: 22047790]
37. Parkin S. Habitus and Drug Using Environments: Health, Place and Lived-Experience. London: Routledge; 2016.

38. Aitken C, Moore D, Higgs P, Kelsall J, Kerger M. The impact of a police crackdown on a street drug scene: evidence from the street. Int J Drug Policy 2002 Sep;13(3):193-202. [doi: 10.1016/s0955-3959(02)00075-0]
39. Cooper H, Moore L, Gruskin S, Krieger N. The impact of a police drug crackdown on drug injectors' ability to practice harm reduction: a qualitative study. Soc Sci Med 2005 Aug;61(3):673-684. [doi: 10.1016/j.socscimed.2004.12.030] [Medline: 15899325]
40. Davis CS, Burris S, Kraut-Becher J, Lynch KG, Metzger D. Effects of an intensive street-level police intervention on syringe exchange program use in Philadelphia, PA. Am J Public Health 2005 Feb;95(2):233-236. [doi: 10.2105/ajph.2003.033563]
41. Friedman S, Cooper LF, Tempalski B, Keem M, Friedman R, Flom P, et al. Relationships of deterrence and law enforcement to drug-related harms among drug injectors in US metropolitan areas. AIDS 2006 Jan 02;20(1):93-99. [doi: 10.1097/01.aids.0000196176.65551.a3] [Medline: 16327324]
42. Kerr T, Small W, Wood E. The public health and social impacts of drug market enforcement: a review of the evidence. Int J Drug Policy 2005 Aug;16(4):210-220. [doi: 10.1016/j.drugpo.2005.04.005]
43. Beletsky L, Heller D, Jenness SM, Neaigus A, Gelpi-Acosta C, Hagan H. Syringe access, syringe sharing, and police encounters among people who inject drugs in New York City: a community-level perspective. Int J Drug Policy 2014 Jan;25(1):105-111 [FREE Full text] [doi: 10.1016/j.drugpo.2013.06.005] [Medline: 23916801]
44. Hayashi K, Ti L, Kaplan K, Suwannawong P, Wood E, Kerr T. Police interference with methadone treatment in Bangkok, Thailand. Int J Drug Policy 2015 Jan;26(1):112-115. [doi: 10.1016/j.drugpo.2014.08.009] [Medline: 25239286]
45. Beletsky L, Cochrane J, Sawyer AL, Serio-Chapman C, Smelyanskaya M, Han J, et al. Police encounters among needle exchange clients in Baltimore: drug law enforcement as a structural determinant of health. Am J Public Health 2015 Sep;105(9):1872-1879. [doi: 10.2105/ajph.2015.302681]
46. Wootson JC. Why This Ohio Sheriff Refuses to Let His Deputies Carry Narcan to Reverse Overdoses. 2017. URL: https://tinyurl.com/yckwyszj [accessed 2021-12-01]
47. Cherkis J, Wing N. Overdose Reversal Drug Naloxone Is Saving Lives, but Not All Police Departments Are on Board. 2015. URL: https://www.huffpost.com/entry/naloxone-police_n_56216b5fe4b02f6a900c6d80 [accessed 2021-12-01]
48. Jacoby JL, Crowley LM, Cannon RD, Weaver KD, Henry-Morrow TK, Henry KA, et al. Pennsylvania law enforcement use of Narcan. Am J Emerg Med 2020 Sep;38(9):1944-1946. [doi: 10.1016/j.ajem.2020.01.051] [Medline: 32057531]
49. Pike E, Tillson M, Staton M, Webster JM. The role of law enforcement officers in responding to the opioid epidemic: a qualitative assessment. Subst Abus 2021 Jan 20;42(4):813-820 [FREE Full text] [doi: 10.1080/08897077.2020.1865243] [Medline: 33471613]
50. White MD, Perrone D, Watts S, Malm A. Moving beyond Narcan: a police, social service, and researcher collaborative response to the opioid crisis. Am J Crim Justice 2021 Jul 03;46(4):626-643 [FREE Full text] [doi: 10.1007/s12103-021-09625-w] [Medline: 34248322]
51. Friedman J, Syvertsen JL, Bourgois P, Bui A, Beletsky L, Pollini R. Intersectional structural vulnerability to abusive policing among people who inject drugs: a mixed methods assessment in California's central valley. Int J Drug Policy 2021 Jan;87:102981 [FREE Full text] [doi: 10.1016/j.drugpo.2020.102981] [Medline: 33129133]
52. Winograd RP, Stringfellow EJ, Phillips SK, Wood CA. Some law enforcement officers' negative attitudes toward overdose victims are exacerbated following overdose education training. Am J Drug Alcohol Abuse 2020 Sep 02;46(5):577-588. [doi: 10.1080/00952990.2020.1793159] [Medline: 32931324]
53. Reichert J, Lurigio A, Weisner L. The administration of naloxone by law enforcement officers: a statewide survey of police chiefs in Illinois. LEEF 2019 Dec 1;19(4):1-14. [doi: 10.19151/leef.2019.1904a]
54. Simmons J, Rajan S, Goldsamt LA, Elliott L. Implementation of online opioid prevention, recognition and response trainings for laypeople: year 1 survey results. Subst Use Misuse 2018 Oct 15;53(12):1997-2002 [FREE Full text] [doi: 10.1080/10826084.2018.1451891] [Medline: 29641944]
55. Simmons J, Rajan S, Goldsamt L, Elliott L. Implementation of online opioid overdose prevention, recognition and response trainings for professional first responders: year 1 survey results. Drug Alcohol Depend 2016 Dec 01;169:1-4. [doi: 10.1016/j.drugalcdep.2016.10.003] [Medline: 27744100]
56. Beletsky L, Abramovitz D, Baker P, Arredondo J, Rangel G, Artamonova I, et al. Reducing police occupational needle stick injury risk following an interactive training: the SHIELD cohort study in Mexico. BMJ Open 2021 Apr 08;11(4):e041629. [doi: 10.1136/bmjopen-2020-041629]
57. Wagner KD, Bovet LJ, Haynes B, Joshua A, Davidson PJ. Training law enforcement to respond to opioid overdose with naloxone: impact on knowledge, attitudes, and interactions with community members. Drug Alcohol Depend 2016 Aug 01;165:22-28. [doi: 10.1016/j.drugalcdep.2016.05.008] [Medline: 27262898]
58. Drug Enforcement Agency. Fentanyl: Safety Recommendations for First Responders. 2017. URL: https://www.dea.gov/documents/2017/2017-11/2017-11-28/fentanyl-safety-recommendations-first-responders [accessed 2021-12-08]
59. Formica SW, Waye KM, Benintendi AO, Yan S, Bagley SM, Beletsky L, et al. Characteristics of post-overdose public health-public safety outreach in Massachusetts. Drug Alcohol Depend 2021 Feb 01;219:108499. [doi: 10.1016/j.drugalcdep.2020.108499] [Medline: 33421800]

60. Drug Enforcement Agency. Joint Intelligence Report: Analysis of Overdose Deaths in Pennsylvania, 2016. 2017. URL: https://www.dea.gov/sites/default/files/2018-07/DEA-PHL-DIR-034-17%20Analysis%20of%20Overdose%20Deaths%20in%20Pennsylvania%202016.pdf [accessed 2022-01-01]
61. Centers for Disease Control and Prevention (CDC). Drug Overdose Deaths: Drug Overdose Deaths Remain High. 2020. URL: https://www.cdc.gov/drugoverdose/data/statedeaths.html [accessed 2021-12-01]
62. Pennsylvania: Opioid-Involved Deaths and Related Harms. 2020. URL: https://www.drugabuse.gov/drug-topics/opioids/opioid-summaries-by-state/pennsylvania-opioid-involved-deaths-related-harms [accessed 2021-12-01]
63. CBS Television (WCAX). The Fix: More Vermonters Sought Help for Addiction during Pandemic. 2021. URL: https://www.wcax.com/2021/07/14/fix-more-vermonters-sought-help-addiction-during-pandemic/ [accessed 2021-12-01]
64. Orlandi MA, Dozier CE, Marta MA. Computer-assisted strategies for substance abuse prevention: opportunities and barriers. J Consult Clin Psychol 1990;58(4):425-431. [doi: 10.1037/0022-006x.58.4.425]
65. Pagliaro L. The history and development of CAI: 1926-1981, an overview. Alberta J Educ Res 1983;29(1):75-84.
66. Lieberman DA, Linn MC. Learning to learn revisited: computers and the development of self-directed learning skills. J Res Comput Educ 2014 Feb 26;23(3):373-395. [doi: 10.1080/08886504.1991.10781968]
67. Amon JJ. The political epidemiology of HIV. J Int AIDS Soc 2014 Jul 23;17(1):19327. [doi: 10.7448/ias.17.1.19327]
68. Rhodes T, Simic M. Transition and the HIV risk environment. BMJ 2005 Jul 23;331(7510):220-223 [FREE Full text] [doi: 10.1136/bmj.331.7510.220] [Medline: 16037463]
69. Global Commission on Drug Policy. The War on Drugs and HIV/AIDS: How the Criminalization of Drug Use Fuels the Global Pandemic. New York: Open Society Foundations; 2021.
70. Terzi T. Police Union Protests Plan to Have New Haven Cops Carry Narcan. 2016. URL: http://fox61.com/2016/07/15/opposition-to-harps-idea-to-have-all-new-haven-cops-carry-narcan/ [accessed 2021-12-01]
71. Benoit WL. Argumentation and credibility appeals in persuasion. South Speech Commun J 2009 Apr;52(2):181-197. [doi: 10.1080/10417948709372687]
72. Petty RE, Cacioppo JT. The effects of involvement on responses to argument quantity and quality: central and peripheral routes to persuasion.c. J Pers Soc Psychol 1984 Jan;46(1):69-81. [doi: 10.1037/0022-3514.46.1.69]
73. Andrews JC, Shimp TA. Effects of involvement, argument strength, and source characteristics on central and peripheral processing of advertising. Psychol Mark 1990;7(3):195-214. [doi: 10.1002/mar.4220070305]
74. Ford I, Norrie J. Pragmatic trials. N Engl J Med 2016 Aug 04;375(5):454-463. [doi: 10.1056/nejmra1510059]
75. Roland M, Torgerson DJ. Understanding controlled trials: what are pragmatic trials? BMJ 1998 Jan 24;316(7127):285-285 [FREE Full text] [doi: 10.1136/bmj.316.7127.285] [Medline: 9472515]
76. Macpherson H. Pragmatic clinical trials. Complement Ther Med 2004 Jun;12(2-3):136-140. [doi: 10.1016/j.ctim.2004.07.043] [Medline: 15561524]
77. Williams AV, Strang J, Marsden J. Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation. Drug Alcohol Depend 2013 Sep 01;132(1-2):383-386. [doi: 10.1016/j.drugalcdep.2013.02.007] [Medline: 23453260]
78. Bennett AS, Bell A, Doe-Simkins M, Elliott L, Pouget E, Davis C. From peers to lay bystanders: findings from a decade of naloxone distribution in Pittsburgh, PA. J Psychoactive Drugs 2018 Feb 09;50(3):240-246. [doi: 10.1080/02791072.2018.1430409] [Medline: 29424656]
79. Guay F, Vallerand RJ, Blanchard C. On the assessment of situational intrinsic and extrinsic motivation: the Situational Motivation Scale (SIMS). Motiv Emot 2000;24(3):175-213. [doi: 10.1037/t12678-000]
80. Ahrnsbrak R, Kroutil L, Harter R. National Survey on Drug Use and Health: Summary of the Effects of the 2015 NSDUH Questionnaire Redesign: Implications for Data Users. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2015.
81. Weathers F, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. PTSD Checklist for DSM-5 (PCL-5). U.S. Department of Veterans Affairs. 2013. URL: https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp [accessed 2021-12-01]
82. Weathers F, Litz BP, Keane TM, Palmieri PA, Marx PB, Schnurr PP. Post-Traumatic Stress Disorder Checklist for Civilians (PCL-C). National Center for PTSD. 1994. URL: https://www.traumainformedcare.chcs.org/resource/post-traumatic-stress-disorder-checklist-for-civilians-pcl-c/ [accessed 2022-02-15]
83. Muthén LK, Muthén BO. MPlus User's Guide. Seventh Edition (1998-2012). 2012. URL: https://www.yumpu.com/en/document/view/45689900/version-7-mplus-users-guide [accessed 2021-12-01]
84. Muthén BO. Beyond SEM: general latent variable modeling. Behaviormetrika 2002 Jan 15;29(1):81-117. [doi: 10.2333/bhmk.29.81]
85. Mackinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: distribution of the product and resampling methods. Multivariate Behav Res 2004 Jan 01;39(1):99-128 [FREE Full text] [doi: 10.1207/s15327906mbr3901_4] [Medline: 20157642]
86. Davison A, Hinkley D. Bootstrap Methods and Their Application. Cambridge, UK: Cambridge University Press; 1997.

87. Fleiss JL, Levin BA, Paik MC. Statistical Methods for Rates and Proportions, Third Edition. 2003. URL: https://onlinelibrary.wiley.com/doi/book/10.1002/0471445428 [accessed 2021-12-01]
88. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009 Jun 29;338(jun29 1):b2393-b2393 [FREE Full text] [doi: 10.1136/bmj.b2393] [Medline: 19564179]
89. Lewis MA, Fitzgerald TM, Zulkiewicz B, Peinado S, Williams PA. Identifying synergies in multilevel interventions. Health Educ Behav 2017 Apr 16;44(2):236-244. [doi: 10.1177/1090198116673994] [Medline: 28330388]
90. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. The qualitative researcher's companion. In: Bryman A, Burgess R, editors. Analyzing Qualitative Data. London: Routledge; 2002.
91. Saks M. Researching Health: Qualitative, Quantitative and Mixed Methods. Thousand Oaks, CA: Sage; 2007.
92. Lingard L, Albert M, Levinson W. Grounded theory, mixed methods, and action research. BMJ 2008 Aug 07;337(aug07 3):a567-a567. [doi: 10.1136/bmj.39602.690162.47] [Medline: 18687728]
93. Morgan DL. Practical strategies for combining qualitative and quantitative methods: applications to health research. Qual Health Res 1998 May 01;8(3):362-376. [doi: 10.1177/104973239800800307] [Medline: 10558337]
94. Kuh DL, Wadsworth M, Hardy R. Women's health in midlife: the influence of the menopause, social factors and health in earlier life. Br J Obstet Gynaecol 1997 Aug;104(8):923-933. [doi: 10.1111/j.1471-0528.1997.tb14352.x] [Medline: 9255084]
95. Kuh D. In: Ben-Shlomo Y, editor. A Life Course Approach to Chronic Disease Epidemiology. Vol. 2. USA: Oxford University Press; 2004.
96. Magnusson D, Cairns DB. Developmental science: toward a unified framework. In: Cairns DB, Elder GH, Costello EJ, editors. Developmental Science. Cambridge, UK: Cambridge University Press; 1996:7-30.
97. Willis S, Reid JD. Life in the Middle: Psychological and Social Development in Middle Age. Cambridge, MA: Academic Press; 1999.
98. Power C, Hertzman C. Social and biological pathways linking early life and adult disease. Br Med Bull 1997 Jan 01;53(1):210-221. [doi: 10.1093/oxfordjournals.bmb.a011601] [Medline: 9158295]
99. Morse JM, Niehaus L. Mixed Method Design: Principles and Procedures. Vol. 4. Oxfordshire, England: Routledge; 2009.
100. Creswell JW. In: Clark VLP, editor. Designing and Conducting Mixed Methods Research. Thousand Oaks, CA: Sage; 2007.
101. Creswell JW, Klassen AC, Plano Clark VL, Clegg Smith K. Best practices for mixed methods research in the health sciences. Qual Soc Work 2013;12(4):541-545.

Abbreviations

ELM: elaboration likelihood model of persuasion
GNN: GetNaloxoneNow.org
HBV: hepatitis B virus
HCV: hepatitis C virus
NSI: needle stick injury
OD: overdose
OEND: overdose education and naloxone distribution
OPS: Opioids and Police Safety Study
ORR: occupational risk reduction
OUD: opioid use disorder
PWID: people who inject drugs
PWUD: people who use drugs
PWUO: people who use opioids
RET: risk environment theory

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Protocol

Evaluating an Evidence-Based Parenting Intervention Among Filipino Parents: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Filipino Americans underuse mental health and preventive care services even though studies have indicated that Filipino youth experience high rates of suicidal ideation, substance abuse, and teen pregnancies, whereas adults experience immigration stress, discrimination, and depression. Evidence-based parenting interventions provided in early childhood have proven to be effective in preventing the onset and escalation of child mental health disorders. In a pilot randomized controlled trial, we found that participation in the Incredible Years Basic Parent Training Program (IY) improved parenting stress and positive parenting practices and decreased child internalizing and externalizing symptoms among Filipino families. A fully powered trial is needed to determine the efficacy of IY as a prevention program among Filipino families.

Objective: The aims of this study are to describe the design and rationale of a randomized controlled trial evaluating the effects of the web-based IY program among parents recruited from multiple community-based settings and its impact on parenting practices, parenting stress, and child problem behavior among Filipino Americans and describe the impact of COVID-19 on our study protocols.

Methods: This study uses a randomized controlled 2-arm individually randomized group treatment pretest–posttest design for 180 parent–child dyads. Individuals are eligible if they are ≥18 years, live in California, and have at least one Filipino child aged 8-12 years. Consenting participants are randomly allocated to receive either the 12-week IY parenting intervention (intervention arm) or American Academy of Pediatrics' Bright Future handouts and placed on a waitlist to receive IY posttrial (waitlist control arm). Primary outcomes include the Parent Practices Interview and the Parenting Stress Index. Secondary outcomes will be measured using the Child Behavior Checklist (completed by parent) and will include child internalizing and externalizing behaviors and total problems. Data are collected at baseline and 3- and 6-month follow-ups.

Results: Changes made to the protocol owing to COVID-19 include administration of surveys remotely and implementation of the intervention on the web. The pandemic has provided an opportunity to evaluate the effectiveness of a web-based version of IY that may improve access and increase use of the intervention. Recruitment and data collection procedures are still ongoing and are expected to be completed by December 2022.

Conclusions: Our research will determine whether IY promotes positive parenting practices and prevents child internalizing and externalizing behaviors in healthy but high-risk populations such as Filipino families. It will also uplift cultural narratives and add to the evidence base for web-based parenting programs and their implementation in real-world settings. If found efficacious,

IY has the potential to prevent behavioral health disparities in this understudied and high-risk Filipino population and can be scaled, adapted, and implemented in other at-risk racial and ethnic minority communities.

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International Registered Report Identifier (IRRID): DERR1-10.2196/21867

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KEYWORDS

Filipino; mental health; prevention; parenting practices; community health

Introduction

Filipino Mental Health

Filipino Americans are the third largest Asian American subgroup in the United States, with the highest concentration living in Los Angeles, California [1]. Despite their numbers, Filipinos have been described as an *invisible minority* and remain understudied owing to the lack of disaggregated research regarding their health status and needs [1-3]. In contrast to the *model minority myth* ascribed to Asians in general [4,5], US-born Filipino youth exhibit higher rates of mental health problems than non-Hispanic White youth [6]. The few studies on Filipino youth reveal exceedingly high rates of adolescent suicidal ideation and attempts compared with non-Hispanic White, Latinx, and African American individuals [2,7-9]. Filipino youth also have higher rates of behavioral problems such as conduct disorder, substance use, high-school dropout, and teen births than other Asian subgroups and have higher rates of depressive symptoms compared with non-Hispanic White individuals [2,8,10,11].

Filipino families also face acculturative and intergenerational challenges, parental separation owing to immigration, family conflict, parental mental health disorders, child maltreatment, loss of social status, discrimination, and high rates of major and postpartum depression [12-14]. The COVID-19 pandemic has exacerbated these issues and placed Filipino children at risk for future behavioral and mental health problems by increasing familial stressors and disrupting many avenues to access health services [15-17]. It has also revealed gaps in our existing approach to the prevention of perinatal depression and child mental health issues.

Despite these behavioral problems, Filipinos are less likely than non-Hispanic White individuals to participate in mental health care and preventive care use, including engagement in parenting interventions [10,18-20]. Barriers to participation include cultural stigma associated with parenting and mental health and time constraints among parents who often work multiple jobs [2,7,9,11,19]. For Filipinos, 85% of whom are affiliated with the Catholic Church [21], the clergy play a critical role in their efforts to manage personal problems [22,23] and, thus, have the potential to serve as gatekeepers to behavioral health and preventive services, including parenting programs. Schools, primary care providers, and community-based organizations may also serve as intervention gatekeepers. Conducting clinical trials in familiar and geographically accessible real-world settings may reduce some of the psychological and logistical barriers to participation and increase motivation to participate [24].

Evidence-Based Parenting Programs

Evidence-based parenting interventions in early childhood have proven to be effective in preventing the onset and escalation of child mental and behavioral health disorders [25]. Many parenting programs target suboptimal parent–child relationships and harsh discipline, two critical risk factors for behavioral health problems among youth [26,27]. Parenting practices strongly affect child behavior problems, perhaps even playing a causal role [28]. The relationship between the antisocial traits of parents and their children is mediated in part by specific parenting practice [29]. There is a great deal of evidence that parenting has a powerful effect on improving functioning and reducing impairments [30]. Child behavior also affects parenting in a transactional manner [31-34]. Children's challenging behaviors (eg, high activity level and poor emotion regulation, attention, and impulse control skills) can elicit coercive or detached parenting, with low nurturance and affection [35]. This parenting style may lead to an exacerbation of the child's behavior problems [28,30,36-39].

In contrast, parental affection, supervision, and firm behavioral control predict long-term positive outcomes [37,40-43]. Parent training programs alter parents' behavior and, presumably in response, children's behavior [44,45]. The training program we are implementing prevents challenging child behaviors early and acts to interrupt this dysfunctional coercive cycle before the child's behaviors become entrenched into an identifiable impairment and eligible for standard treatment models [46,47].

Incredible Years School Age Advance and Basic Parent Training Program

Incredible Years Basic Parent Training Program (IY) is one of the best-studied and highly regarded parent training programs, with previous research highlighting the efficacy of the School Age Basic Parenting Training Program in the Filipino community [19,48-50]. The IY Advance Training Program includes topics focused on effective communication skills and based on community feedback, was suggested to be offered to Filipino families. Current evidence suggests that parent behavior-management programs such as IY are a viable treatment for reducing depressive symptoms in young children [51,52]. Over the past 11 years, Javier et al have conducted a series of studies to pinpoint parent training as a community-identified solution to prevent Filipino adolescent behavioral health problems and disparities [49]; pilot-test IY to assess the efficacy, feasibility, and acceptability of this

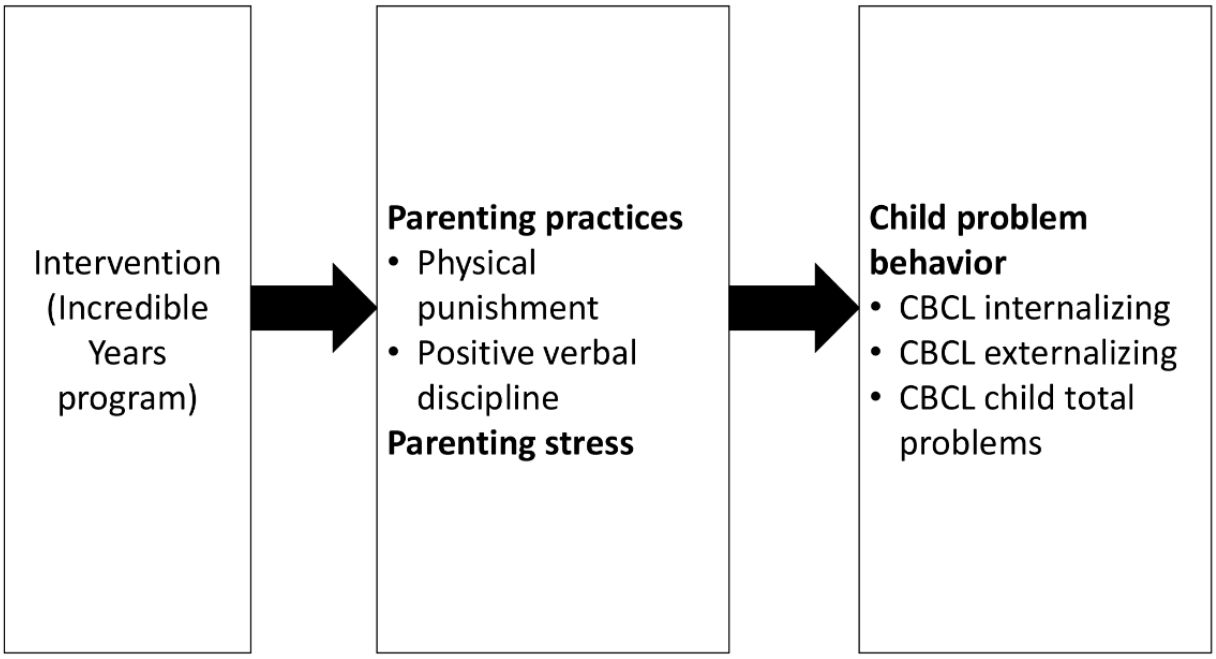
prevention program in community settings in the Filipino population [50]; and develop a theory-based motivational video to increase Filipino parent enrollment rates in IY [53].

The success of these pilots underscores our ability to build trust with community organizations serving large Filipino populations and to overcome logistical challenges involved in implementing the intervention. Previous research conducted by project investigators justify the need to prevent behavioral problems among Filipino youth [2,10,54]. A prevention trial offering the IY School Age Basic and Advance Parent Training Program is needed to determine whether this 12-week combined intervention improves positive parenting practices and internalizing symptoms in children at higher risk for future depression, such as Filipinos.

Theoretical or Conceptual Model

The conceptual model of the IY program in Figure 1 depicts the study hypotheses, that is, how IY affects parenting practices, parenting stress (intermediate outcomes), and child problem behavior (long-term outcomes).

Figure 1. Conceptual model of Incredible Years program theory. CBCL: Child Behavior Checklist.



Social learning theory suggests that early childhood internalizing symptoms may have roots in dysfunctional parenting behaviors and family environments [55]. For instance, depressive behaviors may be both modeled and selectively reinforced by parents [56]. IY targets some of the mechanisms and risk factors for internalizing distress in early childhood: harsh and unpredictable or critical parenting behaviors [57,58]. Parents also learn cognitive strategies for themselves, such as self-praise, coping thoughts, how to challenge negative thoughts, and how to get support that they are encouraged to model for and teach their children. Finally, they learn how to be more positive and nurturing through academic, social, and emotional coaching.

The knowledge gained from this trial will contribute to the scientific literature on preventive and early intervention programs for children at risk for future behavioral problems and to the literature on implementing evidence-based parenting interventions in real-world settings. Very few proven interventions that target Filipino parents are currently available. The data will also provide important information to understand the processes underlying the effects of IY on parenting practices and subsequent child problem behavior among Filipino families. The importance of this research rests on its potential to prevent behavioral health disparities in this understudied and high-risk population.

Hypotheses

The purpose of this study is to describe the design and rationale of a randomized controlled trial evaluating the effects of a 12-week prevention program that includes content from the School Age Advance and Basic Parent Training Program on parenting practices, parenting stress, and child problem behavior among Filipino American families in a community-based setting. Our central hypothesis, based on social learning theory, is that IY will provide efficient parent training, resulting in significant improvements in parenting practices, parenting stress, and child behavioral problems among the intervention group compared with the control group. This hypothesis is supported by a previous study in which we determined initial estimates of effect sizes attributable to the intervention [50].

We hypothesize that parents will report improvements in positive parenting practices, parenting stress, and child problem behavior after IY as compared with baseline and the control condition.

Methods

Overview

This pilot trial is funded by grants from the Robert Wood Johnson Foundation Clinical Scholars Program and the University of Southern California Keck School of Medicine

COVID-19 and Bridge Funding Program. Trial enrollment was initiated in July 2018 and is ongoing.

Ethics Approval

This study was approved by the Children's Hospital of Los Angeles Institutional Review Board (Study ID CHLA-18-00066).

Trial Population

Inclusion and Exclusion Criteria

An individual is eligible to participate if he or she is (1) is aged ≥18 years and (2) identifies as a parent of at least one Filipino child aged 8-12 years. The inclusion criteria for the 180 Filipino American children are as follows: (1) aged between 8 and 12 years and (2) identify as Filipino or half-Filipino. Exclusion criteria include the following: (1) parent plans to move out of California during the next 9 months, (2) parent does not speak English, and (3) parent has completed IY in the past.

We are only including individuals who can speak English because according to the US Census Bureau data for Historic Filipinotown, a large proportion of the Filipino households (80%) are fluent in English [1]. This is primarily owing to the effects of American colonialism in the Philippines, during which an English-only curriculum was implemented. As the majority of Filipinos in Southern California are foreign-born, they have been educated in these institutions in which they were able to learn English. In a previous IY study that offered both consent forms and surveys in Tagalog, 100% of participants chose to use English forms [48].

Outreach and Recruitment

We are outreaching to Filipino parents of children aged 8-12 years from community sites (ie, churches, schools, primary care programs, after-school programs, and community-based organizations) serving Filipino families in California. The sample includes US citizens, permanent residents, and newer immigrants to ensure diversity in the range of socioeconomic status and length of stay in the United States. Prospective study participants are recruited via (1) announcements at regularly scheduled events with parents; (2) mailed letters, which include an endorsement by the community partner, a description of the study, and contact information so that parents can call if they would like to participate; (3) snowball sampling techniques; (4) study website with promotional video; and (5) use of social media.

To address barriers to participation, we use a parent engagement intervention video to promote recruitment. A screening instrument is used to screen potential participants for eligibility and obtain information regarding reasons for refusing to participate in the study. We provide gift card incentives for each survey completed; parents receive US $40 per survey and children receive US $10 per survey. Demographic information, including income, educational level, profession, immigration status, and insurance status, is obtained at baseline. Flyers, unaddressed letters, and email descriptions of the study are provided to partnering organizations for their staff to distribute to Filipino families. Parent addresses or emails are not given to study personnel without parental consent.

Snowball sampling is a nonprobability sampling technique where existing study participants recruit future participants from among their acquaintances and colleagues. We will use this method if we are unable to recruit enough participants from community sites. In these cases, to assure that names are not provided to researchers without their permission, participants may be asked to talk to their friends about this project. Participants are also asked to give their friends our contact information if they wish to become a part of the project. A flyer may be given to the participant to pass on to other potential respondents. The flyer can be used to contact the research team if the referred person is interested in participating in the study. If an individual is interested in participating, eligibility is confirmed using the inclusion and exclusion criteria. We also have a study website where parents may view the video we developed to promote participation in IY.

Once a parent is found to meet the study criteria and expresses an interest in the study, he or she is provided with a detailed description of the study and informed consent is obtained before the administration of preintervention surveys. If families decline to participate, verbal permission is obtained to ask about demographic information and the reason for refusal. A database of stated reasons for refusing and demographics is anonymously maintained and used to aid future recruitment efforts and compare participants with study refusals.

Intervention

Study Design

This pilot study is an individually randomized controlled group treatment trial involving 180 parents of children aged 8-12 years to test the effects of IY implemented in community settings on parenting practices, parenting stress, child behavioral symptoms, and child functional status. Parents are informed of the randomized designs as part of the recruitment and consent procedures. Parents are randomly assigned in a 1:1 allocation with blocked randomization into either the intervention or control arm, resulting in 90 parent–child dyads in both the intervention and control groups. The trial statistician (WM) created the randomization list (using SAS [version 9.4; SAS Institute, Inc]). Research staff conducting data entry and collection are blinded to each participant's randomized assignment.

IY Structure

Before delivering IY in this population, the researchers asked community members to pinpoint health issues they wanted to address through the use of a community-academic partnership and a community advisory board composed of participating Filipino parents and community partners [22]. Together, they came up with the solution of using evidence-based parenting programs to improve child mental health and behavioral issues. The use of community partners allows for increased capacity to outreach to Filipino American families across California.

A total of 2 parent group leaders who have completed the certified training in IY are responsible for delivering the intervention and cofacilitating each parenting workshop. To ensure adequate understanding of Filipino culture and parenting styles, at least one facilitator for each group must identify as

Filipino. To track IY participation, parent group leaders record attendance after each session. Parents attend sessions without their child, and each group typically includes up to 15 parents. During each session, the leaders provide education on parenting strategies, play videos illustrating effective and ineffective parenting, incorporate role-playing exercises, and facilitate discussion about participants' own personal experiences, opinions, and thoughts related to the session's content to enhance their parenting skills.

IY sessions are offered to parents in the intervention group immediately after randomization. There are 12 weekly intervention classes, 2 hours each, for IY. Session topics are shown in Table 1. Sessions 1-6 include topics from the basic program, and sessions 7-12 include topics from the advance program.

Table 1. Session schedule of the Incredible Years program.

Week	Topic
1	Welcome, parent goals, and parental attention
2	Special time or parental attention
3	Social, emotion, and persistence coaching
4	Effective praise
5	Tangible rewards
6	Rules, responsibilities, and routines
7	Clear limit setting and ignoring misbehavior
8	Listening attentively
9	Speaking up
10	Communicating more positively to oneself and others; part 1
11	Communicating more positively to oneself and others; part 2
12	Giving and getting support, graduation, and celebration

We offer make-up sessions for parents missing a weekly session immediately before the next week's session. For example, if a parent misses week 1 session, they are invited to arrive 30 minutes early for week 2 session to go over last week's materials and concepts. The rationale for this is to ensure that the parents are exposed to the materials and concepts as much as possible. Overall, the IY curriculum builds upon principles discussed during the previous weeks.

Comparator

Immediately after randomization, control participants are emailed and mailed written parent education materials from the American Academy of Pediatrics Bright Futures program. These materials include general parenting advice with age group–specific tips on how parents can support their child's development and social and academic success. Parents in the control group are placed on a 3-month waitlist for the IY and are offered the 12 sessions after they have completed the follow-up assessments and intervention group classes end.

Outcomes

Our main hypothesis is that the IY will provide efficient parent training, resulting in significant improvements in parenting practices, parenting stress (primary outcomes), child problem behavior, and COVID-19–related stress (secondary outcomes).

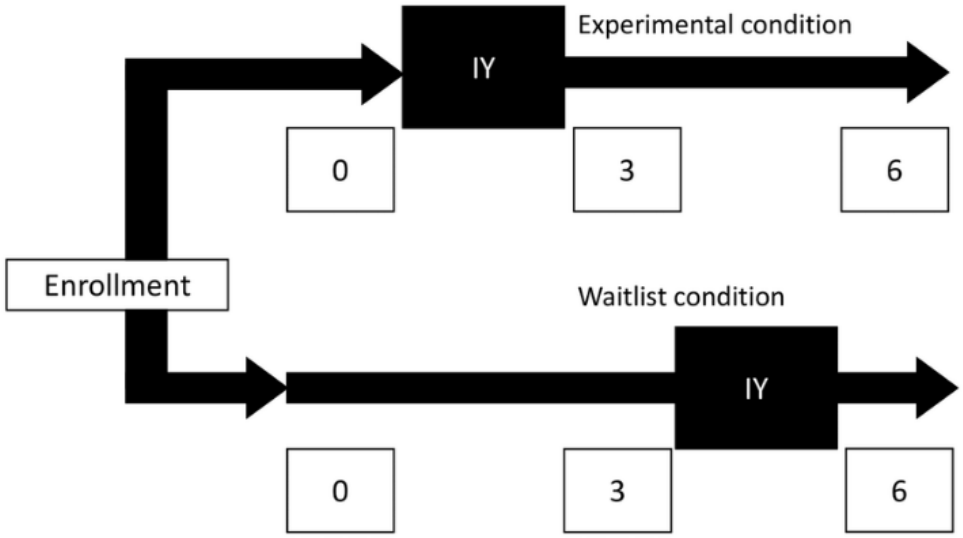
To evaluate primary outcomes, we use the Parenting Practices Inventory [52] to assess parenting practices and physical punishment and the Parenting Stress Index–Short Form [59] to assess parenting stress. To evaluate secondary outcomes, we use the Child Behavior Checklist for Ages 6 to 18 [60]: Externalizing and Internalizing domains and Total Problems (Parent, Child). The reliability and validity of these measures have been described in the literature, with all measures previously validated in multicultural populations. Finally, owing to the COVID-19 pandemic, we also measure parental COVID-19–related stress using the Epidemic–Pandemic Impacts Inventory [61]. To assess consumer perspectives, we use parent satisfaction and participation data in IY evaluation surveys.

Data Collection

Overview

Data collection occurs at three timepoints: at baseline, at 3-month follow-up, and at 6-month follow-up. Figure 2 provides a data collection timeline for both the intervention and waitlist control groups. Data are obtained using process evaluation tracking systems and parent- and child-report instruments.

Figure 2. Data collection timeline. IY: Incredible Years Parent Training Program; 0: baseline assessment (wave 1); 3: 3-month follow-up (wave 2); 6: 6-month follow-up (wave 3).



Parents and children complete the assessments by answering the survey questions. During each interview, the interviewer reads the survey questions found in the assessment forms and records participant responses. The control group completes preintervention and postintervention assessments during the same period as the intervention group. Survey data are entered into a Research Electronic Data Capture trial database and Achenbach System of Empirically Based Assessment–Web databases. The method of data collection (in-person, phone, or web-based) and intervention delivery (in-person or on the internet) is recorded in the data set.

Baseline

After consent is obtained, outcomes assessments and demographic information, including income, educational level, profession, immigration status, insurance status, and levels of enculturation, are gathered for all participants at baseline. Assessments are scored immediately following the group that week and entered into the database.

3-Month Follow-up

After the intervention group's 12-week IY program ends 3 months after baseline, all participants including the control group complete postintervention questionnaires.

6-Month Follow-up

All participants complete another postintervention questionnaire 6 months after baseline. This time frame also marks the end of the IY classes for control group participants, so the control group are asked to complete evaluations pertaining to their experience in IY.

Protocol Changes Owing to COVID-19

Before the pandemic, all parenting sessions were held at various community-based settings. Owing to restrictions on in-person activities, the research team adapted the IY program to be held over Zoom, a web-based video conferencing platform that is compliant with the Health Insurance Portability and Accountability Act of 1996. Group leaders use presentation slides, Zoom chat functioning, discussion synopsis, breakout groups, and educational video clips, to ensure appropriate delivery of session material in a web-based format.

In addition, all surveys were previously administered in person at Children's Hospital, Los Angeles. During the COVID-19 outbreak, all surveys were transitioned to be temporarily conducted over the phone or Zoom. Telephone and video surveys are administered by the interviewer in a quiet and private location, and participants are asked to take the call in a place that maintains their privacy.

We provide the option to use video call interviews for survey administration over a Health Insurance Portability and Accountability Act-compliant version of Zoom. The purpose of using Zoom is to ease the fatigue and comprehension of parents by allowing participants to read the survey questions via screenshare capabilities. Participants may have the option to remotely control entering their own answers if internet capabilities allow for remote control during screensharing. Interviewers screenshare the web-based Research Electronic Data Capture survey form and allow participants to read survey questions and select their answers that appear on the screen. Interviewers remain on the web to set up the screenshare of the survey and answer any questions that come up. Both telephone and video interviews are temporary to adjust to social distancing recommendations owing to COVID-19.

Once precautionary measures regarding COVID-19 are no longer required, in-person surveys with answers written on paper can resume. At that time, the option to conduct surveys through a video or telephone call may be provided to 3- or 6-month follow-up surveys as an alternative to the in-person survey as a means of increasing retention.

Statistical Analysis

Power and Sample Size

Data from our preliminary pilot study were used to estimate sample size for a comparison of intervention group means in clustered data (clustering within individual IY groups). We used a Cohen *d* effect size of 0.55, intraclass correlation of 0.04, and

coefficient of variation of 0.16 in cluster (IY group) sizes. Given this is a pilot study, each primary outcome and all secondary outcomes will be tested at α=.05. Using PASS software, sample sizes of 72 in each group (total sample 144), with an estimated 9 separate IY groups with an average of 8 participants in each group and 2-sided α of .05 will achieve 82% power to detect the intervention group effect size of at least 0.55. Predicting an annual attrition rate of 20%, a full sample of 180 participants is required.

Process Evaluation

We will document participants' and facilitators' experiences to ensure the appropriateness and cultural relevance of the intervention. Parent satisfaction and evaluation are also measured as part of process evaluation after program participation. Qualitative methods, such as field notes are used to document and analyze the intervention's implementation and acceptability in the target population.

Analysis Plan

Before beginning hypothesis testing, data will be screened using univariate analyses (eg, mean, SD, plausible range and value, skewness, and kurtosis), patterns of correlation and covariance, and checks for multicollinearity and singularity of variables. Transformation of variables will be conducted as needed to reduce the effects of valid outliers or violations of normality. Participants will be analyzed by their randomized intervention group, regardless of adherence. Randomized groups will be compared on baseline values of demographic factors and trial primary and secondary outcomes; standardized group differences will be computed for each baseline variable as a standardized assessment of the magnitude of group differences. In this individually randomized group treatment trial, mixed effects linear models will be used to test the IY intervention effect on trial outcomes, accounting for correlated trial outcomes owing to participants clustered within individual IY groups. Mixed model random effects include random intercepts at the individual IY group level and separate random error terms for the IY and control participants. The model incorporates heteroscedasticity between IY versus control participants, as the modeled variance in the IY condition incorporates both group- and individual-level variability and differs from that of the waitlist condition. Fixed effects include the primary independent variable of the randomized group (IY vs waitlist); model covariates will include the baseline value of the trial outcome and baseline factors that differ between randomized groups.

Given the COVID-19 pandemic, we will analyze data from in-person intervention delivery versus web-based delivery separately. As mentioned above, we added a measure of COVID-19–related stress, the Epidemic–Pandemic Impacts Inventory-II. The number of COVID-19–related experiences endorsed will be summed within domains (work or employment, home life, social activities and isolation, changes in emotions and physical health and infection, and positive change) as a cumulative risk index or using an in-person clustering method to identify unique profiles of experiences.

Results

Recruitment and data collection procedures are ongoing and are expected to complete by December 2022; we plan to complete data analyses by June 2023. As of December 2021, in total 103 have completed data collection in person and 60 have completed data collection on the web.

Our central hypothesis is that IY will provide efficient parent training, resulting in significant improvements in parenting practices, parenting stress, and child behavioral problems. This hypothesis is supported by a previous study in which we determined the initial estimates of effect sizes attributable to the intervention [50]. Findings of the pilot study revealed that IY had a positive impact on parenting stress, positive verbal discipline, physical punishment, and parent perceptions of their child's externalizing symptoms, internalizing symptoms, and number of problematic behaviors [50].

Once data analysis is complete, results will be disseminated to individual partnering organizations and study participants, summarizing the results of the study. In addition, we will invite partnering organizations to a community forum aimed at sharing the results of the study and obtaining community feedback. Findings will also be submitted to a peer-reviewed journal and presented at academic conferences.

This study will provide a knowledge base for the translation of specific family-focused behavioral interventions to real-world practice settings with greater emphasis on maximizing the available resources within the contexts of local care settings (primary care settings, churches, schools, and community social service agencies) to better meet the needs of multiple stakeholders.

Discussion

Challenges

A few challenges arose during the study, one major obstacle being the COVID-19 pandemic. Owing to restrictions, we transitioned from in-person intervention implementation and providing the parenting group sessions in community spaces to the current remote delivery of the intervention. We worked with our community advisory board to develop the web-based protocol, and overall, families found it to be acceptable on the web. Of note, we also used materials developed by the IY developer to transition the program to the web (ie, use of web-based evaluations, tips for parenting group leaders to engage families virtually, and use of midweek individual phone calls to follow up with parents). Data collection including informed consent procedures and survey administration also transitioned from in-person to phone or Zoom conferencing communications. Unexpectedly, through the use of web-based platforms during the pandemic, we have been able to expand our outreach to different families across California and reduce time and transportation barriers to participating in the IY intervention. This web-based format seems to be more acceptable to families as it has helped overcome barriers such as transportation, commuting time to sites where in-person

delivery occurred, child care, and the need for social distancing given the COVID-19 pandemic.

Another obstacle we faced was trial delay associated with use of a true community–academic partnership with numerous community partners and organizations helping to address mental health disparities in our communities. Some community partners involved have their own institutional review board and research process, which adds time to the overall regulatory review and approval. Development of statewide partnerships also requires significant time and effort, particularly when working with multidisciplinary teams including school districts, primary care clinics, and other community organizations.

Comparison With Previous Work

Our previous work piloting IY as a community-based prevention program in partnership with gatekeepers and our community advisory board has made it possible to overcome stigma and time-related barriers [19,50]. We were also able to reach a population of at-risk children who have never been diagnosed or referred for behavioral health treatment, thus embodying the goal of prevention and early intervention. Although multiple studies have used churches and other community-based settings as means of engaging underserved, minority populations in mental health and preventative health programs [49,50,54,62-67], to our knowledge, no effectiveness trials among Filipinos have evaluated the IY as a prevention program offered in such settings. Moreover, few culturally appropriate programs specific to Filipino families exist.

To the best of our knowledge, this will also be the first study to examine the efficacy of IY as a web-based prevention program used to improve parenting practices and internalizing symptoms in school-aged children. Many of the previous studies using IY were performed with clinically referred patients and in primary care settings [68-71]. If we are able to determine that web-based IY also improves internalizing symptoms, this single intervention may be considered for use with other ethnic groups as a universal prevention strategy for healthy populations at risk for multiple behavioral problems (both externalizing and internalizing disorders).

Future Directions

Results should suggest ways to increase the population-level effectiveness of parenting programs for minority and immigrant populations, who could benefit from such programs but tend to participate at low rates. These strategies will be used to design a future implementation trial that is attentive to the needs and preferences of parents and community stakeholders. Such strategies are critical in alleviating and eradicating behavioral health disparities seen in these populations. In addition, by transporting and evaluating effective interventions to a variety of community settings, we can provide critical information to health policy makers and public health leaders focused on making decisions about whether these interventions should be sustained.

Conclusions

The knowledge gained from this trial will contribute to the scientific literature on preventive and early intervention programs for children at high risk for future behavioral problems as well as on the implementation of evidence-based parenting interventions in real-world settings. Very few proven interventions that target Filipino parents are available. The data will also provide important information to understand the processes underlying how IY affects parenting practices and subsequent child problem behavior among Filipino families.

This research will impact the well-being of Filipino youth and society as a whole by expanding the cultural narratives and the evidence base supporting web-based parenting interventions during middle childhood to prevent behavioral health disparities. It will allow us to identify and resolve challenges involved in implementing a behavioral parenting intervention in a large and growing immigrant population. The real value of this project is that it attempts to bridge the differences between immigrant parents and youth growing up in the United States and can serve as a model for promoting mental health equity among other immigrant communities affected by behavioral health disparities.

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Authors' Contributions

SRM and JRJ took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, proposed analysis plan, and final draft of the manuscript. JRJ, WM, LP, and MK conceived and planned this study and provided overall supervision to this project.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Report from the USC Keck School of Medicine COVID-19 and Bridge Funding Program: Reviewer 1.
[PDF File (Adobe PDF File), 49 KB - resprot_v11i2e21867_app1.pdf]

Multimedia Appendix 2
Peer Review Report from the USC Keck School of Medicine COVID-19 and Bridge Funding Program: Reviewer 2.
[PDF File (Adobe PDF File), 51 KB - resprot_v11i2e21867_app2.pdf]

References

1. Hoeffel E, Rastogi S, Ouk KM, Shahid H. The Asian Population: 2010. 2010 Census Briefs. 2012. URL: https://www.census.gov/prod/cen2010/briefs/c2010br-11.pdf [accessed 2022-01-21]
2. Javier JR, Huffman LC, Mendoza FS. Filipino child health in the United States: do health and health care disparities exist? Prev Chronic Dis 2007 Apr;4(2):A36 [FREE Full text] [Medline: 17362627]
3. Nadal K, Monzones J. Filipino Americans and neuropsychology. In: Fujii DE, editor. The Neuropsychology of Asian Americans (Studies on Neuropsychology, Neurology and Cognition). Oxfordshire, United Kingdom: Taylor & Francis; 2010:47-70.
4. Choi Y, Lahey B. Testing the model minority stereotype: youth behaviors across racial and ethnic groups. Soc Serv Rev 2006 Sep 01;80(3):419-452 [FREE Full text] [doi: 10.1086/505288] [Medline: 21572913]
5. Kim PY, Lee D. Internalized model minority myth, Asian values, and help-seeking attitudes among Asian American students. Cultur Divers Ethnic Minor Psychol 2014 Jan;20(1):98-106. [doi: 10.1037/a0033351] [Medline: 23914745]
6. Buenavista TL. Issues affecting U.S. Filipino student access to postsecondary education: a critical race theory perspective. J Educ Stud Placed Risk 2010 Apr 20;15(1-2):114-126. [doi: 10.1080/10824661003635093]
7. Kuroki Y. Risk factors for suicidal behaviors among Filipino Americans: a data mining approach. Am J Orthopsychiatry 2015 Jan;85(1):34-42. [doi: 10.1037/ort0000018] [Medline: 25110976]
8. Maramba D. Family and educational environments: Contexts and counterstories of Filipino Americans. In: Educating Asian Americans: Achievement, Schooling, and Identities (Research on the Education of Asian Pacific Americans). Charlotte, North Carolina: Information Age Publishing; 2013.
9. Wolf DL. Family secrets: transnational struggles among children of Filipino immigrants. Sociol Perspect 2016 Aug 02;40(3):457-482. [doi: 10.2307/1389452]
10. Javier J, Lahiff M, Ferrer R, Huffman L. Examining depressive symptoms and use of counseling in the past year among Filipino and non-Hispanic white adolescents in California. J Dev Behav Pediatr 2010 May;31(4):295-303 [FREE Full text] [doi: 10.1097/DBP.0b013e3181dbadc7] [Medline: 20431400]
11. Willgerodt MA, Thompson EA. Ethnic and generational influences on emotional distress and risk behaviors among Chinese and Filipino American adolescents. Res Nurs Health 2006 Aug;29(4):311-324. [doi: 10.1002/nur.20146] [Medline: 16847910]
12. Hayes DK, Ta VM, Hurwitz EL, Mitchell-Box KM, Fuddy LJ. Disparities in self-reported postpartum depression among Asian, Hawaiian, and Pacific Islander Women in Hawaii: Pregnancy Risk Assessment Monitoring System (PRAMS), 2004-2007. Matern Child Health J 2010 Sep 4;14(5):765-773. [doi: 10.1007/s10995-009-0504-z] [Medline: 19653084]
13. Kim HJ, Park E, Storr CL, Tran K, Juon H. Depression among Asian-American adults in the community: systematic review and meta-analysis. PLoS One 2015 Jun 1;10(6):e0127760 [FREE Full text] [doi: 10.1371/journal.pone.0127760] [Medline: 26029911]
14. Ying Y, Han M. Parental acculturation, parental involvement, intergenerational relationship and adolescent outcomes in immigrant Filipino American families. J Immigr Refug Stud 2008 Oct 11;6(1):112-131. [doi: 10.1080/15362940802119351]
15. Brown SM, Doom JR, Lechuga-Peña S, Watamura SE, Koppels T. Stress and parenting during the global COVID-19 pandemic. Child Abuse Negl 2020 Dec;110(Pt 2):104699 [FREE Full text] [doi: 10.1016/j.chiabu.2020.104699] [Medline: 32859394]
16. Brunier A, Drysdale C. COVID-19 disrupting mental health services in most countries, WHO survey. World Health Organization. 2020. URL: https://www.who.int/news/item/05-10-2020-covid-19-disrupting-mental-health-services-in-most-countries-who-survey [accessed 2021-06-28]
17. Shah SM, Mohammad D, Qureshi MF, Abbas MZ, Aleem S. Prevalence, psychological responses and associated correlates of depression, anxiety and stress in a global population, during the coronavirus disease (COVID-19) pandemic. Community Ment Health J 2021 Jan 27;57(1):101-110 [FREE Full text] [doi: 10.1007/s10597-020-00728-y] [Medline: 33108569]
18. David EJ. Cultural mistrust and mental health help-seeking attitudes among Filipino Americans. Asian Am J Psychol 2010 Mar;1(1):57-66. [doi: 10.1037/a0018814]
19. Flores N, Supan J, Kreutzer CB, Samson A, Coffey DM, Javier JR. Prevention of Filipino youth behavioral health disparities: identifying barriers and facilitators to participating in "Incredible Years," an evidence-based parenting intervention, Los

Angeles, California, 2012. Prev Chronic Dis 2015 Oct 22;12:E178 [FREE Full text] [doi: 10.5888/pcd12.150186] [Medline: 26491813]
20. Yu SM, Huang ZJ, Singh GK. Health status and health services access and utilization among Chinese, Filipino, Japanese, Korean, South Asian, and Vietnamese children in California. Am J Public Health 2010 May;100(5):823-830. [doi: 10.2105/ajph.2009.168948]
21. Marineau M, Tice AD, Taylor-Garcia D, Akinaka KT, Lusk H, Ona F. Culturally sensitive strategies designed to target the silent epidemic of hepatitis B in a Filipino community. Hawaii Med J 2007 Jun;66(6):154-156. [Medline: 17621862]
22. Javier JR, Supan J, Lansang A, Beyer W, Kubicek K, Palinkas LA. Preventing Filipino mental health disparities: Perspectives from adolescents, caregivers, providers, and advocates. Asian American Journal of Psychology 2014;5(4):316-324. [doi: 10.1037/a0036479]
23. Nadal K. Filipino American Psychology: A Handbook of Theory, Research, and Clinical Practice. Hoboken, New Jersey, United States: John Wiley & Sons; 2011.
24. Cunningham CE, Bremner R, Boyle M. Large group community-based parenting programs for families of preschoolers at risk for disruptive behaviour disorders: utilization, cost effectiveness, and outcome. J Child Psychol Psychiatry 1995 Oct;36(7):1141-1159. [doi: 10.1111/j.1469-7610.1995.tb01362.x] [Medline: 8847377]
25. Kato N, Yanagawa T, Fujiwara T, Morawska A. Prevalence of children's mental health problems and the effectiveness of population-level family interventions. J Epidemiol 2015;25(8):507-516. [doi: 10.2188/jea.je20140198]
26. Mackenbach JD, Ringoot AP, van der Ende J, Verhulst FC, Jaddoe VWV, Hofman A, et al. Exploring the relation of harsh parental discipline with child emotional and behavioral problems by using multiple informants. The generation R study. PLoS One 2014 Aug 13;9(8):e104793 [FREE Full text] [doi: 10.1371/journal.pone.0104793] [Medline: 25120014]
27. Ackard DM, Neumark-Sztainer D, Story M, Perry C. Parent-child connectedness and behavioral and emotional health among adolescents. Am J Prev Med 2006 Jan;30(1):59-66. [doi: 10.1016/j.amepre.2005.09.013] [Medline: 16414425]
28. Patterson GR. Continuities—A search for causal mechanisms: Comment on the special section. Developmental Psychology 1998;34(6):1263-1268. [doi: 10.1037/0012-1649.34.6.1263]
29. Patterson G, Dishion T. Multilevel family process models: traits, interactions, and relationships. In: Hinde RA, Stevenson-Hinde J, editors. Relationships within Families: Mutual Influences. Oxford, United Kingdom: Clarendon Press; 1998:283-310.
30. Chronis AM, Chacko A, Fabiano GA, Wymbs BT, Pelham Jr WE. Enhancements to the behavioral parent training paradigm for families of children with ADHD: review and future directions. Clin Child Fam Psychol Rev 2004 Mar;7(1):1-27. [doi: 10.1023/b:ccfp.0000020190.60808.a4]
31. Bates JE, Pettit GS, Dodge KA, Ridge B. Interaction of temperamental resistance to control and restrictive parenting in the development of externalizing behavior. Dev Psychol 1998 Sep;34(5):982-995. [doi: 10.1037/0012-1649.34.5.982]
32. Belsky J, Hsieh KH, Crnic K. Mothering, fathering, and infant negativity as antecedents of boys' externalizing problems and inhibition at age 3 years: differential susceptibility to rearing experience? Dev Psychopathol 1998 Jun 01;10(2):301-319. [doi: 10.1017/s095457949800162x] [Medline: 9635226]
33. Kochanska G. Children's temperament, mothers' discipline, and security of attachment: multiple pathways to emerging internalization. Child Dev 1995 Jun;66(3):597-615. [doi: 10.1111/j.1467-8624.1995.tb00892.x]
34. Kochanska G. Multiple pathways to conscience for children with different temperaments: From toddlerhood to age 5. Developmental Psychology 1997;33(2):228-240. [doi: 10.1037/0012-1649.33.2.228]
35. O'Connor TG, Deater-Deckard K, Fulker D, Rutter M, Plomin R. Genotype–environment correlations in late childhood and early adolescence: antisocial behavioral problems and coercive parenting. Dev Psychol 1998 Sep;34(5):970-981. [doi: 10.1037/0012-1649.34.5.970]
36. Brennan PA, Le Brocque R, Hammen C. Maternal depression, parent-child relationships, and resilient outcomes in adolescence. J Am Acad Child Adolesc Psychiatry 2003 Dec;42(12):1469-1477. [doi: 10.1097/00004583-200312000-00014] [Medline: 14627882]
37. Galambos NL, Barker ET, Almeida DM. Parents do matter: trajectories of change in externalizing and internalizing problems in early adolescence. Child Dev 2003 Mar;74(2):578-594. [doi: 10.1111/1467-8624.7402017] [Medline: 12705574]
38. Loeber R. Disruptive and antisocial behavior in childhood and adolescence: development and risk factors. In: Lösel F, Hurrelmann K, editors. Health Hazards in Adolescence. Berlin: Walter De Gruyter; 1990:233-257.
39. Stormshak EA, Bierman KL, McMahon RJ, Lengua LJ. Parenting practices and child disruptive behavior problems in early elementary school. J Clin Child Psychol 2000 Feb;29(1):17-29. [doi: 10.1207/s15374424jccp2901_3]
40. Patterson GR, Chamberlain P. A functional analysis of resistance during parent training therapy. Clin Psychol Sci Pract 1994;1(1):53-70. [doi: 10.1111/j.1468-2850.1994.tb00006.x]
41. Patterson GR, Forgatch MS. Predicting future clinical adjustment from treatment outcome and process variables. Psychol Assess 1995;7(3):275-285. [doi: 10.1037/1040-3590.7.3.275]
42. Reid M, Webster-Stratton C, Beauchaine T. Parent training in head start: a comparison of program response among African American, Asian American, Caucasian, and Hispanic mothers. Prev Sci Off J Soc Prev Res 2001;2(4):209-227. [doi: 10.1023/A:1013618309070]

43. Tolan PH, Gorman-Smith D, Henry DB. The developmental ecology of urban males' youth violence. Dev Psychol 2003;39(2):274-291. [doi: 10.1037/0012-1649.39.2.274]
44. Brestan EV, Eyberg SM. Effective psychosocial treatments of conduct-disordered children and adolescents: 29 years, 82 studies, and 5,272 kids. J Clin Child Psychol 1998 Jun;27(2):180-189. [doi: 10.1207/s15374424jccp2702_5] [Medline: 9648035]
45. Serketich WJ, Dumas JE. The effectiveness of behavioral parent training to modify antisocial behavior in children: a meta-analysis. Behav Ther 1996;27(2):171-186. [doi: 10.1016/s0005-7894(96)80013-x]
46. Jensen PS, Hoagwood K, Petti T. Outcomes of mental health care for children and adolescents: II. Literature review and application of a comprehensive model. J Am Acad Child Adolesc Psychiatry 1996 Aug;35(8):1064-1077. [doi: 10.1097/00004583-199608000-00018] [Medline: 8755804]
47. Kazdin AE. Effectiveness of psychotherapy with children and adolescents. J Consult Clin Psychol 1991;59(6):785-798. [doi: 10.1037/0022-006x.59.6.785]
48. Javier JR. The Filipino family initiative: preliminary effects of an evidence-based parenting intervention offered in churches on parent and child outcomes. ProQuest. 2015. URL: https://www.proquest.com/docview/2158339877/abstract/E5DFC0FB40C54336PQ/1 [accessed 2021-06-29]
49. Javier JR, Supan J, Lansang A, Beyer W, Kubicek K, Palinkas LA. Preventing Filipino mental health disparities: perspectives from adolescents, caregivers, providers, and advocates. Asian Am J Psychol 2014 Dec;5(4):316-324 [FREE Full text] [doi: 10.1037/a0036479] [Medline: 25667725]
50. Javier JR, Coffey DM, Schrager SM, Palinkas LA, Miranda J. Parenting intervention for prevention of behavioral problems in elementary school-age Filipino-American children: a pilot study in churches. J Dev Behav Pediatr 2016;37(9):737-745. [doi: 10.1097/dbp.0000000000000342]
51. Herman KC, Borden LA, Reinke WM, Webster-Stratton C. The impact of the Incredible Years parent, child, and teacher training programs on children's co-occurring internalizing symptoms. Sch Psychol Q 2011 Sep;26(3):189-201 [FREE Full text] [doi: 10.1037/a0025228] [Medline: 25197205]
52. Webster-Stratton C, Herman KC. The impact of parent behavior-management training on child depressive symptoms. J Couns Psychol 2008 Oct;55(4):473-484. [doi: 10.1037/a0013664] [Medline: 22017554]
53. Javier J, Coffey D, Palinkas L, Kipke M, Miranda J, Schrager S. Promoting enrollment in parenting programs among a Filipino population: a randomized trial. Pediatrics 2019 Feb;143(2):e20180553 [FREE Full text] [doi: 10.1542/peds.2018-0553] [Medline: 30679379]
54. Javier J, Chamberlain L, Rivera K, Gonzalez S, Mendoza F, Huffman L. Lessons learned from a community-academic partnership addressing adolescent pregnancy prevention in Filipino American families. Prog Community Health Partnersh 2010;4(4):305-313 [FREE Full text] [doi: 10.1353/cpr.2010.0023] [Medline: 21169708]
55. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Hoboken, New Jersey, United States: Prentice-Hall, Inc; 1985.
56. Hawkins W, Clarke G, Seeley J. Application of social learning theory to the primary prevention of depression in adolescents. Health Values J Health Behav Educ Promot 1993;17(6):31-39 [FREE Full text]
57. Nelson JR, Stage S, Duppong-Hurley K, Synhorst L, Epstein MH. Risk factors predictive of the problem behavior of children at risk for emotional and behavioral disorders. Except Child 2016 Jul 24;73(3):367-379. [doi: 10.1177/001440290707300306]
58. Scaini S, Palmieri S, Caputi M. The relationship between parenting and internalizing problems in childhood. IntechOpen 2018. [doi: 10.5772/intechopen.73540]
59. Abidin R. Parenting Stress Index, fourth edition short form. PSI-4-SF. 2012. URL: http://www4.parinc.com/Products/Product.aspx?ProductID=PSI-4:SF [accessed 2021-06-28]
60. Achenbach T. Child Behavior Checklist. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology. New York: Springer; 2011:546-552.
61. Grasso D, Briggs-Gowan M, Ford J, Carter A. Epidemic-Pandemic Impacts Inventory (EPII). UConn Health - Department of Psychiatry. 2020. URL: https://health.uconn.edu/psychiatry/child-and-adolescent-psychiatry-outpatient-clinic/family-adversity-and-resilience-research-program/epii/ [accessed 2021-06-28]
62. Aguilar DE, Abesamis-Mendoza N, Ursua R, Divino LA, Cadag K, Gavin NP. Lessons learned and challenges in building a Filipino health coalition. Health Promot Pract 2010 May 19;11(3):428-436 [FREE Full text] [doi: 10.1177/1524839908326381] [Medline: 19098260]
63. Kataoka S, Fuentes S, O'Donoghue VP, Castillo-Campos P, Bonilla A, Halsey K, et al. A community participatory research partnership: the development of a faith-based intervention for children exposed to violence. Ethn Dis 2006;16(1 Suppl 1):89-97. [Medline: 16681132]
64. Maxwell AE, Bastani R, Vida P, Warda US. Results of a randomized trial to increase breast and cervical cancer screening among Filipino American women. Prevent Med 2003 Aug;37(2):102-109. [doi: 10.1016/s0091-7435(03)00088-4]
65. Maxwell AE, Bastani R, Danao LL, Antonio C, Garcia GM, Crespi CM. Results of a community-based randomized trial to increase colorectal cancer screening among Filipino Americans. Am J Public Health 2010 Nov;100(11):2228-2234. [doi: 10.2105/ajph.2009.176230]

66. Ursua R, Aguilar D, Wyatt L, Katigbak C, Islam NS, Tandon SD, et al. A community health worker intervention to improve management of hypertension among Filipino Americans in New York and New Jersey: a pilot study. Ethn Dis 2014;24(1):67-76 [FREE Full text] [Medline: 24620451]
67. Wells KB, Jones L, Chung B, Dixon EL, Tang L, Gilmore J, et al. Community-partnered cluster-randomized comparative effectiveness trial of community engagement and planning or resources for services to address depression disparities. J Gen Intern Med 2013 Oct 07;28(10):1268-1278 [FREE Full text] [doi: 10.1007/s11606-013-2484-3] [Medline: 23649787]
68. Carson MC, Montaño Z, Kelman AR, Coffey DM, Javier JR. Promoting behavioral health equity through implementation of the Incredible Years within primary care. Transl Issues Psychol Sci 2019 Dec;5(4):390-401. [doi: 10.1037/tps0000212]
69. Jones K, Daley D, Hutchings J, Bywater T, Eames C. Efficacy of the Incredible Years Programme as an early intervention for children with conduct problems and ADHD: long-term follow-up. Child Care Health Dev 2008 May;34(3):380-390. [doi: 10.1111/j.1365-2214.2008.00817.x] [Medline: 18410644]
70. McGilloway S, Mhaille GN, Bywater T, Furlong M, Leckey Y, Kelly P, et al. A parenting intervention for childhood behavioral problems: a randomized controlled trial in disadvantaged community-based settings. J Consult Clin Psychol 2012 Feb;80(1):116-127. [doi: 10.1037/a0026304] [Medline: 22148879]
71. Perrin EC, Sheldrick RC, McMenamy JM, Henson BS, Carter AS. Improving parenting skills for families of young children in pediatric settings: a randomized clinical trial. JAMA Pediatr 2014 Jan 01;168(1):16-24. [doi: 10.1001/jamapediatrics.2013.2919] [Medline: 24190691]

Abbreviations

IY: Incredible Years Basic Parent Training Program

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Protocol

Supporting People With Type 2 Diabetes in the Effective Use of Their Medicine Through Mobile Health Technology Integrated With Clinical Care to Reduce Cardiovascular Risk: Protocol for an Effectiveness and Cost-effectiveness Randomized Controlled Trial

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Abstract

Background: Type 2 diabetes is a common lifelong condition that affects over 400 million people worldwide. The use of effective medications and active self-management can reduce the risk of serious complications. However, people often have concerns when starting new medications and face difficulties in taking their medications regularly. Support provided by brief messages delivered through mobile phone–based SMS text messages can be effective in some long-term conditions. We have identified promising behavior change techniques (BCTs) to promote medication adherence in this population via a systematic review and developed SMS text messages that target these BCTs. Feasibility work has shown that these messages have fidelity

to intended BCTs, are acceptable to patients, and are successful in changing the intended determinants of medication adherence. We now plan to test this intervention on a larger scale in a clinical trial.

Objective: The aim of this trial is to determine the effectiveness and cost-effectiveness of this intervention for reducing cardiovascular risk in people with type 2 diabetes by comparing it with usual care.

Methods: The trial will be a 12-month, multicenter, individually randomized controlled trial in primary care and will recruit adults (aged ≥35 years) with type 2 diabetes in England. Consenting participants will be randomized to receive short SMS text messages intended to affect a change in medication adherence 3 to 4 times per week in addition to usual care. The aim is to test the effectiveness and cost-effectiveness of the intervention when it is added to usual care. The primary clinical outcome will be a composite cardiovascular risk measure. Data including patient-reported measures will be collected at baseline, at 13 and 26 weeks, and at the end of the 12-month follow-up period. With 958 participants (479 in each group), the trial is powered at 92.5% to detect a 4–percentage point difference in cardiovascular risk. The analysis will follow a prespecified plan. A nested quantitative and qualitative process analysis will be used to examine the putative mechanisms of behavior change and wider contextual influences. A health economic analysis will be used to assess the cost-effectiveness of the intervention.

Results: The trial has completed the recruitment phase and is in the follow-up phase. The publication of results is anticipated in 2024.

Conclusions: This trial will provide evidence regarding the effectiveness and cost-effectiveness of this intervention for people with type 2 diabetes.

Trial Registration: ISRCTN Registry ISRCTN15952379; https://www.isrctn.com/ISRCTN15952379

International Registered Report Identifier (IRRID): DERR1-10.2196/32918

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KEYWORDS

diabetes; SMS text messages; cardiovascular risk prevention; medication adherence; digital health; randomized controlled trial

Introduction

Type 2 Diabetes and Medication Adherence

Type 2 diabetes is a lifelong condition that can cause serious long-term health problems [1]. It is one of the most common long-term conditions, affecting 422 million people worldwide [2] and 4.7 million people in the United Kingdom [3]. It can lead to major complications, including cardiovascular disease (CVD), renal failure, and neuropathy [1]. The global economic burden of diabetes is projected to reach up to 2.2% of the global gross domestic product [4], and many of these costs are because of preventable complications. Treatments to reduce risks of complications from type 2 diabetes are effective if taken as intended [5,6]. However, concerns about medicines and difficulties in taking them regularly, whether intentional or unintentional, are common [7]. The cost of nonadherence to diabetes medication in the United Kingdom has been estimated at £100 million (US $135 million) per year in avoidable treatment costs alone [8].

Some services, such as pharmacy medication checks, use of blister packaging, written reminders, and routine education, are available to support people in taking their medication regularly, but evidence of their effectiveness and cost-effectiveness is not strong [9]. These services may not be right for everyone and are often targeted at particular groups or designed as *one-off* services. Understanding and improving this situation could make a major contribution to health.

Digital Health Interventions and Brief Messaging

Systematic reviews of SMS text messaging to support adherence to treatment and of mobile health interventions in diabetes have identified some effective interventions [10,11]. There are a few trials testing the impact of brief messaging in type 2 diabetes, but they do not test systematically developed interventions, and many are at risk of bias or have short-term follow-up. However, despite variation in response in different settings and differences in trial design, studies to date have not resolved continuing uncertainty about implementation in routine health care [10,11]. Trials of SMS text messaging for preventing cardiovascular risk and lowering blood pressure have shown clinically relevant changes in outcomes compared with usual care [12,13].

There is substantial evidence that personalized interventions are more effective than generic interventions [14]. Tailored interventions may be seen by recipients as more personally relevant, so they will be more likely to attend to, read, understand, and act on them. In addition, tailored interventions are designed to change the determinants of the target behavior that are relevant to individuals or to small subgroups of individuals; they therefore more precisely target the determinants of the behavior of individuals.

Preliminary Studies

Support Through Mobile Messaging and Digital Health Technology for Diabetes (SuMMiT-D) is a program of work composed of three phases: formative work; a feasibility trial; and a large-scale, pragmatic randomized controlled trial of a mobile phone–based system. The program is intended to develop and evaluate brief, tailored behavior change messages for people with type 2 diabetes, intending to encourage regular use of diabetes medication and persistence, and modify risk factors including glucose, blood pressure, and cholesterol levels, and thus the risk of adverse outcomes, including CVD. The intervention is intended to focus on a broad range of individuals with type 2 diabetes, but those with younger onset diabetes and

using insulin alone were not included, as these features often require different care pathways.

In the formative work for this trial, we identified theoretical constructs and features of intervention content found to be associated with medication adherence in people with type 2 diabetes [15] and mapped them onto a standard taxonomy of behavior change techniques (BCTs), that is, active components of interventions used to promote behavior change [16,17]. Development work aimed to ensure that the overall approach was acceptable to people with type 2 diabetes [15]. We then developed a large set of messages to target each BCT [18], through an expert consensus process and surveys with experts and patients to select messages that had fidelity to the intended BCTs and were acceptable to patients. We carried out a feasibility study and further qualitative work [18,19] and confirmed that the intervention and trial processes were acceptable and feasible [20,21] and that the responses to specific messages matched the response observed in the formative work [22].

Aims

The primary objectives of the main SuMMiT-D trial are to determine the effectiveness and cost-effectiveness of this intervention in reducing cardiovascular risk for people with type 2 diabetes compared with usual care. In addition to the primary objectives to determine the effectiveness and cost-effectiveness, a process evaluation will provide information to further develop and refine the intervention, to explore how it can achieve a wide reach, and to explore how it can be incorporated and embedded in health care pathways. It will also further identify the precise psychological mechanisms of action through which the intervention might change behavior.

Methods

Overview

The SuMMiT-D trial protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trial (Multimedia Appendix 1) and the European Society for Patient Adherence, Compliance, and Persistence Medication Adherence Reporting Guidelines recommendations [23,24].

Patient and Public Involvement

Patient members of the public are integral to this trial. A panel of 11 patient and public involvement (PPI) members with type 2 diabetes was set up for the formative stage of this program of work and continues to inform our work, reviews all patient documentation and research findings, and supports the development and refinement of the intervention.

All patient-facing documents for the SuMMiT-D trial, including the participant information sheet, informed consent form, posters, user guides, and website, were reviewed by PPI panel members. The results of the study will be made available to participants of the trial, PPI panel members, and participating general practices on the trial website.

Research Design

The SuMMiT-D main trial is a primary care–based, 2-arm, parallel group, individually randomized controlled trial with a health economic analysis and an embedded process evaluation. The trial aims to recruit 958 participants from up to 100 general practice sites in England. Participants with type 2 diabetes who provide consent will be randomly allocated to receive individually tailored mobile phone–based messages alongside usual care (intervention) or to usual care alone (usual care).

A process evaluation will be carried out in line with the Medical Research Council (MRC) guidance on process evaluations [25] and will focus on (1) mechanisms (or theory) of change of the intervention, that is, how the intervention produces change in participants and (2) the impact of context on how the intervention works.

An economic analysis will be conducted from the perspective of the National Health Service (NHS) and Personal Social Services. The analysis will be informed by routine and self-report data and will estimate the incremental cost-effectiveness ratio expressed as the cost per quality-adjusted life year (QALY) gained.

Setting

The trial will be conducted in general practices in England. The recruitment of practice sites will be monitored to ensure geographical spread, to include a range of sites with levels of deprivation matching the wider distribution, and to align recruitment with the burden of diabetes in the community.

Intervention

Participants assigned to the intervention group will receive brief health-related SMS text messages based on a systematic review of the evidence identifying determinants of medication-taking behavior [17]. Messages were developed based on a systematic review of the evidence by experts [17] and refined in an iterative process of ensuring acceptability based on patient feedback and demonstration of fidelity to intended behavior change determinants, as rated by an independent group of experts [18]. A more detailed description of the intervention is given in the template for intervention description and replication checklist [26], included in Multimedia Appendix 1. Examples of messages are given in Multimedia Appendix 2 along with the corresponding BCT that the message is intended to target based on the formative work for the trial [18].

The intervention is a digital health system with the following components:

1. Participants will be sent up to 4 automated SMS text messages per week, with an average frequency of 3 per week, related to diabetes management and the use of medicine.
2. The library of SMS text messages uses different groups of BCTs (see supplementary material) to target health-related behavior changes related to the use of medicines, as well as messages targeting other aspects of diabetes care (including diet and exercise).
3. The frequency of messages received using a particular group of BCTs can be modified based on a participant's response

to individual messages by sending an SMS text message in response to a particular message asking for that type of message to be sent more or less often. Participants may incur a cost for sending messages in response depending on their network plan.

4. The style of messages is patient-centered and encourages patients to seek further relevant information (including the use of links where it is possible to select external websites; eg, Diabetes UK).

Outcomes

The primary outcome will be a composite cardiovascular outcome adapted from the equations used for the United Kingdom Prospective Diabetes Study (UKPDS) risk engine [27]. We will evaluate the effect of changes in metabolic outcomes (glucose, blood pressure, and cholesterol levels) on the estimated risk of CVD. We will calculate CVD risk at baseline and at follow-up using the UKPDS risk engine [27]. The UKPDS risk engine is type 2 diabetes–specific and is based on 4540 patients from the UKPDS trial (1977 to 1991). It includes glycated hemoglobin (HbA_{1c}) as a continuous variable and calculates the risk of developing a new coronary heart disease event.

Secondary outcomes will include glycemic control (HbA_{1c}), blood pressure, total and high-density lipoprotein cholesterol (mean and clinically relevant change), self-reported smoking status, resource use, and EuroQol 5-dimension, 5-level (EQ-5D-5L). Participants will be assessed at 13, 26, and 52 weeks (not all measures at all time points), with all measurements and data being collected directly from the participants or via their medical records.

Medication adherence outcomes for antidiabetic medication will be prespecified as a proportion of participants with ≥80% medication available over 1 year, a continuous measure of the proportion of medication available over 1 year defined as the medication possession ratio (MPR), and persistence with a medication calculated from routine electronic health data [28,29]. We will also measure the MPR for statins and blood pressure–lowering medications.

Procedures and Assessments

Potential participants who express interest in taking part in the trial will be screened by the trial team and will provide consent and submit their baseline questionnaires either on the web or on paper according to their preference. Participants will be randomized by the trial team and will receive messages for 52 weeks from randomization to the final follow-up. All participants will be asked to complete questionnaires at baseline, 13 weeks, 26 weeks, and at the end of their 52-week follow-up period. Medical note reviews will be conducted at baseline and 12 months after randomization.

Recruitment

Potential participants will be identified through general practices in the United Kingdom. A short information leaflet will be provided to potential participants using a variety of methods, including posts displayed in waiting areas at participating general practices and given to patients by a practice team member.

Health care professionals will screen their type 2 diabetes clinic lists for identifying potentially eligible patients and invite them to participate in the study. Searches and screening may be performed periodically to enable newly potentially eligible patients to be invited. Potentially eligible patients may be contacted up to three times (by phone, letter, email, or SMS text message).

Expressions of Interest

People interested in taking part in the trial can send their full name by SMS text messages to the trial team to register their interest. If potential participants have any difficulties in registering their interest in the trial in this way, they will be able to call a trial telephone number and will receive support in registering as required.

Screening Assessment

Following an expression of interest, a member of the trial team will contact the potential participant by phone to provide further information about the trial and conduct screening and eligibility.

Inclusion Criteria

The inclusion criteria for eligible participants are as follows:

- Are aged ≥35 years
- Are taking oral glucose-lowering treatment, blood pressure–lowering treatment, or lipid-lowering treatment either alone or in combination
- Have access to a mobile phone and are able, if necessary, with help (eg, relatives, friends, or neighbors), to send, understand, and retrieve brief SMS text messages in the English language

Participants who are using insulin treatment without concomitant use of oral glucose-lowering treatment; who are pregnant, within 3 months postpartum or planning pregnancy during the trial; have a serious medical condition that, in the opinion of the investigator, makes them ineligible; have been admitted to hospital within the last 3 months for hyperglycemia or hypoglycemia; or who use a pharmacist-managed monitored dosage system are ineligible.

Informed Consent

Participants will provide consent either on the web or on paper.

Baseline and Follow-Up Assessments

Questionnaires will be administered (on the web or by post) at the baseline assessment, at 13 weeks and 26 weeks after randomization, and at 52 weeks. The measures and schedules are detailed in Table 1.

Table 1. Schedule of trial outcomes and measures.

Procedures	Visits or data collection time points					
	Screening[a]	Participant expression of interest[b]	13 weeks	26 weeks	52 weeks	Any time point
Screening	✓					
Eligibility assessment		✓				
Informed consent		✓				
Demographics and additional information questionnaire (to include age, gender, and postcode)		✓				
MARS[c] self-report scale—questionnaire		✓			✓	
EQ-5D-5L[d] health status—questionnaire		✓	✓	✓	✓	
Health care use record questionnaire		✓			✓	
Hypothesized mediators of behavior change and technology acceptance questionnaire		✓			✓	
Brief hypothesized mediators of behavior change and technology acceptance questionnaire			✓	✓		
Brief attitudes to diabetes and treatment		✓			✓	
Data collection (including medical history and concomitant medication)		✓			✓	
Randomization		✓				
Text messaging system registration		✓				
Sending of intervention or control messages initiated		✓				
Scheduled and unscheduled contacts		✓	✓	✓	✓	
Adverse event assessments						✓
Routinely collected data[e]						✓

[a]General practitioner to screen list before mail out.

[b]Day expression of interest received or as soon as possible thereafter.

[c]MARS: Medication Adherence Report Scale.

[d]EQ-5D-5L: EuroQol 5-dimension, 5-level.

[e]Routinely collected data: hospital episode statistics from National Health Service Digital, data from medical records for metabolic outcomes, use of primary care services, and medicine costs including drug prescriptions issued.

At the baseline assessment, questionnaires will be the Medication Adherence Report Scale (MARS) [28]; EQ-5D-5L [30], a measure to assess the hypothesized mediators of effect based on developmental work and the technology acceptance model [31]; a resource use questionnaire [8]; and a brief measure of satisfaction with diabetes treatment (Multimedia Appendix 1). Experience of diabetes education, presence of a caregiver and their role in medication administration, duration of diabetes, time since last change in type 2 diabetes medication, if the pharmacy used by the participant automatically requests patients' medication from surgery, self-reported level of education, smoking, age, gender, ethnicity, postcode, NHS number, date of birth, previous use of mobile phones and computers, and details of existing mobile phone, including contract type, will also be recorded.

Follow-up will last for 52 weeks after randomization. The following questionnaires will be completed at 13 and 26 weeks (range ±4 weeks) following randomization: EQ-5D-5L [30] and a brief questionnaire based on the health psychology theory and the technology acceptance model [31].

At 52 weeks (range ±4 weeks) following randomization, the following questionnaires will be completed: MARS, a self-report scale [32]; the EQ-5D-5L [30]; a measure based on the health psychology theory and the technology acceptance model [27]; a health care use record [8]; and a brief measure of satisfaction with diabetes treatment. A full schedule of the measures is shown in Table 1.

Additional Trial Procedures

All participants will receive non–health-related SMS text messages at a frequency of approximately 1 every 4 weeks. These messages will be used to maintain contact and prompt completion of questionnaires. The sending and receipt of messages by mobile phones will be monitored throughout the trial and contact will be made with the participants if problems are identified.

Randomization

Participants will be randomized after consent and when all baseline assessments have been completed. Participants will be allocated in a 1:1 ratio to either the intervention or usual care. Randomization will be performed using a validated, secure web-based randomization program (Sortition [Primary Care Trials Unity, University of Oxford]) provided by the University of Oxford Primary Care Clinical Trials Unit.

Allocation will be carried out with a nondeterministic minimization algorithm to ensure groups are balanced for important baseline prognostic and other factors: study site and age (<65 or ≥65 years); gender (male or female); duration of diabetes (<5 years or ≥5 years); and number of medications (<5 or ≥5). The allocated intervention will be implemented directly by the platform on which the digital health system is run. Apart from the qualitative research team and the engineering team, all other trials and health care staff were blinded to the treatment group. We determined that unblinding would not be required during the trial.

Discontinuation of Intervention or Withdrawal From Trial

Participants can withdraw from the trial at any time. Participants can also choose to pause or stop the receipt of SMS text messages by sending an SMS text message or contacting the trial office by telephone or post. Serious unexpected adverse events related to the intervention are determined by the chief investigator (AF) and reported in line with the local procedures.

Statistical Analysis

Power

A total sample size of 958 participants (479 per group) provides 92.5% power to detect a 4-percentage point change in cardiovascular risk of 4-percentage point change in risk (number needed to treat=25) based on an SD of 15% for cardiovascular risk derived from a primary care diabetes trial in patients with type 2 diabetes, in which reductions between 4% and 7% in estimated 10-year CVD risk were observed with statin treatment [33]. This estimate includes 15% inflation owing to clustering and 20% loss to follow-up at 92.5% power and 5% two-sided level of significance. The sample size also provides the power to detect changes in HbA_{1c} between groups of 4 mmol/mol based on an SD of 15 mmol/mol for patients newly starting glucose-lowering therapy [29]. This number of participants will also provide 80% power to detect an increase in the proportion of medication available from a baseline of 50% to 60.9%.

Analysis

The primary analysis population will include all randomized participants in the treatment arm to which they were assigned, regardless of the intervention received. Those found to be ineligible after randomization will be excluded from the analysis. For the primary and secondary outcomes, HbA_{1c} values will be included if they are between 3 and 12 months after randomization. The other data collected via notes review (cholesterol and blood pressure) will be included if between 6 weeks and 12 months post randomization.

Baseline variables will be presented by a randomized group using frequencies (with percentages) for binary and categorical variables and means (and SD) or medians (with lower and upper quartiles) for continuous variables.

The primary outcome will be analyzed using a multiple linear regression model. The model will adjust for baseline score, experience of diabetes education (yes or no), and minimization factors as fixed effects. Depending on the results of a preliminary exploration of the site, a mixed effect model will be used instead of a site fitted as a random effect. The adjusted difference in means between the 2 groups will be presented along with its associated 95% CI and *P* value.

Secondary continuous outcomes that are collected at 13, 26, and 52 weeks will be analyzed using a mixed effect model that includes a time × treatment interaction so that the treatment effect can be estimated at each time point; otherwise, the outcomes will be analyzed in a similar way to the primary outcome.

Similarly, binary outcomes measured at multiple time points will be analyzed using a generalized linear model (adjusting for the same factors listed earlier).

Missing data will be reported with reasons given where available, and the missing data pattern will be explored.

Economic Analysis

The health economic analysis will be embedded in the clinical trial. The principal aim will be to assess the cost-effectiveness of the intervention as compared with usual care and will be accomplished by adopting an England NHS and Personal Social Services perspective, estimating total costs, and benefits expressed in QALYs. The intervention will be microcosted. The use of health care resources by participants of the trial will be estimated from self-reported questionnaires, hospital episode statistics, and Egton Medical Information Systems data and will be costed using current prices. Health utilities will be estimated using methods specified by the National Institute for Clinical Excellence at the time of analysis.

A health economic analysis plan will be agreed upon before the analysis, which will primarily be over the time horizon of the trial, and secondarily over a lifetime. QALYs over 1 year will be estimated directly from the clinical trial, and a trial-based incremental cost-effectiveness ratio will be calculated as the ratio of the difference in mean costs to the difference in QALYs. The joint uncertainty in costs and benefits will be considered through the application of bootstrapping and estimation of the cost-effectiveness acceptability curve.

If the intervention is determined to be clinically effective, costs and outcomes will be extrapolated using the UKPDS model [34]. Costs and outcomes accruing after the first year will be discounted according to the rate specified by the National Institute for Clinical Excellence at the time of analysis. The modeled extrapolation will be subject to probabilistic sensitivity analysis to characterize parameter uncertainty and present the probability of the adherence intervention being cost-effective. The health economic analysis will be reported according to the

Consolidated Health Economic Evaluation Reporting Standards checklist [35].

Process Evaluation

A process evaluation will be carried out in line with the MRC guidance on process evaluations [25] and an updated MRC framework [36]. The process evaluation will have quantitative and qualitative elements and will focus on (1) mechanisms (or theory) of change of the intervention, that is, how the intervention produces change in participants and (2) the impact of context on how the intervention works.

Participants

Participants who provide consent to take part in the embedded qualitative study will be purposefully sampled by characteristics including, but not limited to, age, gender, duration of diabetes, medication use (duration and number), current adherence, and familiarity with digital devices, with the aim of a maximum variation sample within the sampling framework of the trial.

Up to 60 participants will be recruited from the intervention group in 2 waves. The initial wave of up to 30 participants will be recruited for 2 interviews, at 1-month and 12-month follow-ups to explore any change after initial exposure to the intervention, and potential long-term change after 12 months. Up to an additional 30 participants will be recruited for interviews at 12 months following the analysis of the interim measures. This will allow purposive sampling based on any changes in psychological constructs.

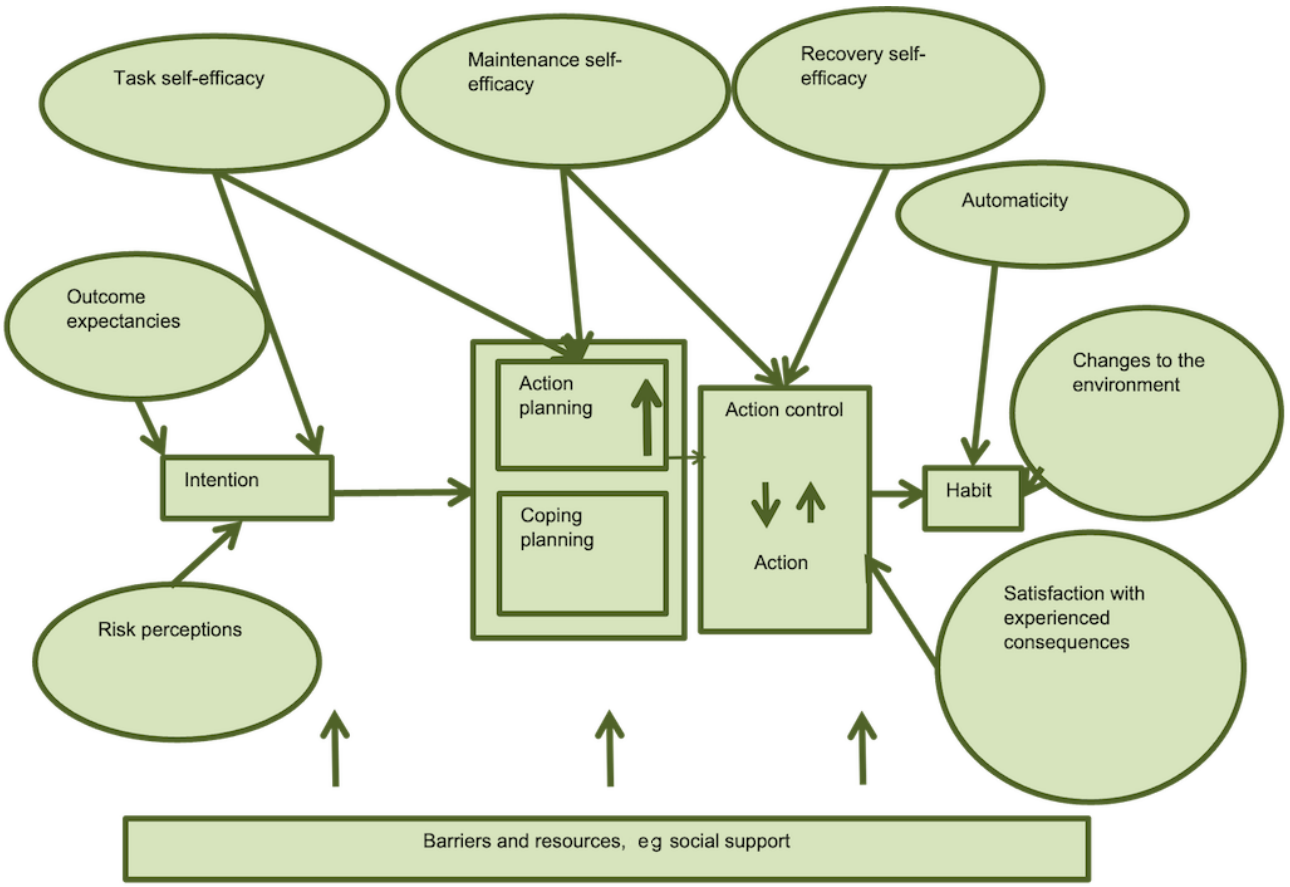
Prompts in the interview guide will be informed by anticipated themes derived from the existing literature and our previous qualitative studies, but consistent with inductive qualitative research methodology, we will also invite stories of the experience of participants in the trial without imposing a strictly limited preconceived topic guide. Further areas for questioning will be added as necessary as new themes emerge from early interviews. Participants will be invited to share their views on how they engaged with the system, the messaging system content, and will be invited to describe how the system was implemented in daily life. This will support the identification of issues surrounding potential attrition.

All interviews will be audio-recorded (with consent), transcribed verbatim, and analyzed thematically [37]. We will involve people with diabetes closely in both the development of the interview guide and in testing and refining our interpretation of the data to ensure that the analysis is as relevant and credible to eventual users as possible.

Quantitative Data in the Process Analysis

The trial will include brief questionnaires to assess the key behavior change constructs in which the messages are targeted at changing (Multimedia Appendix 2). An assessment will be made of the use of the system (messages received and responses) from routinely collected electronic data. In line with MRC guidance [36], we have developed a logic model (Figure 1) that indicates how the intervention will produce changes in behavior and thereby cardiovascular risk based on the Health Action Process Approach [38] and developmental work.

Figure 1. Process evaluation: logic model.



Three mediation analyses based on instrumental variable techniques [39-41] will be used to explore the extent to which changes in the behavior change constructs can explain any impact of the intervention on medication adherence measured by (1) MPR and (2) self-reported MARS and health measured by (3) the composite cardiovascular outcome. The constructs to be included are intention, action planning, coping planning, action control, habit, task self-efficacy, maintenance self-efficacy, recovery self-efficacy, automaticity, changes to the environment, satisfaction with experienced consequences, risk perceptions, outcome expectancies, social support, and patient activation. Relevant covariates will be included in the models, including age, gender, and index of multiple deprivation.

Qualitative Data in the Process Analysis

Interview data will be used to further explore the psychological mechanisms by probing what actions and feelings the intervention may result in, and the contextual factors that may influence how the intervention works for an individual. A content analysis of previous qualitative work has identified potential contextual factors and mechanisms that may influence how the SuMMiT-D intervention is working or not working. The connection between these and the effects of the intervention will be probed in these interviews. In accordance with recent guidelines related to potential measurement reactivity within trials, we have considered the effects these interviews may have on the trial outcomes and have taken steps to mitigate these [42]. All 52-week interviews will be conducted following quantitative data collection. The timing of the 4-week interviews has been chosen to allow exploration of initial changes in response to the messages while still leaving an appropriate gap between the interview and follow-up measurement (11 months). Sensitivity analyses will be considered as an option to examine the potential effects of being interviewed at the interim and final outcome points.

Data Management

All trial data will be entered into electronic case report forms. The clinical database is built on the Research Electronic Data Capture, a secure, web-based application designed to support data capture for research studies [43].

Ethics and Dissemination

The trial will be conducted according to the principles of the Declaration of Helsinki and in accordance with other relevant national guidelines, regulations, acts, and good clinical practice guidelines. The University of Oxford sponsors the trial.

The role of the Trial Steering Committee is taken on by the National Institute for Health Research Programme Steering Committee. The composition of the Trial Steering Committee is presented in Multimedia Appendix 3. The sponsor and funder determined this as a trial at low risk, and a Data Monitoring Committee has not been set up, with the Trial Steering Committee monitoring any problems arising. Ethical approval was obtained from the West of Scotland Research Ethics Committee 05.

The trial is sponsored by the University of Oxford, Clinical Trial and Research Governance Unit, Boundary Brook House, Headington, Oxford, United Kingdom. The sponsor and funder have no role in the study design, collection, management, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication.

Data Sharing and Dissemination

Access to quantitative trial data will be made available following the publication of primary results through a publicly accessible repository. Qualitative data cannot be made openly available because of ethical concerns. Access conditions will be available from the repository. Trial findings will be made available on the International Standard Randomised Controlled Trial Number website as soon as possible and before publication. The participants will be informed of the findings. The findings will be communicated by conferences and social media.

Dissemination Plan

The results of this trial will be submitted to a peer-reviewed journal for publication, through conference presentations, publications of process evaluation, and qualitative work, and on the SuMMiT-D trial website.

Results

Recruitment to the SuMMiT-D trial began with the first participant randomized on March 23, 2021. General practices across England have agreed to identify and invite participants to participate in the study, and participants have been recruited from 42 general practices. The reporting of the trial is anticipated in 2024.

Discussion

Principal Findings

The SuMMiT-D trial is a large-scale randomized controlled trial that aims to estimate the clinical and cost-effectiveness of the SMS text messaging intervention compared with usual care. It addresses the need to develop and better understand scalable interventions that can address the continuing challenge of suboptimal medication adherence through the increasing capability of mobile phones and digital platforms.The trial is pragmatic in design and can provide information about the impact of brief messaging on people with diabetes with SMS text messages that have been systematically developed to use established BCTs. Although the trial focuses on selecting a population having type 2 diabetes, many, if not most, of these people will have other medical conditions; thus, it has broader applicability to a wide population of people who have type 2 diabetes in addition to other conditions rather than excluding those individuals.

Conclusions

If effective, this intervention could help reduce the burden of complications and increase the costs associated with nonadherence. Alongside this trial, we are also looking at how this intervention, and those like it, could best be embedded in routine clinical care. This research could also offer a model for

technology-based self-management support that could be extended to other aspects of diabetes care and other long-term conditions.

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Authors' Contributions

Each author has contributed significantly to and is willing to take public responsibility for one or more aspects of the study. AF, LL, and DF conceived the study; AF, DF, PB, NN, YKB, LL, RR, VW, JM, BG, CV, LT, DAH, RH, and LMY were involved in planning the study. All authors are involved in carrying out the study. LJ, SR, YKB, YC, RC, CP, CK, NN, and JA are involved in data collection. AF and LJ wrote the initial draft of this manuscript; all authors provided revisions and approved the final version.

Conflicts of Interest

LT reports personal fees from Sensyne Health; he also worked part-time for the company and shared options in it. CV reports salary support from Sensyne Health, and RH reports speaker engagements with honoraria from the following companies outside the submitted work: AbbVie, Abbott, Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Biogen, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Sharp Dohme, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi, Shire Pharmaceuticals, Teva, and UCB. RH is a director of Spoonful of Sugar Ltd, a University College London Business company providing consultancy on treatment engagement and patient support programs to health care policy makers, providers, and industry.

Multimedia Appendix 1
Standard Protocol Items: Template for Intervention, Description, and Replication checklist and Recommendations for Interventional Trials checklist.
[DOCX File , 4658 KB - resprot_v11i2e32918_app1.docx]

Multimedia Appendix 2
Study-specific questionnaires and example text messages.
[DOCX File , 4628 KB - resprot_v11i2e32918_app2.docx]

Multimedia Appendix 3
Study governance.
[DOCX File , 38 KB - resprot_v11i2e32918_app3.docx]

Multimedia Appendix 4
Peer review report.
[PDF File (Adobe PDF File), 91 KB - resprot_v11i2e32918_app4.pdf]

References

1. UK Prospective Diabetes Study Group. UK prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995 Nov;44(11):1249-1258. [Medline: 7589820]
2. Global Report on Diabetes. Geneva: World Health Organisation; 2016.
3. Us, diabetes and a lot of facts and stats. Diabetes UK. 2019. URL: https://www.diabetes.org.uk/resources-s3/2019-11/facts-stats-update-oct-2019.pdf [accessed 2021-12-27]
4. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, et al. Global economic burden of diabetes in adults: projections from 2015 to 2030. Diabetes Care 2018 May;41(5):963-970. [doi: 10.2337/dc17-1962] [Medline: 29475843]

5. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364(9435):685-696. [doi: 10.1016/S0140-6736(04)16895-5] [Medline: 15325833]
6. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. Br Med J 1998 Sep 12;317(7160):713-720. [doi: 10.1136/bmj.317.7160.713]
7. McSharry J, McGowan L, Farmer AJ, French DP. Perceptions and experiences of taking oral medications for the treatment of Type 2 diabetes mellitus: a systematic review and meta-synthesis of qualitative studies. Diabet Med 2016 Oct;33(10):1330-1338. [doi: 10.1111/dme.13152] [Medline: 27150899]
8. Salas M, Hughes D, Zuluaga A, Vardeva K, Lebmeier M. Costs of medication nonadherence in patients with diabetes mellitus: a systematic review and critical analysis of the literature. Value Health 2009 Sep;12(6):915-922 [FREE Full text] [doi: 10.1111/j.1524-4733.2009.00539.x] [Medline: 19402848]
9. Patient adherence to medicines. Academy of Medical Sciences. 2015. URL: https://acmedsci.ac.uk/policy/policy-projects/patient-adherence-to-medicines [accessed 2021-01-05]
10. Ricci-Cabello I, Bobrow K, Islam SM, Chow CK, Maddison R, Whittaker R, et al. Examining development processes for text messaging interventions to prevent cardiovascular disease: systematic literature review. JMIR Mhealth Uhealth 2019 Mar 29;7(3):e12191 [FREE Full text] [doi: 10.2196/12191] [Medline: 30924790]
11. Farmer AJ, McSharry J, Rowbotham S, McGowan L, Ricci-Cabello I, French DP. Effects of interventions promoting monitoring of medication use and brief messaging on medication adherence for people with Type 2 diabetes: a systematic review of randomized trials. Diabet Med 2016 May;33(5):565-579. [doi: 10.1111/dme.12987] [Medline: 26470750]
12. Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. J Am Med Assoc 2015;314(12):1255-1263. [doi: 10.1001/jama.2015.10945] [Medline: 26393848]
13. Bobrow K, Farmer AJ, Springer D, Shanyinde M, Yu L, Brennan T, et al. Mobile phone text messages to support treatment adherence in adults with high blood pressure (SMS-Text adherence Support [StAR]): a single-blind, randomized trial. Circulation 2016 Feb 09;133(6):592-600 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.115.017530] [Medline: 26769742]
14. Kassavou A, Sutton S. Automated telecommunication interventions to promote adherence to cardio-metabolic medications: meta-analysis of effectiveness and meta-regression of behaviour change techniques. Health Psychol Rev 2018 Mar;12(1):25-42. [doi: 10.1080/17437199.2017.1365617] [Medline: 28805162]
15. Bartlett YK, Newhouse N, Long HA, Farmer AJ, French DP. What do people with type 2 diabetes want from a brief messaging system to support medication adherence? Patient Prefer Adher 2019 Sep 30;13:1629-1640 [FREE Full text] [doi: 10.2147/PPA.S217843] [Medline: 31686789]
16. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
17. Long H, Bartlett YK, Farmer AJ, French DP. Identifying brief message content for interventions delivered via mobile devices to improve medication adherence in people with type 2 diabetes mellitus: a rapid systematic review. J Med Internet Res 2019 Jan 09;21(1):e10421 [FREE Full text] [doi: 10.2196/10421] [Medline: 30626562]
18. Bartlett YK, Farmer A, Rea R, French DP. Use of brief messages based on behavior change techniques to encourage medication adherence in people with type 2 diabetes: developmental studies. J Med Internet Res 2020 May 13;22(5):e15989 [FREE Full text] [doi: 10.2196/15989] [Medline: 32401214]
19. Farmer A, Allen J, Bartlett K, Bower P, Chi Y, French D, SuMMiT-D Collaborative Group. Supporting people with type 2 diabetes in effective use of their medicine through mobile health technology integrated with clinical care (SuMMiT-D Feasibility): a randomised feasibility trial protocol. BMJ Open 2019 Dec 29;9(12):e033504 [FREE Full text] [doi: 10.1136/bmjopen-2019-033504] [Medline: 31888938]
20. Chi Y, Velardo C, Allen J, Robinson S, Riga E, Judge D, et al. System architecture for "Support Through Mobile Messaging and Digital Health Technology for Diabetes" (SuMMiT-D): design and performance in pilot and randomized controlled feasibility studies. JMIR Form Res 2021 Mar 26;5(3):e18460 [FREE Full text] [doi: 10.2196/18460] [Medline: 33769299]
21. Bartlett YK, Kenning C, Crosland J, Newhouse N, Miles LM, Williams V, et al. Understanding acceptability in the context of text messages to encourage medication adherence in people with type 2 diabetes. BMC Health Serv Res 2021 Jun 28;21(1):608 [FREE Full text] [doi: 10.1186/s12913-021-06663-2] [Medline: 34182988]
22. Bartlett YK, Farmer AJ, Newhouse N, Miles LM, Kenning C, French DP. Effects of using a text message intervention on psychological constructs and association between changes to psychological constructs and medication adherence in people with type 2 diabetes: results from a randomised controlled feasibility study. JMIR Form Res (forthcoming) 2021. [doi: 10.2196/30058]
23. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]

24. De Geest S, Zullig LL, Dunbar-Jacob J, Helmy R, Hughes DA, Wilson IB, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Ann Intern Med 2018 Jul 03;169(1):30-35 [FREE Full text] [doi: 10.7326/M18-0543] [Medline: 29946690]
25. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. Br Med J 2015 Mar 19;350:h1258 [FREE Full text] [doi: 10.1136/bmj.h1258] [Medline: 25791983]
26. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. Br Med J 2014 Mar 07;348:g1687. [doi: 10.1136/bmj.g1687] [Medline: 24609605]
27. Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001 Dec;101(6):671-679. [Medline: 11724655]
28. Farmer AJ, Rodgers LR, Lonergan M, Shields B, Weedon MN, Donnelly L, et al. Adherence to oral glucose-lowering therapies and associations with 1-year HbA1c: a retrospective cohort analysis in a large primary care database. Diabetes Care 2016 Feb;39(2):258-263 [FREE Full text] [doi: 10.2337/dc15-1194] [Medline: 26681714]
29. Shields BM, Hattersley AT, Farmer AJ. Identifying routine clinical predictors of non-adherence to second-line therapies in type 2 diabetes: a retrospective cohort analysis in a large primary care database. Diabetes Obes Metab 2020 Jan;22(1):59-65 [FREE Full text] [doi: 10.1111/dom.13865] [Medline: 31468676]
30. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011 Dec;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
31. Venkatesh V, Davis FD. A theoretical extension of the technology acceptance model: four longitudinal field studies. Manag Sci 2000 Feb;46(2):186-204. [doi: 10.1287/mnsc.46.2.186.11926]
32. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 1999 Dec;47(6):555-567. [doi: 10.1016/s0022-3999(99)00057-4] [Medline: 10661603]
33. Holman RR, Paul S, Farmer A, Tucker L, Stratton IM, Neil HA, Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes Study Group. Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes (AFORRD): a randomised controlled trial. Diabetologia 2009 Jan;52(1):50-59. [doi: 10.1007/s00125-008-1179-5] [Medline: 19002433]
34. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, UK Prospective Diabetes Study (UKDPS) Group. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004 Oct;47(10):1747-1759. [doi: 10.1007/s00125-004-1527-z] [Medline: 15517152]
35. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Br Med J 2013 Mar 25;346:f1049 [FREE Full text] [doi: 10.1136/bmj.f1049] [Medline: 23529982]
36. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. Br Med J 2021 Sep 30;374:n2061 [FREE Full text] [doi: 10.1136/bmj.n2061] [Medline: 34593508]
37. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
38. Schwarzer R. Modeling health behavior change: how to predict and modify the adoption and maintenance of health behaviors. Appl Psychol 2008 Jan;57(1):1-29 [FREE Full text] [doi: 10.1111/j.1464-0597.2007.00325.x]
39. Dunn G, Emsley R, Liu H, Landau S. Integrating biomarker information within trials to evaluate treatment mechanisms and efficacy for personalised medicine. Clin Trials 2013 Oct;10(5):709-719 [FREE Full text] [doi: 10.1177/1740774513499651] [Medline: 24000376]
40. Dunn G, Emsley R, Liu H, Landau S, Green J, White I, et al. Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: a methodological research programme. Health Technol Assess 2015 Nov;19(93):1-115 [FREE Full text] [doi: 10.3310/hta19930] [Medline: 26560448]
41. Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. Stat Methods Med Res 2010 Jun;19(3):237-270. [doi: 10.1177/0962280209105014] [Medline: 19608601]
42. French DP, Miles LM, Elbourne D, Farmer A, Gulliford M, Locock L, MERIT Collaborative Group. Reducing bias in trials due to reactions to measurement: experts produced recommendations informed by evidence. J Clin Epidemiol 2021 Nov;139:130-139 [FREE Full text] [doi: 10.1016/j.jclinepi.2021.06.028] [Medline: 34229092]
43. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]

Abbreviations

BCT: behavior change technique
CVD: cardiovascular disease
EQ-5D-5L: EuroQol 5-dimension, 5-level
HbA_{1c}: glycated hemoglobin
MARS: Medication Adherence Report Scale
MPR: medication possession ratio
MRC: Medical Research Council
NHS: National Health Service
NIHR: National Institute for Health Research
PPI: patient and public involvement
QALY: quality-adjusted life year
SuMMiT-D: Support Through Mobile Messaging and Digital Health Technology for Diabetes
UKPDS: United Kingdom Prospective Diabetes Study

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Protocol

Parent SMART (Substance Misuse in Adolescents in Residential Treatment): Protocol of a Randomized Effectiveness Trial of a Technology-Assisted Parenting Intervention

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Abstract

Background: Adolescents in residential substance use treatment are at extremely high risk for relapse following discharge to the community. Parenting practices, including parental monitoring and parent-adolescent communication, have been established as key predictors of adolescent substance use outcomes and relapse. However, traditional office-based therapy may not be feasible for parents who face structural and systemic barriers. There is a clear need for effective, accessible, and scalable interventions for parents of adolescents receiving residential substance use treatment. In a prior pilot randomized controlled trial, we tested Parent SMART (Substance Misuse among Adolescents in Residential Treatment)—a technology-assisted parenting intervention informed by extensive formative research—as an adjunct to residential treatment as usual (TAU). Parent SMART demonstrated high feasibility and acceptability, as well as evidence of effectiveness in improving parental monitoring and communication.

Objective: This protocol paper describes a fully-powered randomized controlled pragmatic effectiveness trial of Parent SMART as an adjunct to residential TAU. We hypothesize that families who receive Parent SMART will demonstrate greater improvements in parenting skills, reductions in adolescent substance use, and reductions in adolescent problem behaviors relative to families that receive residential TAU. We will test the exploratory hypothesis that reductions in adolescent substance use will be partially mediated by improvements in parenting skills.

Methods: Adolescent-parent dyads (n = 220 dyads; 440 total) will be randomized to either residential TAU only or Parent SMART+TAU. Parents randomized to Parent SMART will receive access to a networking forum, an off-the-shelf computer program called Parenting Wisely, and up to four telehealth coaching calls. Multimethod follow-up assessments consisting of self-reported parent and adolescent measures, a parent-adolescent in vivo interaction task, and 8-panel urine screens will be conducted 6, 12, and 24 weeks postdischarge from residential care. Measures will assess parenting skills, adolescent substance use, and adolescent problem behaviors. Analyses will be conducted using latent change score structural equation modeling.

Results: The trial was funded in August 2021; ethics approval was obtained in August 2020, prior to funding. Due to concerns with the administrative interface in the pilot trial, the Parent SMART networking forum is currently being rebuilt by a different vendor. The programming is scheduled to be completed by December 2021, with recruitment beginning in February 2022.

Conclusions: The proposed research has the potential to advance the field by serving a high-need, underserved population during a vital treatment juncture; targeting parenting practices (putative mediators) that have been shown to predict adolescent substance use outcomes; addressing barriers to accessing continuing care; and testing a highly scalable intervention model.

Trial Registration: ClinicalTrials.gov NCT05169385; https://clinicaltrials.gov/ct2/show/NCT05169385

International Registered Report Identifier (IRRID): PRR1-10.2196/35934

(JMIR Res Protoc 2022;11(2):e35934) doi:10.2196/35934

KEYWORDS

adolescent; residential; technology-assisted; substance use; parent; randomized controlled trial; RCT; intervention; eHealth; problem behaviour; problem behavior

Introduction

Background

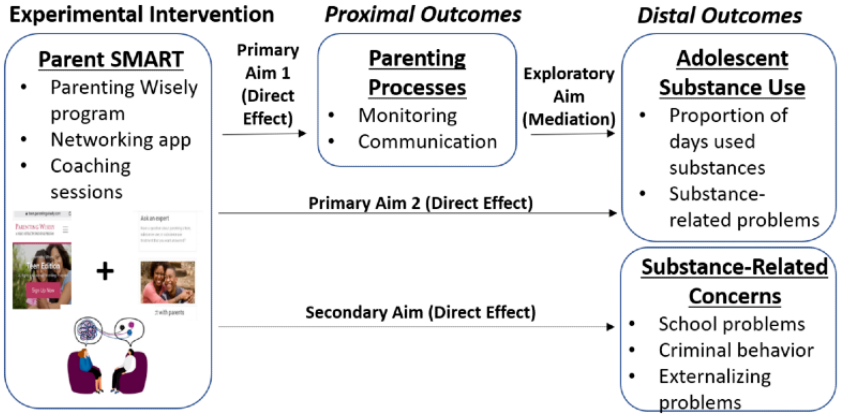
Adolescents with substance use disorders requiring a residential level of care typically present with severe symptoms and an array of co-occurring mental health, behavioral, motivational, legal, and environmental problems [1,2]. While a number of studies have found that residential treatment is associated with an acute reduction in symptoms and co-occurring problems [3,4], long-term outcomes of this population are far less encouraging [5]. Longitudinal studies indicate that the majority of adolescents will relapse within 90 days of discharge [6]. Such poor outcomes are likely at least partially attributable to the fact that only about 35%-45% of adolescents receive any continuing care [7,8].

To improve adolescent outcomes, it has been argued that continuing care interventions should move beyond solely including the adolescent to actively targeting parent engagement. Multiple systematic and meta-analytic reviews [9-12] have demonstrated that substance use interventions that include parents significantly outperform adolescent-only approaches. In recognition of this empirical support, the Residential Care Consortium released a white paper advocating that residential programs improve parent engagement, particularly prior to and following discharge to the community when disruptions in care are common [13]. Further research has suggested that adolescent substance use interventions targeting parental monitoring and communication, two key parenting processes that are protective against adolescent substance use [14,15], are associated with better adolescent outcomes than interventions targeting parent education only [16-18].

Building upon the extant research highlighting how positive parenting skills protect against adolescent substance use [19-21], as well as the research demonstrating the challenges with parent engagement in traditional office-based sessions [22,23], we developed a technology-assisted parenting intervention called Parent SMART (Substance Misuse among Adolescents in Residential Treatment). Parent SMART was designed as an adjunct to residential treatment for adolescents with substance-related problems. It consists of three elements—an online parent skills program, a parent networking forum, and telehealth coaching sessions. The online parenting skills program is an off-the-shelf product [24,25], whereas the networking forum and telehealth coaching sessions were specifically designed in response to formative research with parents of adolescents in residential treatment [26].

We previously tested the Parent SMART intervention via a pilot randomized controlled trial with 61 parent-adolescent dyads across two residential programs (one acute care and one standard residential care) [27]. Results of the pilot trial met or exceeded all of the recruitment, retention, acceptability, feasibility, and fidelity benchmarks established a priori as evidence that the intervention was worthy of further study in a larger trial. Parent SMART demonstrated excellent acceptability and feasibility, with parents who received Parent SMART reporting significantly higher levels of satisfaction and greater likelihood of recommending the services they had received than those who received residential treatment alone [27]. In addition, Parent SMART was associated with significant improvements in parental monitoring and communication, measured via both self-report scales and a behavioral intervention task, across both residential settings [28]. Among adolescents in the acute care setting, Parent SMART was also associated with significant reductions in days of binge drinking and school-related problems; we were underpowered to detect differences in the standard residential care setting, but a number of significant time effects were observed, revealing encouraging reductions in days of substance use, substance-related problems, and high-risk behaviors among adolescents in both conditions [27]. Building upon this prior work, the current protocol describes a fully-powered, randomized controlled trial testing the effectiveness of Parent SMART as an adjunct to residential TAU on parenting skills, adolescent substance use, and problems commonly related to substance use such as school truancy, externalizing behavior, sexual risk behavior, and criminal involvement [10]. A conceptual overview of the study's specific aims is presented visually (Figure 1) and elaborated upon as follows.

Figure 1. Overview of protocol aims. Parent SMART: Substance Misuse in Adolescents in Residential Treatment.



Specific Aims

Primary aim 1: Evaluate the effectiveness of Parent SMART+TAU versus TAU on proximal parenting outcomes. Hypothesis 1 is that, relative to those in TAU, parents receiving Parent SMART+TAU will exhibit greater improvements in parental monitoring and communication at 6, 12, and 24 weeks postdischarge from residential care.

Primary aim 2: Evaluate the effectiveness of Parent SMART+TAU versus TAU on distal adolescent substance outcomes. Hypothesis 2 is that, relative to those in TAU, adolescents whose parents receive Parent SMART+TAU will show greater reductions in the proportion of days substances were used outside a controlled environment and substance-related problems at 6, 12, and 24 weeks postdischarge from residential care.

Secondary aim: Evaluate the effectiveness of Parent SMART+TAU versus TAU on distal adolescent problem behavior outcomes commonly related to substance use: school problems, externalizing behaviors, sexual risk behavior, and criminal involvement. Hypothesis 3 is that adolescents whose parents receive Parent SMART+TAU will have greater reductions in a range of problem behaviors, including school truancy, externalizing behavior, risky sexual behavior, and criminal involvement at 6, 12, and 24 weeks postdischarge from residential, relative to adolescents in TAU.

Exploratory aim: Evaluate the extent to which change in parenting processes mediates change in adolescent substance outcomes. An exploratory hypothesis is that change in parenting processes (ie, communication, monitoring) at 6-weeks postdischarge from residential care will partially mediate primary adolescent substance use outcomes at 12 and 24 weeks.

Methods

Study Design and Ethical Considerations

Parent-adolescent dyads will be assigned to receive either residential TAU or Parent SMART+ residential TAU on a 1:1 schedule using a two-arm, parallel-group, randomized trial design. The Brown University Institutional Review Board has approved all study procedures described herein (ID# 2006002748). The study is registered in clinicaltrials.gov (NCT05169385). The timing of key study elements, including randomization and parent-adolescent assessments, is depicted in Table 1.

Table 1. Timing of key protocol elements.

	Residential treatment				Postdischarge period		
Timepoint	Enrollment	Baseline assessment	Allocation	Residential stay (2-45 Days)	6 weeks	12 weeks	24 weeks
Enrollment							
Informed consent/assent	X						
Masked allocation			X				
Control condition							
Residential treatment as usual				X			
Parent SMART condition							
Parenting Wisely program				X	X	X	
Parent networking app				X	X	X	
Telehealth coaching sessions				X	X		
Assessment of primary aim 1							
Parental monitoring questionnaire		X			X	X	X
Parental communication questionnaire		X			X	X	X
Family assessment task		X			X	X	X
Assessment of primary aim 2							
Proportion days used substances		X			X	X	X
Substance-related problem scale		X			X	X	X
Urine screens					X	X	X
Assessment of secondary aim							
School-related problem scale		X			X	X	X
Behavioral complexity scale		X			X	X	X
Risky behavior scale		X			X	X	X
Crime and violence scale		X			X	X	X

Inclusion Criteria

A total of 440 participants—220 parent-adolescent dyads—will participate in this trial. Parent inclusion criteria are: (1) parent or legal guardian of adolescent aged 12-18 years admitted to residential treatment due to concerns about substance use; (2) will be primary guardian living with adolescent after their discharge from residential treatment; (3) fluent in English or Spanish; and (4) willing and able to complete a structured assessment prior to the adolescent's discharge from residential treatment. Adolescents whose parents qualify are eligible to participate as long as they are willing to participate in the research and able to complete a structured assessment prior to their discharge from residential treatment.

Recruitment

Parents will be referred to the study via a residential intake coordinator at the partner facility (see residential TAU), who will briefly inform parents about the study during the intake process. Interested parents will be given a consent to contact form on a study tablet to review and sign. The consent to contact form will provide a brief overview of the study and will collect the parent's preferred contact information so that research staff can contact the parent at a later time. The research staff will then contact the parent to describe the study risks and benefits and complete a brief eligibility screener. Interested parents who qualify will provide informed consent to participate using electronic consent forms; parents of adolescent minors will also provide informed parental consent for their child to participate. The research staff will then work with staff at the residential facility to schedule a time to speak with the adolescent via phone or Zoom to describe the study and to complete a brief screener. Interested adolescents will provide informed assent (for those age 13-17 years) or informed consent (for those age 18 years) via electronic forms. Parents and adolescents must independently provide consent and assent, respectively, for an adolescent-parent dyad to enroll in the study.

Anticipated Participant Demographics

Based on the participants enrolled in the pilot trial [27], parents are expected to be predominantly biological mothers (about

80%), with the remainder comprised of biological fathers, adopted parents, and other legal guardians. For adolescent characteristics, we expect approximately 10% of adolescents to identify their gender as nonbinary, with the remainder identifying as male (45%) or female (45%). We anticipate about 25% of adolescents will identify as Hispanic. We expect adolescents to self-identify in the following racial categories: White (65%), Black or African-American (12%), Multiracial (15%), and Asian or Asian American (2%). We expect about 6% of adolescents to select "prefer not to answer" as their preferred race.

Randomization

Parent-adolescent dyads will be randomized immediately after completing the baseline assessment using the urn randomization method [29], which systematically biases randomization in favor of balance across conditions. Dyad randomization will be balanced according to adolescent biological sex at birth (male vs female), planned length of stay in residential (0-10 days vs 10+ days), and parent's preferred language (English vs Spanish). Random assignments will be made using an Excel urn generator developed by Stout and colleagues for Project MATCH [22]. Parents will be informed about their treatment assignment shortly after randomization. Residential staff and study research staff conducting follow-up assessments will be blind to the condition.

Interventions

Residential TAU

TAU consists of the standard residential services offered to adolescents at our partner facility and will be received by families in both conditions. The partner residential treatment program, Rosecrance Health Network, offers residential treatment for adolescents at two locations, one in Rockville, Illinois, and one in Sioux City, Iowa. Length of stay ranges from 2 to 45 days, depending on the adolescent's level of need and insurance coverage. Adolescents at Rosecrance Health Network receive about 15 hours of educational programming and 25 hours of treatment per week in a predominantly group-therapy model based on dialectical behavioral therapy [30]. Each adolescent is also assigned a primary counselor who checks in with them at least twice per week. Medication management is offered by a nurse practitioner or psychiatrist as needed. Prior to discharge, parents receive standard discharge planning, which consists of a customized relapse prevention plan as well as either a referral to a new outpatient therapy provider or a return to a prior outpatient therapy provider. Families receive referrals to a psychiatrist or local self-help group as indicated. Postdischarge, families are encouraged to phone the intake coordinator for further referrals or support.

Following randomization, parents will be given an educational pamphlet about adolescent substance use, parenting skills, and local community resources, consistent with usual resource provision at the partner site.

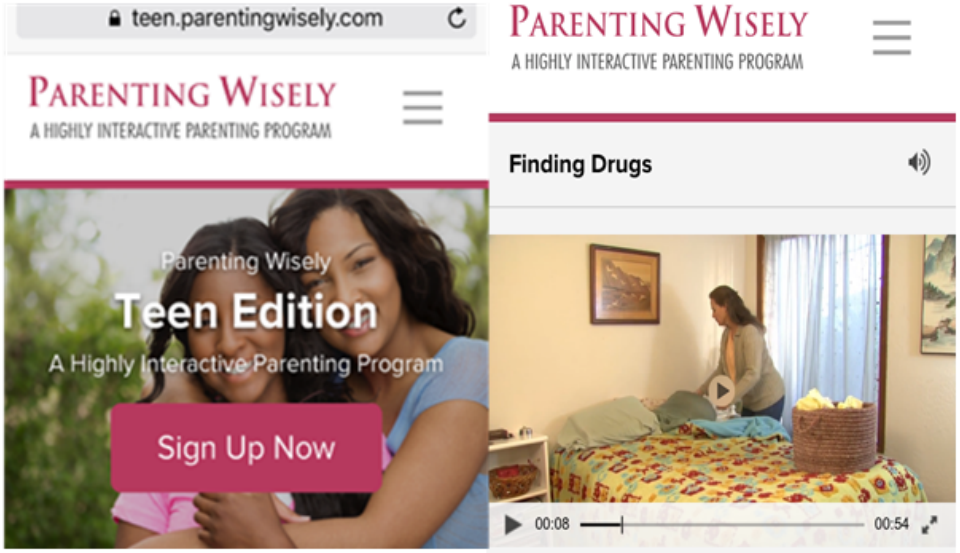
Parent SMART

Parents randomized to Parent SMART will receive a technology-assisted intervention containing three core elements, which were packaged in response to formative feedback described extensively [26] and tested in the pilot trial [27,28]. All three elements are available in both English and Spanish.

Online Parent Skills Program

Parents will receive a 24-week subscription to an off-the-shelf, online parent skills program called Parenting Wisely (Figure 2) shortly after randomization to Parent SMART. Parenting Wisely (Ser Padres Con Sabiduría) is a self-administered, multimedia online program that has demonstrated effectiveness in reducing youth problem behavior across multiple independent studies [24,31-33]. The program contains nine modules, each of which corresponds with a common family problem (eg, finding drugs, monitoring of friends, sibling conflict, etc). Core skills emphasized across the Parenting Wisely modules include two communication skills (I-Statements and Reflective Listening) and two monitoring skills (Contracting and Asking Key Questions). The program also comes with a workbook that outlines all the vignettes, along with a glossary of terms, sample behavior charts, and practice exercises.

Figure 2. Parenting Wisely computer program.



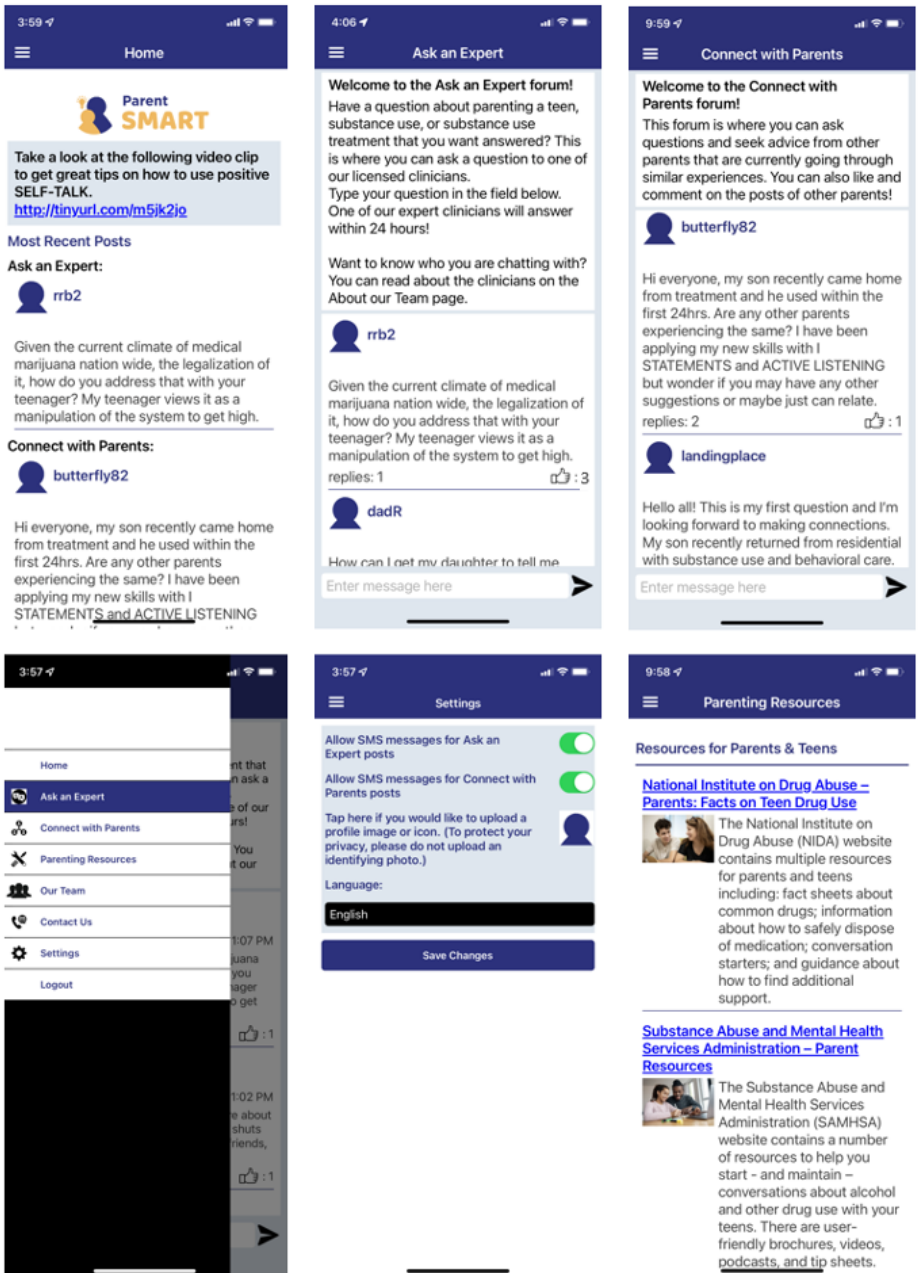
After selecting a module, parents are shown a video clip depicting a family struggling with that problem. Parents then select from three possible video vignette solutions, only one of which demonstrates an effective approach. Parents then receive feedback via video enactment of their chosen solution. The video enactment labels specific parenting skills, explains why the solution was either effective or ineffective and discusses how effective parenting skills (eg, monitoring and communication) can protect against common family problems.

The full Parenting Wisely program takes 3-5 hours to complete depending on user speed and depth of use. Parents will have a unique login, which will allow the research team to monitor their usage. In the pilot trial, 83% of the parents randomized to Parent SMART completed at least two modules, and 33% completed at least five modules. Overall, parents completed a mean of 3.8 modules (SD 2.3, range 1-9 completed modules) [28].

Networking Forum

Parents will also receive access to a networking forum containing two main channels (Ask an Expert and Connect with Parents) along with parenting resources, information about the study team, and customizable settings (Figure 3). The Ask an Expert channel allows parents to pose questions to a team of licensed clinical psychologists, whereas the Connect with Parents channel enables parents to pose questions and comments to other parents of adolescents in residential treatment. The networking forum will be accessible via smartphone app or web browser. The smartphone app will use push notifications to send a daily "Tip of the Day!" offering encouragement, reminders to use the forum, and/or links to Parenting Wisely videos; if the push notification is not opened, parents will receive the notification via SMS message two hours later. In the settings tab, parents can also subscribe to SMS notifications every time someone posts in one of the two main channels.

Figure 3. Parent SMART (Substance Misuse in Adolescents in Residential Treatment) app interface.



The networking forum has been carefully designed so that parents can view all content (including push notifications and SMS messages) in either English or Spanish, using a mix of static content that is pretranslated (eg, page headings and team bios) and user-generated content that is translated via a Google translator set-in. Parents will select their preferred language in the forum's user settings. A bilingual expert moderator will review and correct translation errors. This will allow Spanish-speaking parents to interact with posts by English-speaking parents in both forums and vice versa with minimal disruption. On an ongoing basis, the expert moderator will review all posts submitted to both channels to remove any potentially identifiable information or objectionable material.

Posts submitted to the Ask an Expert forum will be answered by a team of expert adolescent clinical psychologists to ensure continuous coverage. Responses to parent questions will follow a specific formula: validation of concern, reference to a specific Parenting Wisely core skill, and reference to a specific Parenting Wisely module(s) most relevant to the concern. By contrast, posts submitted to Connect with Parents will be viewed by other parents, who can "like" posts or provide comments.

In the pilot trial, 21 of the 30 parents (70%) randomized to Parent SMART posted a total of 16 times in Ask an Expert and 50 times in Connect with Parents. Qualitative analysis of the posts revealed five key themes: parenting skills, parent support, managing the transition home from residential care, adolescent substance use, and family functioning [34]. Parents will be told to expect replies within 24 hours; the average lag time in our pilot trial was 1 to 2 hours.

Coaching Sessions

Telehealth coaching sessions will be offered to support the customization of the content in the Parenting Wisely computer program and encourage engagement in the networking forum. Each session will consist of the rationale for a specific parenting skill, review of a Parenting Wisely module, practice applying the skill to a specific problem, and consideration of questions that the parent would like answered via the networking app. Focal parenting skills covered will align exactly with the Parenting Wisely skills to address parental monitoring (I-Statements and Reflective Listening) and communication (Contracting and Asking Key Questions). Parents will be asked to schedule sessions at times when they can access the internet to view Parenting Wisely modules. The initial 60-minute session will consist of an orientation to the Parenting Wisely program and networking app. Subsequent 45-minute sessions will follow the same basic outline without the orientation. When parents have questions or introduce problems/ concerns about their teen, the coach will first provide validation and then discuss how the parents' problems can be addressed using a specific Parenting Wisely core skill. For homework, parents will be encouraged to complete Parenting Wisely modules that map onto their unique concerns (with reference to specific pages of the parent workbook for additional practice) and to use the networking forum to solicit feedback from either an expert or another parent.

In the pilot trial, 29 of the 30 parents randomized to Parent SMART initiated coaching sessions. On average, parents attended 2.7 coaching sessions, out of a maximum of 4 (SD 1.1, range 1-4) [27].

Parent SMART Coach Training, Fidelity and Competence

Parent SMART sessions will be delivered by BA-level or MA-level coaches, consistent with the approach used in the pilot trial. At least one counselor fluent in Spanish will be available at all times. A licensed clinical psychologist (protocol Principal Investigator), with expertise in training front-line community counselors, developed the training materials and will lead an initial 2-hour training. Prior to the training, coaches will be asked to review the Parent SMART manual, complete two modules in the online Parenting Wisely program, visit the parenting networking forum, and listen to two prerecorded coaching sessions that demonstrate all session elements. During the training session, coaches will conduct multiple role plays of the sessions to gain practice delivering the intervention content.

Before being assigned Parent SMART+TAU participants, each coach must submit two audio-recorded role plays that meet adherence and competence benchmarks. Counselor adherence to each Parent SMART session will be rated via study-specific adherence checklists that range from 0 (no elements covered) to 15 (all elements covered), with the target level of adherence set at 80% coverage. Competency will be rated via the well-validated 6-item "General Therapeutic Skills" subscale of the Cognitive Therapy Rating Scale [35,36]. Items will be scored on 6-point Likert scales ranging from 1 to 6 and then averaged; a mean score ≥4 will indicate competence. All sessions will be rated for adherence and competence by research staff trained in the rating process, with at least 25% of sessions double coded. A different licensed clinical psychologist (second author) will lead weekly supervision meetings with coaches, focused on tailoring sessions to address each family's unique presenting concerns.

A total of 78 sessions occurred in the pilot trial: all were rated on the coach's adherence to protocol and competence by a single coder, and 33% were double coded. In total, 87% of sessions met the adherence, and 100% met the competence benchmark [27]. Agreement between coders was excellent: inter-rater reliability measured via the intraclass correlation coefficient was 0.92 for adherence and 0.86 for competence.

Study Assessments

Parents and adolescents will complete a baseline assessment shortly after admission to the partner facility. Follow-ups will be conducted by research staff blind to condition at 6, 12, and 24 weeks postdischarge. The baseline assessment will be approximately 90-120 minutes for adolescents and 45-60 minutes for parents; each follow-up assessment will take approximately 60 minutes for adolescents and 30 minutes for parents. If a parent loses physical custody of the adolescent postdischarge, adolescent data will still be collected, and parent data will be classified as missing; administration of the full parent battery will be resumed if the parent regains physical custody. If an adolescent turns 18 over the course of the 24-week

follow-up period, then the adolescent will be reconsented as an adult at the next relevant follow-up visit.

Primary Aim 1: Parenting

To address primary aim 1, we will conduct a multimodal assessment of parental monitoring and parental communication. Specifically, we will use parent and adolescent report measures with strong psychometric properties, as well as an in vivo family assessment task. Prior research suggests that adolescent report of parent behavior is more predictive of adolescent risk behavior than parents' self-reported behavior [14]. As such, adolescent reports will be used to capture parent behaviors, whereas parent self-report will be used to measure adolescent behaviors.

Parent Monitoring Questionnaire

The Parental Monitoring Questionnaire [37] is a 24-item youth and parent-reported measure containing three subscales. We will use the following versions of the subscales to assess dimensions of parental monitoring: child disclosure (parent report), parent solicitation (adolescent report), and parental control (adolescent report). Subscales were reliable in our pilot trial (α=.76-.87) and have been shown to correlate with adolescent mental health problems, deviant peer relationships, and family discord [37].

Parent-Adolescent Communication Scale

The Parent-Adolescent Communication Scale [38] is an adolescent and parent reported measure with two subscales. The adolescent-reported version only will be used to assess positive (general family communication) and negative (problems with family communication) aspects of parent-adolescent communication. Subscales had good reliability (α=.71-.92) in our pilot [28] and have been shown to correlate with adolescent engagement in risk behavior [38].

Family Assessment Task

The family assessment task (FAsTask) is an audio-recorded family problem-solving task that will be used to provide an in vivo assessment of parenting skills. Three tasks (5 minutes each) will assess parental monitoring and communication: (1) limit setting: parents lead a discussion about a time they had to set a limit); (2) substance use norms: parents lead a discussion on family views about substance use; and (3) monitoring and listening: adolescent leads a discussion about a time they were unsupervised with their peers and parents react. Each item will be rated on a 9-point Likert scale by trained research staff blind to condition using a structured codebook initially developed by Dishion and colleagues [39] and adapted by the research team. Ratings between 1 and 3 will indicate poor parenting skills, ratings >3 to <6 will indicate average parenting skills, and ratings of 6 and above will indicate strong parenting skills. Individual ratings will yield five distinct scale scores: limit setting (10 items), parent substance use beliefs (4 items), parent substance use communication (6 items), adolescent disclosure (7 items), and parental monitoring (9 items).

In the pilot trial, 20% of FAsTasks were double coded with an excellent mean inter-rater reliability of 94%. Moreover, the FAsTask was sensitive to change, with all five subscales demonstrating significant time by treatment condition interactions, favoring Parent SMART+TAU relative to the TAU-only condition in our pilot trial [28].

Primary Aim 2: Substance Use

Adolescent substance use will be assessed via the Global Appraisal of Individual Needs-Core (GAIN) [40], a well-validated, structured, comprehensive interview. The GAIN has intake and follow-up versions, which each contain over 100 analyzable scales across eight sections (background, substance use, mental health, physical health, risk behaviors, legal, vocational, and environmental). We do not obtain corroboration from parents or peers since parents often underestimate adolescent use [41-43] and since peer corroboration raises issues of confidentiality and unintentional harm [44]. We will assure adolescents of confidentiality, as self-reported substance use has shown reliability when confidentiality is assured [45].

Proportion of Days Substances Used Outside a Controlled Environment (Past 90 Days)

A series of GAIN items will evaluate days of substance use over the past 90 days, as well as days the adolescent was in a controlled environment (eg, residential treatment or justice facility). This will allow calculation of the proportion of days that the adolescent was outside of a controlled environment on which substances were used. The GAIN days of use items have shown excellent comparability [46] to the well-validated Timeline Follow-Back Interview [47,48]. Like the Timeline Follow-back, the GAIN will assess days of alcohol and drug use using a calendar with temporal cues (eg, holidays and special events) to facilitate recall. The proportion of days all substances are used and separate days of binge drinking, marijuana, all other drugs, stimulant, and opioid use will be examined.

Substance-Related Problems Scale

The GAIN substance-related problem scale will be used to obtain a count of substance use symptoms experienced over the past 90 days in line with the latest diagnostic criteria for a substance use disorder [49]. Diagnoses made from this scale have demonstrated good test-retest reliability (κ=.55) [50] and accurately predict independent, blind staff ratings of the presence of substance use disorder (κ=.91) [51]. Reliability in our pilot trial (α=.78) [27] was consistent with prior studies using the same items (α=.76) [51].

Urine Drug Screens

Urine drug screens will be used to corroborate self-reported abstinence and gauge under-reporting of substance use in adolescents. Urine screens will be collected via 8-panel dip urine screens at the 12-month and 24-month follow assessments (75% testing rate in our pilot trial). Samples will be tested for metabolites of marijuana, cocaine, amphetamines, methamphetamines, barbiturates, phencyclidine, opiates, and benzodiazepines.

Secondary Aim: Adolescent Problem Behavior

GAIN scales will be used to assess common behaviors often linked to adolescent substance use [52-55]; higher scores indicate more problems. Consistent with the substance use scales, these scales will use a 90-day recall. Of note, in the pilot trial, we used an abbreviated version of the GAIN that contained

briefer versions of some of these scales; thus, we report psychometric data from the measure validation data trial.

Behavioral Complexity Scale

This scale counts 33 externalizing behaviors, including symptoms of conduct, inattention, and hyperactivity. The full scale has good test reliability for total symptoms (*r*s=.7-.8) and strong internal consistency (α=.94) [40].

School-Related Problems

This four-item scale counts school-related problems, including truancy, chronic tardiness, poor grades, and cutting class. The full scale has demonstrated significant associations with adolescent employment problems, substance use, and cumulative stress in prior studies [56].

Risky Sexual Behavior

This three-item scale evaluates the number of risky sex-related behaviors, including sexual activity with multiple partners, unprotected sex, and sex while under the influence of alcohol or drugs. The full scale has demonstrated concordance with adolescent substance use and mental health problems in prior studies [40].

General Crime Scale

This 31-item scale assesses the number of behaviors the adolescent engaged in indicative of general conflict, as well as property, interpersonal, and drug crime. Test-retest reliability of the full scale has been shown to be excellent with strong internal consistency (α=.90) [40].

Covariates: Demographics

Parent and adolescent sociodemographics will be assessed and controlled for as covariates. Parents will complete a routine sociodemographic form. Adolescents will complete the GAIN Background section, which collects routine sociodemographic variables including age, sex, gender identity, ethnicity, race, and grade in school. Items in other GAIN sections indicate the adolescent's history of substance use or mental health treatment utilization, data that will be used to control for treatment received.

Data Analysis Plan

Overview

The data analysis plan contains periodic data quality checks, early generation of analysis variables, and mock study table generation to provide a check on completeness of study data. The study statistician will be blind to treatment conditions and follow a protocol established a priori.

Hypotheses will be tested with a latent change score modeling [57] approach estimated within a structural equation modeling framework [58]. The structural equation modeling framework allows direct estimating and testing hypotheses of interest, including treatment effects and mechanisms of action across multiple outcome variables. Compared to latent growth modeling, latent change score modeling is flexible (ie, not structured) with respect to the shape of the trajectory of change. This approach avoids misspecification of the change trajectory and allows for the testing of mediation hypotheses (exploratory aim). As a mixed repeated measures approach based on maximum likelihood estimation, the model produces unbiased effect estimates and standard errors under the missing at random assumption. The missing at random assumption is less restrictive than the missing completely at random assumption that is implicit in complete case or carry-forward methods for missing data and consistent with the intent-to-treat principle [59]. We will focus on intent-to-treat analyses to optimize rigor and account for the fact that families randomized to Parent SMART may engage in passive activities, such as lurking in the app or reading push notifications. Supplementary completer analyses will assess effects among those who complete at least two telehealth coaching sessions and two Parenting Wisely modules. Analyses will also control for contact time (eg, number of modules completed, number of posts in the app, and number of sessions attended) as a covariate in analyses of primary and secondary outcomes. The full analysis plan will be coded and executed on collected data at the end of Year 1 to identify errors so final analyses can be completed quickly.

Primary aims 1 and 2 and the secondary aim compare trajectories of change using data from baseline, 6, 12, and 24 weeks follow-up on parenting processes, adolescent substance use, and adolescent problems, respectively. These aims will be evaluated in latent change score models with separate change effects for each of the adjacent time points [57]. For each aim (primary aims 1-2 and secondary aim), multiple outcomes are specified. For example, primary aim 1 specifies parental communication (two subscales) and parental monitoring (three subscales). Primary aim 2 includes days of substance use as well as problems related to substance use. A single latent variable at each time point will be used to define a composite outcome reflecting shared covariance among the multiple outcome indicators. Measurement invariance will be tested over time, and noninvariance will be assumed if necessary. "Point-in-time analyses" will be conducted to assess preliminary effects at 6 weeks and then at 12 weeks.

The exploratory aim examining potential mediators will be evaluated by bringing outcome models together in a single multivariate model. The exploratory hypothesis posits that positive changes in parenting processes at 6 weeks will be related to reductions in adolescent substance use and adolescent problems at 12 and 24 weeks. A bivariate change score model will evaluate change in parenting processes and change in adolescent substance use and related problems simultaneously and introduce a residual covariance term describing the association of change in parenting and change in adolescent outcomes. Time lagged regression coefficients will then be applied to test whether a change in parenting processes at 6 weeks leads to lower adolescent substance use and adolescent problems at 12 and 24 weeks. Examples of such an approach to evaluating mediation and moderation effects in the context of randomized trials can be found in McArdle and Prindle [60].

Power

The study's primary and secondary aims were specifically powered to detect small to medium effect sizes on the Time*Condition interactions, based on: (1) the effect sizes detected in our pilot trial, which were small to medium in size,

and which matched the proposed population in terms of severity; and (2) the effect sizes of the online parenting program on parenting processes detected in prior clinical trials, which were medium to large [24,32,33]. With a sample size of 220 dyads, we will have 80% power to detect a 0.38 standard deviation effect size or larger with a type I error risk of .05.

Results

This pragmatic effectiveness trial received notice of grant award on August 1, 2021. Ethics approval was obtained a full year prior to funding, in August 2020. Due to concerns with the administrative interface in the pilot trial surfaced by the study investigators, the Parent SMART networking app is currently being rebuilt by a new vendor, Mooseworks Software LLC. The programming has been fully completed as of December 22, 2021, and demonstrations are scheduled with the recruitment partner in January 2022. Recruitment is scheduled to commence in February 2022.

Discussion

Summary

Given the poor long-term outcomes of adolescents in residential care [1,2,51], strategies to improve adolescent substance use treatment outcomes following discharge are sorely needed. This pragmatic effectiveness trial will compare residential TAU to a multicomponent technology-assisted parenting intervention that has shown strong evidence of feasibility and acceptability [27] as well as preliminary effectiveness in improving parent-adolescent communication and parental monitoring. This trial will specifically address calls for improvements to residential care for adolescents put forth by the Residential Care Consortium [13] by promoting the engagement of parents during the transition from residential treatment to continuing care.

Potential Strengths and Limitations

This pragmatic effectiveness trial is characterized by a number of strengths. Most notably, Parent SMART is a novel technology-assisted intervention that was developed based on extensive formative research with parents, adolescents, and residential treatment staff and is supported by encouraging data from a rigorous pilot randomized controlled trial. This study will build upon the successful pilot trial by conducting a fully-powered evaluation of the intervention's effects on parental monitoring, parent-adolescent communication, adolescent substance use, and adolescent behavioral outcomes. Moreover, this study will move beyond simply testing the effectiveness of the intervention by specifying and examining putative mediators of change. Finally, the Parent SMART intervention is highly scalable: it augments an off-the-shelf intervention with a parent networking app and telehealth sessions that require limited training to deliver. Future work will seek to test different delivery models of Parent SMART to support long-term sustainability: (1) delivery by trained residential staff who bill for services, and (2) delivery by outside vendors, purchased as part of a technology package paid for by the residential center as part of the bundled rate.

In addition to these strengths, several limitations should be considered. A key limitation is that the Parent SMART+TAU and TAU conditions do not offer an equivalent dose of contact time. As a result, favorable results associated with Parent SMART may be attributable to a higher overall dose of treatment. This decision was made because our goal was to assess whether the package intervention was a feasible, acceptable, and effective adjunct to residential services delivered under real-world conditions. A related limitation is that Parent SMART is a bundled, multicomponent intervention, which will limit the ability to determine which aspects of the intervention (ie, the computer program, parent networking app, telehealth sessions) are driving observed effects. To mitigate these limitations, we will carefully control for each type of contact time (eg, number of telehealth sessions completed, time spent in the app, number of parenting skills modules completed) in analyses of primary and secondary outcomes.

Conclusions

If found to be effective, Parent SMART could offer a relatively low-cost, highly scalable adjunctive strategy to engage parents of adolescents receiving residential treatment. Layering in an adjunctive technology-assisted intervention could potentially extend the reach of residential TAU and promote engagement in continuing care during a time when adolescents are at especially high risk of relapse. Parent SMART could offer highly significant public health benefits by improving vital parenting processes shown to protect against substance use and substance-related problems during the vulnerable transition from residential care to the community. Future investigations should seek to evaluate the feasibility, acceptability, and preliminary effectiveness of Parent SMART intervention in settings where adolescents receive comparable stabilization and support, such as partial hospital and intensive outpatient programs.

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Authors' Contributions

SJB led the writing of the grant proposal and the preparation of this manuscript. LMK contributed to converting the protocol to manuscript form. All co-investigators (SAH, TJ, AS, JCW, and TW) contributed to the grant proposal. All authors reviewed multiple drafts of the protocol in manuscript form and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 147 KB - resprot_v11i2e35934_app1.pdf]

References

1. Reif S, George P, Braude L, Dougherty RH, Daniels AS, Ghose SS, et al. Residential Treatment for Individuals With Substance Use Disorders: Assessing the Evidence. Psychiatric Services 2014 Mar;65(3):301-312. [doi: 10.1176/appi.ps.201300242]
2. Uliaszek AA, Hamdullahpur K, Mills L. Examining the Effectiveness of Residential Treatment Among Adolescents With Problem Substance Use. Journal of Child & Adolescent Substance Abuse 2019 Nov 01;28(4):221-228. [doi: 10.1080/1067828x.2019.1682736]
3. Ringle JL, Huefner JC, James S, Pick R, Thompson RW. 12-month follow-up outcomes for youth departing an integrated residential continuum of care. Children and Youth Services Review 2012 Apr;34(4):675-679. [doi: 10.1016/j.childyouth.2011.12.013]
4. Harder AT. Residential Care and Cure: Achieving Enduring Behavior Change with Youth by Using a Self-determination, Common Factors and Motivational Interviewing Approach. Residential Treatment for Children & Youth 2018 Nov;35(4):317-335. [doi: 10.1080/0886571x.2018.1460006]
5. Kapp S, Rand A, Damman J. Clinical Gains for Youth in Psychiatric Residential Treatment Facilities: Results from a State-Wide Performance Information System. Residential Treatment for Children and Youth 2015 Jan 12;32(1):37-57. [doi: 10.1080/0886571X.2015.1004287]
6. Passetti LL, Godley MD, Kaminer Y. Continuing Care for Adolescents in Treatment for Substance Use Disorders. Child and Adolescent Psychiatric Clinics of North America 2016 Oct;25(4):669-684. [doi: 10.1016/j.chc.2016.06.003]
7. Godley S, Godley M, Dennis M. The Assertive Aftercare Protocol for adolescent substance abusers. In: Innovations in Adolescent Substance Abuse Interventions. Elsevier; 2001:311-329.
8. Godley M, Godley S. Assertive continuing care for adolescents. In: Addiction recovery management: Theory, research and practice. In: Humana Press; 2011:103-126.
9. Becker SJ, Curry JF. Outpatient interventions for adolescent substance abuse: A quality of evidence review. Journal of Consulting and Clinical Psychology 2008 Aug;76(4):531-543. [doi: 10.1037/0022-006x.76.4.531]
10. Hogue A, Henderson CE, Becker SJ, Knight DK. Evidence Base on Outpatient Behavioral Treatments for Adolescent Substance Use, 2014–2017: Outcomes, Treatment Delivery, and Promising Horizons. Journal of Clinical Child & Adolescent Psychology 2018 Jun 12;47(4):499-526. [doi: 10.1080/15374416.2018.1466307]
11. Tanner-Smith EE, Wilson SJ, Lipsey MW. The comparative effectiveness of outpatient treatment for adolescent substance abuse: A meta-analysis. Journal of Substance Abuse Treatment 2013 Feb;44(2):145-158. [doi: 10.1016/j.jsat.2012.05.006]
12. Steele D, Becker S, Danko K. Interventions for Substance Use Disorders in Adolescents: A Systematic Review. In: A Systematic Review. (Comparative Effectiveness Review, No. 225.). Rockville, MD: Agency for Healthcare Research and Quality (US); 2020:A.
13. Affronti ML, Levison-Johnson J. The Future of Family Engagement in Residential Care Settings. Residential Treatment For Children and Youth 2009 Nov 12;26(4):257-304. [doi: 10.1080/08865710903382571]
14. Rusby JC, Light JM, Crowley R, Westling E. Influence of parent–youth relationship, parental monitoring, and parent substance use on adolescent substance use onset. Journal of Family Psychology 2018 Apr;32(3):310-320. [doi: 10.1037/fam0000350]
15. Carver H, Elliott L, Kennedy C, Hanley J. Parent–child connectedness and communication in relation to alcohol, tobacco and drug use in adolescence: An integrative review of the literature. Drugs: Education, Prevention and Policy 2016 Sep 26;24(2):119-133. [doi: 10.1080/09687637.2016.1221060]
16. Benchaya MC, Moreira TDC, Constant HMRM, Pereira NM, Freese L, Ferigolo M, et al. Role of Parenting Styles in Adolescent Substance Use Cessation: Results from a Brazilian Prospective Study. IJERPH 2019 Sep 16;16(18):3432. [doi: 10.3390/ijerph16183432]
17. Vakalahi HF. Adolescent Substance Use and Family-Based Risk and Protective Factors: A Literature Review. J Drug Educ 2016 Jul 21;31(1):29-46. [doi: 10.2190/qp75-p9ar-nuvj-fjcb]

18. Tobler AL, Komro KA. Trajectories or Parental Monitoring and Communication and Effects on Drug Use Among Urban Young Adolescents. Journal of Adolescent Health 2010 Jun;46(6):560-568. [doi: 10.1016/j.jadohealth.2009.12.008]
19. Ryan J, Roman NV, Okwany A. The Effects of Parental Monitoring and Communication on Adolescent Substance Use and Risky Sexual Activity: A Systematic Review. TOFAMSJ 2015 Mar 31;7(1):12-27. [doi: 10.2174/1874922401507010012]
20. Lac A, Crano WD. Monitoring Matters. Perspect Psychol Sci 2009 Nov 01;4(6):578-586. [doi: 10.1111/j.1745-6924.2009.01166.x]
21. Goliath V, Pretorius B. PEER RISK AND PROTECTIVE FACTORS IN ADOLESCENCE: IMPLICATIONS FOR DRUG USE PREVENTION. SWORK 2016 Mar;52(1):113-129. [doi: 10.15270/52-1-482]
22. Ventura AS, Bagley SM. To Improve Substance Use Disorder Prevention, Treatment and Recovery: Engage the Family. J Addict Med 2017;11(5):339-341. [doi: 10.1097/ADM.0000000000000331] [Medline: 28787300]
23. Ryan-Pettes SR, Lange LL, Magnuson KI. Mobile Phone Access and Preference for Technology-Assisted Aftercare Among Low-Income Caregivers of Teens Enrolled in Outpatient Substance Use Treatment: Questionnaire Study. JMIR Mhealth Uhealth 2019 Sep 26;7(9):e12407. [doi: 10.2196/12407]
24. Kacir CD, Gordon DA. Parenting Adolescents Wisely: The Effectiveness of an Interactive Videodisk Parent Training Program in Appalachia. Child & Family Behavior Therapy 2008 Oct 21;21(4):1-22. [doi: 10.1300/j019v21n04_01]
25. Feil EG, Gordon D, Waldron H, Jones LB, Widdop C. Development and Pilot Testing of an Internet-based Version of Parenting Wisely. Fam Psychol 2011 Apr;27(2):22-26 [FREE Full text] [Medline: 30246175]
26. Becker SJ, Hernandez L, Spirito A, Conrad S. Technology-assisted intervention for parents of adolescents in residential substance use treatment: protocol of an open trial and pilot randomized trial. Addict Sci Clin Pract 2017 Jan 3;12(1):1-13. [doi: 10.1186/s13722-016-0067-4]
27. Becker SJ, Helseth SA, Janssen T, Kelly LM, Escobar KI, Souza T, et al. Parent SMART (Substance Misuse in Adolescents in Residential Treatment): Pilot randomized trial of a technology-assisted parenting intervention. Journal of Substance Abuse Treatment 2021 Aug;127:108457. [doi: 10.1016/j.jsat.2021.108457]
28. Becker SJ, Helseth SA, Janssen T, Kelly LM, Escobar K, Spirito A. Parent Smart: Effects of a Technology-Assisted Intervention for Parents of Adolescents in Residential Substance Use Treatment on Parental Monitoring and Communication. Evidence-Based Practice in Child and Adolescent Mental Health 2021 Oct 13;6(4):459-472. [doi: 10.1080/23794925.2021.1961644]
29. Stout RL, Wirtz PW, Carbonari JP, Del Boca FK. Ensuring balanced distribution of prognostic factors in treatment outcome research. J. Stud. Alcohol Suppl 1994 Dec(s12):70-75. [doi: 10.15288/jsas.1994.s12.70]
30. McCredie MN, Quinn CA, Covington M. Dialectical Behavior Therapy in Adolescent Residential Treatment: Outcomes and Effectiveness. Residential Treatment for Children & Youth 2017 May 19;34(2):84-106. [doi: 10.1080/0886571x.2016.1271291]
31. Cotter KL, Bacallao M, Smokowski PR, Robertson CIB. Parenting Interventions Implementation Science. Research on Social Work Practice 2013 May 31;23(6):639-650. [doi: 10.1177/1049731513490811]
32. Stalker KC, Rose RA, Bacallao M, Smokowski PR. Parenting Wisely Six Months Later: How Implementation Delivery Impacts Program Effects at Follow-Up. J Primary Prevent 2018 Feb 16;39(2):129-153. [doi: 10.1007/s10935-017-0495-2]
33. Cefai J, Smith D, Pushak RE. Parenting Wisely: Parent Training via CD-ROM with an Australian Sample. Child and Family Behavior Therapy 2010 Mar 03;32(1):17-33. [doi: 10.1080/07317100903539709]
34. Helseth SA, Scott K, Escobar KI, Jimenez F, Becker SJ. What parents of adolescents in residential substance use treatment want from continuing care: A content analysis of online forum posts. Substance Abuse 2021 May 04;42(4):1049-1058. [doi: 10.1080/08897077.2021.1915916]
35. Dobson K, Shaw B, Vallis T. Reliability of a measure of the quality of cognitive therapy. Br J Clin Psychol 1985;24(4):295-300. [doi: 10.1111/j.2044-8260.1985.tb00662.x]
36. Young J, Beck A. Cognitive Therapy Scale Rating Manual. University of Pennsylvania 1980:1-24. [doi: 10.1037/t00834-000]
37. Stattin H, Kerr M. Parental Monitoring: A Reinterpretation. Child Development 2000 Jul;71(4):1072-1085. [doi: 10.1111/1467-8624.00210]
38. Barnes HL, Olson DH. Parent-Adolescent Communication and the Circumplex Model. Child Development 1985 Apr;56(2):438. [doi: 10.2307/1129732]
39. Dishion T, Kavanagh K. Intervening in Adolescent Problem Behavior: A Family-Centered Approach. New York: Guilford Press; 2003:A.
40. Dennis M, White M, Titus J, Unsicker M. Administration Guide for the Gain and Related Measures (Version 5). Normal, Illinois: Chestnut Health Systems; 2008:A.
41. Cantwell DP, Lewinsohn PM, Rohde P, Seeley JR. Correspondence between adolescent report and parent report of psychiatric diagnostic data. J Am Acad Child Adolesc Psychiatry 1997 May;36(5):610-619. [doi: 10.1097/00004583-199705000-00011] [Medline: 9136495]
42. Velting DM, Shaffer D, Gould MS, Garfinkel R, Fisher P, Davies M. Parent-victim agreement in adolescent suicide research. J Am Acad Child Adolesc Psychiatry 1998 Nov;37(11):1161-1166. [doi: 10.1097/00004583-199811000-00015] [Medline: 9808927]

43. Fisher SL, Bucholz KK, Reich W, Fox L, Kuperman S, Kramer J, et al. Teenagers Are Right–Parents Do Not Know Much: An Analysis of Adolescent–Parent Agreement on Reports of Adolescent Substance Use, Abuse, and Dependence. Alcoholism Clin Exp Res 2006 Oct;30(10):1699-1710. [doi: 10.1111/j.1530-0277.2006.00205.x]
44. Dishion TJ, McCord J, Poulin F. When interventions harm: Peer groups and problem behavior. American Psychologist 1999;54(9):755-764. [doi: 10.1037/0003-066x.54.9.755]
45. Needle R, McCubbin H, Lorence J, Hochhauser M. Reliability and Validity of Adolescent Self-Reported Drug Use in a Family-Based Study: A Methodological Report. International Journal of the Addictions 2009 Jul 03;18(7):901-912. [doi: 10.3109/10826088309033058]
46. Dennis M, Funk R, Godley S, Godley M, Waldron H. Cross-validation of the alcohol and cannabis use measures in the Global Appraisal of Individual Needs (GAIN) and Timeline Followback (TLFB; Form 90) among adolescents in substance abuse treatment. Addiction. Suppl 2004;99:2-128. [doi: 10.1111/j.1360-0443.2004.00859.x]
47. Sobell L, Sobell M. Timeline follow-back: A technique for assessing self-reported alcohol consumption. In: Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Humana Press; 1992:41-72.
48. Sobell L, Sobell M. Timeline Followback User's Guide: A Calendar Method for Assessing Alcohol and Drug Use. Toronto: Addiction Research Foundation; 1996:A.
49. American PA. Diagnostic and Statistical Manual of Mental Disorders. 5th ed 2013:A. [doi: 10.1176/appi.books.9780890425596]
50. Dennis M, Dawud-Noursi S, Muck R, McDermeit M. The need for developing and evaluating adolescent treatment models. In: Adolescent Substance Abuse Treatment in the United States: Exemplary Models from a National Evaluation Study. In: Haworth Press; 2003:3-34.
51. Shane PA, Jasiukaitis P, Green RS. Treatment outcomes among adolescents with substance abuse problems: the relationship between comorbidities and post-treatment substance involvement. Evaluation and Program Planning 2003 Nov;26(4):393-402. [doi: 10.1016/s0149-7189(03)00055-7]
52. Henggeler SW, Clingempeel WG, Brondino MJ, Pickrel SG. Four-year follow-up of multisystemic therapy with substance-abusing and substance-dependent juvenile offenders. J Am Acad Child Adolesc Psychiatry 2002 Jul;41(7):868-874. [doi: 10.1097/00004583-200207000-00021] [Medline: 12108813]
53. Henry KL, Huizinga DH. Truancy's Effect on the Onset of Drug Use among Urban Adolescents Placed at Risk. Journal of Adolescent Health 2007 Apr;40(4):358.e9-358.e17. [doi: 10.1016/j.jadohealth.2006.11.138]
54. Pedersen MU, Thomsen KR, Heradstveit O, Skogen JC, Hesse M, Jones S. Externalizing behavior problems are related to substance use in adolescents across six samples from Nordic countries. Eur Child Adolesc Psychiatry 2018 Apr 4;27(12):1551-1561. [doi: 10.1007/s00787-018-1148-6]
55. Oshri A, Tubman JG, Burnette ML. Childhood Maltreatment Histories, Alcohol and Other Drug Use Symptoms, and Sexual Risk Behavior in a Treatment Sample of Adolescents. Am J Public Health 2012 May;102(S2):S250-S257. [doi: 10.2105/ajph.2011.300628]
56. Titus J, Feeney T, Smith D, Rivers T, Kelly L, Dennis M. GAIN Q3 3.2. In: Administration, Clinical Interpretation, and Brief Intervention. Normal, Illinois: Chestnut Health Systems; 2013.
57. McArdle JJ. Latent Variable Modeling of Differences and Changes with Longitudinal Data. Annu. Rev. Psychol 2009 Jan 01;60(1):577-605. [doi: 10.1146/annurev.psych.60.110707.163612]
58. Muthén BO. Beyond SEM: General Latent Variable Modeling. Behaviormetrika 2002 Jan 15;29(1):81-117. [doi: 10.2333/bhmk.29.81]
59. Ware JH, Harrington D, Hunter DJ, D'Agostino RB. Missing Data. N Engl J Med 2012 Oct 04;367(14):1353-1354. [doi: 10.1056/nejmsm1210043]
60. McArdle JJ, Prindle JJ. A latent change score analysis of a randomized clinical trial in reasoning training. Psychology and Aging 2008;23(4):702-719. [doi: 10.1037/a0014349]

Abbreviations

FAsTask: Family Assessment Task
GAIN: Global Appraisal of Individual Needs
Parent SMART: Substance Misuse among Adolescents in Residential Treatment
TAU: treatment as usual

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Protocol

The Effects of Modified Intermittent Fasting in Psoriasis (MANGO): Protocol for a Two-Arm Pilot Randomized Controlled Open Cross-over Study

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Abstract

Background: Psoriasis is a complex disease associated with multiple comorbidities, including metabolic syndrome and leaky gut syndrome. Dietary lifestyle interventions have been reported to affect the disease in terms of lesional severity. It remains unclear how diets affect these comorbidities and the general health in psoriasis patients. Modified intermittent fasting (MIF) on 2 nonconsecutive days has shown beneficial effects on metabolic parameters. A significant advantage of MIF over the currently investigated dietary changes is its feasibility.

Objective: Here, we aim to study the effects of MIF on skin, gut, and metabolic health in psoriasis patients.

Methods: A 2-arm pilot randomized controlled open cross-over study will be performed in 24 patients with psoriasis. Patients will be randomized 1:1 to either start with 12 weeks of MIF and go on a subsequent regular diet for another 12 weeks or start with 12 weeks of regular diet and do subsequent MIF for 12 weeks. The following parameters will be assessed: demographics, disease phenotype, medical and familial history, psoriasis severity, dermatology-specific and general quality of life, nutritional and physical habits, mental and intestinal health, intestinal and cutaneous integrity, inflammatory and metabolic markers, and satisfaction.

Results: A total of 24 participants have been enrolled in the study. The final visit is foreseen for June 2021.

Conclusions: The aim is to uncover the effects of MIF on psoriasis severity and gut health integrity through clinical and molecular investigation. More precisely, we want to map the evolution of the different markers, such as psoriasis severity, permeability, and inflammation, in response to MIF as compared to a regular diet,. Understanding how dietary lifestyles can affect epithelial lineages, such as the skin and gut, will greatly improve our understanding of the development of psoriasis and may offer a nonpharmacological venue for treatments.

Trial Registration: ClinicalTrials.gov NCT04418791; https://clinicaltrials.gov/ct2/show/NCT04418791

International Registered Report Identifier (IRRID): DERR1-10.2196/26405

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KEYWORDS

psoriasis; leaky gut; gut-skin axis; dietary intervention; intermittent fasting

Introduction

Psoriasis is a prevalent and chronic skin disease characterized by red, scaly, and thickened skin lesions. The extent of the lesions determines the severity of the disease and is commonly defined by the Psoriasis Area and Severity Index (PASI). The disease has a significant impact on quality of life (QoL) [1]. Currently, no cure is available, and the disease is mainly treated symptomatically.

Psoriasis is a complex and multifactorial disease that remains to be understood more thoroughly. Although genetic factors such as polymorphisms in *PSORS1-9*, *IL12B*, *IL23R*, and *IL28RA* play a role [2], disease development and severity is also heavily affected by factors such as obesity, stress, and smoking [3-11]. Our current understanding of its pathophysiology has led to the development of drugs targeting disease-mediating cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-17, and the subunits of IL-23 p40 and p19. Interestingly, the same cytokines also play important roles in comorbidities associated with psoriasis [12,13]. Indeed, the disease complexity is evident from the associated physical and mental comorbidities, including cardiovascular diseases, metabolic syndrome, depression, and leaky gut syndrome [14-25]. The latter is especially interesting since it is characterized by an impaired intestinal barrier and hence shows parallels with psoriatic skin, which is also characterized by an impaired cutaneous barrier. The link between the gut and skin has been postulated several times and has been termed the gut-skin axis [26,27]. In the psoriasiform "imiquimod" murine model, we have shown that gut-mediated inflammation drove the extent of the cutaneous lesions and was mediated by the production of type I interferon beta (IFN-β) [28], underscoring that gut health can affect skin health. In humans, intestinal permeability in psoriasis has been reported previously [24,29,30], highlighting the existence of an aberrant gut-skin axis in the disease as well.

The effect of dietary interventions has not been investigated in psoriasis related to this gut-skin axis, as the focus has mainly been on the skin only. Indeed, different studies have been conducted to investigate the effects of diets in psoriasis. For instance, a gluten-free diet was associated with a positive effect on psoriasis severity in patients who tested positive for gluten sensitivity [31,32]. Another study investigating a diet aimed at weight loss showed a favorable outcome on psoriasis and QoL, especially in patients with obesity [33]. This confirmed the findings of an earlier study that combined diet with physical exercise for weight loss [34]. Interestingly, treatment response can be improved by a very low-calorie ketogenic diet [35]. We also reported that treatment response to secukinumab, an IL-17 blocker for psoriasis treatment, may be negatively impacted by weight [36]. Recently, long-term weight loss was found favorable for psoriasis [37]. In 2019, a fasting diet related to Ramadan was conducted in which participants had their meals and drinks, including water, only during evening hours [38]. This diet was found to be favorable for psoriasis, especially in patients treated with apremilast or mTOR inhibitors. More recently, an aggressive ketogenic weight-loss program led to a significant reduction in disease severity in drug-naive psoriasis patients who were overweight or obese [39]. Despite the positive effects of dietary changes on psoriasis outcomes, feasibility for daily implementation and effectiveness heavily depend on adherence. Gibson and Sainsbury propose strategies to increase adherence, including avoiding overcompensation of caloric restrictions and tailoring to the individual's needs [40]. Here, we aim to investigate the effects of modified intermittent fasting (MIF), more specifically the 5:2 diet. In this diet, participants restrict their caloric uptake to 500 kilocalories (kcal) on 2 nonconsecutive days per week. MIF has been associated with positive outcomes on plasma insulin levels, fat-to-lean ratio, and other cardiovascular disease risk factors [41-44], yet its effects on psoriasis and gut health remains to be investigated. It has a successful adherence rate, as it reduces the drive to overcompensate the calorie restriction and allows the individual to incorporate the calorie-restricting days to their own scheme (tailored), reflecting the conditions postulated by Gibson and Sainsbury for optimal adherence [40].

Here, we present the protocol of the study titled "The Effects of Modified Intermittent Fasting in Psoriasis (MANGO): Protocol for a Two-Arm Pilot Randomized Controlled Open Cross-Over Study" to investigate the effects of a dietary intervention on the gut-skin axis in patients with psoriasis. The MANGO study will provide mechanistic evidence to help determine whether there is a link between gut health and psoriatic lesions, offer insight into the benefit of MIF in psoriasis management, and potentially begin a landmark shift in the holistic view of chronic skin disease.

Methods

Research Hypothesis

We aim to investigate the impact of a MIF diet in patients affected by mild psoriasis on skin and gut health based on various markers. The main hypothesis is that a 5:2 diet over the course of 12 weeks will improve skin lesions and gut health biomarkers in comparison to a standard diet.

Primary Objective

The primary objective of this study is to compare MIF with a standard diet in terms of the proportion of patients obtaining an improvement in absolute PASI score from baseline during or at the end of the 12-week postintervention period to prove the superiority of MIF.

Secondary Objectives

The secondary objective of this study is to compare MIF with a standard diet during or at the end of the 12-week postintervention period in the following aspects: differences in total body fat, weight, BMI, and waist circumference during and after intervention to baseline; differences in inflammation markers in serum and skin during and after intervention to baseline; differences in metabolic markers in serum and skin during and after intervention to baseline; differences in permeability markers in serum, skin, gut, and feces during and after intervention to baseline; correlation to dietary intake and disease severity; and score of participants' rating of satisfaction with the intervention.

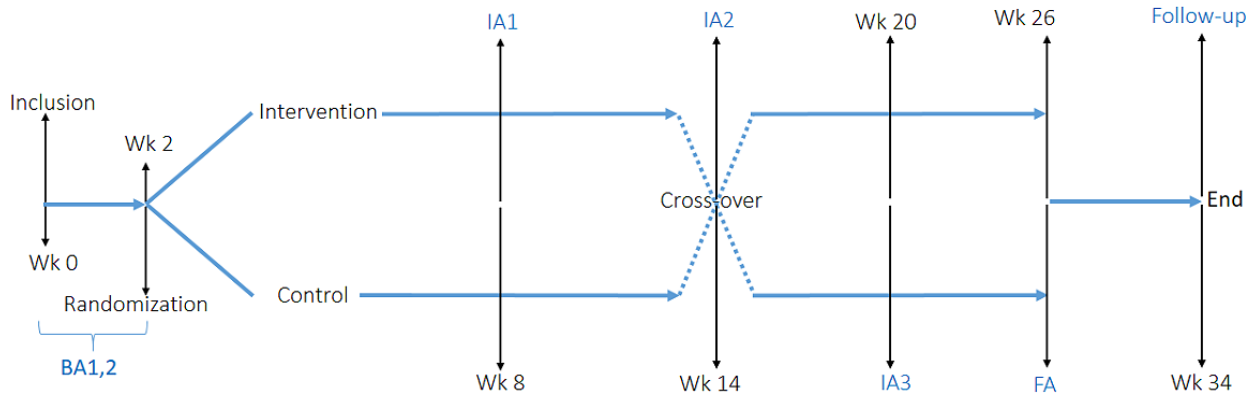
Finally, the number of participants who complete the study or single intervention window successfully will also be assessed to give us insights into the feasibility of the diet.

Study Design

We will use an open randomized controlled cross-over clinical trial to test the effects of MIF on the gut-skin axis in 24 adults with psoriasis. The total study duration will be 34 weeks: 2 moments will be included as baseline prior to randomization (week 0 and 2). Randomization will be performed with the REDCap (Vanderbilt University) randomization module upon inclusion. Postrandomization, patients will be assigned to either the intervention or control arm. This study will use a cross-over design, and patients will switch arms at week 14 (Figure 1). Evaluations will include clinical, biochemical, and patient-reported outcomes. Intermediate time points will be included at weeks 8 and 20. Each participant will be in the study for a total of 26 weeks, with a single follow-up at week 34 after completion of the second arm. The entire trial will run for 12 months with a recruitment period of 3 months.

This study has been registered on clinicaltrials.gov (NCT04418791) and has been approved by the ethics committee of the Ghent University Hospital (B6702020000141). The trial will be conducted according to the Declaration of Helsinki. Informed consent will be obtained verbally as well as in writing.

Figure 1. Open randomized controlled cross-over clinical trial to test the effects of modified intermittent fasting on the gut-skin axis in adults with psoriasis. Cross-over includes a 12-week intervention period and a 12-week control period. Evaluations include clinical and biochemical parameters. Intermediate time points are included. BA: baseline analysis; FA: final analysis; IA: intermediate analysis; Wk: week.



Recruitment, Eligibility, and Randomization

Study participants are patients who attend the PsoPlus clinic at the Department of Dermatology at the Ghent University Hospital or who are willing to attend the PsoPlus clinic for the study visits. An additional call will be launched through the Flemish Psoriasis League for people with psoriasis to be screened and enrolled. A recruitment target of a maximum of 24 adults will be recruited through consecutive sampling. Participants should have a clinical diagnosis of mild psoriasis vulgaris. Mild psoriasis is defined as a score of 10 or less based on the PASI. The eligibility criteria are further detailed in Textbox 1. Participants who meet any of the exclusion criteria at the time of enrollment or during the study period will be excluded from study participation. Participants will be allocated in a 1:1 manner to the control or intervention arm under stratified randomization with variable permuted blocks, and the concealment of allocation will be based on age, gender, and BMI, with a maximum of 15 participants per arm.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Between 18 and 70 years old
- Clinically diagnosed psoriasis by a dermatologist
- Predominantly present with psoriasis vulgaris
- Present with Psoriasis Area and Severity Index (PASI) ≤ 10 at time of enrollment
- Reported stable weight (< 5% weight loss/gain) for the past 3 months
- Treated exclusively with topical treatment for psoriasis at the time of enrollment and throughout study
- Able to give informed consent
- Willing and able to comply with study procedure
- Willing and able to use MyFitnessPal app to record diet during intervention period
- Willing and able to attend all scheduled visits through the study period
- Willing and able to provide blood, cutaneous, and fecal samples as stated in the procedure
- Willing to apply measures to prevent pregnancy throughout study period

Exclusion criteria

- Present with type 1 or 2 diabetes mellitus
- Present with a history of cardiac condition(s)
- Present with comorbidities that cannot be combined with the intervention (eg, cancer)
- History of or current eating disorder (anorexia, bulimia, etc; screening via the *Diagnostic and Statistical Manual Method for Mental Disorders, Fifth Edition* if indicated)
- Malnourished patients (screening via the *Malnutrition Universal Screening Tool* if indicated)
- Present with gout
- Pregnant, having pregnancy plans, or breastfeeding
- Use of diuretics at time of sampling
- Use of anti-, pre-, and/or probiotics in the 3 months prior to enrollment or during the study period

Study Interventions

Upon inclusion, participants are expected to record their dietary and exercise habits for 2 full weeks using the MyFitnessPal app. Baseline measurements will consist of 2 different time points: inclusion (week 0) and randomization (week 2), which will be averaged for analysis. Upon randomization, participants will be assigned to either the control or intervention arm in a 1:1 ratio. The intervention consists of a dietary intervention based on the 5:2 fasting diet. Participants will perform MIF, for which they will be asked to consume a total of 500 kcal in a window of 6 hours or less from 8:00 AM to 2:00 PM, twice per week on 2 nonconsecutive days. Participants will receive a leaflet with examples of what 500 kcal constitutes. This intervention will last for 12 weeks, starting from randomization. The control arm resembles the baseline period, in which participants can eat without restriction for 12 weeks. A digital food diary will be completed using the MyFitnessPal app, and participants will be asked to use the TARGID tag [45] present in the app's database. Participants are expected to record their dietary and exercise habits twice a week through the MyFitnessPal app (on the fasting days in the intervention arm). The Food Frequency Questionnaire will be used during all visits to assess and record any dietary changes. Clinical evaluation will be performed during PsoPlus consultations held at the Department of Dermatology at the Ghent University Hospital by the treating dermatologist and specialized nurse. Questionnaires regarding QoL will be completed in the waiting room prior to the consultation, while questionnaires regarding dietary and exercise habits will be completed at home by the patient. Demographic and clinical data will be collected in addition to serum, skin (via tape stripping), feces, MyFitnessPal app, and patient-reported outcomes from questionnaires (Multimedia Appendix 1).

Outcome Measures

Multimedia Appendix 1 lists the parameters per study visit. During the study, data on demographics will be collected and will include age, gender, and medical and familial history. Furthermore, the disease phenotype will be assessed, and psoriasis severity will be evaluated by an independent assessor. In addition to psoriasis-related parameters, the clinical assessment will include metabolic parameters such as weight, waist circumference, BMI, and total body fat. Lifestyle habits will be registered: patients will keep a diary of their diet twice a week in the online MyFitnessPal app; in the intervention arm, this will be done on the fasting days. General diet and physical exercise habits will be recorded via the Food Frequency Questionnaire and the International Physical Activity

Questionnaire, respectively. Questionnaires will also be used to evaluate QoL and mental health, including Dermatology Life Quality Index, EuroQol-5 Dimension-5 Level, Hospital Anxiety and Depression Scale, Beck's Depression Index, Perceived Stress Scale, and the Visual Analogue Scale for satisfaction.

Cutaneous barrier integrity will be checked through the measurement of transepidermal water loss at 2 different body sites: 1 perilesional and 1 nonlesional site. These will be documented to ensure measurement at the same body sites throughout the study.

Intestinal barrier integrity will be assessed in 2 serological and fecal samples. Permeability markers zonulin, claudin-3, and ileal fatty acid-binding protein (I-FABP) will be quantified in serum, and calprotectin (S100A8/S100A9) will be measured in both serum and stool samples. Participants will also be asked to report on intestinal symptoms based on the Dutch questionnaire for irritable bowel syndrome (Prikkelbaar Darm Syndroom Questionnaire).

Serological levels of inflammatory and metabolic messengers such as IL-6, TNF-α, leptin, and adiponectin will be measured in serum and skin. The latter will be collected through skin tape stripping at the same body sites where transepidermal water loss measurement is performed.

Finally, microbiome sampling will be performed through cutaneous and fecal samples for future follow-up projects.

Study visits will be planned on the fasting days, and participants will be scheduled in this manner to account for circadian rhythm and reduce intraindividual variability.

Sample Size Calculations

The sample size was determined by power analyses and the available study budget. It was calculated with the power calculator on the Melanoma and Skin Cancer Trial website, with a 2-tailed *t* test and α at .05 and power at 0.80. The predicted effect size was estimated based on a prior study of intermittent fasting [38]. We estimated that at a 2-sided *P* value of .05 and with 80% power, we would need 16 participants to complete the study to detect a within-individual effect size of 0.75 SDs. We estimated a dropout rate of 20%, leading to a sample size of 20 participants. To minimize dropouts, recruiting personnel will emphasize considering the requirements of the study before enrollment begins. In cases of dropouts, extra participants will be recruited to maintain statistical power.

Statistical Analysis

The primary aim is to explore the effect of MIF on mild psoriasis. Secondary outcomes include changes from baseline to selected time-points during and postintervention in QoL, body weight, BMI, total body fat, inflammation and metabolic markers in serum and skin, and permeability markers in serum and feces. Furthermore, differences in dietary and physical exercise habits will be investigated. Comparisons will be made within a single arm (paired) and between both arms (unpaired).The chi-square test and Mann-Whitney test will be used to compare groups, and regression-binary logistics will be performed with identified independent variables to determine their influence on the outcome. Demographics will be analyzed as confounding variables. Cytokine data that are not normally distributed and differences in cytokine levels between groups will be analyzed using the nonparametric Mann-Whitney test. Correlations will be assessed using Spearman rank correlation. For each group, we will use multivariate logistic regression modeling to detect associations between cytokine levels and the primary end point, and to adjust for confounding effects of age, sex, and the intervention. Cytokine data will be log-transformed prior to use in multivariate models. Pre-existing differences between groups at baseline will be examined using a 1-way analysis of variance featuring a factor for diet allocation. Significant differences emerging from these tests will be explored using appropriate post hoc tests to adjust for multiple comparisons and to isolate the source(s) of variance. In addition to these analyses at the group level, individual responses will also be closely examined for outliers that may affect interpretation. Further analysis, such as subgroup analysis, may also be conducted in light of patterns emerging in the final data set. Baseline characteristics of participants who withdraw during the fasting intervention will also be compared against the final population with t tests being used to assess tolerability. *P* values will be reported to 4 decimal places with *P* values less than .0001 being reported as *P*<.001. A *P* value <.05 will be considered statistically significant. Data analysis will be executed with SPSS 23.0 (IBM Corp) and GraphPad Prism (GraphPad Software Inc).

Dissemination of Project Findings

The findings of this study will be disseminated by various means, determined by the target audience. To reach the academic dermatology community, we will publish the results in a scientific international peer-reviewed dermatology journal and present our findings at (inter)national congresses with a focus on dermatology and psoriasis. The psoriasis patient community will receive information on the results through the National Psoriasis Foundation and the Flemish Psoriasis League, including a laymen summary of the findings. Lastly, we will reach the general public by communicating the main results through the research team's social media channels.

Results

The study initiation was delayed due to the COVID-19 pandemic. Active recruitment of patients began in July 2020, and the first patient was included in October 2020. As of December 2020, we enrolled a total of 24 patients. The last patient visit is foreseen in June 2021, and results are expected to be published December 2021.

Discussion

Recently, psoriasis has been accepted to be a multimorbid disease with a large impact from lifestyle factors. Obesity has been found to be an independent predictor for the development of psoriasis and to be associated with disease severity [46]. A growing body of evidence suggests the existence of a gut-skin axis, which may also be of importance in psoriasis, revealing the need to urgently address the question of how diet may affect the disease. To our knowledge, the MANGO study is the first comprehensive trial to investigate the effects of MIF on

cutaneous, intestinal, and mental health in a cohort of people with psoriasis.

We expect that the MIF intervention will have beneficial effects on psoriatic lesions and be associated with favorable changes in metabolic parameters. We anticipate to detect shifts in intestinal parameters that may be associated with skin improvement. In addition, the data generated from this trial will inform the design of future large-scale trials to evaluate the presence and role of the gut-skin axis in psoriasis. The study additionally includes collection of cutaneous and fecal samples for future microbiome analysis if the intervention proves beneficial.

To overcome the difficulty of diet-based interventions in terms of confounding factors and the small sample size, we have chosen the design of a prospective cross-over randomized trial. As such, each patient will be monitored over more than 6 months and serve as his or her own control. Another strength of this study is the combination of clinical, biochemical, and patient-reported outcomes for cutaneous, intestinal, and mental parameters. Moreover, since some parameters can vary, the study includes 2 baseline points in order to assess normal variation. We opted to perform the pilot trial in a cohort of patients with mild psoriasis who are not on systemic agents to reduce any confounding effects of immunomodulators that may directly impact the outcomes. Lastly, since we introduced a restrictive time window for the consumption of the 500 kcal on fasting days, we will be able to reduce confounding effects of the circadian rhythm [47]. A potential limitation includes health bias among participants.

Results from this study may have multidimensional consequences and assets. On the one hand, beneficial effects of fasting may be potentially viewed as a nonpharmacological add-on treatment for psoriasis. A subset of psoriasis patients dislike pharmacological treatments and therefore opt to gain additional control over their disease through a diet. On the other hand, evidence that a free intervention may have health benefits in patients requiring costly drugs such as biologics may give rise to a moral dilemma: how do we define health responsibility in terms of lifestyle with the rise of health care costs? This debate, applicable to many other (chronic) illnesses, is highly relevant and should not be postponed. It should take place in the near future, with a multidisciplinary panel in a transparent manner in order to interpret the results from comparable trials.

To conclude, if patients with psoriasis tolerate MIF well and experience improvement, there is potential for the diet to be widely adopted by those with psoriasis in a sustainable manner. In addition, MIF may provide a positive impact on their general health, as this diet has already proven to be effective in obesity and seems to be also effective in diabetes [48]—two common comorbidities associated with psoriasis. Given this, we may discern the importance of the gut-skin axis and use it to our advantage in the disease management of psoriasis.

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Authors' Contributions

LG drafted the manuscript and designed the figures. NH, NM, SA, SDH, and JL contributed to the writing of the manuscript. LG designed the trial in collaboration with NH, NM, SDH and JL. All authors revised the final version of the article before submitting it.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of all parameters collected at each visit divided into clinical, lifestyle-related, and biochemical parameters.
[DOCX File , 19 KB - resprot_v11i2e26405_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from the National Psoriasis Foundation.
[PDF File (Adobe PDF File), 112 KB - resprot_v11i2e26405_app2.pdf]

References

1. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol 2001;137(3):280-284.
2. O'Rielly DD, Rahman P. Genetic, Epigenetic and Pharmacogenetic Aspects of Psoriasis and Psoriatic Arthritis. Rheum Dis Clin North Am 2015 Nov;41(4):623-642. [doi: 10.1016/j.rdc.2015.07.002] [Medline: 26476223]

3. Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili A, et al. Cigarette Smoking, Body Mass Index, and Stressful Life Events as Risk Factors for Psoriasis: Results from an Italian Case–Control Study. Journal of Investigative Dermatology 2005 Jul;125(1):61-67. [doi: 10.1111/j.0022-202X.2005.23681.x]
4. Fortes C, Mastroeni S, Leffondré K, Sampogna F, Melchi F, Mazzotti E, et al. Relationship between smoking and the clinical severity of psoriasis. Arch Dermatol 2005 Dec;141(12):1580-1584. [doi: 10.1001/archderm.141.12.1580] [Medline: 16365261]
5. Naldi L. Psoriasis and smoking: links and risks. Psoriasis (Auckl) 2016 May;6:65-71. [doi: 10.2147/ptt.s85189]
6. Fordham B, Griffiths C, Bundy C. A pilot study examining mindfulness-based cognitive therapy in psoriasis. Psychol Health Med 2015;20(1):121-127. [doi: 10.1080/13548506.2014.902483] [Medline: 24684520]
7. Malhotra S, Mehta V. Role of stressful life events in induction or exacerbation of psoriasis and chronic urticaria. Indian J Dermatol Venereol Leprol 2008;74(6):594-599. [doi: 10.4103/0378-6323.45100] [Medline: 19171981]
8. Martín-Brufau R, Romero-Brufau S, Martín-Gorgojo A, Brufau Redondo C, Corbalan J, Ulnik J. Psoriasis lesions are associated with specific types of emotions. Emotional profile in psoriasis. Eur J Dermatol 2015;25(4):329-334. [doi: 10.1684/ejd.2015.2577] [Medline: 26065886]
9. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med 2007;167(15):1670-1675. [doi: 10.1001/archinte.167.15.1670] [Medline: 17698691]
10. Langan SM, Seminara NM, Shin DB, Troxel AB, Kimmel SE, Mehta NN, et al. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. J Invest Dermatol 2012 Mar;132(3 Pt 1):556-562 [FREE Full text] [doi: 10.1038/jid.2011.365] [Medline: 22113483]
11. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutr Diabetes 2012 Dec 03;2:e54 [FREE Full text] [doi: 10.1038/nutd.2012.26] [Medline: 23208415]
12. Paroutoglou K, Papadavid E, Christodoulatos GS, Dalamaga M. Deciphering the Association Between Psoriasis and Obesity: Current Evidence and Treatment Considerations. Curr Obes Rep 2020 Sep;9(3):165-178. [doi: 10.1007/s13679-020-00380-3] [Medline: 32418186]
13. Gardner LC, Grantham HJ, Reynolds NJ. IL-17 May Be a Key Cytokine Linking Psoriasis and Hyperglycemia. J Invest Dermatol 2019 Jun;139(6):1214-1216 [FREE Full text] [doi: 10.1016/j.jid.2019.02.038] [Medline: 31126427]
14. Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. J Am Acad Dermatol 2013 Dec;69(6):1014-1024. [doi: 10.1016/j.jaad.2013.06.053] [Medline: 24238156]
15. Gaeta M, Castelvecchio S, Ricci C, Pigatto P, Pellissero G, Cappato R. Role of psoriasis as independent predictor of cardiovascular disease: a meta-regression analysis. Int J Cardiol 2013 Oct 03;168(3):2282-2288. [doi: 10.1016/j.ijcard.2013.01.197] [Medline: 23490084]
16. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J Hypertens 2013 Mar;31(3):433-42; discussion 442. [doi: 10.1097/HJH.0b013e32835bcce1] [Medline: 23249828]
17. Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, et al. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol 2013 Aug;27 Suppl 3:12-29. [doi: 10.1111/jdv.12163] [Medline: 23845149]
18. Singh S, Young P, Armstrong AW. Relationship between psoriasis and metabolic syndrome: a systematic review. G Ital Dermatol Venereol 2016 Dec;151(6):663-677. [Medline: 27589483]
19. Rodríguez-Zúñiga MJM, Cortez-Franco F, Quijano-Gomero E. Association of Psoriasis and Metabolic Syndrome in Latin America: A Systematic Review and Meta-Analysis. Actas Dermosifiliogr 2017 May;108(4):326-334 [FREE Full text] [doi: 10.1016/j.ad.2016.11.009] [Medline: 28117050]
20. Pietrzak D, Pietrzak A, Krasowska D, Makara-Studzińska M, Madej A, Baranowska M, et al. Depressiveness, measured with Beck Depression Inventory, in patients with psoriasis. J Affect Disord 2017 Feb;209:229-234. [doi: 10.1016/j.jad.2016.11.045] [Medline: 27930916]
21. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GB, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol 2015 Apr;135(4):984-991 [FREE Full text] [doi: 10.1038/jid.2014.530] [Medline: 25521458]
22. Humbert P, Bidet A, Treffel P, Drobacheff C, Agache P. Intestinal permeability in patients with psoriasis. Journal of Dermatological Science 1991 Jul;2(4):324-326. [doi: 10.1016/0923-1811(91)90057-5]
23. Mcmillin DL, Richards DG, Mein EA, Nelson CD. Systemic aspects of psoriasis. Integrative Medicine 2000 Mar;2(2-3):105-113. [doi: 10.1016/s1096-2190(00)00010-x]
24. Hamilton I, Fairris GM, Rothwell J, Cunliffe WJ, Dixon MF, Axon ATR. Small Intestinal Permeability in Dermatological Disease. QJM: An International Journal of Medicine 1985;56(3-4):559-567. [doi: 10.1093/oxfordjournals.qjmed.a067901]
25. Sanchez IM, Jiang W, Yang EJ, Singh RK, Beck K, Liu C, et al. Enteropathy in Psoriasis: A Systematic Review of Gastrointestinal Disease Epidemiology and Subclinical Inflammatory and Functional Gut Alterations. Curr Derm Rep 2018 Feb 13;7(1):59-74. [doi: 10.1007/s13671-018-0213-1]

26. Ali IA, Foolad N, Sivamani RK. Considering the Gut-Skin Axis for Dermatological Diseases. Austin J Dermatolog 2014;1(5):1024.
27. O'Neill CA, Monteleone G, McLaughlin JT, Paus R. The gut-skin axis in health and disease: A paradigm with therapeutic implications. Bioessays 2016 Nov;38(11):1167-1176. [doi: 10.1002/bies.201600008] [Medline: 27554239]
28. Grine L, Steeland S, Van Ryckeghem S, Ballegeer M, Lienenklaus S, Weiss S, et al. Topical imiquimod yields systemic effects due to unintended oral uptake. Sci Rep 2016 Jan 28;6:20134 [FREE Full text] [doi: 10.1038/srep20134] [Medline: 26818707]
29. Humbert P, Bidet A, Treffel P, Drobacheff C, Agache P. Intestinal permeability in patients with psoriasis. Journal of Dermatological Science 1991 Jul;2(4):324-326. [doi: 10.1016/0923-1811(91)90057-5]
30. Sikora M, Chrabąszcz M, Maciejewski C, Zaremba M, Waśkiel A, Olszewska M, et al. Intestinal barrier integrity in patients with plaque psoriasis. J Dermatol 2018 Dec;45(12):1468-1470. [doi: 10.1111/1346-8138.14647] [Medline: 30222202]
31. Michaëlsson G, Gerdén B, Hagforsen E, Nilsson B, Pihl-Lundin I, Kraaz W, et al. Psoriasis patients with antibodies to gliadin can be improved by a gluten-free diet. Br J Dermatol 2000 Jan;142(1):44-51. [doi: 10.1046/j.1365-2133.2000.03240.x] [Medline: 10651693]
32. Michaëlsson G, Ahs S, Hammarström I, Lundin IP, Hagforsen E. Gluten-free diet in psoriasis patients with antibodies to gliadin results in decreased expression of tissue transglutaminase and fewer Ki67+ cells in the dermis. Acta Derm Venereol 2003;83(6):425-429 [FREE Full text] [doi: 10.1080/00015550310015022] [Medline: 14690336]
33. Ford AR, Siegel M, Bagel J, Cordoro KM, Garg A, Gottlieb A, et al. Dietary recommendations for adults with psoriasis or psoriatic arthritis from the medical board of the national psoriasis foundation: a systematic review. JAMA Dermatol 2018 Aug 01;154(8):934-950. [doi: 10.1001/jamadermatol.2018.1412] [Medline: 29926091]
34. Naldi L, Conti A, Cazzaniga S, Patrizi A, Pazzaglia M, Lanzoni A, Psoriasis Emilia Romagna Study Group. Diet and physical exercise in psoriasis: a randomized controlled trial. Br J Dermatol 2014 Mar;170(3):634-642. [doi: 10.1111/bjd.12735] [Medline: 24641585]
35. Castaldo G, Galdo G, Rotondi Aufiero F, Cereda E. Very low-calorie ketogenic diet may allow restoring response to systemic therapy in relapsing plaque psoriasis. Obes Res Clin Pract 2016;10(3):348-352. [doi: 10.1016/j.orcp.2015.10.008] [Medline: 26559897]
36. Soenen R, Meulewaeter E, Grine L, Van den Berghe N, Brouwers E, Speeckaert R, et al. Defining a Minimal Effective Serum Trough Concentration of Secukinumab in Psoriasis: A Step toward Personalized Therapy. J Invest Dermatol 2019 Oct;139(10):2232-2235.e1 [FREE Full text] [doi: 10.1016/j.jid.2019.04.012] [Medline: 31067484]
37. Jensen P, Christensen R, Zachariae C, Geiker NR, Schaadt BK, Stender S, et al. Long-term effects of weight reduction on the severity of psoriasis in a cohort derived from a randomized trial: a prospective observational follow-up study. Am J Clin Nutr 2016 Aug;104(2):259-265. [doi: 10.3945/ajcn.115.125849] [Medline: 27334236]
38. Damiani G, Watad A, Bridgewood C, Pigatto P, Pacifico A, Malagoli P, et al. The impact of ramadan fasting on the reduction of PASI score, in moderate-to-severe psoriatic patients: a real-life multicenter study. Nutrients 2019 Jan 27;11(2):1-10 [FREE Full text] [doi: 10.3390/nu11020277] [Medline: 30691245]
39. Castaldo G, Rastrelli L, Galdo G, Molettieri P, Rotondi Aufiero F, Cereda E. Aggressive weight-loss program with a ketogenic induction phase for the treatment of chronic plaque psoriasis: a proof-of-concept, single-arm, open-label clinical trial. Nutrition 2020 Jun;74:110757. [doi: 10.1016/j.nut.2020.110757] [Medline: 32222582]
40. Gibson A, Sainsbury A. Strategies to Improve Adherence to Dietary Weight Loss Interventions in Research and Real-World Settings. Behav Sci (Basel) 2017 Jul 11;7(3):44 [FREE Full text] [doi: 10.3390/bs7030044] [Medline: 28696389]
41. Wegman MP, Guo MH, Bennion DM, Shankar MN, Chrzanowski SM, Goldberg LA, et al. Practicality of intermittent fasting in humans and its effect on oxidative stress and genes related to aging and metabolism. Rejuvenation Res 2015 Apr;18(2):162-172 [FREE Full text] [doi: 10.1089/rej.2014.1624] [Medline: 25546413]
42. Tripolt NJ, Stekovic S, Aberer F, Url J, Pferschy PN, Schröder S, et al. Intermittent Fasting (Alternate Day Fasting) in Healthy, Non-obese Adults: Protocol for a Cohort Trial with an Embedded Randomized Controlled Pilot Trial. Adv Ther 2018 Aug;35(8):1265-1283 [FREE Full text] [doi: 10.1007/s12325-018-0746-5] [Medline: 30046988]
43. Stekovic S, Hofer SJ, Tripolt N, Aon MA, Royer P, Pein L, et al. Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans. Cell Metab 2019 Sep 03;30(3):462-476.e6 [FREE Full text] [doi: 10.1016/j.cmet.2019.07.016] [Medline: 31471173]
44. Tinsley GM, La Bounty PM. Effects of intermittent fasting on body composition and clinical health markers in humans. Nutr Rev 2015 Oct;73(10):661-674. [doi: 10.1093/nutrit/nuv041] [Medline: 26374764]
45. Evenepoel C, Clevers E, Deroover L, Matthys C, Verbeke K. Dietary assessment with the online platform MyFitnessPal: a reliable method? Proc. Nutr. Soc 2020 Jun 10;79(OCE2):E506. [doi: 10.1017/s0029665120004541]
46. Kunz M, Simon JC, Saalbach A. Psoriasis: Obesity and Fatty Acids. Front Immunol 2019;10:1807 [FREE Full text] [doi: 10.3389/fimmu.2019.01807] [Medline: 31417571]
47. Patterson RE, Sears DD. Metabolic Effects of Intermittent Fasting. Annu Rev Nutr 2017 Aug 21;37:371-393. [doi: 10.1146/annurev-nutr-071816-064634] [Medline: 28715993]

48. Zubrzycki A, Cierpka-Kmiec K, Kmiec Z, Wronska A. The role of low-calorie diets and intermittent fasting in the treatment of obesity and type-2 diabetes. J Physiol Pharmacol 2018 Oct;69(5):663-683 [FREE Full text] [doi: 10.26402/jpp.2018.5.02] [Medline: 30683819]

Abbreviations

I-FABP: ileal fatty acid-binding protein
IL: interleukin
INF: interferon
kcal: kilocalorie
MANGO: Modified Intermittent Fasting in Psoriasis
MIF: modified intermittent fasting
PASI: Psoriasis Area and Severity Index
QoL: quality of life
TNF: tumor necrosis factor

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Protocol

Patient-Led Mass Screening for Atrial Fibrillation in the Older Population Using Handheld Electrocardiographic Devices Integrated With a Clinician-Coordinated Remote Central Monitoring System: Protocol for a Randomized Controlled Trial and Process Evaluation

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Abstract

Background: Atrial fibrillation (AF) is common in older people and increases the risk of stroke. The feasibility and effectiveness of the implementation of a patient-led AF screening program for older people are unknown.

Objective: This study aims to examine the feasibility and effectiveness of an AF screening program comprising patient-led monitoring of single-lead electrocardiograms (ECGs) with clinician-coordinated central monitoring to diagnose AF among community-dwelling people aged ≥75 years in Australia.

Methods: This is a nationwide randomized controlled implementation trial conducted via the internet and remotely among 200 community-dwelling adults aged ≥75 years with no known AF. Randomization will be performed in a 1:1 allocation ratio for the intervention versus control. Intervention group participants will be enrolled in the monitoring program at randomization. They will receive a handheld single-lead ECG device and training on the self-recording of ECGs on weekdays and submit their ECGs via their smartphones. The control group participants will receive usual care from their general practitioners for the initial 6 months and then commence the 6-month monitoring program. The ECGs will be reviewed centrally by trained personnel. Participants and their general practitioners will be notified of AF and other clinically significant ECG abnormalities.

Results: This study will establish the feasibility and effectiveness of implementing the intervention in this patient population. The primary clinical outcome is the AF detection rate, and the primary feasibility outcome is the patient satisfaction score. Other

outcomes include appropriate use of anticoagulant therapy, participant recruitment rate, program engagement (eg, frequency of ECG transmission), agreement in ECG interpretation between the device automatic algorithm and clinicians, the proportion of participants who complete the trial and number of dropouts, and the impact of frailty on feasibility and outcomes. We will conduct a qualitative evaluation to examine the barriers to and acceptability and enablers of implementation. Ethics approval was obtained from the human research ethics committee at the University of Sydney (project number 2020/680). The results will be disseminated via conventional scientific forums, including peer-reviewed publications and presentations at national and international conferences.

Conclusions: By incorporating an integrated health care approach involving patient empowerment, centralized clinician-coordinated ECG monitoring, and facilitation of primary care and specialist services, it is possible to diagnose and treat AF early to reduce stroke risk. This study will provide new information on how to implement AF screening using digital health technology practicably and feasibly for older and frail populations residing in the community.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12621000184875; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380877

International Registered Report Identifier (IRRID): DERR1-10.2196/34778

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KEYWORDS

atrial fibrillation; screening; handheld; electrocardiogram; ECG; acceptability; user perception; user experience; barrier; enabler; older adults; elderly; feasibility; effectiveness; implementation; monitoring; aging; cardiovascular; cardiology; heart disease; mobile phone

Introduction

Background

The prevalence and incidence of atrial fibrillation (AF) increase with age and is common among older people [1-4]. A recent study estimated that the global prevalence of AF is 59.7 million [4]. Approximately 70% of individuals with AF are aged between 65 and 85 years [5]. AF has been reported to account for 36% of all ischemic strokes, of which 85% are inadequately anticoagulated [6]. If AF is detected early and managed with appropriate anticoagulation therapy, the stroke risk and subsequent stroke-related disability and mortality can be reduced significantly [7]. Unfortunately, it was estimated that 1% of the general population and 1.4% of people aged ≥65 years were living with undiagnosed AF, as reported in a systematic review that combined data from 30 cross-sectional studies (n=122,571) [8]. Hence, the opportunity for anticoagulation therapy to reduce stroke risk for these patients is missed.

Several guidelines have recommended opportunistic screening for AF [9-12]. However, studies suggest that one-off opportunistic screening approaches have a low yield for identifying AF. For example, a recent cluster randomized trial of opportunistic screening using pulse palpation, electronic blood pressure measurement with an AF algorithm, and a handheld single-lead electrocardiogram (ECG) device versus usual care for detection of AF in primary care patients (involving 9218 patients in the intention-to-screen group, 55% women, mean age 75.2 years vs 9526 patients in the usual care group, 54.3% women, mean age 75.0 years) found that opportunistic screening did not improve AF detection compared with usual care [13]. On the contrary, repeated heart rhythm monitoring over a duration increased the yield of AF detection. Petryszyn et al [14] reported in a systematic review that repeated heart rhythm monitoring with ECG devices over periods ranging from 2 weeks to 12 months had higher AF detection rates compared with one-off opportunistic screening approaches: 2.1% (95% CI 1.5-2.8) with repeated ECG screening versus 1.2% (95% CI 0.8-1.6) with opportunistic screening (P<.05). Although many guidelines advocate the use of 12-lead ECG for opportunistic screening, these may limit locations where screening may occur and demand a higher skill level to operate 12-lead ECG devices [15,16]. Mobile single-lead handheld ECG devices are easier to use with better time efficiency compared with 12-lead ECG machines, and these single-lead handheld ECG devices have been used in several AF screening studies [15].

Recent systematic reviews, including 8180 single-lead ECG tracings, show that mobile handheld single-lead ECG devices have high accuracy for diagnosing AF [17]. These devices are available to the public and clinicians. However, a national survey reported that although general practitioners (GPs) are aware of the devices, they rarely conduct AF screening in their busy clinical practice [18]. Clinician-led AF screening faces barriers because clinicians are facing competing clinical priorities and time constraints [19]. Alternative strategies for early detection and management of AF are needed. Patient-led AF screening through self-recording of single-lead ECG using mobile handheld ECG devices could be an alternative. A randomized controlled trial (RCT) involving 7173 community-dwelling older people aged 75 to 76 years in Sweden reported that screening using patient-activated intermittent ECG recordings with a handheld ECG device (Zenicor) twice daily over 2 weeks, when the participants noticed palpitations, increased new AF detection fourfold [20]. Similarly, in an RCT of AF screening using a handheld ECG device (AliveCor Kardia) in 1001 participants aged ≥65 years and with CHADS-VASc (congestive heart failure, hypertension, age ≥75 [double score], diabetes, stroke [double score], vascular disease, age 65 to 74 and sex category) score ≥2, the detection rate of new AF after 12 months was 3.8% in the monitored group versus 0.1% in the control group (hazard ratio 3.9, 95% CI 1.4-10.4; P=.007) [21]. Another RCT of AF screening using a 2-week ambulatory ECG patch (Zio XT), one at baseline and another at 3 months in 856 participants aged ≥75 years with hypertension, increased new

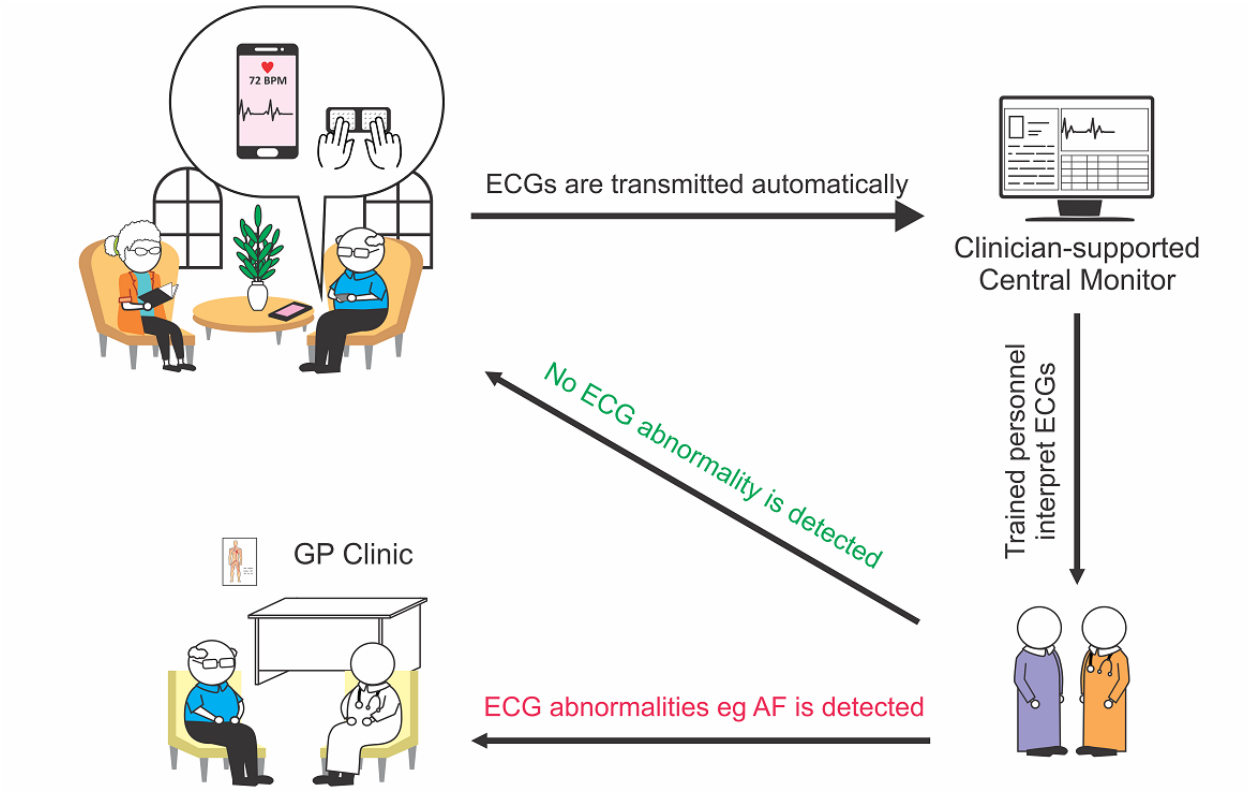
AF detection rate 10 folds (5.3% in the monitored group vs 0.5% in the control group; relative risk: 11.2; 95% CI, 2.7-47.1; *P*=.001) [22]. These studies [20-22] suggest the potential of patient-led approaches to AF screening but still leave questions on how to implement these approaches and the generalizability of these approaches. Unanswered questions about the implementation of AF screening programs include whether such programs can be implemented alongside existing health care systems; whether regular self-screening with mobile devices is feasible and acceptable in older adults; what is the feasibility, resource use, and clinician acceptability of real-world implementation of such programs; what is the time taken by services overseeing and monitoring such programs in terms of reviewing and interpreting large amounts of ECG data; and what strategies can be applied to optimize the use of resources. In addition, there is less data on the barriers to and enablers of the implementation of such programs, longer self-monitoring periods, and implementation in subgroups (such as older people who are frail and people living in remote areas) in which these strategies may not work. A recent systematic review reported that the prevalence of frailty in patients with AF was up to 75% [23]. More studies are needed to better assess whether such mobile health devices can be used effectively and implemented in programs at a large scale among older people who are frail.

There is also a lack of information about the role and importance of patient empowerment with respect to the implementation of AF screening. The World Health Organization promotes patient empowerment (ie, training patients to perform and engage in health-related behaviors within their familiar setting) as it can potentially lead to positive health outcomes [24]. Patient empowerment can be incorporated in patient-led AF screening by training patients to self-record single-lead ECGs. However, patient empowerment has its limitations; that is, patients face automated ECG interpretation results that are often beyond their competence to understand and act upon, and it is impractical to have every ECG result individually and regularly checked by their clinicians. A centralized monitoring system is a feasible way of remotely monitoring a patient's heart rhythm [25].

The processes of the screening program can vary in their actual implementation because of diverse contexts and participant characteristics (both patients and clinicians); for example, participants may be incapable of or not engage in performing self-recording of ECG, or they may not follow up with (or do not have access to) their clinician after a clinically significant abnormality is detected and notified. Process variations can affect outcomes. Therefore, it is important to evaluate the processes with the aim of better understanding why variations occur and how to improve the processes to achieve an effective intervention and identify contextually relevant strategies to scale up the screening program to benefit larger populations.

In summary, there are gaps in our knowledge regarding the feasibility, effectiveness, and acceptability of patient-led AF screening by remote patient self-recording with centralized clinician-supported monitoring of single-lead ECGs in older community-dwelling people who are frail. The Mass AF screening program (Figure 1) is designed for implementation among community-dwelling people aged ≥75 years. It comprises the provision of a handheld ECG device and training of participants to self-screen on weekdays and transmit ECGs for review by a central monitoring team. We aim to implement and evaluate this AF self-screening program in which older people in the community are empowered to perform repeated heart rhythm monitoring using a single-lead handheld ECG device and connected with health care providers who review and support the diagnosis of AF and management by primary care and specialist services. We hypothesize that the proposed self-screening model of care may lead to several positive outcomes, including a feasible and scalable model for implementing patient-led AF screening in community-dwelling older people, improved patient satisfaction by empowering them with the relevant knowledge and skills to perform self-screening [24], and thereby higher adherence to the screening program [26,27].

Figure 1. Overview of the *Mass AF* screening program: patient-led self-recording of electrocardiograms (ECGs) with the clinician-coordinated centralized system. AF: atrial fibrillation; GP: general practitioner.



Objective

Our study objectives are to (1) compare AF ascertainment rates in the intervention and control groups; (2) evaluate the feasibility of the intervention, including assessing participant satisfaction, acceptability, barriers, and enablers and how frailty influences these assessments; and (3) assess agreements between the ECG device automatic algorithm and clinician interpretation.

Alongside these objectives, the specific objectives of the process evaluations are as follows:

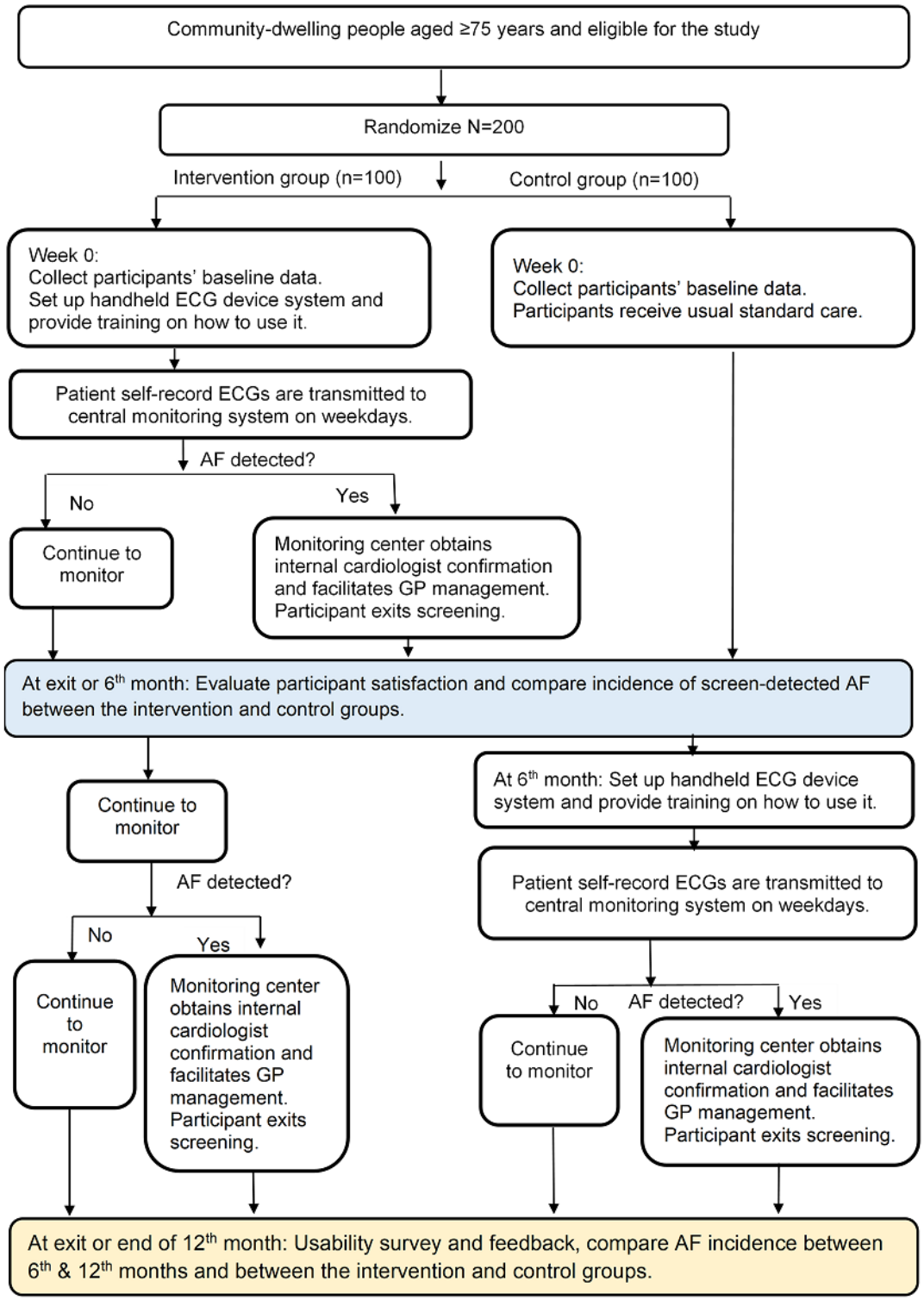
1. To assess the fidelity of the screening program (ie, whether the intervention was delivered as intended), participant engagement with the intervention in terms of the frequency of ECG recordings, and reach (eg, the socioeconomic and frailty profiles of participants and how these profiles affect the engagement and outcomes)
2. To evaluate the feasibility of the screening program from the perspective of participants and clinicians to gain a deeper understanding of barriers and enablers; this includes an examination of the mechanisms of impact; that is, an examination of the potential causal mechanisms through which the intervention results in the adoption of self-screening by understanding how patients and clinicians interact with the screening program
3. To explore any factors external to the screening program that may have affected implementation (ie, the community-dwelling environment, access to health care services, and GP views and attitudes), including identification of resources and implementation processes required for effective uptake and implementation of the screening program

Methods

Study Design

This is a 2-arm, randomized, open-label, waitlist-controlled trial in community-dwelling people aged ≥75 years. We will also conduct a process evaluation of this study. Randomization in the ratio of 1:1 is stratified by participant frailty status (frail or nonfrail; Multimedia Appendix 1). Participant frailty was determined using the FRAIL (Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight) scale based on five components: *fatigue*, *resistance* (inability to climb stairs), *ambulation* (inability to walk a certain distance), *illness*, and *loss of weight* [28,29]. The intervention group will commence the monitoring program for 12 months upon enrollment. The control group will be waitlisted for the first 6 months and then commence the monitoring program in the subsequent 6 months. The steps involved for enrollment, randomization, intervention, control, and exit from the program are outlined in the study flowchart (Figure 2), and descriptions of the screening program are provided in the following sections.

Figure 2. Flowchart of the *Mass AF* screening program. AF: atrial fibrillation; ECG: electrocardiogram; GP: general practitioner.



Study Population

Our target population involves older people living independently in the community outside of a hospital, nursing home, or similar institutional residence. The inclusion criteria are as follows: community-dwelling people aged ≥75 years, having a smartphone or electronic device that can operate the AliveCor Kardia mobile app, and being able to understand instructions in English. Individuals with the following conditions will be excluded: previously confirmed diagnosis of AF, having an implantable cardiac monitor, pacemaker or defibrillator, dementia, inability to provide informed consent, and those with a medical illness with an anticipated life expectancy of <3 months.

Intervention Group: AF Self-screening and Monitoring Program

Participants allocated to the intervention will immediately commence the monitoring program. They will be provided with a small handheld single-lead Kardia ECG device (AliveCor

Inc), which has been cleared by the Food and Drug Administration and approved by the Therapeutics Goods Administration. After the participants receive the device, they will receive a phone call from research assistants who will help them to set up the device, including downloading the Kardia app to the mobile phone, setting up reminders to record ECG in the app, and setting up a Kardia user account. The research assistants will create a participant profile in the central monitoring portal, which will generate a unique 12-digit code for the participant. Research assistants will inform participants of their unique 12-digit code via SMS text message or over the phone. The participant will enter the 12-digit code in their Kardia user account, and once this step is completed, the Kardia user account will be connected to the central monitoring portal. Participants can commence recording the ECGs, which will be transmitted to their personal profiles in the central monitoring portal.

Research assistants will take participants through the steps of recording an ECG. Participants will record a single-lead ECG trace by placing 2 fingers of each hand steadily on 2 small touchpads (3 cm × 3 cm) of the device for 30 seconds on weekdays. The ECG device will be connected to the mobile phone wirelessly via the Kardia app that they have downloaded. An ECG trace will appear on the participants' mobile phones, and participants will be able to record notes in the ECG trace. We will encourage them to note the activities they performed before recording the ECG. The ECG and notes will be automatically transmitted to the central monitoring portal. The training conducted over the telephone or video call between research assistants and participants will take approximately 30 to 60 minutes per participant. In the context of the COVID-19 pandemic, all study-related procedures will be conducted remotely using phone calls or video calls (if participants have access to and prefer this modality). To ensure that participants are confident in using the device, research assistants will call each participant to confirm that they are able to record an ECG. Participants will be encouraged to have a family member who may assist them in the process. After the training, participants will also receive an SMS text message with a weblink to an instructional video created by the device manufacturer. The short training video will serve as a reference for participants to refresh their memory on how to record a single-lead ECG. The research team will contact participants if they have not recorded any ECGs for 3 consecutive days to find out and address the causes, if possible.

Before commencing the study, participants will be advised that in the event of experiencing symptoms (eg, syncope, chest pain, palpitations, and shortness of breath) that are severe in nature or that are of concern to the participants, to present to their local medical physician or hospital for assessment as soon as possible.

Control Group: Usual Care During Waiting Period

Participants allocated to the control group will have usual care and be told that they have been waitlisted to start the monitoring program in 6 months. During the 6-month waiting period, it is expected that participants in the waitlist group will visit their GPs as per their usual health care needs, and their GPs will provide care and referrals as usual.

Sample Size

In computing the sample size required to assess the primary feasibility outcome, we will evaluate the proportion of participants reporting being satisfied or very satisfied that their heart rhythm was monitored in the past 6 months in the intervention group versus the control group. We arbitrarily set that 50% of the participants in the control group will be satisfied or very satisfied. With reference to the literature that reported a proportion of 67% [30] to 82% [31] of older people were satisfied or very satisfied with the use of technology-enabled monitoring at home, we postulate that there will be an absolute 30% increase in satisfaction in the intervention group compared with the control group. Our study will have 80% power, using a 5% level of significance, to detect an absolute difference of 30% in satisfaction between the 2 groups. A sample size of 100 participants aged ≥75 years is required to assess the primary feasibility outcome

To calculate the sample size required to evaluate the primary clinical outcome of AF detection rate, we set an AF detection rate of 10% in the intervention group and 1% in the control group, in accordance with a recent study [22]. At 80% power, a 2-sided test, and α .05, we estimate that a sample of 200 participants will be needed to detect a significant difference in AF detection between the intervention and control groups. Therefore, a total of 200 participants will be recruited for this trial to assess the primary clinical outcome.

Randomization

Participants will be randomized to the intervention or control group on a 1:1 basis stratified by baseline measure of frailty (ie, frail or not frail according to the FRAIL score) [28,29] and using permuted blocks of sizes 4 and 6. The statistician has generated a randomization list using the RandomiseR package in R software (R Foundation for Statistical Computing) [32]. The randomization list will be input into the REDCap (Research Electronic Data Capture) [33] database, which captures participant demographic and baseline data and survey findings (Multimedia Appendix 1). The statistician and principal investigators will be unaware of patient allocation until after the completion of the study.

Recruitment

A multipronged approach will be used to identify potential participants. We will use clinician networks (eg, GPs, cardiologists, geriatricians, and allied health professionals) and a variety of direct approaches to the community to recruit a wide spectrum of participants from various demographic backgrounds living in wide geographical areas across Australia. Communications will be sent to practice managers seeking their assistance in disseminating introductory letters, leaflets, flyers, and posters to their clinicians. The practice managers may also disseminate the information to their patients through their usual channels of communication, including displaying them in waiting rooms, websites, newsletters, or in electronic format or hard copy. The decision to contact the research team will be at the discretion of the patients. In addition, a direct community approach will be used. The research poster and leaflets will be disseminated in local community centers such as the Returned

and Services League Australia and places of worship. People interested in the study will initiate contact with the study team directly by email or phone to receive further information. We will also list the study with third-party recruiters such as HealthMatch [34] and Join US [35]. Individuals who contact the research team will be screened for eligibility and provided with further explanations about the study. We will inform GPs about their patients who enroll in the study.

Participant Consent and Enrollment

The research team will confirm the eligibility of interested individuals against the inclusion and exclusion criteria over the phone. Eligible individuals will be provided with participant information statements and consent information and given time to read the information. Research personnel will answer individuals' questions. Participants will provide verbal consent to a member of the research team who will electronically sign off the consent form and keep the form in the secured university computer drive.

ECG Central Monitoring System

Qualified and trained study personnel, including a cardiac technician and clinical monitoring personnel with medical qualifications, will remotely review all ECGs and compare their diagnosis with the device's automated diagnostic algorithm. If the ECGs are normal or have minimal abnormalities and the personnel are certain of their diagnosis, the ECGs will not be referred to a cardiologist. However, the personnel will refer all abnormal ECGs for diagnosis confirmation, or uncertain ECG abnormalities for clarification of diagnosis, to cardiologists or cardiac electrophysiology specialists. Participants' ECGs will be classified into *low, moderate, high, and severe abnormalities* and managed as shown in Table 1. The research team will notify the participants and their GPs of AF or other clinically significant ECG abnormalities. A copy of an abnormal ECG will be forwarded to their GP. When an AF diagnosis is confirmed by the research team, the participant will be advised to see their GP. The participant will exit the screening program or opt to continue the monitoring program. The research team will contact the GP to obtain information about the treatment given to the patient.

Table 1. Electrocardiogram (ECG) classification and management plan.

ECG findings	Classification	The study team will take the following actions
First-degree heart block	Low critical abnormality	• If PR interval >300 milliseconds, notify and send ECG to GP[a] within a week • If PR interval is between 201 and 300 milliseconds, notify and send ECG to GP within the duration of participant's enrollment in the study
Ectopic heartbeats (atrial ectopic and ventricular ectopic)	Low critical abnormality	• As these are common and noncritical findings, notify GP at the end of the study
Atrial fibrillation, atrial flutter, nonsustained ventricular tachycardia, bradycardia <40 bpm[b], second-degree heart block, nonsustained supraventricular tachycardia	Moderate critical abnormality	• Notify and send ECG to GP within a week • Advise patients to see their GP as soon as possible • Contact patient to confirm review with their GP in the subsequent week
Significant ECG abnormalities that need urgent medical attention (eg, suspected ST elevation)	High critical abnormality	• Consult cardiologists in the research team to confirm the diagnosis, and where necessary, adjudicate suspect ECGs • Notify and send ECG to GP within 3 working days • Advise patients to see their GP as soon as possible • Contact patient to confirm review with their GP in the subsequent week
Potentially life-threatening arrhythmia or abnormality (eg, third-degree heart block)	Severe abnormality	• Consult cardiologists in the research team to confirm diagnosis • Advise patients to present to their local emergency department immediately • Notify and send ECG to GP on the same day • Contact patient to confirm review with their GP in the subsequent week
ECGs without any of the above abnormalities	Normal	• Review ECG report (including normal and the above abnormal findings) in monthly team meeting

[a]GP: general practitioner.

[b]bpm: beats per minute.

Data Collection

All study procedures have been designed to be conducted remotely using telephone or video calls. At baseline, we will obtain information on sociodemographics, self-reported weight and height, and concurrent medical conditions and medications and data to assess stroke risk, frailty, and activities of daily living. At the end of the program, we will conduct a usability survey of all participants via phone calls to obtain information related to their experiences with the screening program and obtain further information on any adverse events while participating in the program (Multimedia Appendix 1). All GPs who have patients enrolled in the study will be invited to provide their feedback in a survey (Multimedia Appendix 2). All

electronic data and documents related to participants and the project will be securely stored in the university computer drive accessible by authorized research team members only.

Qualitative Evaluations

We have followed the Medical Research Council guidelines in designing the process evaluation [36]. Participants' and GPs' expectations and experiences of the screening program may be influenced by various contextual factors such as the participants' social and cultural background and the GPs' clinical practice resource and setting. Using a theoretical lens of critical realism [37], we will provide an explanatory analysis of the perceptions, experiences, and interactions with contextual factors that participants describe (ie, what works for whom and under what circumstances).

After participants have used the handheld ECG device for a minimum of 3 months, the research team will invite several participants in both groups (≥10 participants to achieve thematic saturation) to attend an in-depth semistructured interview to explore their views and feedback on the study. The semistructured interview will explore the participants' feedback on their experiences with using the ECG device, use of the device for detecting irregular heart rhythm, participants' perceptions of this remote screening method, and their access to health services generally (Multimedia Appendix 1). The invitation will be based on purposive sampling to obtain representative participants from a wide spectrum of demographic groups, that is, male or female, rural or urban, and frail or not frail.

GPs will be invited to a one-on-one in-depth interview, which will take approximately 20 to 30 minutes. The interviews will be audio recorded and transcribed by the research team. We plan to recruit at least eight GPs for this interview. A sample of 8 GPs is considered appropriate for the exploratory interviews [38]. However, more GPs will be recruited if thematic saturation is not achieved. The semistructured interviews will explore GPs' views with respect to AF screening generally and in screening people aged ≥75 years particularly, their views of the patient-led self-screening in this research study, their knowledge of the use of mobile health devices (including handheld ECG devices) in clinical practice, and their views on using the handheld ECG device (ie, AliveCor Kardia) for AF screening in this study. In alignment with a critical realism [37] approach, the interview questions will explore GPs' contextual factors and their interaction with patient participants and the research team with the aim of exploring GPs' perception of their roles and barriers to and acceptability and enablers of this patient-led self-recording of a single-lead ECG program (Multimedia Appendix 2).

Outcome Measurements

The clinical outcomes include (1) new AF detected over 6 and 12 months and (2) appropriate use of anticoagulant therapy. The feasibility outcomes include (1) participant satisfaction that their heart rhythm was monitored in the past 6 months; (2) participant recruitment rate; (3) frequency of ECG transmission to the central monitor; (4) proportion of participants who complete the program; (5) proportion of dropouts (exit the program prematurely) and reasons; (6) actual costs of the screening program; (6) agreement between the ECG device's automatic algorithm and clinician interpretation; (7) usability assessment; (8) participant acceptability and barriers to and enablers of implementation; and (9) impact of frailty on feasibility assessments and outcomes.

Analysis

All analyses will be conducted according to the principle of intention-to-treat. Continuous variables will be presented as mean (SD) or median with IQR and categorical variables as frequency and percentage. The key outcomes, namely participant satisfaction in the AF screening program, usability of the screening program, and the incidence of new AF detected over 6 and 12 months, will be reported as frequency and percentages and will be compared between the intervention and control groups using the chi-square test. Comparisons between groups (intervention and control) for other outcomes will be assessed using the chi-square test or Fisher exact test for categorical variables and Student *t* test or Mann-Whitney test for continuous variables as appropriate. We will consider 2-tailed $P<.05$ as statistically significant. The agreement between the ECG device automatic algorithm and clinician interpretation will be evaluated using κ statistics. Subgroup analyses will be performed based on age, gender, and location. Subgroup analysis by frailty will be performed to examine the potential impact of frailty on the outcomes, feasibility, and acceptability of the program. The actual operational costs of delivering the project will be recorded and verified using invoices and receipts, including the costs of personnel involved in interpreting ECGs, which will be computed based on their hourly wages and the time they spent in their roles in this program. The resultant costs will be compared with the costs reported in the literature on the costs associated with the detection of AF in a similar older population. Missing data will be identified, and its causes will be described. Sensitivity analysis will be performed to examine the robustness of the findings [39].

Qualitative evaluation will be reported according to the COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines [40]. Interviews with patients and GPs will be thematically analyzed using an inductive approach [41]. Themes will be interpreted through the critical realism lens [37] and compared with the literature [42,43]. We will triangulate the quantitative and qualitative findings [44] from patient participants and GPs to acquire an in-depth understanding of the barriers to and enablers of implementing the screening program.

The process evaluation components [36], explanatory data, and anticipated outcomes are summarized in Table 2.

The quantitative and qualitative analysis approach and methods are summarized in Textbox 1.

Table 2. Process evaluation—implementation processes, mechanisms of impact, and contexts.

Process evaluation components	Descriptions	Methods and explanatory data	Anticipated outcomes
Implementation processes	• Fidelity of implementation • Participation in intervention • Reach	• Participant enrollment and characteristics, including socioeconomic status and frailty • Participant engagement (number of self-recorded ECGs[a]) • Clinician characteristics and involvement	• Participants who are engaged with the intervention and satisfied with the program
Mechanisms of impact (how does intervention help adoption of AF[b] self-screening)	• Barriers and enablers	• Participant engagement and satisfaction • Participant survey and interview • Clinician survey and interview	• A feasible screening program
Context (how do factors external to the intervention affect uptake and implementation)	• Participants' overall health • Community-dwelling environment • Access to health care services • General practitioner views and attitudes	• Comorbidities, frailty, and functional status • Participant demographic data, survey, and interview • Clinician survey and interview	• Identification of resources and implementation processes required for effective uptake and implementation of the screening program • A contextualized feasible screening program

[a]ECG: electrocardiogram.

[b]AF: atrial fibrillation.

Textbox 1. Description of analysis methods on outcome measures compared between the intervention group and waitlist control group.

New atrial fibrillation detected

- Frequency of occurrence and proportions at 6 months—via electrocardiogram collected at the central monitor (during intervention) and self-report and confirmation with medical records or electrocardiogram (during waitlist control period)

Appropriate use of anticoagulant therapy

- Frequency of occurrence and proportion of participants with new atrial fibrillation treated with anticoagulant appropriately—via confirmation with general practitioners or participants' self-reported anticoagulant medication use assessed by using an interviewer-administered questionnaire at 6 months

Participant satisfaction at the sixth month

- Frequency of occurrence and proportion of participants reporting being satisfied or very satisfied—assessed via an interviewer-administered questionnaire at 6 months

Participant recruitment rate

- Number of participants recruited over time—via log sheet
- Cumulative frequency graph over time

Electrocardiogram transmission to the central monitor

- Frequency of electrocardiogram transmission per participant over the enrollment period—electronic logs of all transmissions to the central monitor
- The time the participant transmitted the electrocardiogram—histogram of electrocardiogram transmission time distribution

Participants who completed the program

- Number and proportion of participants who completed the program—via log sheet

Proportion of dropouts (exit program prematurely) and reasons

- Number and proportion of dropouts and reasons—via log sheet

Actual costs of the screening program

- Operational costs (eg, electrocardiogram devices, subscription fee to Kardia monitoring portal, and mail postages) recorded and verified using invoices and receipts
- Costs of personnel involved in interpreting electrocardiograms computed based on their hourly wage and the time they spent in their roles in this program—data collected prospectively and throughout program implementation

Agreement in electrocardiogram interpretations

- Number of consultations and percentages of agreement between the monitoring personnel and cardiologists in clarifying uncertain electrocardiogram abnormalities—logs of all interactions

Usability assessment at the 12th month

- Responses to the Usability questionnaire will be assessed by 5-point Likert scale—via self-report questionnaires (Multimedia Appendix 1)

Participant acceptability and barriers to and enablers of implementation

- In-depth one-on-one interview with participants (Multimedia Appendix 1) and general practitioners (Multimedia Appendix 2)
- Thematic analysis

Impact of frailty on feasibility assessments and the outcomes

- Frailty assessed by the 5-item FRAIL (Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight) scale (Multimedia Appendix 1)

Ethics and Dissemination

This study was approved by the human research ethics committee of the University of Sydney (reference number 2020/680). The study is conducted in full conformance with principles of the International Committee on Harmonization of Good Clinical Practice and *Declaration of Helsinki* Good Clinical Practice guidelines and within the laws and regulations of the Australian National Health and Medical Research Council.

Results

This study was funded by a National Heart Foundation Vanguard grant awarded in October 2019. The study was approved by the

human research ethics committee of the University of Sydney in November 2020. The first participant was enrolled in May 2021. As of December 2021, a total of 112 participants have been enrolled. Data analysis and results are expected to be published in December 2023.

Discussion

Anticipated Strengths

This patient-led AF screening in the community is different from clinician-led opportunistic screening. In this model of screening, participants are trained and empowered to self-record ECGs instead of awaiting clinicians to screen them opportunistically. The centralized remote monitoring team will facilitate patient access to see their GPs.

Drawing on the strengths of quantitative and qualitative methodologies [45], this study will provide evidence for AF detection rates, participant satisfaction, and feasibility of implementing this program using a telephone, a video interface, and the internet for older people, including people who are frail, with the potential to extend to other vulnerable groups such as people with disabilities, people who are socially isolated or because of the COVID-19 pandemic lockdown, and those who live in remote areas.

Participant satisfaction scores often reflect the convergence and gap between participant expectations and actual experiences [46], and satisfaction scores also measure how well the intervention was received by participants [31]; hence, satisfaction is a commonly evaluated outcome in clinical trials [46]. Nonetheless, satisfaction scores would not provide insights into participant experiences, which provide contextualized feedback to improve the screening program. We complement this with in-depth one-on-one semistructured interviews with participants and GPs to explore their insights on barriers and enablers.

This is a prospective RCT design. The waitlist-controlled design provides equitable access to all participants in a mass screening strategy. It is a simple, acceptable, and noninvasive screening strategy that can be implemented regardless of geographical location. Our novel approach in promoting patient-empowered self-screening integrated with a clinician-coordinated centralized system will provide patients with integrated care that facilitates access to GPs and specialist services. Patients will receive training to use the device, and they will be reminded to perform their routine ECGs if they have not done so for 3 consecutive days. This type of interaction and reminder system has been proven to yield positive health outcomes such as engagement in positive health behaviors [47]. Performing self-screening could raise awareness of self-care and improve patient confidence in self-care, which is a form of patient empowerment that is promoted by the World Health Organization [24].

We anticipate that this study will provide data on whether implementation of this type of community-based model of care is feasible and acceptable to patients and health providers in the community. At study completion, the results will be shared with the Heart Foundation (study funder), policy makers, health providers, consumers, and other stakeholders. Access to ECG monitoring devices for future screening programs is dependent on feasibility from a cost perspective, as well as aspects of whether this would be a barrier to implementation. We will conduct a qualitative analysis to understand participants' perceptions of the value of the monitoring device to their well-being, as well as the affordability of the device.

Anticipated Research Outcomes and Impacts on Clinical Practice and Policy

This study will provide information on the usability of and costs associated with AF mass screening in Australian people aged ≥75 years. It will also provide evidence of AF incidence in older people in Australia. This can potentially facilitate the development of a national screening program for AF in older people and people who are frail.

Screening for AF is more likely to occur in the community or general practice setting than in the hospital setting. It took an average of 10.6 minutes to acquire a 12-lead ECG in a general practice setting (including the time preparing the patient for ECG acquisition and placing the electrodes correctly on the patient) [48]. In contrast, this patient-empowered self-screening potentially reduces time constraints faced by clinicians as patients are empowered to self-record ECGs in the community rather than clinicians spending the additional time acquiring ECGs opportunistically in a busy clinical setting. In this program, GPs can access help from the participating cardiology team to confirm the diagnosis and facilitate appropriate management of new AF if necessary. This could enhance access and interaction between GPs and cardiologists in providing integrated care to patients to achieve better health outcomes.

Anticipated Challenges and Limitations

All study procedures have been designed to be conducted remotely by telephone or video interface to facilitate this study in the context of the COVID-19 pandemic. Therefore, the collection of baseline data and medical history relies on participants' self-reported information. There is a potential for loss to follow-up in older patients who are frail; for example, participants do not record ECGs. We will attempt to minimize this by following up with patients when no ECG is received for 3 consecutive days. There may be a potential selection bias in this study based on the inclusion criteria. For example, this trial is limited to older people who can understand English and have a smartphone. These participants may come from higher socioeconomic communities and represent a more motivated cohort than the general population of older people.

Conclusions

The findings from this implementation study will guide the development of practical and attainable solutions to address a gap in AF screening among older people in the community and other vulnerable groups. In addition, this study will explore the experiences and feedback from participants and clinicians and provide new knowledge on the processes involved in the implementation of the screening program and how processes can be improved, replicated, and scaled up to reach larger populations.

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Authors' Contributions

KCW, TNN, and CKC prepared the study protocol, which was discussed, reviewed, and approved by the entire study team. KCW, TNN, SM, and CKC established the sample size, randomization, and statistical analysis plan. KCW consulted with SAT to formulate the qualitative methodology, including the evaluation framework, and incorporated them with the statistical analysis plan. KCW discussed with ST about establishing the electrocardiogram (ECG) monitoring, management, and escalation plan. ST, ABI, and KCW will monitor the ECGs in the central monitoring system. CKC and SK will adjudicate and confirm the diagnosis of ECGs with uncertain abnormalities. KCW will communicate with patients and clinicians when atrial fibrillation or clinically significant ECG abnormalities are detected. KCW will conduct interviews with the participants and clinicians. MJB and another research assistant will recruit participants, train participants to use the ECG device, and record participant data in the REDCap (Research Electronic Data Capture) system. KCW will analyze the ECG data from the ECG central monitoring system. VG will oversee the study, facilitate participant recruitment, liaise with the ethics and government authorities of the university, and ensure overall conduct and compliance of the study as per the approved protocol. CKC, TNN, SK, TU and RIL are project supervisors. KCW will lead the overall implementation and evaluation of the study. KCW and TNN will perform the overall process evaluation of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient participant data collection at baseline, 6-month follow-up, and 12-month completion of the program and semistructured interview guide.
[PDF File (Adobe PDF File), 138 KB - resprot_v11i2e34778_app1.pdf]

Multimedia Appendix 2
General practitioner data form and semistructured interview guide.
[PDF File (Adobe PDF File), 50 KB - resprot_v11i2e34778_app2.pdf]

References

1. Andrade JG, Macle L, Nattel S, Verma A, Cairns J. Contemporary Atrial Fibrillation Management: a comparison of the current AHA/ACC/HRS, CCS, and ESC guidelines. Can J Cardiol 2017 Aug;33(8):965-976. [doi: 10.1016/j.cjca.2017.06.002] [Medline: 28754397]
2. Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, Stewart S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. Med J Aust 2015 Jan 19;202(1):32-35. [doi: 10.5694/mja14.00238] [Medline: 25588442]
3. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006 Apr;27(8):949-953. [doi: 10.1093/eurheartj/ehi825] [Medline: 16527828]
4. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. J Am Coll Cardiol 2020 Dec 22;76(25):2982-3021 [FREE Full text] [doi: 10.1016/j.jacc.2020.11.010] [Medline: 33309175]
5. Feinberg W, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995 Mar 13;155(5):469-473. [Medline: 7864703]
6. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, et al. Adelaide stroke incidence study. Stroke 2013 May;44(5):1226-1231. [doi: 10.1161/strokeaha.113.675140]

7. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):531-575 [FREE Full text] [doi: 10.1378/chest.11-2304] [Medline: 22315271]
8. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. Thromb Haemost 2013 Aug;110(2):213-222. [doi: 10.1160/TH13-02-0165] [Medline: 23595785]
9. NHFA CSANZ Atrial Fibrillation Guideline Working Group, Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. Heart Lung Circ 2018 Oct;27(10):1209-1266 [FREE Full text] [doi: 10.1016/j.hlc.2018.06.1043] [Medline: 30077228]
10. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, AF-Screen Collaborators. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. Circulation 2017 May 09;135(19):1851-1867. [doi: 10.1161/CIRCULATIONAHA.116.026693] [Medline: 28483832]
11. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg 2016 Nov;50(5):1-88. [doi: 10.1093/ejcts/ezw313] [Medline: 27663299]
12. Mairesse G, Moran P, Van Gelder IC, Elsner C, Rosenqvist M, Mant J, ESC Scientific Document Group. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). Europace 2017 Oct 01;19(10):1589-1623. [doi: 10.1093/europace/eux177] [Medline: 29048522]
13. Uittenbogaart SB, van Gurp NV, Lucassen WA, Winkens B, Nielen M, Erkens PM, et al. Opportunistic screening versus usual care for detection of atrial fibrillation in primary care: cluster randomised controlled trial. Br Med J 2020 Sep 16;370:m3208 [FREE Full text] [doi: 10.1136/bmj.m3208] [Medline: 32938633]
14. Petryszyn P, Niewinski P, Staniak A, Piotrowski P, Well A, Well M, et al. Effectiveness of screening for atrial fibrillation and its determinants. A meta-analysis. PLoS One 2019 Mar 20;14(3):e0213198 [FREE Full text] [doi: 10.1371/journal.pone.0213198] [Medline: 30893323]
15. Walker A, Muhlestein J. Smartphone electrocardiogram monitoring: current perspectives. Adv Health Care Technol 2018 Jun;Volume 4:15-24. [doi: 10.2147/ahct.s138445]
16. Wong K, Thiagalingam A, Kumar S, Marschner S, Kunwar R, Bailey J, et al. User perceptions and experiences of a handheld 12-lead electrocardiographic device in a clinical setting: usability evaluation. JMIR Cardio 2021 Aug 26;5(2):e21186 [FREE Full text] [doi: 10.2196/21186] [Medline: 34435958]
17. Wong KC, Klimis H, Lowres N, von Huben A, Marschner S, Chow CK. Diagnostic accuracy of handheld electrocardiogram devices in detecting atrial fibrillation in adults in community versus hospital settings: a systematic review and meta-analysis. Heart 2020 Aug 11;106(16):1211-1217. [doi: 10.1136/heartjnl-2020-316611] [Medline: 32393588]
18. Wong KC, Kok C, Marschner S, Usherwood T, Chow CK. Screening for atrial fibrillation and other arrhythmias in primary care. BMC Fam Pract 2020 May 06;21(1):79 [FREE Full text] [doi: 10.1186/s12875-020-01151-8] [Medline: 32375662]
19. Orchard J, Li J, Freedman B, Webster R, Salkeld G, Hespe C, et al. Atrial fibrillation screen, management, and guideline-recommended therapy in the rural primary care setting: a cross-sectional study and cost-effectiveness analysis of ehealth tools to support all stages of screening. J Am Heart Assoc 2020 Sep 15;9(18):e017080 [FREE Full text] [doi: 10.1161/JAHA.120.017080] [Medline: 32865129]
20. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. Circulation 2015 Jun 23;131(25):2176-2184. [doi: 10.1161/CIRCULATIONAHA.114.014343] [Medline: 25910800]
21. Halcox JP, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. Circulation 2017 Nov 07;136(19):1784-1794. [doi: 10.1161/CIRCULATIONAHA.117.030583] [Medline: 28851729]
22. Gladstone DJ, Wachter R, Schmalstieg-Bahr K, Quinn FR, Hummers E, Ivers N, SCREEN-AF Investigators and Coordinators. Screening for atrial fibrillation in the older population: a randomized clinical trial. JAMA Cardiol 2021 May 01;6(5):558-567. [doi: 10.1001/jamacardio.2021.0038] [Medline: 33625468]
23. Villani ER, Tummolo AM, Palmer K, Gravina EM, Vetrano DL, Bernabei R, et al. Frailty and atrial fibrillation: a systematic review. Eur J Intern Med 2018 Oct;56:33-38. [doi: 10.1016/j.ejim.2018.04.018] [Medline: 29936074]
24. Patient empowerment and health care. WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care. 2009. URL: https://www.ncbi.nlm.nih.gov/books/NBK144022/ [accessed 2020-10-01]
25. Health Quality Ontario. Remote monitoring of implantable cardioverter-defibrillators, cardiac resynchronization therapy and permanent pacemakers: a health technology assessment. Ont Health Technol Assess Ser 2018;18(7):1-199 [FREE Full text] [Medline: 30443279]

26. Fuertes JN, Anand P, Haggerty G, Kestenbaum M, Rosenblum GC. The physician-patient working alliance and patient psychological attachment, adherence, outcome expectations, and satisfaction in a sample of rheumatology patients. Behav Med 2015 Sep 03;41(2):60-68. [doi: 10.1080/08964289.2013.875885] [Medline: 24354470]
27. Pflugeisen BM, Rebar S, Reedy A, Pierce R, Amoroso PJ. Assessment of clinical trial participant patient satisfaction: a call to action. Trials 2016 Oct 06;17(1):483 [FREE Full text] [doi: 10.1186/s13063-016-1616-6] [Medline: 27716378]
28. Kojima G. Frailty defined by FRAIL Scale as a predictor of mortality: a systematic review and meta-analysis. J Am Med Dir Assoc 2018 Jun;19(6):480-483. [doi: 10.1016/j.jamda.2018.04.006] [Medline: 29793675]
29. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012 Jul 11;16(7):601-608 [FREE Full text] [doi: 10.1007/s12603-012-0084-2] [Medline: 22836700]
30. Woodend AK, Sherrard H, Fraser M, Stuewe L, Cheung T, Struthers C. Telehome monitoring in patients with cardiac disease who are at high risk of readmission. Heart Lung 2008 Jan;37(1):36-45. [doi: 10.1016/j.hrtlng.2007.04.004] [Medline: 18206525]
31. Chae YM, Lee JH, Ho SH, Kim HJ, Jun KH, Won JU. Patient satisfaction with telemedicine in home health services for the elderly. Int J Med Inform 2001 May;61(2-3):167-173. [doi: 10.1016/s1386-5056(01)00139-3] [Medline: 11311671]
32. Uschner D, Schindler D, Hilgers R, Heussen N. randomizeR: an R package for the assessment and implementation of randomization in clinical trials. J Stat Soft 2018;85(8):22. [doi: 10.18637/jss.v085.i08]
33. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
34. Find clinical trials for you. Health Match. 2021. URL: https://healthmatch.io/ [accessed 2022-01-19]
35. Join Us. 2021. URL: https://www.joinus.org.au/ [accessed 2022-01-19]
36. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. Br Med J 2015 Mar 19;350(mar19 6):h1258 [FREE Full text] [doi: 10.1136/bmj.h1258] [Medline: 25791983]
37. Bhaskar R. Reclaiming Reality: A Critical Introduction to Contemporary Philosophy. London, UK: Routledge; 2011.
38. Vasileiou K, Barnett J, Thorpe S, Young T. Characterising and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. BMC Med Res Methodol 2018 Nov 21;18(1):148 [FREE Full text] [doi: 10.1186/s12874-018-0594-7] [Medline: 30463515]
39. Dziura J, Post LA, Zhao Q, Fu Z, Peduzzi P. Strategies for dealing with missing data in clinical trials: from design to analysis. Yale J Biol Med 2013 Sep;86(3):343-358 [FREE Full text] [Medline: 24058309]
40. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007 Dec 16;19(6):349-357. [doi: 10.1093/intqhc/mzm042] [Medline: 17872937]
41. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
42. Byrne D. Complexity Theory and the Social Sciences: An Introduction. London, UK: Routledge; 1998.
43. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013 Sep 18;13(1):117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
44. Patton MQ. Qualitative Research & Evaluation Methods: Integrating Theory and Practice, 4th Edition. Thousand Oaks, CA: SAGE Publications; 2014.
45. Creswell JW, Hirose M. Mixed methods and survey research in family medicine and community health. Fam Med Community Health 2019 Mar 28;7(2):e000086 [FREE Full text] [doi: 10.1136/fmch-2018-000086] [Medline: 32148709]
46. Leonardsen AL, Hardeland C, Helgesen AK, Grøndahl VA. Patient experiences with technology enabled care across healthcare settings- a systematic review. BMC Health Serv Res 2020 Aug 24;20(1):779 [FREE Full text] [doi: 10.1186/s12913-020-05633-4] [Medline: 32838784]
47. Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. J Am Med Assoc 2015 Sep 22;314(12):1255-1263. [doi: 10.1001/jama.2015.10945] [Medline: 26393848]
48. Somerville S, Somerville J, Croft P, Lewis M. Atrial fibrillation: a comparison of methods to identify cases in general practice. Br J Gen Pract 2000 Sep;50(458):727-729 [FREE Full text] [Medline: 11050790]

Abbreviations

AF: atrial fibrillation
CHADS-VASc: congestive heart failure, hypertension, age ≥75 (double score), diabetes, stroke (double score), vascular disease, age 65 to 74 and sex category
COREQ: Consolidated Criteria for Reporting Qualitative Research

ECG: electrocardiogram
FRAIL: Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight
GP: general practitioner
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Functionality and Quality of Asthma mHealth Apps and Their Consistency With International Guidelines: Protocol for a Systematic Search and Evaluation of Mobile Apps

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Abstract

Background: Asthma is a chronic respiratory disorder that requires long-term pharmacotherapy and patient empowerment to manage the condition and recognize and respond to asthma exacerbations. Mobile health (mHealth) apps represent a potential medium through which patients can improve their ability to self-manage their asthma. Few studies have conducted a systematic evaluation of asthma mobile apps for quality and functionality using a validated tool. None of these reviews have systematically assessed these apps for their content and evaluated them against the available international best practice guidelines.

Objective: The objective of this study is to conduct a systematic search and evaluation of adult-targeted asthma mHealth apps. As part of this review, the potential of an mHealth app to improve asthma self-management and the overall quality of the app will be evaluated using the Mobile App Rating Scale framework, and the quality of the information within an app will be evaluated using the current Global Initiative for Asthma guidelines as a reference.

Methods: A stepwise methodological approach was taken in creating this review. First, the most recent Global Initiative for Asthma guidelines were independently reviewed by 2 authors to identify key recommendations that could be feasibly incorporated into an mHealth app. A previously developed asthma assessment framework was identified and was modified to suit our research and ensure that all of these identified recommendations were included. In total, 2 popular app stores were reviewed to identify potential mHealth apps. These apps were screened based on predefined inclusion and exclusion criteria. Suitable apps were then evaluated. Technical information was obtained from publicly available information. The next step was to perform an app quality assessment using the validated Mobile App Rating Scale framework to objectively determine the quality of an app. App functionality was assessed using the Intercontinental Medical Statistics Institute for Health Informatics Functionality Scoring System. Finally, the mHealth apps were assessed using our developed checklist.

Results: Funding has been received for the project from the Respiratory Department at Northern Health, Victoria. Three reviewers have been recruited to systematically evaluate the apps. The results of this study are expected in 2022.

Conclusions: To our knowledge, this review represents the first study to examine all mHealth apps available in Australia that are targeted to adults with asthma for their functionality, quality, and consistency with international best practice guidelines. Although this review will only be conducted on mHealth apps available in Australia, many apps are available worldwide; thus, this study should be largely generalizable to other English-speaking regions and users. The results of this review will help to fill gaps in the literature and assist clinicians in providing evidence-based advice to patients wishing to use mHealth apps as part of their asthma self-management.

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KEYWORDS

asthma; mHealth; mobile phone; applications; self-management; chronic disease; respiratory; smartphone; asthma app

Introduction

Background

Asthma is a chronic respiratory disorder that is clinically defined as a combination of typical respiratory symptoms (outlined below) and significant variable reversible airflow limitation [1]. Symptoms that people with asthma can experience include periods of shortness of breath, cough, wheezing, and chest tightness. When the frequency or severity of these symptoms increases compared with a patient's baseline respiratory status, it represents an *asthma exacerbation* or *flare-up* [2].

Asthma is a significant worldwide chronic health issue affecting 1% to 18% of the global population [3]. In Australia, 2.7 million people have asthma, representing 11% of the total population [4]. A 2012 survey of Australians with asthma found that 10% of them had presented to an emergency department ≥1 time for asthma-related symptoms, and 29% reported an urgent health care visit (to either a general practitioner or emergency facility) [4]. Asthma accounts for 34% of Australia's burden of disease because of respiratory conditions and 2.5% of Australia's total burden of disease [4]. Australian adults with asthma are more likely to describe themselves as having a poor quality of life compared with those without asthma and are less likely to rate their health status as excellent or very good. This trend is more pronounced among those with severe or poorly controlled asthma [4]. When observing the total cost that asthma has on the Australian health system, it is evident that hospital-related costs outweigh non–hospital-related costs (Aus $205 million/year [approximately US $150 million] vs Aus $163 million/year [approximately US $120 million]) [4]. Theoretically, reducing exacerbations would reduce the requirement for hospitalizations, unplanned primary care presentations, and indirect costs such as work absenteeism, and thus assist in bringing these costs down.

The Global Initiative for Asthma (GINA) guidelines represent regularly updated guidelines based on reviews of the available scientific literature by an international panel of experts [3]. It is from these guidelines that many local asthma management guidelines stem from. In addition to pharmacotherapy for asthma management, the GINA guidelines advise that a key aspect of treatment is educating patients on recognizing symptoms of asthma exacerbations and learning when and how to self-manage them [3]. Mobile health (mHealth) apps represent a potential medium through which patients can improve their ability to self-manage their asthma. From the most recent Deloitte [5] review of Australia's telecommunication status, 89% of the Australian population uses smartphones. This widespread, almost ubiquitous use of smartphones, and the apps that run on them, represents an opportunity to empower patients to track asthma symptoms, learn about their condition, and undertake practical self-management strategies. A number of systematic evaluations of asthma mobile apps have been conducted; however, to our knowledge, none have assessed all available apps for the presence and quality of information that they provide compared with available best practice management guidelines in a systematic way [6-8].

This review will look at both free and paid asthma mHealth apps targeted toward adults with asthma available from the Apple App Store (iOS) and Google Play Store (Android) and examine the functionality and quality of these apps and the consistency of these available apps with recommendations from the GINA guidelines, making it the first review of its kind. All of the review processes will be conducted on apps available in the region of the researchers, Australia. Although mobile apps are often published across multiple regions in the same language, different regions can have different apps available on their stores. As such, some identified mHealth apps may not be available in all regions, whereas others available in other regions may not be available in Australia. However, given that most apps identified in this review will also be available in other English-speaking regions, the results should be largely generalizable to these regions.

Objective

The objective of this study is to conduct a systematic search and evaluation of the available English-language mHealth apps targeted to adults with asthma, assess their potential for improving asthma self-management, and assess the quality of the information they provide using the current GINA guidelines as a reference.

Methods

Overview

The methodology of how we will achieve these research objectives is explained in this section. First, the GINA guidelines were read by 2 medical professionals (BR and KS) to identify and establish a consensus of key recommendations in the guidelines that could be feasibly incorporated into an app for asthma management. Next, mobile apps in the selected app stores will be identified. After identification, we will screen the apps based on the selection criteria. Finally, we will evaluate the quality and functionality of the mHealth apps and extract this information into a database.

Study Setting

This study will be conducted in Australia by medical practitioners, medical students, and digital health researchers. It will assess mHealth apps presented in English on Australian mobile app stores. Given that the clinicians involved in this research are adult physicians, and the management principles of asthma vary significantly between adult and pediatric populations, only those mHealth apps targeted toward adults

with asthma will be evaluated. Where possible, we have followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews [9]. Given that this is a protocol and is a review of mobile apps instead of journal articles, some of the items in the guideline checklist are not relevant to this protocol.

Review of the GINA Guidelines to Establish That the Recommendations Are Feasible for Incorporation Into an mHealth App

We will use the established Mobile App Rating Scale (MARS) to assess the usability and overall quality of an app, as detailed in the section below. Although this framework is helpful for reviewing general app features and quality, it does not possess information specific to asthma management. There is no validated peer-reviewed asthma mHealth app checklist or framework. However, a previously developed asthma app assessment framework from Guan et al [10] has been created by researchers in China. The framework developed by these researchers has not been derived and validated into an instrument since its production; however, it was developed in a systematic fashion using a Delphi survey technique and by consulting a number of different respiratory specialists [10]. Although this represents a solid and well–thought-out framework, there were a number of issues identified with only using this framework for our study. First, it includes a number of topics regarding the utility and usability of an app. For our study, we have elected to use the validated MARS assessment framework to look at these areas. Thus, looking at these topics doubles the information that is already being looked at. Second, we wanted to ensure that the recommendations identified from the GINA guidelines were in the checklist. Although the framework by Guan et al [10] has been developed by numerous respiratory specialists, it never specifically references these global guidelines in its development. We want to ensure current best practice guidelines are met and thus have used these guidelines. Third, given that this checklist was developed by overseas practitioners, we wanted to ensure that it was still applicable to Australian and Western clinicians and patients. Finally, this is not a validated tool, and as such, caution is warranted when using this framework. For these reasons, we sought to have 2 clinicians review the current international best practice asthma guidelines to establish which recommendations could be feasibly incorporated into an mHealth app and develop our own checklist, which we will meld with aspects of the framework by Guan et al [10].

This was conducted independently by 2 of the primary team members: the first and final authors. The 2020 GINA guidelines were read in full, and each reviewer noted recommendations from the GINA that they believed could be incorporated into an asthma app for patients. We hoped to capture all relevant recommendations that could feasibly be integrated into a mobile app by conducting this process in an independent manner with reviewers at different stages in their respiratory medicine careers. After each author had identified their recommendations, they came together to see if a consensus could be reached on them. If no consensus could be reached, the plan was for an independent senior member of the team to review the identified recommendations to make a decision. However, this was not required. The authors either identified the same or similar recommendations or agreed with the recommendations that the other authors identified that they did not. The identified recommendations from each author and the recommendations where a consensus was reached, which represent the final identified recommendations, are shown in Table 1.

Therefore, we will develop a checklist from these identified recommendations and a modified version of the framework by Guan et al [10] to ensure that all of our recognized recommendations are included and that the information we intend to obtain using other measures (ie, the MARS framework) is not. This checklist will be demonstrated later in this protocol.

The presence or absence of the features derived from the checklist by Guan et al [10] and the GINA guidelines will be used as a marker of the information quality of the app. Given that we are modifying their checklist, we will not assign the weighting that Guan et al [10] attributed to certain framework groups. Furthermore, given that these apps are for use by patients with asthma and not health professionals, what a patient considers important may, and often does, differ from their health professional. Thus, the weighting does not hold as much relevance in our study as the subgroups have been weighted by physician impression of importance. Therefore, our checklist only examines whether an asthma app does or does not contain information or features developed using the GINA guidelines or the framework by Guan et al [10]. We will assess these apps using both our developed checklist and the MARS framework.

Table 1. Recommendations identified from the Global Initiative for Asthma guidelines that could feasibly be incorporated into a mobile health app.

Reviewer 1	Reviewer 2	Consensus reached?
Assess symptom control (eg, ACQ[a])	Support for assessing symptom control over a 4-week period	Support for assessing symptom control over a 4-week period looking at the frequency of asthma symptoms, night waking because of asthma, frequency of SABA[b] use, and any activity limitation because of asthma; uses recognized screening, symptom control or numerical asthma control tools, and peak flow measurement
Ability to self-track symptoms with or without peak flow	—[c]	Encourages patients to track symptoms and peak flow measurements
Risk factors for future exacerbations	Helps users identify the future risk of exacerbations	Helps users identify the risk of future exacerbations
Screening for comorbidities and education regarding managing them	Screens for comorbidities and assists patients with managing them	Screens for relevant comorbidities and educates patients on the management of these
Inhaler technique with or without video	Provides education on appropriate inhaler techniques	Provides education on appropriate inhaler techniques with visual aids
Ability to record action plan	Provides an area for patients to keep and refer to their written action plan	Provides an area for patients to keep and refer to their written action plan
Reminder to engage with primary care	Reminds users to see their health care provider for management and review of their asthma	Provides reminders to users to see their health care provider for management and review of their asthma
—	Specifically provides the suggestion to see a health care provider if a patient is using a SABA alone	Specifically provides the suggestion to see a health care provider if a patient is using a SABA alone
Medication adherence	Prompts users to adhere to controller medications even when symptoms are infrequent	Prompts users to adhere to controller medications even when symptoms are infrequent
General asthma education	Provides knowledge on general asthma information, management of asthma, modifiable risk factors and strategies to address them, and when to see a health care provider	Provides knowledge on general asthma information, management of asthma, modifiable risk factors and strategies to address them, when to see a health care provider, and identification and management of comorbidities
Help with activating action plan	Provides advice on when to refer to a patient's asthma action plan based on self-monitoring of symptoms or PEF[d]	Provides advice on when to refer to a patient's asthma action plan based on self-monitoring of symptoms or PEF
—	Prompts patient to see primary HCP[e] if features of an asthma exacerbation (symptoms and SABA use) are identified via the app	Prompts patient to see primary HCP if features of an asthma exacerbation (symptoms and SABA use) are identified via the app

[a]ACQ: Asthma Control Questionnaire.

[b]SABA: short-acting β-agonist.

[c]Not available. Recommendation identified by one reviewer but not the other.

[d]PEF: peak expiratory flow.

[e]HCP: health care provider.

Identification, Screening, and Selection of Mobile Apps for Review

This review will include both free and paid apps from the two most popular app stores in Australia across iOS and Android operating systems: the Apple App Store and Google Play Store.

Our approach to identifying these apps will follow the approach used in similar studies [6-8]. We will use the search bar in each of the stores and input the term *asthma*. This is a broad search category that will yield a number of results, some irrelevant to our review. However, the point of this is to capture all apps for review. This search will occur on August 10, 2021, in Melbourne, Australia. At the time of publication, this has already occurred.

All reviewers will be instructed to ensure that their operating system is up to date before commencing the following steps.

In total, 2 reviewers will search both app stores independently on the same day. One of the reviewers will be the primary author, and the second is a final year medical student with interest in digital health. These are 2 of the 3 people who will review the apps later in the study. Having 2 independent reviewers will aid quality assurance at this point of the review and reduce the risk of selection bias. The primary author of the study will review these apps, as will a final year medical student who is yet to be recruited. Screenshots will be taken of the results pages and sent to the primary researcher for record keeping. After obtaining the results for this search term, each reviewer will input the information into a Microsoft Excel

spreadsheet (see Multimedia Appendix 1 for an example) in the order that they appear in the search results. The reviewers will then compare their results to ensure that they have captured all the available apps. If an app has been missed, the reviewers will need to recheck the stores until they have identified all available apps.

Screening of the apps identified in the previous step will occur next. This process will be comparable with similar reviews that have looked at the quality of mobile apps for diabetes self-management [11]. For all apps identified above, the same 2 reviewers will individually look at the app title, description, and attached photos, looking to identify inclusion and exclusion criteria for the app to undergo further evaluation.

An identified asthma app will be included in the evaluation stage if all of the following apply: (1) its primary role is related to asthma, (2) it is targeted to those with asthma, (3) it can be run on mobile phones, and (4) it is in English.

Apps will be excluded if any of the following apply: (1) it is not primarily related to asthma, (2) it is primarily targeted toward health care professionals (as stated in the product description), (3) it is not in English, and (4) it is targeted toward pediatric patients.

This information will be entered into a Microsoft Excel spreadsheet for record keeping (Multimedia Appendix 2).

Next, all apps included and not excluded at this stage will be downloaded by a third reviewer. The purpose of this is to identify apps that do not install properly or function after downloading. In the event of a suspected app malfunction, the reviewer will alert another reviewer, who will also attempt to download and operate the app. The purpose of this is to eliminate the risk that it is just the individual reviewer's phone that is malfunctioning. If both reviewers cannot properly install or get the app to function after download, it will be eliminated from the review.

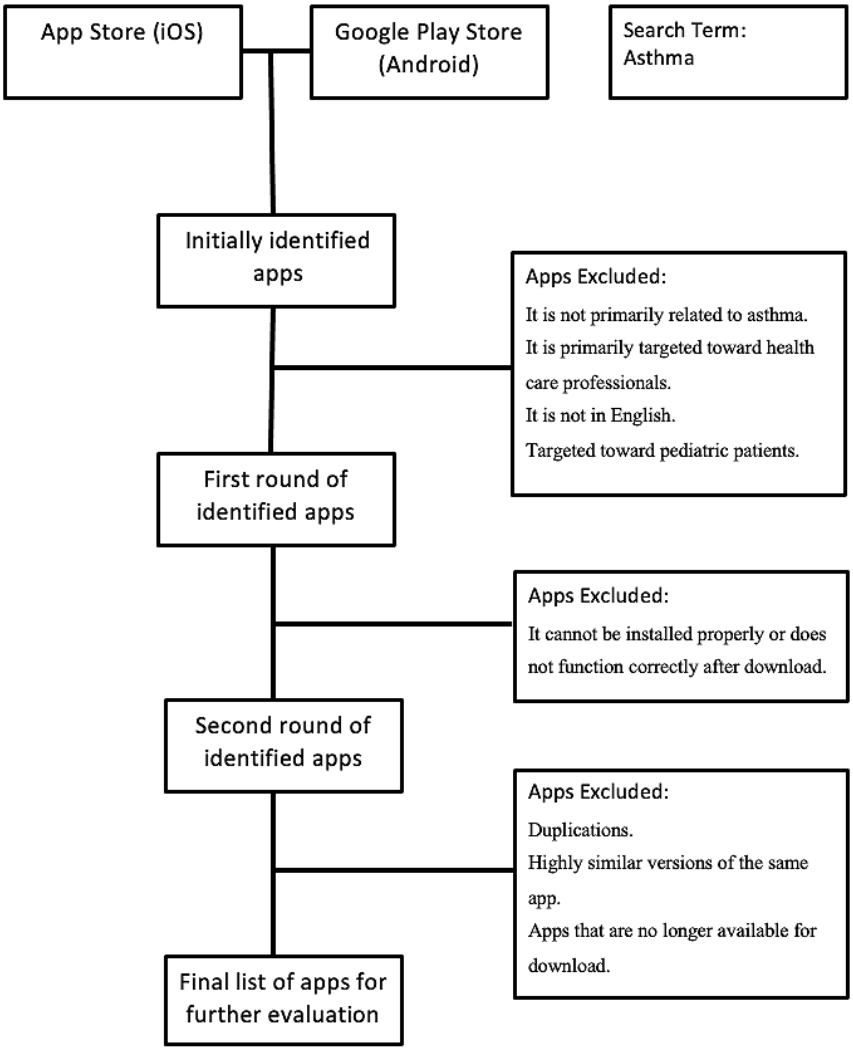
If, at any stage up to this point, discrepancies exist between the reviewers where they cannot reach a consensus, the app will be reviewed by a senior team member to make the final decision.

Finally, a last round of screening will be conducted by a third member of the research team. Here, the following apps will be removed from the review:

1. Duplications (ie, those apps that are available from both stores)
   - In the event that an app is available on both stores, the most updated version of the app will be kept.
   - In the event of an app having the same update date on both stores, it will be left to the discretion of the reviewer as to which app of the 2 is included for further review.
2. Highly similar versions of the same app (eg, a pro version)
   - In the event of this occurring, the pro version will be kept. This is as our primary goal is to assess for best-quality asthma apps.
3. Apps that are no longer available for download

After this, we will have a complete list of apps to be reviewed in the evaluation and data extraction. Figure 1 shows a flowchart of the screening process of these apps.

Figure 1. Flowchart of the screening process of apps to arrive at a final list for further evaluation.



App Evaluation and Data Extraction

Overview

An internet database will be established on Qualtrics (Qualtrics International Inc) to standardize data extraction. This will allow the various researchers to review and enter data from their various places of work. From this software, we will be able to export the information for the analysis of the results later in the study.

As with previous studies that have conducted a similar review of mHealth apps, 2 assessors will review the description of each of the apps selected above, download it, and use the app for a minimum of 20 minutes to be familiar with all functions of the app [11]. There will be a total of 3 app reviewers in this project. Using a web-based team generator, all apps suitable for evaluation will be randomly allocated to assessors so that each app will be appraised by 2 reviewers. The combination of this random allocation and having each app evaluated by 2 reviewers independently will help reduce bias. At the same time, ensuring that each reviewer does not have an inordinate number of apps to assess will serve to prevent overburdening the reviewer with workload to optimize task performance.

The reviewers will subsequently conduct the evaluation and enter the data into the Qualtrics database. Each reviewer will perform this process individually. If, at any stage, a reviewer has a question regarding a certain feature of an app and how to assess it, they will be advised to talk to one of the senior members of the team not involved in the review process.

There are 4 key aspects of the app evaluation and data extraction process. Below are the summaries of these, with the checklists provided in Multimedia Appendix 3 and a step-by-step guide to data collection in Multimedia Appendix 4 [3,12-14].

Technical Information About the App

The first step of data collection will involve gathering basic technical information about the app. The decision of which technical information to include is based on prior app review studies [6,11,15]. This will be derived from publicly available information in the in-store app descriptions and any in-app information sections. If required, the app developer's website will be consulted. Data that will be collected regarding the

technical information include the app name, date of release, date of update, developer, developer affiliations, price, rating, number of ratings, platform or platforms, size of the app, and number of downloads. The main purpose of this category is for descriptive purposes when discussing the other findings of the review [15]. This checklist is provided in Multimedia Appendix 3.

App Quality Assessment

This assessment will be completed using the validated MARS to objectively determine the quality of the apps selected above [15,16]. This scale has 4 separate domains that are assessed to evaluate mobile app quality. These are engagement, functionality, esthetics, and information quality [15,16]. A total of 19 items, each with a 5-point scale regarding the quality in these 4 domains, makes up the MARS [15]. This framework is presented in Multimedia Appendix 3. Once this has been completed for an app, a mean score for that domain and the overall MARS will be calculated. Following these objective questions, there are subjective questions to evaluate user satisfaction and the perceived impact of the app on the user's knowledge, attitude, motivation to change, the likelihood of change, and awareness of the importance of changing their asthma self-management [15].

App Functionality

App functionality refers to what the app can do for a user and is an important marker of whether an app offers much benefit to users and the overall quality of an app. Although the MARS framework looks at the overall quality of a mobile app, it predominantly focuses on performance, ease of use, gestural design navigation, and navigation of the app [15]. For this reason, the Intercontinental Medical Statistics Institute for Health Informatics Functionality Scoring System, henceforth known as the *IMS functionality score*, will be used. This score has been developed by the above institute and is based on 7 functionality criteria and 4 subcategories in the *record* functionality criterion. This score focuses on the scope of functions, including the ability of the app to inform, instruct, record, display, guide, remind or alert, and communicate information [11,17]. Each app is assessed for having or not having these functions and is then given a total functionality score between 0 and 11 [17]. This scoring system is presented in Multimedia Appendix 3.

Presence of App Features Consistent With Asthma Guidelines

A review of the available literature using the CINAHL, MEDLINE, Embase, and PubMed databases was performed to look at the work previous studies conducting a review of asthma apps have done. Although we were able to identify a study that developed a framework for the assessment of asthma smartphone apps, no validated checklists or instruments were identified [10]. In the study, the researchers surveyed the professionals involved to develop an attributed weight of importance for each item using a Delphi survey technique [10]. As discussed above, although derived from parts of the framework by Guan et al [10], our checklist will not be identical to theirs. The main functions of the app that we will be interested in assessing in our checklist include asthma information, self-management skill training (including peak flow use, inhaler technique, and nonpharmacological strategies), monitoring of asthma symptoms, risk evaluation, and prompting (medication reminders and referring to action plan reminders and suggestions for seeking health advice).

The checklist that we developed and that will be used is provided in Multimedia Appendix 3.

Each of the selected apps will be assessed using this checklist, and the data will be extracted into the database discussed above. Where significant differences in judgment are identified, a senior team member not involved in the original review will be alerted and review the app to make the final decision.

Reviewer Training

A training session will be organized among all the reviewers before the initial data extraction. This training session will be similar to the one performed by Gong et al [11] for their diabetes app review. The goals of this session will be to ensure all participants (1) understand the scope and purpose of the study, (2) understand this study protocol and have read it in full, (3) understand how to search for apps on the Google Play Store and Apple App Store, (4) understand how to extract information from these apps, and (5) understand how to enter data into our web-based database.

This training will be in the form of a web-based lecture; step-by-step examples via screen sharing features; and, finally, case studies, with reviewers expected to use the protocol to assess 5 apps. If the reviewers reach ≥90% agreement, the main study can begin. If the reviewers are <90% in agreement, a further 5 apps will be assessed. If this is an ongoing issue, then the protocol will be examined for flaws and areas of improvement. This session will be conducted in 2 components. In the first session, BR will talk with the other 2 reviewers regarding asthma self-management and how to complete the created checklist. The second session will be run by EG, who has extensive experience in mHealth app reviews and the use of the MARS framework and will instruct reviewers on how to use this appropriately.

A step-by-step reference guide has also been created to inform reviewers on how to fill out the various frameworks and checklists involved in the study. This is provided in Multimedia Appendix 4.

Quality Assurance, Data Management, and Data Analysis

Quality control is ensured by a number of different methods. First, adequate training will be provided to all the researchers. Second, the selected apps will be allocated to reviewers by web-based random allocation software in an effort to reduce selection bias. Third, 2 reviewers have assessed all mobile apps independently. Finally, discrepancies in opinion between reviewers will be solved by a third senior team member. A total of 2 different major app databases will be used to reduce the risk of selection bias. Given that this is a review of apps and not articles, there are no unpublished or gray literature searches that need to be done, reducing the risk of publication bias.

All data will be entered into either our Microsoft Excel spreadsheet during the screening process or the web-based database when evaluating the apps. These will be stored on a cloud-based system to which only the team has access.

Once ready, the data will be retrieved from these sources, and a descriptive analysis will be performed using data analysis software.

Results

The above information will be collected in the web-based Qualtrics database and Microsoft Excel spreadsheet. Once completed, all of these data will be downloaded for subsequent analysis. This analysis will comprise a descriptive analysis and calculation of the mean and SD. In the event of skewed data distribution, the IQR and median will be calculated. Given that each app will be double-rated by 2 separate reviewers, interrater reliability scores will be calculated.

At this stage, we plan to conduct all data analyses using Stata statistical software version 14 (StataCorp LLC). We will generate visual figures to demonstrate the results in an easy-to-interpret, visually friendly manner using Microsoft Excel (version 16, Office 365). This study is expected to conclude in late 2022.

Discussion

Comparison With Prior Work

This is not the first review of available mHealth asthma apps. Prior studies that have conducted these assessments have primarily focused on evaluating the quality and functionality of apps using the MARS framework, as we do in this study [6-8]. From a review of the literature over the past 5 years, only 2 prior studies were found to have conducted some sort of assessment of the alignment of apps with asthma self-management principles. Both of these studies only looked at free apps, eliminating a number of apps from review [8,18]. The data collection for both reviews occurred >4 years ago [8,18]. In the rapidly developing marketplace of mobile apps, a number of new apps have been released in this time. Our review will look at both free and paid apps and provide an updated assessment, given that our data collection will take place in 2021. Furthermore, Househ et al [18] did not assess apps from the Apple App Store, focusing only on the Google Play Store, and therefore did not fully assess the breadth of available English-language apps in the marketplace. These authors evaluated whether apps included or did not include information consistent with GINA guidelines as per a checklist created by 1 author [18]. However, this was limited to asthma information and education and did not include further features such as the ability of an app to track information, provide asthma skill training, or personalize information. This review also did not examine the overall app quality using the validated MARS framework [18]. Our review benefits from having 2 independent clinicians review the guidelines to establish all GINA self-management recommendations that could be feasibly incorporated into an mHealth app and review app quality using the MARS framework. Furthermore, we will examine not only the presence of information but also the presence or absence of the ability to track asthma symptoms and provide reminders and skill training and all features derived from the GINA guidelines that are provided in Multimedia Appendix 3. As part of their app review, Tan et al [8] established a framework for assessing the alignment of mHealth apps with the theoretical principles of self-management of allergic rhinitis or asthma [8]. A total of 6 asthma self-management principles were identified based on a literature review and author consensus [8]. Our review has taken the further step of specifically deriving the self-management principles from the international best practice GINA guidelines and creating a more extensive checklist looking at these principles. Therefore, the inclusion of paid apps, the creation of an asthma self-management principle checklist derived from international best practice guidelines, and the up-to-date nature of this study will make our study unique.

Projected Significance

The projected significance of this review is 3-fold. First, it adds to the body of literature on this topic. The systematic approach that we have taken in developing the methodology for this project and the asthma self-management principle checklist will result in a robust evaluation of the quality and content alignment with guidelines of the available mHealth apps. Second, by examining the consistency of these apps with international best practice guidelines, the results will assist clinicians in providing evidence-based advice to adult patients wishing to use mHealth apps as part of their asthma self-management. Finally, by performing this review, we will be able to identify what asthma mHealth apps do well in and what they need improvement in. This will assist in the future development of evidence-based asthma mHealth apps and future research.

Conclusions

This review represents the first study to our knowledge to examine all English-language mHealth apps available in Australia that are targeted to adults with asthma for their functionality, quality, and consistency with international best practice guidelines. Most apps identified in this review will also be available in other English-speaking regions; thus, the results should be largely generalizable to these regions. The results of this review will help fill gaps in the literature and assist clinicians in providing evidence-based advice to adult patients wishing to use mHealth apps as part of their asthma self-management. Furthermore, it will assist in identifying current gaps in the quality and content of available mHealth apps to develop robust, evidence-based asthma mHealth apps in the future.

Acknowledgments

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Authors' Contributions

BO and KS conceived this study. BR developed this protocol by adapting a previously created protocol by EG for a diabetes mHealth app review project. KS and BR reviewed the GINA guidelines to establish key recommendations that could be feasibly incorporated into a mHealth app. BO and KS provided valuable guidance and advice in the development of this protocol, subsequent data collection, and manuscript development. BR and 2 medical students, DZ and EP, will be the app reviewers for this project. BR will be the primary author of the manuscripts written from the information obtained using this protocol. EG and BR will also provide training to all the reviewers of the project. All authors contributed to the refinement of the study protocol and the approval of the final manuscript. The Respiratory Research Team at the Northern Hospital assisted in providing general advice to the authors.

Conflicts of Interest

The Northern Health Respiratory Department is providing funding for this study. The head of this department, KS, is a key author of this paper. The department does not have competing or fiduciary interests that would be affected by the results of this study. KS is not responsible for directly reviewing the apps included in the study or for the data analysis.

Multimedia Appendix 1
Example of a table for recording app store search results.
[DOCX File , 21 KB - resprot_v11i2e33103_app1.docx]

Multimedia Appendix 2
Table for determining inclusion or exclusion of an app.
[DOCX File , 16 KB - resprot_v11i2e33103_app2.docx]

Multimedia Appendix 3
Data extraction forms (technical information, Mobile App Rating Scale, Intercontinental Medical Statistics functionality score, and asthma assessment checklist).
[DOCX File , 47 KB - resprot_v11i2e33103_app3.docx]

Multimedia Appendix 4
Stepwise guide on the key steps of data extraction and evaluation.
[DOCX File , 162 KB - resprot_v11i2e33103_app4.docx]

References

1. Australian asthma handbook. National Asthma Council. 2021. URL: https://www.asthmahandbook.org.au/diagnosis/adults [accessed 2021-01-04]
2. Reddel HK, Taylor DR, Bateman ED, Boulet L, Boushey HA, Busse WW, American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009 Jul 1;180(1):59-99. [doi: 10.1164/rccm.200801-060ST] [Medline: 19535666]
3. Global strategy for asthma management and prevention. Global Initiative for Asthma (GINA). 2020. URL: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf [accessed 2022-01-05]
4. Commonwealth Government of Australia. Asthma. Australian Institute of Health and Welfare. 2020. URL: https://www.aihw.gov.au/reports/chronic-respiratory-conditions/asthma/contents/asthma [accessed 2022-01-04]
5. Mobile nation 2019: the 5G future. Deloitte. 2019. URL: https://www2.deloitte.com/content/dam/Deloitte/au/Documents/Economics/deloitte-au-economics-mobile-nation-2019-080419.pdf [accessed 2022-01-04]
6. Tinschert P, Jakob R, Barata F, Kramer J, Kowatsch T. The potential of mobile apps for improving asthma self-management: a review of publicly available and well-adopted asthma apps. JMIR Mhealth Uhealth 2017 Aug 02;5(8):e113 [FREE Full text] [doi: 10.2196/mhealth.7177] [Medline: 28768606]
7. Ramsey RR, Caromody JK, Voorhees SE, Warning A, Cushing CC, Guilbert TW, et al. A systematic evaluation of asthma management apps examining behavior change techniques. J Allergy Clin Immunol Pract 2019;7(8):2583-2591. [doi: 10.1016/j.jaip.2019.03.041] [Medline: 30954644]

8. Tan R, Cvetkovski B, Kritikos V, O'Hehir RE, Lourenço O, Bousquet J, et al. Identifying an effective mobile health application for the self-management of allergic rhinitis and asthma in Australia. J Asthma 2020 Oct;57(10):1128-1139. [doi: 10.1080/02770903.2019.1640728] [Medline: 31274044]
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021 Mar 29;10(1):89 [FREE Full text] [doi: 10.1186/s13643-021-01626-4] [Medline: 33781348]
10. Guan Z, Sun L, Xiao Q, Wang Y. Constructing an assessment framework for the quality of asthma smartphone applications. BMC Med Inform Decis Mak 2019 Oct 15;19(1):192 [FREE Full text] [doi: 10.1186/s12911-019-0923-8] [Medline: 31615493]
11. Gong E, Zhang Z, Jin X, Liu Y, Zhong L, Wu Y, et al. Quality, functionality, and features of Chinese mobile apps for diabetes self-management: systematic search and evaluation of mobile apps. JMIR Mhealth Uhealth 2020 Apr 07;8(4):e14836 [FREE Full text] [doi: 10.2196/14836] [Medline: 32255432]
12. Pinnock H. Supported self-management for asthma. Breathe (Sheff) 2015 Jun;11(2):98-109 [FREE Full text] [doi: 10.1183/20734735.015614] [Medline: 26306110]
13. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet 2018 Feb 24;391(10122):783-800. [doi: 10.1016/S0140-6736(17)33311-1] [Medline: 29273246]
14. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95. [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
15. Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile app rating scale: a new tool for assessing the quality of health mobile apps. JMIR Mhealth Uhealth 2015;3(1):e27 [FREE Full text] [doi: 10.2196/mhealth.3422] [Medline: 25760773]
16. Terhorst Y, Philippi P, Sander LB, Schultchen D, Paganini S, Bardus M, et al. Validation of the Mobile Application Rating Scale (MARS). PLoS One 2020;15(11):e0241480 [FREE Full text] [doi: 10.1371/journal.pone.0241480] [Medline: 33137123]
17. Aitken M, Gauntlett C. Patient apps for improved healthcare : from novelty to mainstream. IMS Institute for Healthcare Informatics. 2013. URL: http://ignacioriesgo.es/wp-content/uploads/2014/03/iihi_patient_apps_report_editora_39_2_1.pdf [accessed 2022-01-04]
18. Househ M, Hossain N, Jamal A, Zakaria N, Elmetwally A, Alsalamah M, et al. A cross-sectional content analysis of Android applications for asthma. Health Informatics J 2017 Jun 03;23(2):83-95 [FREE Full text] [doi: 10.1177/1460458215627289] [Medline: 26940137]

Abbreviations

GINA: Global Initiative for Asthma
MARS: Mobile App Rating Scale
mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Promoting Resilience and Well-being Through Co-design (The PRIDE Project): Protocol for the Development and Preliminary Evaluation of a Prototype Resilience-Based Intervention for Sexual and Gender Minority Youth

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Abstract

Background: Sexual and gender minority youth (SGMY) are at an increased risk of a range of mental health problems. However, few evidence-informed interventions have been developed specifically to support their mental well-being. Interventions that are evidence-informed for the general population and are fine-tuned specifically with SGMY in mind proffer considerable potential. A particular opportunity lies in the delivery of engaging interventions on the web, where the focus is on enhancing the coping skills and building the resilience of SGMY, in a way that is directly relevant to their experiences. On the basis of earlier work related to an intervention called Rainbow SPARX (Smart, Positive, Active, Realistic, X-factor thoughts), we seek to create a new resource, especially for SGMY in the United Kingdom.

Objective: This project has 3 main objectives. First, together with SGMY as well as key adult experts, we aim to co-design a media-rich evidence-informed web-based SGMY well-being prototype toolkit aimed at those aged between 13 and 19 years. Second, we will explore how the web-based toolkit can be used within public health systems in the United Kingdom by SGMY and potentially other relevant stakeholders. Third, we aim to conduct a preliminary evaluation of the toolkit, which will inform the design of a future effectiveness study.

Methods: The first objective will be met by conducting the following: approximately 10 interviews with SGMY and 15 interviews with adult experts, a scoping review of studies focused on psychosocial coping strategies for SGMY, and co-design workshops with approximately 20 SGMY, which will inform the creation of the prototype toolkit. The second objective will be met by carrying out interviews with approximately 5 selected adult experts and 10 SGMY to explore how the toolkit can be best used and to determine the parameters and user-generated standards for a future effectiveness trial. The final objective will be met with a small-scale process evaluation, using the think out loud methodology, conducted with approximately 10 SGMY.

Results: The study commenced on September 1, 2021, and data gathering for phase 1 began in October 2021.

Conclusions: A considerable body of work has described the issues faced by the SGMY. However, there is a dearth of research seeking to develop interventions for SGMY so that they can thrive. This project aims to co-design such an intervention.

Trial Registration: Research Registry Reference researchregistry6815; https://www.researchregistry.com/browse-the-registry#home/registrationdetails/609e81bda4a706001c94b63a/

International Registered Report Identifier (IRRID): PRR1-10.2196/31036

(JMIR Res Protoc 2022;11(2):e31036) doi:10.2196/31036

KEYWORDS

LGBT; e-therapy; depression; adolescent; youth; online; sexuality; gender; resilience; public health

Introduction

Background

It has been estimated that up to 10% of the adolescent population are sexual and gender minority youth (SGMY), as determined by the results of a range of population-based samples [1,2]. Despite rapid social progress, SGMY often experience abuse, bullying, and victimization. For example, the United Kingdom's nationally representative Millennium Cohort Study of almost 10,000 adolescents reported that sexual minority youth had twice the odds of being verbally abused (odds ratio 2.25) and physically assaulted (odds ratio 2.15) in the past year compared with their heterosexual peers [3]. Less has been documented regarding the mistreatment of gender minority youth, which draws on population-based data. However, reports that do exist highlight a particularly disturbing picture of abuse and discrimination [4,5]. Abuse, mistreatment, and socially hostile environments are thought to be key drivers that impact the mental health of SGMY [6,7]. This, by extension, places them at a considerable risk of depression and other mental health problems. For instance, a meta-analysis of population-based studies (predominantly from the United States) that included 165,380 adolescents highlighted that sexual minority youth had almost 3 times the odds of depressive symptoms and depressive disorder (odds ratio 2.94) compared with their heterosexual peers [1]. Population-based estimates of depression among gender minority youth are even more concerning, with a nationally representative study of secondary school students in New Zealand reporting that transgender adolescents had almost 6 times the odds of clinically significant depressive symptoms (odds ratio 5.7) compared with their peers who were not transgender (ie, were cisgender) [8]. Therefore, a pressing public health challenge is addressing the adverse effects of social violence experienced by these adolescents in the context of a heteropatriarchal society, which places them at greater risk of mental ill-health.

Typically, SGMY cannot simply leave the harmful social environments that impact their mental health owing to practical constraints, including their economic dependence on their families. Many are geographically isolated away from the SGMY supports clustered in cities, and most will not have parents who are sexual and gender minority (SGM) individuals. Further exacerbating these challenges is evidence that SGMY appear to be *coming out* at a younger age [9] when they will have had fewer opportunities to develop effective strategies to cope with stigma processes [7]. Hence, there is an urgent need for widely accessible and targeted help to assist these adolescents in developing the best possible skills to thrive. This need has been reinforced in policy documents. For example, public health policy in England prioritizes the "reduced development and exacerbation of mental health problems, including among high-risk groups and children and adolescents" [10].

There are published studies on strategies to improve harmful social environments, including student-led clubs for SGMY and antibullying interventions delivered face-to-face by SGMY organizations in secondary schools (eg, [11,12]). However, these interventions often miss those who most need them [13]. This includes SGMY in the most challenging environments, not because they are necessarily hard to reach but, as seen with other underserved populations, they will be easy to neglect [13]. As a result, the initiatives to improve the social milieu for SGMY tend to be deployed in environments already supportive of SGMY.

Although SGM people have previously been identified as a *high-risk* population in terms of suicide by the UK government [14], few evidence-informed interventions have been developed specifically for SGMY. In addition, SGM individuals are poorly served by the options available to them in terms of effective *mainstream* interventions [15-17], with SGMY frequently perceiving health care providers as unhelpful [18]. To date, most research in the field has focused on describing the issues SGMY face and not on possible solutions [19,20]. It is already known that SGMY frequently seek informal support on the web [18], but 2 systematic reviews focused on psychosocial treatments published in 2018 and 2019 identified only a single evaluated digital tool to support the mental well-being of SGMY [19,20], and this tool, *Rainbow SPARX* (Smart, Positive, Active, Realistic, X-factor thoughts), was developed in New Zealand [21]. A third more inclusive systematic review was published in 2020 [22]. This review sought to provide an overview of all digital health interventions that aimed to address the mental, physical, or sexual health–related concerns of SGMY. Most of the interventions identified (17 of the 24) targeted the management or risk reduction of sexually transmitted infections, with only 5 interventions primarily targeting mental health–related problems [22]. Of these 5 interventions, 1 focused on drug abuse prevention, 2 targeted nonspecific aspects of psychological well-being using YouTube videos and expressive writing techniques, and 2 targeted internalizing symptoms or problems. The 2 interventions focused on internalizing symptoms were Rainbow SPARX and TODAY! [23]. The TODAY! intervention, from the United States, is an app that offers young sexual minority men techniques that they can use to manage their symptoms of depression and anxiety. It has been subjected to usability testing, and the qualitative data gathered from this testing will be used to inform the later stages of this intervention's development [23]. The paucity of identified digital tools for SGMY is somewhat surprising given that a UK Department of Health commissioned report has highlighted SGMY's strong preference to access help on the web. In this report, 82.3% (n=572 SGMY) of participants indicated that they would be *likely* or *very likely* to choose help in this format. This was followed by a preference for face-to-face assistance (n=355 SGMY, 51.1%) and then mobile (eg, SMS text messaging) forms of support (n=297 SGMY, 43.2%) [18].

Evidence-informed web-based interventions are rarely made available to young people, for instance Rainbow SPARX has not been used outside of a research context. This intervention was co-designed together with SGMY [24] and evaluated in a mixed methods open trial [21,25]. Most recently, a further intervention for SGMY has been delivered digitally for young people (aged 14-29 years) in Canada, also within a research context [26]. The intervention *AFFIRM Online* consists of 8 sessions facilitated by an SGM clinician and is provided on the web in a synchronous manner [26]. Arguably, requiring SGM clinician facilitation limits the intervention's ability to potentially support large numbers of SGMY. Therefore, interventions that are evidence-informed, widely accessible, and fine-tuned with SGMY in mind (eg, with strategies that assist them in managing SGM stigma and victimization) offer considerable potential. This is especially so if delivered on the web as self-help, while harnessing innovations in multimedia design and with a focus on enhancing coping skills.

Objectives

This project has three main objectives:

1. To co-design a media-rich evidence-informed web-based SGMY well-being prototype toolkit together with SGMY as well as key adult experts
2. To explore how the web-based toolkit can be used within public health systems in the United Kingdom by SGMY, and potentially other relevant stakeholders
3. To conduct a preliminary evaluation of the toolkit, which will inform the design of a future effectiveness study

Methods

Target Population and Outcomes

We have decided to cocreate a toolkit for SGMY as a combined group and not a separate resource for either sexual minority youth or gender minority youth. We have come to this decision based on our experiences of attempting to initially focus exclusively on sexual minority young people for Rainbow SPARX-related work, but where we eventually found a focus on SGMY was optimal. In particular, during the recruitment phase of the open trial of Rainbow SPARX, gender minority youth also wanted to participate (and were included) [21]. Moreover, during the trial period, some participants' gender and sexual identities were not static and evolved (understandably given that they were all adolescents). Therefore, we think that a focus on SGMY as a whole is preferable, given the developmental factors and so that we are inclusive of young people who will be fluid, questioning, or unsure of their sexual identity or gender identity. As such, we believe that an inclusive and combined approach will present the best opportunity to reduce the barriers and enhance inclusion in this research.

The target outcome for the toolkit is the improved overall well-being of SGMY. At this stage, we have deliberately not stipulated anything more detailed in terms of outcomes, as the outcomes will be confirmed during the CONCEPT stage (see Table 1 for a summary of the project's stages). For instance, during the IDENTIFY to POSITION stages of the project, SGMY may highlight a preference for a reduced focus on managing symptoms of depression, which has been a key outcome or focus of digital interventions for SGMY to date (eg, for Rainbow SPARX [21], TODAY! [23], and AFFIRM Online [26]). Instead, SGMY may recommend, for example, that behavioral strategies to better handle peer bullying be a major focus of the toolkit. To determine what SGMY believe should be the specific target outcomes, we will use a modified nominal group technique [27]. For instance, SGMY will be asked to rank the importance of certain features or outcomes based on responses using a Likert scale (eg, a feature or outcome is ranked from 1=very important to 5=not at all important). This technique has been successfully used in focus groups or workshops (eg, [28]), as well as prior related work where young people (aged 16-25 years) codeveloped user-generated quality standards for youth mental health services in primary health care settings [29].

Table 1. Overview of the study's stages[a].

	IDENTIFY	DEFINE	POSITION	CONCEPT	CREATE	USE
Methods which enable the active participation of adolescents	*How do SGMY*[b]*see the biggest systemic and environmental problems?* Based on: phase 1 interviews with SGMY & data from published studies	*How do the problems [from IDENTIFY] manifest in the lives of SGMY & how do they cope?* Phase 1 interviews with SGMY [& 'card sorting' hierarchy of problems]	*How should the evidence-informed coping strategies be communicated to SGMY?* Co-design workshop 1 with SGMY [to include creating scenarios & discussing 'look & feel']	*What would motivate SGMY to use the online toolkit?* Co-design workshop 1 [to include creating storyboards & generating design ideas]	*How should it/could it be improved?* Co-design workshop 2 [to include providing corrective feedback on rough cuts of the audio-visual materials & toolkit prototypes]	*Is the online toolkit successful from the perspective of SGMY?* In-depth process evaluation [to include interviews with SGMY with no prior knowledge of the toolkit]
Evidence-informed research activities	*What do adult experts see as the biggest environmental problems?* Consultations and interviews with adult experts	*Literature review.* Scoping review to determine evidence-informed coping strategies for SGMY	*Determine the best online & creative techniques.* Confirm the behavioral theories most relevant to the overall project	*Stakeholder consultation with adult experts.* What should be the process, impact, and outcome indicators?	*Develop protocols for possible future randomised controlled trial.* Build and test data collection within toolkit	*Determine toolkit's applicability & evaluate toolkit.* Interviews with adult experts to establish toolkit's use

[a]Stages as informed by the earlier work of Hagen and colleagues [30].

[b]SGMY: sexual and gender minority youth.

Participants and Their Recruitment

The participants will consist of SGMY and key adult expert stakeholders.

SGMY Participants

We will recruit approximately 40 SGMY aged between 13 and 19 years residing in the United Kingdom. SGMY will be recruited via youth workers, including those based at the SGMY centers who have already expressed an interest in being involved in this study. These centers are based in a range of geographic locations, including a large urban area where the SGMY using their services are diverse in terms of their ethnicity, socioeconomic status, sexual identity (eg, they may identify as lesbian, gay, bisexual, or *questioning*), and gender identity. As a result, we expect to have cisgender male, cisgender female, and transgender participants (eg, transgender women, transgender men, and nonbinary young people) participating.

Key Adult Expert Participants

These participants (all resident in the United Kingdom) will consist of the following:

- Health and social care professionals (eg, SGM youth workers, public health practitioners, and other health care providers)
- Other publicly employed professionals with an interest in SGMY mistreatment prevention (eg, specialist teachers, experts on bullying prevention, and SGM police officers)
- Professionals who commission health and social care services (eg, staff working in a clinical commissioning group or local authority)
- Parents of adolescents interested in supporting the well-being of SGMY

Approximately 20 adult participants will be recruited via organizations that have endorsed this study and have agreed to support its implementation (eg, SGMY centers, 2 county councils in Southern England, and a center for police and policing research). The parents will be recruited via the networks of the Promoting Resilience and Well-being Through Co-design (PRIDE) team members (eg, support groups for SGM staff and parent groups hosted by a university). We will recruit a range of adult experts, including those who are likely to be SGM themselves. We believe that adult participants who are heterosexual and cisgender will also contribute meaningfully to the study, first, because of their roles (eg, there is a fairly limited number of health and social care commissioners) and, second, because of their expertise and practical experience (eg, some practitioners are highly skilled at working with SGMY and are heterosexual and cisgender).

Toolkit

It is envisaged that the toolkit will have the following characteristics:

- Be accessible (ie, conform to Web Content Accessibility Guidelines 2.1) and the website will be responsive by assuming a different structure as needed for desktop, mobile, and device use;
- Have embedded standardized assessments and measures (see the Measures section for further details);
- Involve a degree of interactivity, which might include gamification elements (eg, a *points-based system* that could be amassed as the user attempts to support the SGMY *characters* in the most helpful way possible) as gamification is thought to improve engagement with mental health interventions [31]; and
- Include short dramatizations in video format as part of relatable vignettes that are embedded into the toolkit. For

example, it is anticipated that 3 vignettes will be created, each focused on a specific challenge, such as X who is a professional and SGMY ally struggling to support a young person being bullied because of being bisexual, Y who is preparing to tell their parents they are gender nonbinary, and Z who is being pressured into attending prayer-based *therapy* (to *become straight*).

To maintain the confidentiality and safety of participants, the proposed web-based toolkit and the associated video material will be filmed with actors who constitute the *characters*. Nonetheless, attempts will be made to situate filmed scenes in realistic environments to promote the engagement and uptake of materials.

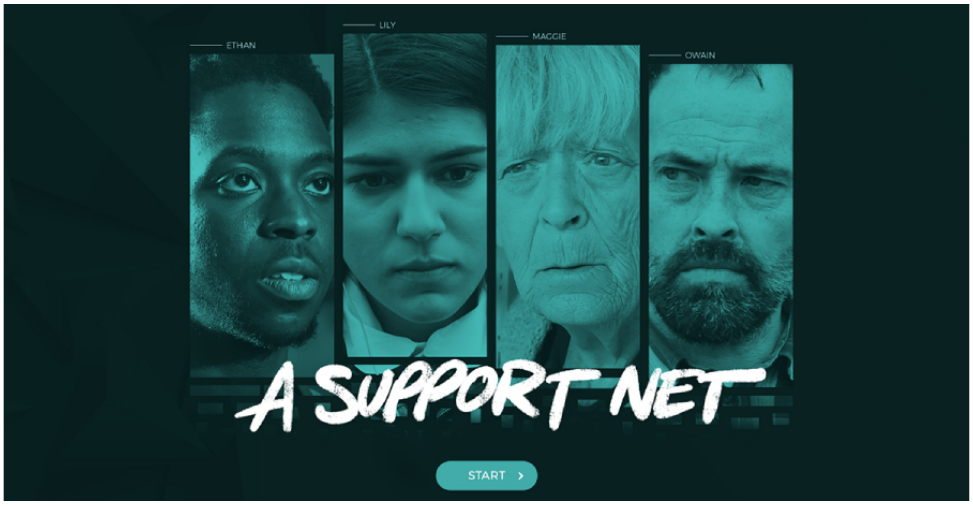
The toolkit will also build upon and advance aspects of the work already conducted in relation to Rainbow SPARX [21,25]. This 7-level form of computerized cognitive behavioral therapy (CBT) was designed to treat depression in SGMY and was based on the original version of SPARX, a serious game-based intervention [32]. The differences between SPARX and Rainbow SPARX are mostly script-related and account for 5.9% of the overall program script (ie, the minigames, characters, and weekly homework tasks remained the same) [21]. The main version of SPARX has been enhanced and updated for web-based delivery, and it is currently delivered free of charge in New Zealand. However, Rainbow SPARX has not been updated since 2009, nor has it been used outside of a research context. Prior research conducted with SGMY has reinforced issues or challenges to do with Rainbow SPARX, which is why we are developing a new bespoke toolkit specifically for SGMY in the United Kingdom. In particular, user feedback from SGMY about Rainbow SPARX has reinforced that substantial changes are required [25,33], and it has not been possible to address all the key issues to ensure it is optimally acceptable to SGMY in the United Kingdom. The salient issues previously identified include the following:

- There is insufficient SGMY-specific content in Rainbow SPARX [25,33]. In particular, the intervention did not satisfactorily address issues or topics of relevance for SGMY. For example, an SGMY research participant in the United Kingdom who had reviewed the intervention stated,"...You can't just change a few words around and have a slightly different message at the start and say 'oh yeah it's a completely different game for LGBT [i.e. SGM] people'..." [33].
- The look and feel of Rainbow SPARX needs to be improved and updated [33]. A specific issue that needs to be addressed for SGMY is the forced sex binary inherent in the intervention (ie, the user can only customize a male or female avatar with no other options; see Figure 1 for details).
- The intervention should be made accessible across a range of platforms [33] so that it can be delivered on mobile phones, computers, and tablets.

Figure 1. Rainbow SPARX (Smart, Positive, Active, Realistic, X-factor thoughts) characters (the female character dressed in red holding a staff and the male character immediately beside her are the avatars).

Perhaps unsurprisingly then, when SGMY reviewing Rainbow SPARX (in its original format) in 2017 in the United Kingdom were asked if they would use the intervention if they were *feeling down*, only 38% (8/21) of participants indicated that they would do so [33]. This was among a sample for an exploratory qualitative study where 86% (18/21) of participants reported that they had felt down or low in the past (ie, they were ideally placed to assess an intervention for mild to moderate depression in SGMY) [33]. Given this feedback, we have decided that our new toolkit will not be an adaptation of an existing *mainstream* program such as SPARX, but instead it will be entirely *rainbow* in its focus. The PRIDE toolkit will be designed together with SGMY at the forefront, in an overdue effort to meaningfully center those who have been marginalized in terms of their mental health needs. Rainbow SPARX was designed with SGMY in New Zealand and is a fantasy-based serious game. However, consultation sessions with SGMY in the United Kingdom has indicated that they would prefer an intervention that reflects the United Kingdom's contemporary context and is *real life* in terms of its look and feel (eg, as in A Support Net; Figure 2). Informed by earlier feedback from SGMY, we have codeveloped a new open educational web-based resource in a *real-life* style together with SGMY. This web-based resource is called "How to be a better LGBTQI+ [lesbian, gay, bisexual, trans, queer, intersex and other SGM persons] ally," and it is delivered via the OpenLearn platform [34]. This recent work has helped inspire the toolkit development aspects of this study. However, despite the identified shortcomings of Rainbow SPARX, the intervention has meritorious aspects, as acknowledged previously by SGMY [25]. We are therefore keen to assess whether the new toolkit also provides self-help that is delivered in a novel format, has positive and likable *characters*, and offers helpful tips or strategies for coping [25].

Figure 2. Landing page for *A Support Net* with the lead characters *Ethan*, *Lily*, *Maggie*, and *Owain* depicted.



Underpinning Theoretical Concepts and Key Principles

The toolkit will be informed by several underpinning theoretical concepts and key principles, which will also support the design of the toolkit's process evaluation and the parameters of a future effectiveness study.

CBT Principles

The general principles of CBT are the same for all groups, and CBT specifically for SGMY has been used effectively over a number of years (eg, [35,36]). However, CBT for SGMY requires some adaptation in order for the toolkit to adequately consider the unique challenges faced by these young people (eg, biphobia and the pervasiveness of cisheteronormativity).

Minority Stress

In the context of this project, we recognize that the mistreatment and high levels of stress that SGMY face place them at a greater risk of mental health problems [37]. It will therefore be explicit in the toolkit that we do not consider that SGMY are *lesser* or *more problematic* relative to their cisgender and heterosexual peers; rather, it is toxic social environments that place SGMY at elevated risk of mental ill-health.

Resilience

This is a person's ability to *bounce back* in the face of adversity. Prior research has indicated that higher self-reported resilience is associated with lower levels of depression and anxiety [38]. Furthermore, resilience is thought to have a mitigating effect on depressive symptoms among people who have experienced challenging life events during childhood [38]. The aim of resiliency training in the toolkit will be to enhance an SGMY's *bounce back*, resulting in the strongest possible capacity to recover from stressful events.

Co-design Principles

For this project, we will use the youth co-design participatory framework outlined by Hagen et al [30], an approach summarized for this project in further detail in Table 1 and the *Procedures* section.

Normalization Process Theory

This is a framework that can be used to describe and assess the implementation potential of complex interventions [39]. By using normalization process theory, we aim to think through the pertinent issues of implementation while designing the toolkit (eg, how it can fit within the practices of professionals supporting its use in local communities).

Procedures

This project has 3 main objectives with 3 corresponding phases.

Phase 1

In the first phase, the objective is to co-design a media-rich evidence-informed web-based SGMY well-being prototype toolkit together with SGMY as well as key adult experts. In addition to the cocreation of contributions with SGMY at all stages of the project, there will also be input from key adult expert stakeholders. This will span the IDENTIFY, CONCEPT, and USE stages using the co-design stages or steps as outlined by Hagen et al [30] (see also Table 1 for an overview of all the stages and Table 2 for a summary in Gantt chart format). It is envisaged that the toolkit will include custom-made audiovisual materials in the form of dramatizations to illustrate key points from the vignettes created during the POSITION and CONCEPT stages, for example, dramatizations in a style as adopted in *A Support Net*—a free mental health literacy resource with >30,000 users to date developed by PRIDE team members and delivered via the Open University's OpenLearn platform [40] (Figure 2). There will also be components specifically designed to enhance engagement as recommended by SGMY during the CONCEPT and CREATE stages (eg, a points-based rewards system).

Table 2. Summary Gantt Chart for the study.

Milestones	Before the study starts			Study month																
Project Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Milestone 1: ethics approval sought and obtained	✓	✓	✓																		
Milestone 2: appoint 2 advisory groups		✓	✓																		
Milestone 3: phase 1 (step 1) complete scoping review				✓	✓	✓	✓														
Milestone 4: phase 1 (step 1) SGMY[a] interviews or focus groups					✓	✓	✓														
Milestone 5: phase 1 (step 1) interviews with adult experts					✓	✓	✓														
Milestone 6: phase 1 (Step 1) confirm theoretical framework				✓	✓	✓	✓	✓													
Milestone 7: phase 1 (step 2) 1st SGMY co-design workshops									✓	✓											
Milestone 8: phase 1 (Step 2) dramatizations filmed & prototype ready											✓	✓									
Milestone 9: phase 1 (Step 2) 2nd SGMY co-design workshops													✓	✓							
Milestone 10: phase 2 Refined prototype ready for evaluation															✓	✓					
Milestone 11: phase 2 Confirm assessments for evaluation													✓	✓	✓						
Milestone 12: phase 3 Process evaluation completed																	✓	✓	✓		
Milestone 13: phase 3 Interviews with SGMY & adult experts																		✓	✓		
Milestone 14: phase 3 draft initial protocol for future trial																		✓	✓		
Milestone 15: create summary report for SGMY and for adult experts																			✓	✓	✓
Milestone 16: create academic outputs																			✓	✓	✓
Advisory group meetings (×3)				✓					✓									✓			

[a]SGMY: sexual and gender minority youth.

The novel web-based toolkit will be underpinned by a new framework of useful and evidence-informed cognitive and behavioral coping strategies. The framework will draw upon practice wisdom from expert practitioners in SGMY mental well-being (in the IDENTIFY stage), from the *expert by experience* solutions offered by SGMY (in the DEFINE stage), and from the scoping review, which will appraise the peer-reviewed literature (also in the DEFINE stage). For instance, content is likely to include evidence-informed strategies to improve a young person's psychological and physical health (eg, behavioral activation challenges involving physical exercise as has been previously employed in Rainbow SPARX [21]).

To draw upon the experiences of a range of SGMY from diverse backgrounds, the co-design workshops are planned to be on the web with participants from SGMY organizations (where many members are Black, Asian, or from another minority ethnic group). Ideally, some adolescents questioning their sexuality or gender identity will take part in this project. However, if they are *currently unsure*, these youth are less likely to participate, which is an issue also identified in earlier research [41]. Hence, while we will proactively attempt to recruit questioning youth, we will also ask all SGMY participants to reflect on their early experiences of *coming out* in developing the intervention so that we surface issues of salience for questioning adolescents. Composite vignettes for the audiovisual materials and the related scenarios will be developed with SGMY (during the POSITION to CREATE stages).

The key activities in phase 1 will occur in 2 concurrent steps.

Step 1 will consist of interviews with SGMY and adult experts as well as a scoping review focused on identifying adaptive psychosocial coping strategies for SGMY (all conducted during the IDENTIFY and DEFINE stages of the study). The four key activities will be as follows:

1. Informed by an earlier scoping review and subsequent conceptual framework from Colpitts and Gahagan [42,43], we will conduct a scoping review that describes the challenges in SGMY's social and environmental systems and establishes the recommended strategies for building resilience. In addition, the measures used in the studies identified during the scoping review will be assessed for their suitability for use during the process evaluation of the toolkit in phase 3.
2. Informed by our prior work, advice from practitioners with expertise in cognitive and behavioral coping strategies for SGM individuals, as well as other contributions including those from the scoping review, we will develop a framework of the components and behavior change techniques required to enhance resilience in SGMY.
3. We will conduct web-based (or face-to-face, if feasible) interviews (or focus groups—depending on participants' preferences) with SGMY focusing on the common environmental problems SGMY experience and the associated stress management strategies frequently used by SGMY (n=10).
4. We will conduct web-based (or face-to-face, if feasible) interviews with adult experts to ascertain how the web-based toolkit could be used in community settings and public health systems (as well as by SGMY), including, for example by, (1) health and social care commissioners (n=5); (2) parents of adolescents supportive of SGMY (n=5); and (3) practitioners (eg, SGM youth workers, school pastoral care workers, police officers, child and adolescent mental health services clinicians; n=5). The interviews with adult experts will also include determining adaptive resilience and stress management strategies for SGMY.

Step 2 will involve co-designing the toolkit (for work across the POSITION, CONCEPT, and CREATE stages). The key activity will be working collaboratively with SGMY (n=20) during at least two sessions to cocreate the web-based toolkit at participatory web-based co-design workshops. SGMY user requirements and preferences will be used to inform the work of the contracted information technology specialists, so that they can produce the prototype toolkit. Audiovisual material will be developed based on vignettes created together with SGMY.

Phase 2

The second main objective of this project is to explore how the toolkit can be used within public health systems in the United Kingdom by SGMY. We will establish how the toolkit could be used by SGMY and potentially by others (eg, health and social care professionals). For example, the toolkit may also be useful for professionals' future continuing professional development activities.

The two key activities in phase 2 during the CONCEPT and CREATE stages are as follows:

1. Completing the initial build of the prototype toolkit and refining this as needed based on SGMY feedback (n=20, ie, the SGMY participants from phase 1, step 2)
2. Determining SGMYs' (n=20) and adult experts' (n=15, ie, from phase 1, step 1) user-defined key criteria for success (eg, SGMY may determine that the toolkit's engagement potential is especially important) and potentially the standardized assessments for the toolkit (eg, the measures to be used)

Phase 3

The third main objective of this project is to plan the potential delivery of the intervention and determine the design and measures for a future effectiveness study, as well as further implementation of the toolkit. Assuming that *stop/go* decision criteria to determine if the toolkit warrants an effectiveness study are met (criteria developed during the CREATE stage) and based on the in-depth process evaluation conducted in the USE stage, we will submit a bid for an effectiveness randomized controlled trial to the National Institute for Health Research in the United Kingdom (or another relevant funder).

The key activities in phase 3 during the USE stage are as follows:

1. An in-depth process evaluation will be conducted with (n=10) SGMY not involved in the IDENTIFY to CREATE stages of the project. Data will then be gathered directly from the prototype toolkit (eg, the psychological measures

data) and during recorded interviews. During interviews, SGMY will be asked to think out loud while interacting with the toolkit, as informed by an earlier evaluation conducted with young sexual minority men by Fleming et al [23]. Therefore, SGMY participants will use the toolkit in a time-bound lab-based session (eg, during 2 mornings of possible use) where SGMY may elect to only use the PRIDE toolkit for a much shorter period (eg, 40 minutes each morning). This will yield less in the way of potential real-world use data, but given the think out loud methodology, this is a pragmatic approach allowing for some limited use data to be obtained.

2. Interviews will also be carried out with selected adult experts, including commissioners of health and social care services, to establish the feasibility of implementation at scale, to confirm outcome measures, and to determine how the toolkit can be best used in public health systems (n=5). The interviews will help inform the design of a possible future effectiveness study.

Measures

The measures to be embedded into the actual toolkit will be determined during phase 1 of the project. Indicative measures include assessments previously used in evaluating Rainbow SPARX, such as the following:

- The Kazdin Hopelessness Scale for Children, which is a 17-item self-report questionnaire assessing hopelessness [44]
- The Mood and Feelings Questionnaire, which is a 33-item self-report questionnaire designed to detect depression in clinical populations [45]
- The Pediatric Quality of Life and Satisfaction Questionnaire, which is a 15-item self-report questionnaire addressing satisfaction with current life [46]

Other options that are suitable for adolescents and focus on well-being are as follows:

- The World Health Organization-5 Well-being Index, which is a 5-item measure of overall well-being [47]
- The University of California Los Angeles Loneliness Scale for Adolescents, which is a 20-item self-report measure [48]
- The Warwick-Edinburgh Mental Well-being Scale, which is a 14-item positive mental health measure [49]

Proposed Analyses

The analyses will be carried out with regard to the 3 main objectives of the project in the following ways.

Objective 1

Together with *SGMY* as well as key adult experts, we aim to co-design a media-rich evidence-informed web-based *SGMY* well-being prototype toolkit aimed at those aged 13 to 19 years. The data pertaining to this objective will include interviews, focus groups, and a scoping review. We will use a general inductive approach for data analysis of transcribed interviews and focus groups [50,51]. The summarized results from the scoping review, together with the themes and subthemes derived from the interviews and focus groups, will lead to the creation of a novel and timely theoretical framework for evidence-informed cognitive and behavioral coping strategies for SGMY. We anticipate that this framework will be relevant to others working to support the mental health of SGMY in the United Kingdom and further afield.

Objective 2

We will explore how the web-based toolkit can be used within public health systems in the UK by *SGMY* and potentially other relevant stakeholders. The data related to this objective consist of transcribed interviews. These transcripts will be analyzed using the framework approach [52], an approach that is closely related to established methods (eg, thematic analysis) and has already been applied in earlier health-related research (eg, [53]). For the PRIDE study, facets of SGMY stressor experiences and exposures will be identified via findings from the existing literature (as part of objective 1). Framework analysis allows for the use of this prior knowledge to gain further depth to a phenomenon; this is done through exploring shared communalities and differences in experiences within the participant group. In this study, we assume there will be areas of tension in which experiences are qualitatively different for SGMY participants, by virtue of their membership in a particular subgroup or social identity (eg, sexual minority vs gender minority differences). Unlike some qualitative analytic methods that engender homogeneity in sampling to explore the aims (eg, interpretative phenomenological analysis) [54], framework analysis is well suited to analyses conducted with heterogeneous participant groups. Thus, participants' shared experiences, as well as diversity of experiences, can be explored [55]. The approach involves working through stages to develop themes (as with thematic analysis), but then the themes are further refined in an iterative fashion, eventually leading to the development of a robust conceptual framework. The analyses pertaining to implementation are guided by the normalization process theory [39]. In addition to the themes and subthemes identified from the interviews, recommendations for future plans for the toolkit will be developed with SGMY and stakeholders to build into the project opportunities for novel and unforeseen ways to use and access the toolkit.

Objective 3

We aim to conduct a preliminary evaluation of the acceptability, feasibility, and impact of the toolkit, which will inform the design of a future effectiveness study. Semistructured interviews using the *think out loud* methodology will be conducted. These will include questions related to the following: participants' views about the acceptability of the toolkit; the extent to which the toolkit adequately addresses the specific needs of SGMY, including those with diverse characteristics (eg, in regard to the user-generated criteria for the toolkit's perceived *success*); areas for improvement; the feasibility of using it in different real-world contexts; and the possible impacts of the toolkit on users. The transcribed interviews will be analyzed using the general inductive approach [50,51]. Preliminary use data will also be examined, including the time spent using the toolkit and the extent to which different components were used. Preliminary information about the potential impact of the intervention will be gained by examining the effect sizes of pre- to

postintervention use changes in the primary outcome measure (to be determined) and potentially other self-report measures.

Study Team

The PRIDE team consists of a project coordinator and researchers with expertise in youth mental health, SGM well-being, intervention development and implementation, and public health research. This team will work with 2 advisory groups. One advisory group will consist of at least four SGMY advisors. The second advisory group comprises adult experts, including academics and others, with practice and policy expertise in areas such as e-therapies, SGM public health, and SGM youth work. Both advisory groups will be involved from project initiation to completion, including the planning of the subsequent effectiveness study (which is beyond the scope of this protocol).

Ethics and Consent

A favorable opinion from the Open University's human research ethics committee will be obtained before participants are recruited for this study. SGMY and key adult experts participating in this study will provide written consent before participating. The consent form and participant information sheet for SGMY participants will be reviewed by SGMY and refined to ensure that it is presented in a way that is age-appropriate and easy to understand. It will also contain the contact details for SGMY supports (eg, telephone-based helplines) and suggestions on how to seek SGMY-appropriate psychosocial support if required.

Involving adolescents interested in this study who are aged <16 years are likely to present ethical challenges, because these younger adolescents will be required to have written consent from a parent or legal guardian (as well as their own written consent). This presents problems for younger SGMY who are not yet *out* regarding their SGMY status. Therefore, only those younger SGMY with the coconsent of a parent or legal guardian can participate. As a result, the sample of SGMY is likely to be skewed toward older adolescents in this study, and those who are younger will already be *out* with supportive families.

Results

This study was funded in March 2021. We received a favorable opinion for our ethics application for phase 1 of the study from the Open University's human research ethics committee in August 2021. We will apply for further approval for phases 2 and 3. The study commenced on September 1, 2021. Participant recruitment for the study began in October 2021, and all data for the study should be gathered by early 2023 (see Table 2 for details).

Discussion

Principal Findings

There has been considerable research describing the mental health challenges SGMY face, but little research has been conducted on interventions designed to make a difference for SGMY. For example, 2 prior systematic reviews of psychosocial treatments have previously identified only a single evaluated digital tool to support the mental well-being of SGMY [19,20], and a third more recent and inclusive systematic review highlighted only 5 interventions that broadly targeted mental health–related problems [22]. Fortunately, this situation is rapidly changing, with a recent research protocol highlighting an emerging interest in gamified health interventions for SGM individuals [56]. For example, an intervention is being pilot-tested among SGMY (aged 14-18 years) in the United States, with the aim of improving help-seeking behavior and coping [57]. Our proposed toolkit is therefore timely and could be useful in the United Kingdom, where there is an absence of evidence-informed digital interventions to support the well-being of SGMY. This project is funded by the UK's Medical Research Council under the Public Health Intervention Development scheme. This scheme involves developing a novel intervention, and coproduction with relevant stakeholders is expected. Within the rules of the scheme, limited resources (approximately 15% of the project's overall costs) are directed toward acceptability and feasibility research. Therefore, the emphasis of this project is directed toward creating a new toolkit (during phases 1 and 2), with only a preliminary emphasis placed on evaluation (in phase 3).

The focus of our work, and the limited earlier intervention research focused on SGMY in this field, has been directed at an individual level. For instance, *Rainbow SPARX* [21] and *AFFIRM Online* [26] have sought to reduce symptomatology, such as depressive symptoms, among individual SGMY. However, there are wider systemic issues that require attention in the United Kingdom and elsewhere, because SGMY are forced to live in a challenging heteropatriarchal society. As a result, SGMY are frequently *problematized*, whereas insufficient effort is directed at addressing the negative environments that mean SGMY are more likely to have mental health problems. In short, more research should be conducted to improve the overall milieu for SGMY. This is because earlier work, drawing on population-based research, has already demonstrated that schools that are more supportive of SGMY lead to a reduction in risk in terms of depression and suicidality for SGMY [6]. Although it is envisaged that our toolkit will focus on individual SGMY, it could also potentially be used by others (eg, health and social care professionals) for their continuing professional development. Thus, the toolkit could reach a *wider audience* that might also assist in helping change certain environments.

Our decision to focus on the larger (heterogeneous) SGMY population versus being more specifically focused on either sexual minority or gender minority youth is a limitation of this study, given some of the challenges unique to each of these 2 main groups. However, the use of a framework analytic method for qualitative data interpretation allows for the exploration of group commonalities and differences [55], which might mitigate some of the limitations related to being able to identify key differences between subgroups in the overall SGMY sample. As a consequence, our intention is to cocreate a toolkit that will be meaningful and acceptable to both sexual as well as gender minority youth. In addition to drawing on shared experiences of stressors SGMY face, our qualitative work will also explore areas of tension, in which gender and sexual minority young people discuss issues that they perceive differentiate SGMY

subgroups, for example, specific stressors that vary along group divides. We will attempt to recruit a range of SGMY participants and include those who live outside of the largest cities in the United Kingdom, but a probable limitation of this study will be an overrepresentation of SGMY participants from *LGBTQ+ (lesbian, gay, bisexual, trans, queer) friendly* urban areas. Our relatively short timescale poses other challenges for both the intervention and its evaluation, as well as its possible real-world implementation [58]. This is because, for digital toolkits, technology is evolving rapidly and interventions that are not updated (or refined following trials) risk becoming dated even before an eventual roll-out [59]. Consequently, a *new* toolkit could become much less appealing to SGMY by the time it is available outside of research settings. Another challenge in this rapidly changing field is that interventions are required to keep pace with technology (eg, work across a range of devices and operating systems) while also demonstrating effectiveness. These challenges have already been reinforced as key issues in relation to digital interventions for young people [58].

Conclusions

SGMY are underserved in terms of mental health service provision, and these young people have already highlighted the value of support on the web [33]. Our proposed project seeks to coproduce an engaging media-rich evidence-informed well-being prototype toolkit for this unique subpopulation. SGMY will be central to the creation of the toolkit, which will require an effectiveness trial after this initial work is completed.

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Conflicts of Interest

SPARX (Smart, Positive, Active, Realistic, X-factor thoughts) and Rainbow SPARX are cited in the manuscript. The intellectual property for SPARX is held by UniServices at The University of Auckland. Any proceeds from licensing or selling SPARX outside of New Zealand will be shared in part with UniServices, The University of Auckland and SPARX's developers (which includes ML).

References

1. Lucassen MF, Stasiak K, Samra R, Frampton CM, Merry SN. Sexual minority youth and depressive symptoms or depressive disorder: a systematic review and meta-analysis of population-based studies. Aust N Z J Psychiatry 2017 Aug;51(8):774-787. [doi: 10.1177/0004867417713664] [Medline: 28565925]
2. Reisner SL, Poteat T, Keatley J, Cabral M, Mothopeng T, Dunham E, et al. Global health burden and needs of transgender populations: a review. Lancet 2016 Jul 23;388(10042):412-436 [FREE Full text] [doi: 10.1016/S0140-6736(16)00684-X] [Medline: 27323919]
3. Amos R, Manalastas EJ, White R, Bos H, Patalay P. Mental health, social adversity, and health-related outcomes in sexual minority adolescents: a contemporary national cohort study. Lancet Child Adolesc Health 2020 Jan;4(1):36-45. [doi: 10.1016/S2352-4642(19)30339-6] [Medline: 31753807]
4. Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, et al. Transgender people: health at the margins of society. Lancet 2016 Jul 23;388(10042):390-400. [doi: 10.1016/S0140-6736(16)00683-8] [Medline: 27323925]
5. Rimes KA, Goodship N, Ussher G, Baker D, West E. Non-binary and binary transgender youth: comparison of mental health, self-harm, suicidality, substance use and victimization experiences. Int J Transgend 2019;20(2-3):230-240 [FREE Full text] [doi: 10.1080/15532739.2017.1370627] [Medline: 32999609]
6. Denny S, Lucassen M, Stuart J, Fleming T, Bullen P, Peiris-John R, et al. The association between supportive high school environments and depressive symptoms and suicidality among sexual minority students. J Clin Child Adolesc Psychol 2016;45(3):248-261. [doi: 10.1080/15374416.2014.958842] [Medline: 25469988]
7. Gnan GH, Rahman Q, Ussher G, Baker D, West E, Rimes KA. General and LGBTQ-specific factors associated with mental health and suicide risk among LGBTQ students. J Youth Stud 2019 Feb 17;22(10):1393-1408. [doi: 10.1080/13676261.2019.1581361]
8. Clark T, Lucassen M, Bullen P, Denny SJ, Fleming TM, Robinson EM, et al. The health and well-being of transgender high school students: results from the New Zealand adolescent health survey (Youth'12). J Adolesc Health 2014 Jul;55(1):93-99 [FREE Full text] [doi: 10.1016/j.jadohealth.2013.11.008] [Medline: 24438852]
9. Lucassen M, Clark T, Denny S, Fleming TM, Rossen FV, Sheridan J, et al. What has changed from 2001 to 2012 for sexual minority youth in New Zealand? J Paediatr Child Health 2015 Apr;51(4):410-418. [doi: 10.1111/jpc.12727] [Medline: 25209060]

10. PHE Strategy 2020-25. Public Health England. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/831562/PHE_Strategy_2020-25.pdf [accessed 2022-01-18]
11. Burford J, Lucassen MF, Hamilton T. Evaluating a gender diversity workshop to promote positive learning environments. J LGBT Youth 2017 Feb 02;14(2):211-227. [doi: 10.1080/19361653.2016.1264910]
12. Lucassen MF, Burford J. Educating for diversity: an evaluation of a sexuality diversity workshop to address secondary school bullying. Australas Psychiatry 2015 Oct;23(5):544-549. [doi: 10.1177/1039856215592324] [Medline: 26129815]
13. Watt G. The inverse care law revisited: a continuing blot on the record of the National Health Service. Br J Gen Pract 2018 Nov 29;68(677):562-563. [doi: 10.3399/bjgp18x699893]
14. LGBT Action Plan: improving the lives of lesbian, gay, bisexual and transgender people. GOV.UK. URL: https://www.gov.uk/government/publications/lgbt-action-plan-2018-improving-the-lives-of-lesbian-gay-bisexual-and-transgender-people [accessed 2022-01-18]
15. Foy AA, Morris D, Fernandes V, Rimes KA. LGBQ+ adults' experiences of Improving Access to Psychological Therapies and primary care counselling services: informing clinical practice and service delivery. Cognit Behav Therap 2019 Sep 10;12. [doi: 10.1017/s1754470x19000291]
16. Lucassen MF, Stasiak K, Fleming T, Frampton C, Perry Y, Shepherd M, et al. Computerized cognitive behavioural therapy for gender minority adolescents: analysis of the real-world implementation of SPARX in New Zealand. Aust N Z J Psychiatry 2021 Sep;55(9):874-882 [FREE Full text] [doi: 10.1177/0004867420976846] [Medline: 33287554]
17. Rimes KA, Ion D, Wingrove J, Carter B. Sexual orientation differences in psychological treatment outcomes for depression and anxiety: national cohort study. J Consult Clin Psychol 2019 Jul;87(7):577-589. [doi: 10.1037/ccp0000416] [Medline: 31219292]
18. Queer Futures Final Report: Understanding lesbian, gay, bisexual and trans (LGBT) adolescents' suicide, self-harm and help-seeking behaviour. Lancaster University. 2016. URL: https://tinyurl.com/5drrff7v [accessed 2022-01-18]
19. Hobaica S, Alman A, Jackowich S, Kwon P. Empirically based psychological interventions with sexual minority youth: a systematic review. Psychol Sexual Orientation Gender Diversity 2018 Sep 15;5(3):313-323. [doi: 10.1037/sgd0000275]
20. Van Der Pol-Harney E, McAloon J. Psychosocial interventions for mental illness among LGBTQIA youth: a PRISMA-based systematic review. Adolescent Res Rev 2018 Aug 2;4(2):149-168 [FREE Full text] [doi: 10.1007/s40894-018-0090-7]
21. Lucassen M, Merry S, Hatcher S, Frampton C. Rainbow SPARX: a novel approach to addressing depression in sexual minority youth. Cognit Behav Practice 2015 May;22(2):203-216 [FREE Full text] [doi: 10.1016/j.cbpra.2013.12.008]
22. Gilbey D, Morgan H, Lin A, Perry Y. Effectiveness, acceptability, and feasibility of digital health interventions for LGBTIQ+ young people: systematic review. J Med Internet Res 2020 Dec 03;22(12):e20158 [FREE Full text] [doi: 10.2196/20158] [Medline: 33270039]
23. Fleming JB, Hill YN, Burns MN. Usability of a culturally informed mHealth intervention for symptoms of anxiety and depression: feedback from young sexual minority men. JMIR Hum Factors 2017 Aug 25;4(3):e22 [FREE Full text] [doi: 10.2196/humanfactors.7392] [Medline: 28842389]
24. Lucassen M, Hatcher S, Stasiak K, Fleming T, Shepherd M, Merry S. The views of lesbian, gay and bisexual youth regarding computerised self-help for depression: an exploratory study. Advances Mental Health 2014 Dec 17;12(1):22-33 [FREE Full text] [doi: 10.5172/jamh.2013.12.1.22]
25. Lucassen M, Hatcher S, Fleming T, Stasiak K, Shepherd M, Merry S. A qualitative study of sexual minority young people's experiences of computerised therapy for depression. Australas Psychiatry 2015 Jun;23(3):268-273. [doi: 10.1177/1039856215579542] [Medline: 25881962]
26. Craig SL, Leung VW, Pascoe R, Pang N, Iacono G, Austin A, et al. AFFIRM Online: utilising an affirmative cognitive-behavioural digital intervention to improve mental health, access, and engagement among LGBTQA+ youth and young adults. Int J Environ Res Public Health 2021 Feb 05;18(4):1541 [FREE Full text] [doi: 10.3390/ijerph18041541] [Medline: 33562876]
27. Van de Ven AH, Delbecq AL. The nominal group as a research instrument for exploratory health studies. Am J Public Health 1972 Mar;62(3):337-342. [doi: 10.2105/ajph.62.3.337] [Medline: 5011164]
28. Olsen J. The Nominal Group Technique (NGT) as a tool for facilitating pan-disability focus groups and as a new method for quantifying changes in qualitative data. Int J Qual Methods 2019 Jul 26;18:160940691986604. [doi: 10.1177/1609406919866049]
29. Graham T, Rose D, Murray J, Ashworth M, Tylee A. User-generated quality standards for youth mental health in primary care: a participatory research design using mixed methods. BMJ Qual Saf 2014 Oct;23(10):857-866 [FREE Full text] [doi: 10.1136/bmjqs-2014-002842] [Medline: 24920648]
30. Hagen P, Collin P, Metcalf A, Nicholas M, Rahilly K, Swainston N. Participatory Design of Evidence-based Online Youth Mental Health Promotion, Prevention, Early Intervention and Treatment. Melbourne: Young and Well Cooperative Research Centre; 2012.
31. Fleming T, Bavin L, Stasiak K, Hermansson-Webb E, Merry SN, Cheek C, et al. Serious games and gamification for mental health: current status and promising directions. Front Psychiatry 2016;7:215 [FREE Full text] [doi: 10.3389/fpsyt.2016.00215] [Medline: 28119636]

32. Merry S, Stasiak K, Shepherd M, Frampton C, Fleming T, Lucassen M. The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial. BMJ 2012 Apr 18;344:e2598 [FREE Full text] [doi: 10.1136/bmj.e2598] [Medline: 22517917]
33. Lucassen M, Samra R, Iacovides I, Fleming T, Shepherd M, Stasiak K, et al. How LGBT+ young people use the internet in relation to their mental health and envisage the use of e-therapy: exploratory study. JMIR Serious Games 2018 Dec 21;6(4):e11249 [FREE Full text] [doi: 10.2196/11249] [Medline: 30578194]
34. How to be a better LGBTQI+ ally. The Open University. 2021. URL: https://www.open.edu/openlearn/health-sports-psychology/young-peoples-health/how-be-better-lgbtqi-ally [accessed 2022-01-21]
35. Castro-Couch M. Cognitive-behavioral therapies with lesbian, gay, and bisexual clients. Arch Sex Behav 2007 Jun 9;36(4):626-627. [doi: 10.1007/s10508-007-9174-3]
36. Safren SA, Hollander G, Hart TA, Heimberg RG. Cognitive-behavioral therapy with lesbian, gay, and bisexual youth. Cognit Behav Pract 2001 Jun;8(3):215-223. [doi: 10.1016/s1077-7229(01)80056-0]
37. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull 2003 Sep;129(5):674-697 [FREE Full text] [doi: 10.1037/0033-2909.129.5.674] [Medline: 12956539]
38. Joyce S, Shand F, Tighe J, Laurent SJ, Bryant RA, Harvey SB. Road to resilience: a systematic review and meta-analysis of resilience training programmes and interventions. BMJ Open 2018 Jun 14;8(6):e017858 [FREE Full text] [doi: 10.1136/bmjopen-2017-017858] [Medline: 29903782]
39. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med 2010 Oct 20;8:63 [FREE Full text] [doi: 10.1186/1741-7015-8-63] [Medline: 20961442]
40. Lucassen M, Samra R, Axtell-Powell G, Cooke G. 'A Support Net': evaluating a novel mental health-related online educational tool. In: Proceedings of the International Society for Research on Internet Interventions - ISRII: The Next Generation. 2019 Presented at: Proceedings of the International Society for Research on Internet Interventions - ISRII: The Next GenerationAuckland, New Zealand; Feb 13-15, 2019; Auckland, New Zealand.
41. Lucassen MF, Fleming TM, Merry SN. Tips for research recruitment: the views of sexual minority youth. J LGBT Youth 2017 Jan 13;14(1):16-30. [doi: 10.1080/19361653.2016.1256246]
42. Gahagan J, Colpitts E. Understanding and measuring LGBTQ pathways to health: a scoping review of strengths-based health promotion approaches in LGBTQ health research. J Homosex 2017;64(1):95-121. [doi: 10.1080/00918369.2016.1172893] [Medline: 27043161]
43. Colpitts E, Gahagan J. The utility of resilience as a conceptual framework for understanding and measuring LGBTQ health. Int J Equity Health 2016 Apr 06;15:60 [FREE Full text] [doi: 10.1186/s12939-016-0349-1] [Medline: 27048319]
44. Kazdin AE, French NH, Unis AS, Esveldt-Dawson K, Sherick RB. Hopelessness, depression, and suicidal intent among psychiatrically disturbed inpatient children. J Consult Clin Psychol 1983;51(4):504-510. [doi: 10.1037/0022-006x.51.4.504]
45. Kent L, Vostanis P, Feehan C. Detection of major and minor depression in children and adolescents: evaluation of the Mood and Feelings Questionnaire. J Child Psychol Psychiatry 1997 Jul;38(5):565-573. [doi: 10.1111/j.1469-7610.1997.tb01543.x] [Medline: 9255700]
46. Endicott J, Nee J, Yang R, Wohlberg C. Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q): reliability and validity. J Am Acad Child Adolesc Psychiatry 2006 Apr;45(4):401-407. [doi: 10.1097/01.chi.0000198590.38325.81] [Medline: 16601644]
47. Bech P, Olsen LR, Kjoller M, Rasmussen NK. Measuring well-being rather than the absence of distress symptoms: a comparison of the SF-36 Mental Health subscale and the WHO-Five Well-Being Scale. Int J Methods Psychiatr Res 2003;12(2):85-91 [FREE Full text] [doi: 10.1002/mpr.145] [Medline: 12830302]
48. Mahon NE, Yarcheski TJ, Yarcheski A. Validation of the revised UCLA Loneliness Scale for adolescents. Res Nurs Health 1995 Jun;18(3):263-270. [doi: 10.1002/nur.4770180309] [Medline: 7754096]
49. Stewart-Brown S, Platt S, Tennant A, Maheswaran H, Parkinson J, Weich S, et al. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): a valid and reliable tool for measuring mental well-being in diverse populations and projects. J Epidemiol Community Health 2011 Sep 13;65(Suppl 2):A38-A39. [doi: 10.1136/jech.2011.143586.86]
50. Boyatzis R. Transforming Qualitative Information Thematic Analysis and Code Development. Thousand Oaks, California: Sage Publications, Inc; 1998.
51. Thomas D. A general inductive approach for analyzing qualitative evaluation data. Am J Eval 2016 Jun 30;27(2):237-246 [FREE Full text] [doi: 10.1177/1098214005283748]
52. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013 Sep 18;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
53. Mericle AA, de Guzman R, Hemberg J, Yette E, Drabble L, Trocki K. Delivering LGBT-sensitive substance use treatment to sexual minority women. J Gay Lesbian Soc Serv 2018;30(4):393-408 [FREE Full text] [doi: 10.1080/10538720.2018.1512435] [Medline: 31007499]
54. Lyons E, Coyle A. Analysing Qualitative Data in Psychology. London: SAGE Publications; 2016.

55. Qualitative Research Practice A Guide for Social Science Students and Researchers. London: SAGE Publications; 2003.
56. Boyle SC, LaBrie JW. A gamified, social media-inspired, web-based personalized normative feedback alcohol intervention for lesbian, bisexual, and queer-identified women: protocol for a hybrid trial. JMIR Res Protoc 2021 Apr 16;10(4):e24647 [FREE Full text] [doi: 10.2196/24647] [Medline: 33861212]
57. Coulter RW, Sang JM, Louth-Marquez W, Henderson ER, Espelage D, Hunter SC, et al. Pilot testing the feasibility of a game intervention aimed at improving help seeking and coping among sexual and gender minority youth: protocol for a randomized controlled trial. JMIR Res Protoc 2019 Feb 15;8(2):e12164 [FREE Full text] [doi: 10.2196/12164] [Medline: 30767903]
58. Stasiak K, Fleming T, Lucassen M, Shepherd M, Whittaker R, Merry S. Computer-based and online therapy for depression and anxiety in children and adolescents. J Child Adolesc Psychopharmacol 2016 Apr;26(3):235-245. [doi: 10.1089/cap.2015.0029] [Medline: 26465266]
59. Fleming T, Bavin L, Lucassen M, Stasiak K, Hopkins S, Merry S. Beyond the trial: systematic review of real-world uptake and engagement with digital self-help interventions for depression, low mood, or anxiety. J Med Internet Res 2018 Jun 06;20(6):e199 [FREE Full text] [doi: 10.2196/jmir.9275] [Medline: 29875089]

Abbreviations

CBT: cognitive behavioral therapy
LGBTQ+: lesbian, gay, bisexual, trans, queer and other sexual and gender minority persons
LGBTQI+: lesbian, gay, bisexual, trans, queer, intersex and other sexual and gender minority persons
PRIDE: Promoting Resilience and Well-being Through Co-design
SGM: sexual and gender minority
SGMY: sexual and gender minority youth
SPARX: Smart, Positive, Active, Realistic, X-factor thoughts

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Protocol

Kidney Sellers From a Village in Nepal: Protocol for an Ethnographic Study

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Abstract

Background: Kidney selling is a global phenomenon, with higher-income countries functioning as recipients and lower-income countries as donors, reflecting the gaps due to poverty and vulnerability. In recent years, an increasing number of residents in a village near the capital city of Nepal have been selling their kidneys; however, the factors embedded in the local social, cultural, political, and individual context driving kidney selling are poorly understood.

Objective: The aim of this study is to explore the drivers of kidney selling and its consequences in Hokse village in central Nepal, using ethnographic methods and multistakeholder consultations.

Methods: An ethnographic approach will be adopted along with in-depth interviews and key informant interviews among the residents and kidney sellers in the village. Relevant participants in the village will be selected purposively using a snowball approach. The number of participants will be predicated on the principles of data saturation. In addition, consultations with relevant stakeholders will be conducted at various levels, which will include authorities within and outside the village, and policymakers. All interviews will be conducted face to face, audio-recorded for transcription, and subjected to a thematic analysis.

Results: This study was approved by Mahidol University Central Institutional Review Board (MU-CIRB 2020/217.1808) in September 2020 and by Nepal Health Research Council (NHRC 716/2020 PhD) in January 2021. The fieldwork started in February 2021 and the data analysis was completed in September 2021.

Conclusions: This study is expected to provide insight into the reasons underlying the practice of kidney selling based on the example of Hokse village, along with the perspectives of multiple stakeholders.

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KEYWORDS

ethnography; kidney selling; Nepal; qualitative methods; study protocol; bioethics; medical ethics; kidney transplantation; living donors; tissue donors; tissue and organ procurement; transplantation; organ transplant

Introduction

The increasing global demand for kidney transplantation has fueled an illegal kidney trade. In 2011, 10% of all organs for transplant surgeries in the world were trafficked from a total of 100 countries [1,2]. The global phenomenon of the kidney trade finds major buyers in high-income countries and sellers in low- and middle-income countries (LMICs) [3,4]. Kidney selling has been identified in places such as the “shantytowns” of Brazil, which are infamous for “body snatching” [5], and various other

regions such as in South Africa, the Philippines, Israel, Turkey, Moldova, Argentina, Mozambique, Eastern Europe, Egypt, and India. Often, the poor and vulnerable communities in these LMICs are the hotspots for the kidney trade. In Asia, the kidney trade is prominent in China and the Indian subcontinent. Although economic prosperity is rising in these countries, high inequality between the rich and poor is pressing hard on the population. Thus, the poorer segment of the population continues to fall vulnerable to the easy money that can be obtained by selling their kidneys, while being unaware of its adverse consequences [6]. However, little systematic literature exists in exploring the nature of the organ trade, its drivers, and the adversities.

Nepal, a small country sandwiched between China and India, has become notorious for an increasing kidney trade in recent years. The village of Hokse, which lies approximately 50 kilometers east of the capital city, Kathmandu, has a high proportion of villagers who have sold their kidneys. In 2015, a study reported that more than 300 villagers from Hokse had already sold their kidneys for as low as US $200 [2], most of whom had been deceived by brokers with promises of a better future and substantial financial rewards [7]. Consequently, the village has been labeled as the "kidney village," which serves the cheapest kidneys in the world [3]. In addition, two massive earthquakes in 2015 further pushed the villagers of Hokse to extreme poverty and compounded their existing vulnerabilities for kidney selling. An immediate impact of the earthquakes was that the demolished houses needed urgent repair or rebuilding for which some villagers resorted to selling their kidneys [8]. Given the proximity to the capital city and the good road connection, villagers could seek jobs in the city for their livelihood. These social and cultural circumstances further add to the urgency and interest in focusing on Hokse village as a case study for the kidney trade.

Although poverty and economic conditions may seem to be ostensibly prominent reasons for kidney selling, they are invariably entrenched in the local social and cultural context such as money for food, rituals, and dowry [6,7,9-17]. Kidney sellers are often left with an even worse financial situation and physical health after kidney removal [4,6,9-11]. Thus, a deeper analysis of the phenomenon and its drivers, along with the underlying links to the wider structural, social, and cultural factors in the village, is essential. This study was conceived to fully explore the phenomenology in Hokse village, in addition to answering how it differs from other villages that share similar social, economic, and cultural contexts.

The main objective of this study is to explore the drivers of kidney selling and its consequences in Hokse village of the Paanchkhal municipality in central Nepal, using ethnographic methods and multistakeholder consultations. The specific objectives of this study are to: (1) understand the nature and pattern of the kidney trade in the community; (2) explore Hokse residents' perception, concept, and meaning of the kidney and the kidney selling phenomenon; (3) explore various factors driving the kidney trade from multiple stakeholders and actors such as village head leaders, neighbors, and family members; and (4) explore the enabling and impeding factors related to the kidney trade in and beyond Hokse village.

Methods

Study Design and Setting

As a qualitative research design is deemed to be the most appropriate for exploring and understanding the concept of kidney selling, the meaning of the kidney, and the interplay of myriad factors affecting the kidney trade [18], we will employ different qualitative techniques and utilize Hokse village as a case study. Multiple methods of qualitative data collection will be used, including an ethnographic approach in Hokse village and in-depth interviews with kidney sellers and other relevant participants.

The study setting, Hokse village, is located at ward numbers 7 and 8 of Paanchkhal municipality, Kavrepalanchwok district, which is about a 2-hour drive from Kathmandu. There are a total of 1000 households in these wards [19]. The members of Hokse village include different ethnicities such as Bahun, Chettri, Tamang, Sarki, and Danwar, and their livelihoods depend on subsistence farming and daily wage-earning [19]. Given the proximity to the capital city and a good road connection, a natural question arises as to why the villagers choose to sell their kidneys rather than seeking economic opportunities in the capital city.

Study Population and Sampling

Data will be collected from a diverse group of participants. The primary participants for the research will be kidney sellers aged above 18 years (Table 1). In addition, family members, neighbors, relatives, village heads, and permanent residents of the village who are willing to discuss the issue will be included as key informants of the study. Health care providers and local officers of different developmental organizations will also be recruited as our key informants. Other stakeholders such as policymakers at the Ministry of Health, legal workers, and civil society organization staff working in the field of organ and human trafficking for at least 1 year will be included in the study. Similarly, medical personnel involved in transplant medicine in Nepal will be interviewed. We will also interview some border patrol officers posted at an important border checkpoint for at least the previous 6 months. Data from these different types of participants will allow us to gain a holistic view of the phenomenon. However, we will not include altruistic kidney donors or those who undergo the surgery to donate to their family members.

Informed consent will be obtained orally and the prospective participants will be requested to sign the consent form after receiving information about the study. Informed consent in this study will be undertaken thoroughly. For example, informed consent among kidney sellers would be a sensitive issue, and thus all measures for complete and confidential informed consent will be taken into consideration.

A notable aspect of this study is the ethnographic fieldwork in which a researcher will familiarize with the villagers by living in the villages, and will observe and note down the life, culture, and traditions in the village. Such a method does not enable obtaining consent from potential participants as would be done for a survey or qualitative interview. Nonetheless, at minimum,

the researcher can obtain informed consent for all types of interviews. In case of virtual interviews, the researcher will obtain oral consent along with a digital signature of informed consent. However, some of the conversations that occur in a causal fashion as part of everyday life would be considered informal interviews and may not require informed consent.

The primary participants will be given full authority to choose the interview site and decision to be interviewed. An interviewee will be clearly instructed that they can discontinue the interview at any point without providing any justifications. All participants will be anonymized in the collected data and all personal identifiers will be removed from the transcripts.

During the study, a series of purposive sampling efforts will be made to identify the various participants. The purposive sampling technique will allow us to identify and collect information-rich cases for an in-depth study [20]. As the issues around the kidney trade can be culturally sensitive, a snowball approach may be used to identify additional participants until data saturation is reached. However, the sampling design may evolve depending on the circumstances of the data collection period, the opportunities to enroll the relevant participants, and the ability to capture the issues that emerged during the stay in the village. Specifically, we will interview approximately 12 to 20 kidney sellers, ensuring an adequate sample to obtain varied stories of kidney selling [20-23], along with 18-28 key informants and stakeholders (Table 1).

Table 1. Details of the study population, participants, and sample size.

Type of participant	Sample size, n
Primary participants: Kidney sellers of Hokse village	12-20
Key informants	
Family members, neighbors, relatives, village head	10-15
Health care providers and local officers	2-3
Stakeholders	
Transplant unit medical personnel	2-3
Policymakers, legal workers, NGO[a]/INGO[b] workers	3-5
Border checkpoint officers	1-2

[a]NGO: nongovernmental organization.

[b]INGO: international nongovernmental organization.

Research Tools

We will use interview guides for the in-depth interviews and field diaries for the ethnographic study (see Multimedia Appendix 1 for the interview guide). The field diary will be used to record important details of the ethnographic observations such as nonverbal communication, including the personal presentation of the participant, body expressions, gestures, facial expressions, style, and alterations in speech (eg, silences, choking speech, blatant speech, fading speech, cringing and tremors in the speech), laughter, and other manifestations. The principal investigator (BS) will be an integral component of the research who will investigate how local people think, perceive, and justify the kidney selling phenomenon.

Furthermore, every attempt will be made by the researchers to understand the participants and remain at the same level during constructing the meaning and experiences of kidney sellers [24]. This will help to interpret the discussion as shared by the participants. The preliminary conception that kidney selling was highly prevalent in the village to fulfill the basic needs of the poor villagers is incomplete, particularly as there are poorer villages without a kidney trade in Nepal. Understanding the experiences of kidney sellers will be critical in building an emic meaning and concept of the kidney and its trade.

Researchers' Background

The characteristic of the researchers is an important aspect to consider for the research design, data collection, and analysis, as it may have an impact on the participants. The principal investigator (BS) has an educational background in health and social sciences and belongs to a Newar ethnic community in western Nepal, where he has lived near different ethnic groups such as Bahun, Chettri, Magar, Gurung, Darai, and Bote, which is similar to the cultural context of Hokse village [25]. Although all team members of this study are men, this team is well trained to tackle the sensitivity of the research. The team members include an expert medical anthropologist (LS) and a public health specialist (BA) who have expertise and experience around community engagement, along with a researcher (MS) who has experience in gender-related issues. We believe that this research team has the capacity to think critically and add multidisciplinary perspectives to explain the unanticipated circumstances to enrich the data interpretation and its implications. Based on the ongoing data collection and reflection, we will train and incorporate a woman to collect data as to better reflect gender-related issues and when approaching female participants.

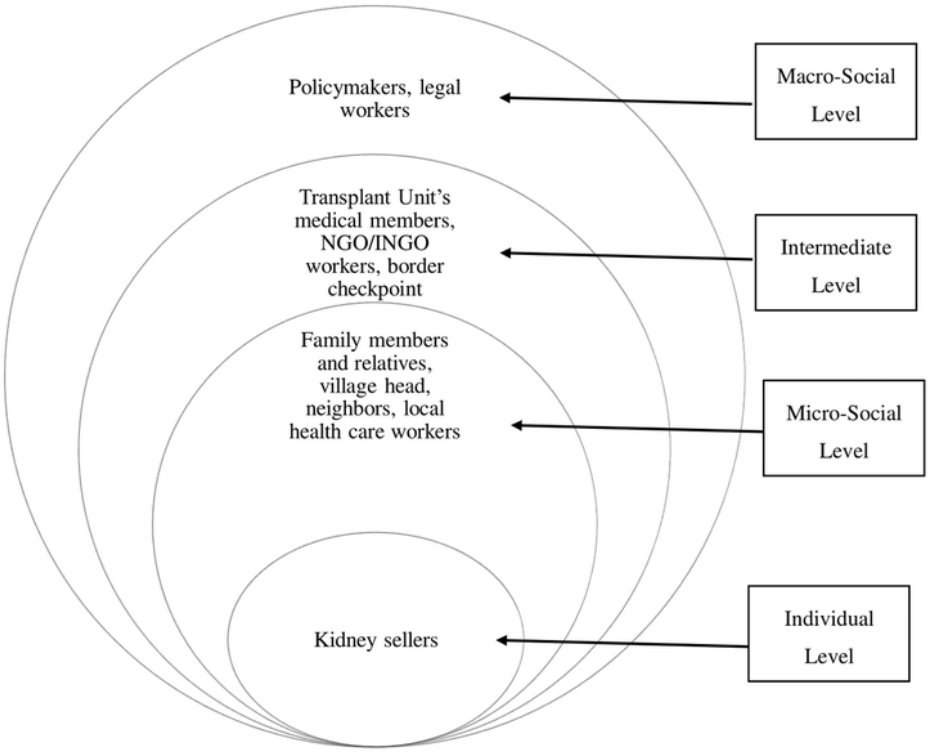
Research Hypothesis

The organ trade in Hokse village is a multifaceted problem that is predicated on individual microlevel to macrolevel factors such as policy and geographical context. This study will attempt to explore this hypothesis using a combination of methods, primarily through ethnography.

The organ trade is not a trade in the conventional sense; it is the selling of human flesh. Thus, its presence in any society is

not a simple phenomenon. As kidney selling is a complex phenomenon, its research warrants a flexible approach. We will use a constructivist perspective, which is one such approach in which human beings are assumed of being able to construct their understanding of the subject and situation. We will also analyze the embedded class and power relations, social inequalities, and social interactions that shape individual decision-making. Using the theoretical lens of critical medical anthropology (CMA), we will delve deeper into the experiences of the kidney sellers to understand and situate their decisions with the power differences and influence of dominant sociocultural and economic forces. Multiple stakeholders and key informants will allow us to understand the web of causation of kidney selling at different levels of analyses as used in CMA, from the individual microlevel to the macro structural level (Figure 1) [26]. CMA highlights the importance of political and economic forces, including the exercise of power in shaping health, disease, illness experience, and health care, which supplements the culturally sensitive analysis of human behavior grounded in anthropological methods.

Figure 1. Participants, key informants, and stakeholders at different levels. NGO: nongovernmental organization; INGO: international nongovernmental organization.



Data Collection Procedures

Entry into the Field

Before drawing up this research protocol, the principal investigator (BS) visited the village twice to explore the feasibility of the study. In the first visit, a few kidney sellers were located with the help of some personal contacts. In the second visit, some key informants were identified and a further network was established. The experiences and connections made in these visits will facilitate a smooth integration into the village for the principal investigator, who will reside there during this research for ethnography. This approach will set a good rapport with the villagers and informal conversations will be conducted with the villagers before diving more deeply into the sensitive topic of kidney selling.

Although we intend to mitigate our preexisting biases before entering the field, our backgrounds and experiences, which are different from those of the villagers, may lead to some inevitable biases. It will be difficult to enter the field with an empty mind as the theoretical knowledge and literature will prompt the researchers to have a preconception [24]. Nevertheless, we will utilize an inductive approach, which is likely to uncover new ideas and observations, giving rise to new knowledge; as a result, new theoretical positions may be derived from our empirical data and observations [27].

Ethnographic Approach

Fieldwork

We will conduct at least 3 months of ethnographic fieldwork in the village. Even though the principal investigator (BS) is from Nepal, spending substantial time in the village is crucial to embed in the community. The fieldwork will be conducted based on the theoretical framework to address the objectives of the research. During fieldwork, observations will be the key tool to understand the different activities of the villagers. New questions and issues are bound to arise during the ethnographic research. The research methods will be adapted to ensure that there is sufficient flexibility to gather crucial details during the ethnography. In addition, we will attempt to understand the power differences and interconnectedness of indigenous health and western medicine during our data collection, which can help us to explain and interpret the data [28]. Because of the current COVID-19 pandemic, we will adopt all national and

local regulations, in addition to undertaking the safety and hygiene measures such as regularly washing hands, using alcohol gel, wearing masks, and social distancing. We will also share our knowledge (related to precautions and preventive measures for COVID-19) to our participants and will not remain in direct physical contact with any participants.

Concerning the risk management related to potential for stigmatization, since a researcher will be based in the village, we will utilize complete confidentiality when setting up interviews and discussion on the topic. No interviews will be openly conducted. An interview will be conducted in a quiet, safe, and enclosed place such as household rooms where others will not be allowed to participate. We will adopt in-depth interview techniques to ensure we have one-on-one interviews.

Considering the current COVID-19 pandemic, we will adjust our plans for data collection as feasible. For instance, we will hire a local Nepali as a research assistant to conduct the ethnographic study. Outside the village, interviews with stakeholders will be conducted remotely through, for example, Skype, Microsoft Teams, and Zoom. All coordination and management of data collection will be remotely managed by the principal investigator (BS) because of current travel restrictions due to the COVID-19 pandemic.

Participant and Key Informant Interviews

Iterative interviews will be conducted with the kidney sellers and their relatives, key informants, local leaders, and concerned people. The interview guide will be used flexibly to adapt according to the contextual situation of each unique participant. The saturation of data will be ascertained after timely discussions with the coinvestigators. As kidney sellers may have experienced harsh social stigma, they may not open up easily when interviewed. The principal investigator will be cognizant of the sensitivity and approach the challenge with empathy and patience. Only after an adequate relationship has been built with the kidney sellers, the principal investigator will attempt to explore the sensitive topics. The use of a snowball approach may be needed to locate further relevant participants based on the understanding that a particular participant might be key to the research topic [29].

Stakeholder Consultations

Different stakeholders will be consulted via semistructured interviews to understand the other actors of the research, as identified in Table 1. The main purpose of involving these stakeholders is to place the experiences of the kidney sellers in the social, cultural, political, and economic context of Nepal. For example, most kidney sellers travel to India through many of the checkpoints on the 1600-kilometer-long porous border that Nepal shares with India in the east, south, and west, where no legal documents are required to cross to the other side. To gain a better sense of how kidney sellers cross the border, the research team will travel to the Nepal-India border and interview the responsible personnel working at the checkpoint. Additionally, considering the COVID-19 pandemic, if stakeholder interviews are not possible as planned, we will request virtual interviews according to the preference of the interviewee.

Researchers' Reflection and Discussion

After the interviews are conducted, the principal investigator will share the preliminary findings with the research team for reflection and further discussion. Based on the team's discussion, the principal investigator may have to further explore particular themes. There may be multiple rounds of discussion and reflections among the investigators. As this research is a form of interpretive ethnography, the chances of revisiting the participants will remain open during the data collection period.

Rigor in Qualitative Data Collection

To ensure the information in qualitative research is reliable and valid, social interaction and trust between the researcher and participants are essential. We will attempt to avoid any bias by being reflexive, separating personal interpretations from the tasks during data collection and interactions with participants, and focusing more on developing an emic perspective [30]. To ensure that the study findings are shaped by the participants and not by researcher biases and interests, a trail of the research steps taken will be documented in the field diary. There will also be constant validity checks by checking for consistencies and inconsistencies in the data reported by participants. Alternative descriptions and explanations will be sought and recorded in the field diaries. Persistent observations during multiple sessions of interviews with different participants will help to triangulate the data and boost the credibility. Furthermore, a coinvestigator (BA) is an expert in the field of kidney selling in Nepal and will help to assess the credibility of the data extracted from the participants. Similarly, a particular focus will be maintained to adhere to the research guidelines and objectives of the research. The field diaries, transcribed data, and themes developed will be reviewed by two qualitative methods experts (LS and BA) to ensure that the interpretation and conclusions drawn are supported by the data.

Data Analysis

The analysis of the data will start from the early phase of the research. The research methods used in this study will require different analyses. For instance, different facets of human experience, beliefs, kinship patterns, and ways of settlement and living, along with social, economic, and cultural factors of the village will be analyzed from the ethnographic findings. The audio-recorded interviews and the field notes will be transcribed first in the Nepali language and then translated to English. The translated English data will be back-translated into the Nepali language to ensure the validity of the translation, which will also help us to retain the nuanced meanings and interpretations. The interview data will be sorted and labeled. The data will be read several times to get a gist of the interviews, and then will be subjected to initial coding, followed by theme-building. The data will be analyzed and interpreted using the lens of CMA.

Content analysis will be conducted independently by two investigators (BS and BA). The initial analysis will be discussed with the participants to ensure that their emic interpretation is retained. NVivo version 10 (QSR International) will be used to manage and analyze the data. The analysis process and findings will be shared with the research team.

Ethics and Dissemination

All participants will be provided with a complete and clear explanation about the research in the local language through an informed consent procedure. The participants will be made aware that their names will not be written anywhere in the document. Their participation will be completely voluntary and they will be clarified about their freedom to opt out of the study at any stage of the research without providing justifications. Audio-recorded files will also be kept in folders of the principal investigator's personal computer and will be password-protected to safeguard the confidentiality of the participants' details. For the best interest of the participants, both the site (home, workplace, or any other place) and the timing of the interview will be decided by the participants to ensure their privacy and freedom.

The output of the research will be disseminated through academic articles published in international peer-reviewed scientific journals. The participants will be notified regarding the sharing of findings to the public domain; however, confidentiality, anonymity (by providing pseudonyms), and privacy of the participants will be ensured. Our research findings will be reported following the COREQ (Checklist for Reporting Qualitative Research) guidelines [31].

The study protocol was reviewed and approved by Mahidol University Central Institutional Review Board (MU-CIRB 2020/217.1808), Thailand, in September 2020, and the Nepal Health Research Council (716/2020 PhD), Nepal, in January 2021.

Results

The fieldwork started in February 2021 and different key informants and stakeholders at international and nongovernmental organizations, transplant units, policymakers, government workers, and legal workers have been identified. The data analysis was completed in September 2021.

Discussion

Projected Significance

Kidney selling is a global phenomenon; however, concentrated selling is rare and warrants urgent attention. The selling of kidneys from one particular village calls for an in-depth and broad exploration of the issue. The few previous studies on the topic have identified social responsibilities such as education, social welfare, dowry, and debt, entrenched in the local social and cultural context, to be crucial drivers of kidney selling [4,6,10-12]; however, these factors alone may not explain the concentrated selling of kidneys in one particular village in Nepal. This research will delve into the factors affecting kidney selling in this village at the micro and macro levels, and seek to answer why and how such a phenomenon is so prevalent in this village. The findings of this study may ultimately help to inform the policy and interventions to reduce organ trafficking in Nepal.

Study Limitations

This study will be conducted particularly in a village with a specific population in rural Nepal, which shows unique characteristics; hence, the data obtained may not be generalizable to other populations inside and outside Nepal. The character and the situation of Nepal and its open border with India may bring about findings that may or may not apply to other parts of the world where kidney selling is found.

Conclusion

This research will explore the reasons for selling kidneys among the residents of Hokse village, which is also known as "the kidney village" in Nepal. This work also attempts to understand the motivations of the individuals from this particular village, including their habits, economic status, employment status, educational attainment, daily activities, behavioral patterns, and understanding of the outer world. We will attempt to determine the social status of the kidney sellers within the village from both sides, kidney sellers and villagers, and to explore whether they are discriminated against or stigmatized in their community. The findings from this research will highlight the characteristics of the phenomenon in the village, including its drivers at micro and macro levels. Future research can build on the findings from this research, including operational and implementation research aiming to mitigate organ trafficking. Findings from this study will help us to establish and challenge our hypothesis and assumptions related to kidney selling in the study village. Moreover, this study can serve as a foundational platform to explore the strands and areas that might emerge but may not have adequate explanatory data. Future research can build from these findings to explore questions and areas that are beyond the scope of the current research.

Authors' Contributions

All authors contributed to the overall study design and specific methodologies. All authors approved the final version for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[PDF File (Adobe PDF File), 182 KB - resprot_v11i2e29364_app1.pdf]

References

1. Shimazono Y. The state of the international organ trade: a provisional picture based on integration of available information. Bull World Health Organ 2007 Dec 01;85(12):955-962 [FREE Full text] [doi: 10.2471/blt.06.039370] [Medline: 18278256]
2. Haken J. Transnational crime in the developing world. Global Financial Integrity. 2011 Feb 08. URL: https://gfintegrity.org/report/briefing-paper-transnational-crime/ [accessed 2022-02-02]
3. Mavrellis C. Transnational crime and the developing world. Global Financial Integrity. 2017 Mar 27. URL: https://gfintegrity.org/report/transnational-crime-and-the-developing-world/ [accessed 2022-02-02]
4. Scheper-Hughes N. The global traffic in human organs 1. Curr Anthropol 2000 Apr;41(2):191-224. [Medline: 10702141]
5. Scheper-Hughes N. Theft of life: the globalization of organ stealing rumours. Anthropol Today 1996 Jun;12(3):3. [doi: 10.2307/2783143]
6. Cohen L. Where it hurts: Indian material for an ethics of organ transplantation. Daedalus 1999;128(4):135-165. [Medline: 11645873]
7. PRI: Destroyed by a quake. Targeted by organ traffickers. Will a monsoon break this village? The Asia Foundation. 2016 Jun 20. URL: https://asiafoundation.org/2016/06/20/pri-destroyed-quake-targeted-organ-traffickers-will-monsoon-break-village/ [accessed 2022-02-02]
8. Cousins S. Nepal: organ trafficking after the earthquake. Lancet 2016 Feb 27;387(10021):833. [doi: 10.1016/S0140-6736(16)00555-9] [Medline: 26972066]
9. Zargooshi J. Quality of life of Iranian kidney "donors". J Urol 2001 Nov;166(5):1790-1799. [Medline: 11586226]
10. Yousaf FN, Purkayastha B. 'I am only half alive': Organ trafficking in Pakistan amid interlocking oppressions. Int Sociol 2015 Oct 02;30(6):637-653. [doi: 10.1177/0268580915605648]
11. Moniruzzaman M. "Living cadavers" in Bangladesh: bioviolence in the human organ bazaar. Med Anthropol Q 2012 Mar;26(1):69-91. [doi: 10.1111/j.1548-1387.2011.01197.x] [Medline: 22574392]
12. Moazam F, Zaman RM, Jafarey AM. Conversations with kidney vendors in Pakistan: an ethnographic study. Hastings Cent Rep 2009;39(3):29-44. [doi: 10.1353/hcr.0.0136] [Medline: 19537621]
13. Mendoza RL. Kidney black markets and legal transplants: are they opposite sides of the same coin? Health Policy 2010 Mar;94(3):255-265. [doi: 10.1016/j.healthpol.2009.10.005] [Medline: 19931205]
14. Adhikari B. Organ and human trafficking in Nepal. Lancet 2016 May 07;387(10031):1907. [doi: 10.1016/S0140-6736(16)30419-6] [Medline: 27203655]
15. Goyal M, Mehta RL, Schneiderman LJ, Sehgal AR. Economic and health consequences of selling a kidney in India. JAMA 2002 Oct 02;288(13):1589-1593. [doi: 10.1001/jama.288.13.1589] [Medline: 12350189]
16. Naqvi SAA, Ali B, Mazhar F, Zafar MN, Rizvi SAH. A socioeconomic survey of kidney vendors in Pakistan. Transpl Int 2007 Nov;20(11):934-939. [doi: 10.1111/j.1432-2277.2007.00529.x] [Medline: 17645418]
17. Moazam F. Bioethics and organ transplantation in a Muslim society: A study in culture, ethnography, and religion. Indiana: Indiana University Press; 2006.
18. Scheper-Hughes N. Parts unknown. Ethnography 2016 Jul 24;5(1):29-73. [doi: 10.1177/1466138104041588]
19. Paanchkhal Municipality. 2020. URL: https://panchkhalmun.gov.np [accessed 2020-09-25]
20. Patton M. Qualitative research and evaluation methods. 3rd Edition. Thousand Oaks, CA: Sage Publications; 2002.
21. Lincoln Y, Guba E. Naturalistic inquiry. Beverly Hills, CA: Sage Publications; 1985:75.
22. Marshall C, Rossman G. Designing qualitative research. 6th Edition. Thousand Oaks, CA: Sage Publications; 2016.
23. McCracken G. The long interview. Thousand Oaks, CA: Sage Publications; 1988:13.
24. Fetterman D. Ethnography: Step-by Step Guide. 3rd Edition. Thousand Oaks, CA: Sage Publications; 2010.
25. Ward profile Government of Nepal 2020. Vyas Municipality. URL: https://vyasmun.gov.np/en [accessed 2020-11-21]
26. Baer HA, Singer M, Johnsen JH. Toward a critical medical anthropology. Soc Sci Med 1986;23(2):95-98. [Medline: 3749976]
27. Stebbins R. Exploratory research in the social sciences. London: Sage Publications; 2001.
28. Guan Y, Gong J, Song B, Li J, Fang S, Tang S, et al. The effect of UV exposure on conventional and degradable microplastics adsorption for Pb (II) in sediment. Chemosphere 2022 Jan;286(Pt 2):131777. [doi: 10.1016/j.chemosphere.2021.131777] [Medline: 34375835]
29. Noy C. Sampling knowledge: the hermeneutics of snowball sampling in qualitative research. Int J Soc Res Method 2008 Oct;11(4):327-344. [doi: 10.1080/13645570701401305]
30. Finlay L, Gough B. Reflexivity: A practical guide for researchers in health and social sciences. United States: John Wiley & Sons; 2008.
31. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007 Dec;19(6):349-357. [doi: 10.1093/intqhc/mzm042] [Medline: 17872937]

Abbreviations

CMA: critical medical anthropology
COREQ: Checklist for Reporting Qualitative Research

LMIC: low- and middle-income country

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Protocol

An mHealth App for Fibromyalgia-like Post–COVID-19 Syndrome: Protocol for the Analysis of User Experience and Clinical Data

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Abstract

Background: Post–COVID-19 syndrome, also referred as "long covid," describes persisting symptoms after SARS-CoV-2 infection, including myalgia, fatigue, respiratory, or neurological symptoms. Objective symptoms are often lacking, thus resembling a fibromyalgia-like syndrome. Digital therapeutics have shown efficiency in similar chronic disorders such as fibromyalgia, offering specific disease monitoring and interventions such as cognitive behavioral therapy or physical and respiratory exercise guidance.

Objective: This protocol aims to study the requirements and features of a new mobile health (mHealth) app among patients with fibromyalgia-like post–COVID-19 syndrome in a clinical trial.

Methods: We created a web application prototype for the post–COVID-19 syndrome called "POCOS," as a web-based rehabilitation tool aiming to improve clinical outcomes. Patients without organ damage or ongoing inflammation will be included in the study. App use will be assessed through user experience questionnaires, focus groups, and clinical data analysis. Subsequently, we will analyze cross-sectional and longitudinal clinical data.

Results: The developed mHealth app consists of a clinically adapted app interface with a simplified patient-reported outcome assessment, monitoring of medical interventions, and disease activity as well as web-based instructions for specific physical and respiratory exercises, stress reduction, and lifestyle instructions. The enrollment of participants is expected to be carried out in November 2021.

Conclusions: User experience plays an important role in digital therapeutics and needs to be clinically tested to allow further improvement. We here describe this process for a new app for the treatment of the fibromyalgia-like post–COVID-19 syndrome and discuss the relevance of the potential outcomes such as natural disease course and disease phenotypes.

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KEYWORDS

post–COVID-19 syndrome; COVID-19; SARS-CoV-2; mobile health; application; user experience; testing; user interface; long-covid syndrome; mHealth; app; user interface; protocol; reinforcement; learning; strategy; symptom; outcome; patient-reported outcome; therapy; rehabilitation; monitoring

Introduction

Post–COVID-19 Syndrome

Post–COVID–19 syndrome is an increasingly recognized symptom complex occurring after SARS-CoV-2 infection, which has also been called "long COVID-19" [1]. It can be described as persisting organ damage; for example, after intensive care treatment for respiratory failure or more frequently by persisting general unspecific symptoms such as fatigue, myalgia, concentration, and sleep disturbance [2]. Owing to its neurotropism, SARS-CoV-2 can cause neural damage and persisting neurologic symptoms including olfactory dysfunction, neuropathic pain, and transient memory loss [3-5]. Objective findings in imaging or functional testing are classically missing. As an example, there is no typical neurological manifestation induced by COVID-19 on magnetic resonance imaging, but a wide range of different patterns are observed in patients [6]. Thus, the diagnosis of post–COVID-19 syndrome is clinical and difficult to monitor [7]. Similar postviral features have also been attributed in the past to other infectious outbreaks; for example, Epstein-Barr Virus or Q fever [8,9]. After the severe acute respiratory syndrome outbreak in 2003, approximately one-third of the infected patients developed reduced tolerance to exercise many months later despite having normal lung function [10]. In the past, postviral myalgic encephalomyelitis (ME) has been considered a synonym for chronic fatigue syndrome [11]. Patients with ME have also experienced neurovegetative and cognitive dysfunction, often fulfilling the classification criteria for fibromyalgia [12]. It remains unclear whether this dysfunction is a stress-related response of the host, or if it occurs owing to ongoing viral replication [13].

The prevalence of post–COVID-19 syndrome is unclear, but it has been already discussed in the literature as an upcoming relevant health problem, for which therapeutic solutions and scalable health care models must be developed [14,15]. The incidence of post–COVID-19 syndrome after SARS-CoV-2 infection is estimated to be 10%-35%. This estimation can reach 85% for hospitalized patients [16]. In this study, we focus on fibromyalgia-like post–COVID-19 syndromes, albeit without ongoing inflammatory activity or objective organ damage.

Digital Therapeutics

The use of medical apps as diagnostic but also therapeutic tools is rapidly increasing, fostered not only by the current pandemic but also by the growing acceptance of mobile health (mHealth) [17-19]. Change in legislation in different countries also permits the prescription of therapeutic medical apps, such as Digital Health Applications (DIGAs) in Germany. DIGAs are digital therapeutic tools that meet high quality standards and proof of clinical benefits. They are officially registered and most of them provide tools for cognitive behavioral therapy, exercise instructions, and lifestyle modifications (habits, nutrition, meditation, etc) [20,21].

The pandemic accelerates the development of digital solutions. The United States and Australia have, for example, established remote care systems for patients with chronic diseases and COVID-19 [22]. Surveys developed in Ontario (Canada) between February and May 2020 showed an increase from approximately 1000 clinical-to-patient video calls per day to 14,000, especially concerning elderly patients [23]. These examples illustrate the progressive implementation of digital therapeutics in the modern society. According to several studies, this new field will become a turning point in global health. Unfortunately, most of these studies also indicate that there is a scarcity of qualitative data in this domain [24-26]. The lack of knowledge in user experience (UX) and other factors such as design or gamification, which could influence consumer engagement, may be considered to facilitate the development of digital health solutions [27]. Notwithstanding the trend toward digital therapeutics, it is evident that more research on designing these apps for optimal usability is required [28].

Many currently existing apps offer the technical requirements but lack protocols for user interface (UI) design [29]. Furthermore, clinical study design including therapeutic apps require specific consideration; for example, where and how therapeutic modules are integrated or how patient-reported outcomes (PROs) can be monitored [30].

UX

UX experiments are key to improve the ergonomics and usability of an app. They occur during the development of the user interface and aim to optimize its usability. UX experiments also help the developer to assess the user's expectations. They are vital in the process of building a suitable app [31].

UX research on therapeutic medical apps is a growing field as UX interferes with adherence and potentially also with clinical outcomes. However, there is a lack of qualitative research on health and medical apps in general [29]. So far, a combination of three theory models for assessing UX for patients with chronic conditions has been postulated: the Technology Acceptance Model (TAM), the Health Information TAM (HITAM), and Health Belief Model [32]. The TAM measures how users accept technology. The HITAM adds to the concepts in the TAM by incorporating the Health Belief Model [32].

Aim and Research Questions

In this study, we aim to understand how patients with fibromyalgia-like post–COVID-19 syndrome might use digital therapeutics at the example of the app "POCOS" and how their experience could be improved in regard to onboarding, data entry, data processing, and illustration as well as therapeutic applications. Furthermore, we aim to translate these findings in the development of an optimized clinically adapted app interface, and we speculate on the potential use of such a device for a better scientific understanding of the post–COVID-19 syndrome. By the term "clinically adapted," we are referring to a patient-centered app architecture tailored to disease-specific needs but also comprehensible and interoperative for clinicians.

The research questions of this study are as follows:

User Experience

- Which symptom or intervention features are considered most important by patients with post–COVID-19 syndrome?
- What is the best way to illustrate disease activity and symptoms?

- Which general therapeutic (medical and paramedical) interventions are considered most useful by patients?
- How often will they use the app over time? What are the best intervals for assessing PROs?
- How useful are online instructions and educational videos?
- What type of therapeutic modules are considered most useful by the patients?
- How useful is a personalized web-based therapy program based on symptom profile and disease activity?

Clinical Outcomes

- What is the natural course of post–COVID-19 syndrome? Can phenotypes be identified?
- What are the risk factors for poor subjective or objective outcomes (doctor's visits or hospitalization)?
- How useful are validated fibromyalgia activity scores, such as the widespread pain index or symptoms severity score for post–COVID-19 syndrome [33]?

Methods

UI Implementation

The web application prototype investigated here is called "POCOS," which stands for post–COVID-19 syndrome. For this purpose, we developed a simplified app interface adapted to assess and treat post–COVID-19 symptoms (Figure 1). The main architecture of this interface is based on different sections resembling a doctor's visit and disease-specific requirements, respectively:

- Assessment of PROs in accordance with the literature [34].
- Medical and paramedical interventions since last data entry (physiotherapy, laboratory analysis, physical activity, and nutritional aspects).
- Monitoring and visualization of symptom courses and personalized fibromyalgia-like post–COVID-19 disease activity scores.
- Web-based therapy modules with animated videos for information, different exercise instructions (physical, respiratory, smelling, etc), muscle relaxation, stress reduction, cognitive behavioral therapies, mindfulness, as well as exchange with peers and health care professionals. The web-based treatment program will be composed in accordance with the leading disease features: fatigue, stress, pain, sleep problems, respiratory problems, neurologic symptoms, etc. It will also include information about what has helped other patients with similar symptoms recently ("What has helped you the most recently?" output) (Tables 1 and 2).

Figure 1. POCOS user interface. Left panel: the "How are you?" screen with electronic patient-reported outcomes and activity. Center panel: the "My result" screen with monitoring of symptom activity and health conditions. Right panel: the "Act & Advice" screen with a personalized training program adapted to the user's symptoms.

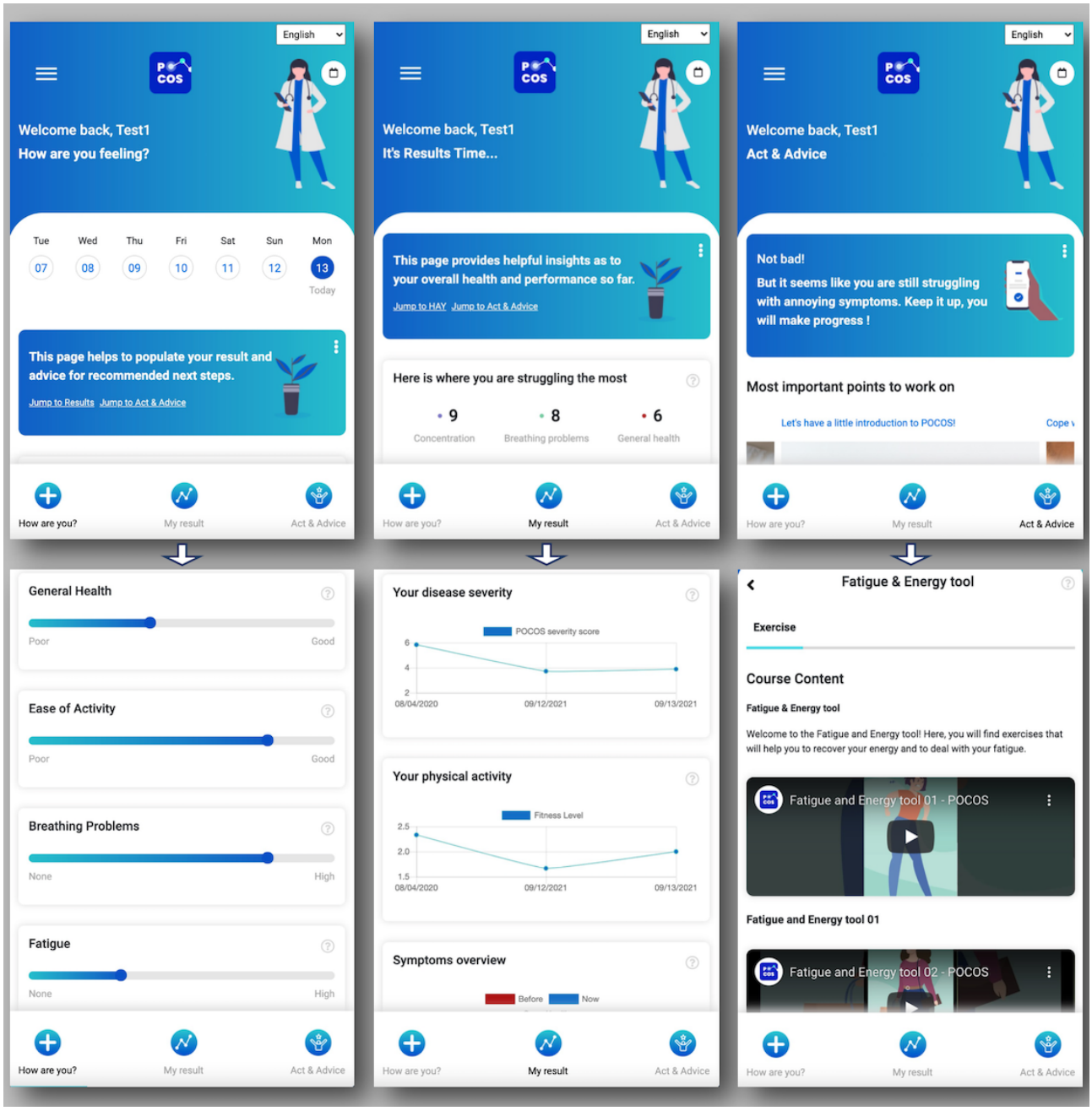


Table 1. Overview of data assessment (onboarding process, patient-reported outcomes, and interventions).

Characteristics	Response type
Onboarding process (only once after first login)	
Age	Birth date input
Gender	M/F
Date of suspected or confirmed COVID-19 infection	Date input
Type of test, if available	ELISA[a] or direct testing
Confinement	Yes/No
(If confinement) Confinement duration	Number of days
(If confinement) Type of confinement place	Small/big flat, house, house with garden
Other infected family members or peers	Yes/No
Initial symptoms	Multiple choice (to be determined)
Psychosocial factors	Multiple choice (to be determined)
Pre-existing disorders	Multiple choice (to be determined)
Smoking	Yes/No
Patient-reported outcomes (daily or weekly)	
General health	Horizontal slider (0-10 scale)
Breathing problems	Horizontal slider (0-10 scale)
Overall pain	Horizontal slider (0-10 scale)
Tender points	Clickable on body diagram (frond and back)
Memory level	Horizontal slider (0-10 scale)
Fatigue	Horizontal slider (0-10 scale)
Concentration	Horizontal slider (0-10 scale)
Ease of activity	Horizontal slider (0-10 scale)
Smelling and taste problems	Horizontal slider (0-10 scale)
Mood	Clickable smileys (1-5 scale)
Interventions (daily or weekly)	
Physical activity (walk, sport, and exercises)	Frequency (once, 2-3 times a week, everyday)
Weight	Numeric
Number of physician visits since the last input	Never, 1-3, >3
Have you been in hospital since last input?	Yes/No
Did you have therapeutic sessions since last input?	Selection (therapy type list, to be determined), frequency
Pain killers use	Frequency (per week)
What has helped you the most recently?	Free text entry
Laboratory values from blood test (if available)	Type of value, value (concentration)
Current medication	Selection (list of drugs available on the market) and frequency taken

[a]ELISA: enzyme-linked immunosorbent assay.

Table 2. Therapy modules, type of content proposed to the patient in each therapy module and corresponding patient-reported outcomes (related patient-related outcomes).

Therapy module	Content types (video/tutorials, images, and text)	Related patient-related outcomes
Respiratory	Respiratory exercises and yoga	Breathing problems, fatigue, ease of activity, and concentration
Relaxation	Yoga, meditation, and physical and relaxation exercises	Breathing problems, fatigue, overall pain, concentration, ease of activity, and mood
Energy	Relaxation exercises, yoga, advice to save energy, and meditation	Fatigue, ease of activity, mood, and overall pain
Pain management	Therapeutic stories to understand pain, yoga, meditation, and relaxation	Overall pain
Memory	Memory exercises, therapeutic stories, and advice to improve memory	Memory level and concentration
Physio	Physical exercises and yoga	Ease of activity, breathing problems, overall pain, and fatigue
Smelling and taste	Smelling and taste exercises, instructions, and self-assessment	Smelling and taste
Mental enhancement	Motivation exercises and positive thinking advice	Mood, concentration, ease of activity, and fatigue

Inclusion and Exclusion Criteria

As no official definition for the post–COVID-19 syndrome exists, we decided to include the following patients: (1) those with a proven SARS-CoV-2 infection (direct test or enzyme-linked immunosorbent assay) and (2) those with persisting symptoms such as pain, fatigue, sleep disturbance, respiratory symptoms, or concentration problems over 3 months [35].

Currently hospitalized patients and those with objective signs of active infection such as fever, increased C-reactive protein, active other viral or bacterial infection, and active immune-mediated, oncologic, or psychiatric disease are not the focus of this study and will be excluded. We will also exclude patients who are hospitalized in intensive care units or those with past or persisting organ dysfunction.

Clinical Data Assessment

Age, gender, family situation, education, and information on the type and duration of confinement during the pandemic will be assessed during the onboarding process. We will record initial COVID-19 symptoms as well as pre-existing disorders including depression, nutritional factors, and smoking (Table 1).

PROs will be assessed as listed in Table 1 and have been selected in accordance with the main symptoms of post–COVID-19 syndrome reported in the literature [2]. They are collected on a daily or weekly basis.

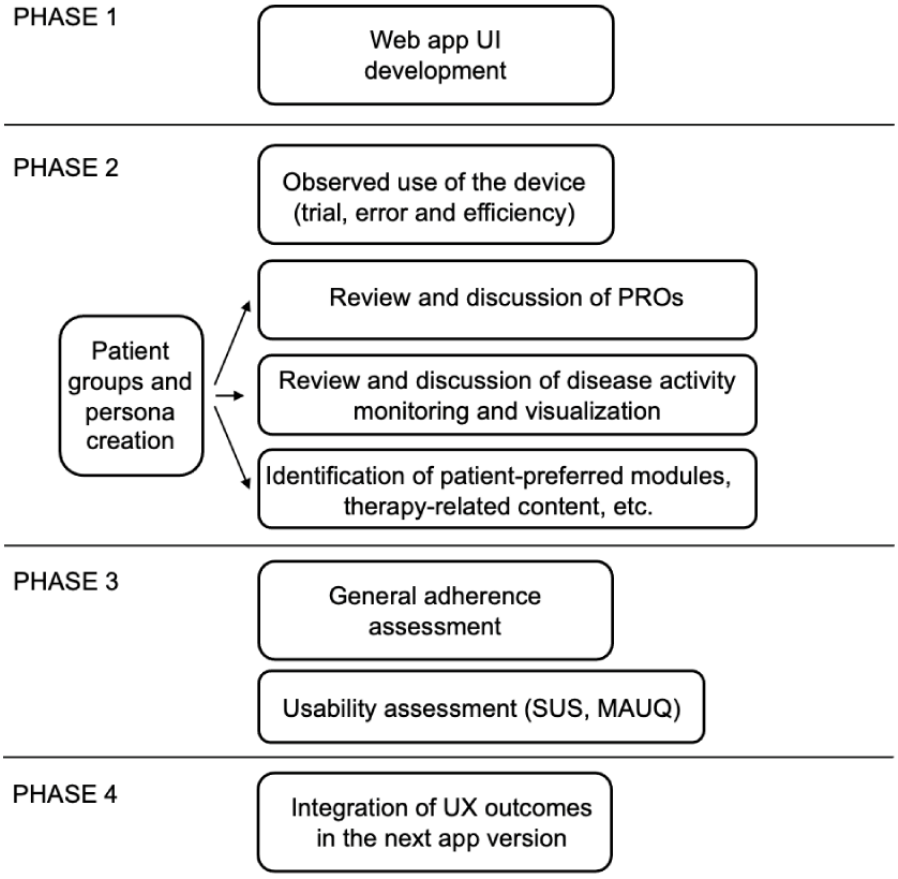
On a daily and weekly basis, we will collect information on work activity and sick leave, doctor visits, medication, and hospitalizations. As a further feature, patients can type in what helped them most in the last week to monitor and share with patients with similar profiles (Table 1). The data will be analyzed cross-sectionally and longitudinally to identify phenotypes and to calculate risk models.

Widespread pain index and the symptom severity score will be assessed on the basis of PROs and clickable body diagrams (Table 1) data [33].

UI/UX Experiments

For UI/UX assessment, we aim to examine the interactions between patients with post–COVID-19 syndrome and the "POCOS" app in terms of quality of experience. UX research will be performed by providing POCOS as an app prototype. The following analyses will be performed (Figure 2): (1) interviews with patients with post–COVID-19 syndrome groups and creation of personas (clustering patient groups by similarities); (2) System Usability Scale (SUS) [36], mHealth App Usability Questionnaire (MAUQ) [37], and the Brief Medication Questionnaire; and (3) observed use of device (task success rate, errors, efficiency, and time spent).

Figure 2. User experience research and the experimental design. MAUQ: mHealth App Usability Questionnaire, PRO: patient-reported outcome, SUS: System Usability Scale, UI: user interface, UX: user experience.



Patient and User Groups

The patients will be selected after obtaining ethical approval. Owing to the changing and diverse nature of diseases, we will further have user personas for each group to test our findings and possible hypothesis. Personas have proven to be a crucial factor when designing user tests through several research. In their research for user preferences and persona design in cardiovascular disease, Haldane et al [38] reported that personas are a key feature of user-centered design and are used in many fields from design to marketing and product, and it aims at understanding large and diverse target audiences. Therefore, our study will also focus on studying personas to identify diverse patient groups.

Personas will be created by patients with post–COVID-19 syndrome in accordance with their needs, their habits, and their challenges while using the app. The personas will be developed on the basis of the most common characteristic of the patient groups. The type of persona is also influenced by Haldane et al [38] as they outline a general approach to mHealth user types.

User Interface Testing

Testing of nonfunctional properties of the app UI, which will lead to nonfunctional app requirements, will be performed. These properties (especially design or esthetics) are likely to affect the users' experiences and are therefore crucial to investigate.

To decide on the color scheme, font, spacing, alignment, images, videos, and sound, we will perform A/B testing with different patient groups. While group A will use the app in blue, group B will use the app in the green. According to previous analyses, the blue color is preferred for promoting the identity of clinics and hospitals, while the green color represents nature and health [39]. After their use of the app, patients will be asked about their preferences on the visual attributes with a questionnaire on design principles and choices, derived from the qualitative research on color theory. The data gathered will help us identify the color and design choice of different age groups and genders.

Along with the rating screen, charts are used for users to reach and monitor their progress. To provide specific patient groups the opportunity to decide on what they see on their screen, we will be using the Card Sorting Method. Cart Sorting is a method that involves screenshots of each app to be printed on cards and presented to the users asking them to place the cards in the order that they thought most appropriate [40].

Interaction and Usability

Interaction and usability investigations will result in the functional requirements of the app. These experiments will lead to the eventual modification, suppression, or validation of the app features. These UX outcomes will then be integrated in the subsequent app version.

Patients will be assigned tasks to complete with the app in a given timeframe. These tasks will include but not be limited to *enter today's mood*, *view chart of the pain*, *go to advices page*,

adjust yesterday's sleep quality, *check last week data*, etc. The tasks will be modified in accordance with the prototype design and ready-to-use features. We will also record the patients' task time to find the optimal speed and which functions seem to take longer for the patients. As they would while using the app on their own, they will be asked to input their symptoms and report on their pain. To complete the task, the user's choice of interaction will be recorded by logging their errors such as tapping instead of double-tapping while inputting text.

Along with the interaction and usability observation, upon completion of each task, users will be administered the SUS [41]. Originally developed by John Brooke in 1986, the SUS facilitates the evaluation of a wide variety of products and features including hardware, software, mobile devices, and apps. It is a 10-item questionnaire that allows us to understand the efficiency of the system and how easily it can be used by the user. After the data are collected, we will be able to score the system and readdress issues with usability if necessary. After each experiment, we will also ask our patients to provide their opinion on the system along with what they liked and what they thought could be improved.

In addition to the SUS, users will also be administered the MAUQ to fill. This 10-15–item questionnaire is specific for mHealth apps and is commonly used and adapted to measure usability [37].

Medical Adherence

The importance of user experience in relation to medical adherence is well-documented within the discipline of health psychology. According to Dayer et al [42], low adherence causes approximately 33%-69% of medication-related hospitalizations and US $100 billion in annual health care costs. Currently, there are no tests to analyze app adherence. Currently available mHealth apps including Med Agenda, Dosecast, and MedSimple use push notifications such as "time to take your medication" for adherence. Furthermore, apps such as Med Agenda, RxmindMe, Dosecast, MedsIQ, PillManager, and MediMemory require a box to be ticked when the patients take their medication. All of these apps have very low ratings on both Apple App Store and Google Play as they do not possess the features they claim to have.

To create patient-based adherence, we will create a survey to ask the user how often they would like to be reminded to use the app (and to provide the PROs). The Brief Medication Questionnaire [43] will be used to explore both patients' medication-taking behavior and barriers to adherence. It has a 5-item "Regime" screen, a 2-item "Belief" screen, and a 2-item "Recall" screen. These screens assess how patients took their medications in the past week, the effectiveness of the drug, and concerning features. The test will help us generate our personas by identifying patients who need assistance with their medications, highlight their concerns, and provide novel insights for improvement and development suggestions.

Clinical Data Analysis

Cross-sectional and prospective characterization of the post–COVID-19 syndrome is key for its understanding and treatment. The POCOS app will collect information on initial COVID-19 infection and subsequent symptoms over time. PROs and medical and paramedical interventions including doctor's visits and hospitalization will be assessed on at least a weekly basis.

Power calculation: at the beginning of 2021, a total of 33,000 individuals survived a SARS-CoV-2 infection in Switzerland. We estimate that 20%-30% of the patients after a SARS-CoV-2 infection experience marked fatigue and reduced quality of life.

Sample size consideration: data will not be analyzed in order to prove certain hypothesis (exploratory data analysis). The minimal required sample size (n) is determined as follows:

$$n \geq N + (N - 1) \times \epsilon^2 z^2 \times p \times q \quad \textbf{(1)}$$

where N is the number of patients who survived a SARS-CoV-2 infection in Switzerland, is the error accuracy (tolerated error), z is the quantile of the standard normal distribution, p is the relative frequency of people with post–COVID-19 syndrome (fatigue of at least >3 months), $q = 1 - p$. In this case, N=33,000, ϵ=5%, z=1.96, p=0.15, and q=0.85; thus, a minimal sample size of 195 individuals is required. A high dropout rate of 25% is assumed, so that a total of 250 patients who survived a SARS-CoV-2 infection will be initially included in the study. Explorative analysis will be performed with cross-tabs and correlations to identify associations. Repeated measurements analyses will be performed to explore multivariate associations between baseline status (adjusting for age, sex, and disease duration) and disease status after 3 or 6 months. Furthermore, logistic regression analysis will be used to analyze multivariate associations among binary endpoints (eg, achievement of remission, myalgia [yes/no], and work incapacity [yes/no]) at 6 and 12 months. We will perform logistic regression analyses adjusting for age, sex, and BMI to identify symptoms at acute infection (anosmia, fever, persistent cough, fatigue, shortness of breath, diarrhea, chest pain, and hoarse voice), which might be associated with the development of post–COVID-19 syndrome. The aim is to set up a model to predict poor outcomes. At a later step, with higher numbers of included individuals, supervised machine learning using labeled data will be used to generate prediction models, feature importance, and heat maps based on classification and regression analyses.

Ethical Considerations

The study proposal has been conditionally accepted by the regional ethical committee. This study is expected to commence in November 2021.

Results

The provisory frond-end development (UI) of the POCOS app has been completed in the form of a clinically adapted architecture (Figure 1). The back-end development is ongoing, especially at the level of data management. A landing website and an introduction video for the app have been prepared. The therapeutic content (videos, articles, and other type of media) has been uploaded on the app. A fully functional version of the app (including web and mobile versions) is expected for the end of September 2021.

Discussion

Expected Findings

We here demonstrate UI development of a new mHealth app for post–COVID-19 syndrome, which focuses on the fibromyalgia-like phenotype. The decision for this phenotype was based on its frequency and difficulty to manage symptoms, taking into account the lack of objective clinical signs and biomarkers. Furthermore, we previously developed and used digital support tools for patients with fibromyalgia and chronic fatigue syndromes at our center. As post–COVID-19 syndrome shares clinical similarities with other common chronic syndromes (fibromyalgia, chronic pain syndrome, chronic fatigue syndrome, and rheumatoid arthritis), this study may also provide insights into interesting elements for digital therapeutics that are applied for other chronic diseases [44-47].

The collection of clinical post–COVID-19 data is crucial for its understanding and symptom management. Potentially, data obtained by this app will facilitate the identification of prognostic markers and markers for disease activity, respectively. A strong point of this protocol is the development of the advanced UI frontend including therapy-related content. Therefore, in an optimized version based on the results obtained from this study, we expect a quick and high user interest.

Limitations

As a limitation, PROs and disease activity markers used in this app have not been validated for the post–COVID-19 syndrome. We would also like to emphasize that this protocol will not provide information on efficacy or safety of this app. In any case, the therapeutic value of this app will have to be tested in a future validation study.

Conclusions

In conclusion, this study will provide new and potentially large-scale information on the outcomes of patients with post–COVID-19 syndrome. The focus of this protocol on UI/UX design will potentially improve the knowledge on interactions between patients and an mHealth interface.

Conflicts of Interest

MB, LB and TH are shareholders of ATREON Société Anonyme.

References

1. Baig A. Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers. J Med Virol 2021 May;93(5):2555-2556. [doi: 10.1002/jmv.26624] [Medline: 33095459]
2. Raveendran A, Jayadevan R, Sashidharan S. Long COVID: An overview. Diabetes Metab Syndr 2021;15(3):869-875 [FREE Full text] [doi: 10.1016/j.dsx.2021.04.007] [Medline: 33892403]
3. Conde Cardona G, Quintana Pájaro LD, Quintero Marzola ID, Ramos Villegas Y, Moscote Salazar LR. Neurotropism of SARS-CoV 2: Mechanisms and manifestations. J Neurol Sci 2020 May 15;412:116824 [FREE Full text] [doi: 10.1016/j.jns.2020.116824] [Medline: 32299010]
4. Hu J, Jolkkonen J, Zhao C. Neurotropism of SARS-CoV-2 and its neuropathological alterations: Similarities with other coronaviruses. Neurosci Biobehav Rev 2020 Dec;119:184-193 [FREE Full text] [doi: 10.1016/j.neubiorev.2020.10.012] [Medline: 33091416]
5. Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 2021 Feb;24(2):168-175. [doi: 10.1038/s41593-020-00758-5] [Medline: 33257876]
6. Kremer S, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, et al. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology 2020 Nov;297(2):E242-E251 [FREE Full text] [doi: 10.1148/radiol.2020202222] [Medline: 32544034]
7. Raveendran AV. Long COVID-19: Challenges in the diagnosis and proposed diagnostic criteria. Diabetes Metab Syndr 2021;15(1):145-146 [FREE Full text] [doi: 10.1016/j.dsx.2020.12.025] [Medline: 33341598]
8. Vernon SD, Whistler T, Cameron B, Hickie IB, Reeves WC, Lloyd A. Preliminary evidence of mitochondrial dysfunction associated with post-infective fatigue after acute infection with Epstein Barr virus. BMC Infect Dis 2006 Jan 31;6:15 [FREE Full text] [doi: 10.1186/1471-2334-6-15] [Medline: 16448567]
9. Ayres J, Flint N, Smith E, Tunnicliffe W, Fletcher T, Hammond K, et al. Post-infection fatigue syndrome following Q fever. QJM 1998 Mar;91(2):105-123. [doi: 10.1093/qjmed/91.2.105] [Medline: 9578893]
10. Ong KC, Ng AW, Lee LS, Kaw G, Kwek SK, Leow MK, et al. Pulmonary function and exercise capacity in survivors of Severe Acute Respiratory Syndrome. Chest 2004 Oct;126(4):868S. [doi: 10.1378/chest.126.4_meetingabstracts.868s-b]
11. Dowsett EG, Ramsay AM, McCartney RA, Bell EJ. Myalgic encephalomyelitis--a persistent enteroviral infection? Postgrad Med J 1990 Jul;66(777):526-530 [FREE Full text] [doi: 10.1136/pgmj.66.777.526] [Medline: 2170962]
12. Natelson B. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Fibromyalgia: Definitions, Similarities, and Differences. Clin Ther 2019 Apr;41(4):612-618 [FREE Full text] [doi: 10.1016/j.clinthera.2018.12.016] [Medline: 30795933]
13. Komaroff AL, Bateman L. Will COVID-19 Lead to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome? Front Med (Lausanne) 2020;7:606824 [FREE Full text] [doi: 10.3389/fmed.2020.606824] [Medline: 33537329]

14. Jiang DH, McCoy RG. Planning for the Post-COVID Syndrome: How Payers Can Mitigate Long-Term Complications of the Pandemic. J Gen Intern Med 2020 Oct;35(10):3036-3039 [FREE Full text] [doi: 10.1007/s11606-020-06042-3] [Medline: 32700223]
15. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med 2021 Apr;27(4):601-615. [doi: 10.1038/s41591-021-01283-z] [Medline: 33753937]
16. Pavli A, Theodoridou M, Maltezou H. Post-COVID Syndrome: Incidence, Clinical Spectrum, and Challenges for Primary Healthcare Professionals. Arch Med Res 2021 Aug;52(6):575-581 [FREE Full text] [doi: 10.1016/j.arcmed.2021.03.010] [Medline: 33962805]
17. Kao C, Liebovitz DM. Consumer Mobile Health Apps: Current State, Barriers, and Future Directions. PM R 2017 May;9(5S):S106-S115. [doi: 10.1016/j.pmrj.2017.02.018] [Medline: 28527495]
18. Peine A, Paffenholz P, Martin L, Dohmen S, Marx G, Loosen SH. Telemedicine in Germany During the COVID-19 Pandemic: Multi-Professional National Survey. J Med Internet Res 2020 Aug 05;22(8):e19745 [FREE Full text] [doi: 10.2196/19745] [Medline: 32568724]
19. Safi S, Danzer G, Schmailzl KJ. Empirical Research on Acceptance of Digital Technologies in Medicine Among Patients and Healthy Users: Questionnaire Study. JMIR Hum Factors 2019 Dec 29;6(4):e13472 [FREE Full text] [doi: 10.2196/13472] [Medline: 31782741]
20. Esser M, Boreham A, Ring C, Schreier J. PNS100 The New Reimbursement Route for Digital Health Applications (DIGA) in Germany: Critical Appraisal and First Evaluation of the Possible Effect on the German Healthcare System. Value in Health 2020 Dec;23:S658-S659 [FREE Full text] [doi: 10.1016/j.jval.2020.08.1544]
21. Gerke S, Stern AD, Minssen T. Germany's digital health reforms in the COVID-19 era: lessons and opportunities for other countries. NPJ Digit Med 2020;3:94 [FREE Full text] [doi: 10.1038/s41746-020-0306-7] [Medline: 32685700]
22. John Leon Singh H, Couch D, Yap K. Mobile Health Apps That Help With COVID-19 Management: Scoping Review. JMIR Nurs 2020;3(1):e20596 [FREE Full text] [doi: 10.2196/20596] [Medline: 32897271]
23. Macleod M. New Normal: Are virtual doctor?s appointments here to stay? CTV News. 2020 May 14. URL: https://www.ctvnews.ca/health/coronavirus/new-normal-are-virtual-doctor-s-appointments-here-to-stay-1.4939255 [accessed 2022-01-31]
24. Dang A, Arora D, Rane P. Role of digital therapeutics and the changing future of healthcare. J Family Med Prim Care 2020 May;9(5):2207-2213 [FREE Full text] [doi: 10.4103/jfmpc.jfmpc_105_20] [Medline: 32754475]
25. Cho C, Lee H. Could Digital Therapeutics be a Game Changer in Psychiatry? Psychiatry Investig 2019 Mar;16(2):97-98 [FREE Full text] [doi: 10.30773/pi.2019.01.20] [Medline: 30808114]
26. Choi MJ, Kim H, Nah H, Kang D. Digital Therapeutics: Emerging New Therapy for Neurologic Deficits after Stroke. J Stroke 2019 Oct;21(3):242-258 [FREE Full text] [doi: 10.5853/jos.2019.01963] [Medline: 31587534]
27. Jeffrey B, Bagala M, Creighton A, Leavey T, Nicholls S, Wood C, et al. Mobile phone applications and their use in the self-management of Type 2 Diabetes Mellitus: a qualitative study among app users and non-app users. Diabetol Metab Syndr 2019;11:84 [FREE Full text] [doi: 10.1186/s13098-019-0480-4] [Medline: 31636719]
28. Xie Z, Kalun Or C. Acceptance of mHealth by Elderly Adults: A Path Analysis. Proc Hum Factors Ergon Soc Annu Meet 2021 Feb 09;64(1):755-759. [doi: 10.1177/1071181320641174]
29. Bitkina O, Kim H, Park J. Usability and user experience of medical devices: An overview of the current state, analysis methodologies, and future challenges. Int J Ind Ergon 2020 Mar;76:102932 [FREE Full text] [doi: 10.1016/j.ergon.2020.102932]
30. Solomon DH, Rudin RS. Digital health technologies: opportunities and challenges in rheumatology. Nat Rev Rheumatol 2020 Sep;16(9):525-535. [doi: 10.1038/s41584-020-0461-x] [Medline: 32709998]
31. Biduski D, Bellei E, Rodriguez J, Zaina L, De Marchi ACB. Assessing long-term user experience on a mobile health application through an in-app embedded conversation-based questionnaire. Comput Hum Behav 2020 Mar;104:106169 [FREE Full text] [doi: 10.1016/j.chb.2019.106169]
32. Anderson K, Burford O, Emmerton L. Mobile Health Apps to Facilitate Self-Care: A Qualitative Study of User Experiences. PLoS One 2016;11(5):e0156164 [FREE Full text] [doi: 10.1371/journal.pone.0156164] [Medline: 27214203]
33. Wolfe F, Clauw DJ, Fitzcharles M, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010 May;62(5):600-610 [FREE Full text] [doi: 10.1002/acr.20140] [Medline: 20461783]
34. Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. Int J Clin Pract 2021 Mar;75(3):e13746 [FREE Full text] [doi: 10.1111/ijcp.13746] [Medline: 32991035]
35. Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res 2020 Oct;6(4):00542 [FREE Full text] [doi: 10.1183/23120541.00542-2020] [Medline: 33257910]
36. Holden RJ. A Simplified System Usability Scale (SUS) for Cognitively Impaired and Older Adults. Proceedings of the International Symposium on Human Factors and Ergonomics in Health Care 2020 Sep 16;9(1):180-182. [doi: 10.1177/2327857920091021]

37. Chumkasian W, Fernandez R, Win K, Petsoglou C, Lord H. Adaptation of the MAUQ and usability evaluation of a mobile phone-based system to promote eye donation. Int J Med Inform 2021 Jul;151:104462. [doi: 10.1016/j.ijmedinf.2021.104462] [Medline: 33933903]
38. Haldane V, Koh JJK, Srivastava A, Teo KWQ, Tan YG, Cheng RX, et al. User Preferences and Persona Design for an mHealth Intervention to Support Adherence to Cardiovascular Disease Medication in Singapore: A Multi-Method Study. JMIR Mhealth Uhealth 2019 May 28;7(5):e10465 [FREE Full text] [doi: 10.2196/10465] [Medline: 31140445]
39. How Great UI Design for Healthcare App Can Help Your Patients. Ego Creative Innovations Limited. 2021 May 18. URL: https://www.ego-cms.com/post/great-healthcare-app-design [accessed 2022-01-31]
40. Gkatzidou V, Giacomin J, Skrypchuk L. Automotive Human Centred Design Methods. Berlin: De Gruyter; 2021.
41. System Usability Scale (SUS). US General Services Administration. Technology Transformation Services. URL: https://www.usability.gov/how-to-and-tools/methods/system-usability-scale.html [accessed 2022-01-31]
42. Dayer L, Heldenbrand S, Anderson P, Gubbins PO, Martin BC. Smartphone medication adherence apps: potential benefits to patients and providers. J Am Pharm Assoc (2003) 2013;53(2):172-181 [FREE Full text] [doi: 10.1331/JAPhA.2013.12202] [Medline: 23571625]
43. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Educ Couns 1999 Jul;37(2):113-124. [doi: 10.1016/s0738-3991(98)00107-4] [Medline: 14528539]
44. Levine DM, Co Z, Newmark LP, Groisser AR, Holmgren AJ, Haas JS, et al. Design and testing of a mobile health application rating tool. NPJ Digit Med 2020;3:74 [FREE Full text] [doi: 10.1038/s41746-020-0268-9] [Medline: 32509971]
45. Ursini F, Ciaffi J, Mancarella L, Lisi L, Brusi V, Cavallari C, et al. Fibromyalgia: a new facet of the post-COVID-19 syndrome spectrum? Results from a web-based survey. RMD Open 2021 Aug;7(3):e001735 [FREE Full text] [doi: 10.1136/rmdopen-2021-001735] [Medline: 34426540]
46. Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: implications for rehabilitation. Br J Anaesth 2020 Oct;125(4):436-440 [FREE Full text] [doi: 10.1016/j.bja.2020.05.021] [Medline: 32560913]
47. Silva Andrade B, Siqueira S, de Assis Soares WR, de Souza Rangel F, Santos NO, Dos Santos Freitas A, et al. Long-COVID and Post-COVID Health Complications: An Up-to-Date Review on Clinical Conditions and Their Possible Molecular Mechanisms. Viruses 2021 Apr 18;13(4):700 [FREE Full text] [doi: 10.3390/v13040700] [Medline: 33919537]

Abbreviations

DIGA: Digital Health Applications
HITAM: Health Information Technology Acceptance Model
MAUQ: mHealth App Usability Questionnaire
ME: myalgic encephalomyelitis
mHealth: mobile health
SUS: System Usability Scale
TAM: Technology Acceptance Model
UI: user interface
UX: user experience

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Protocol

Investigating Genetic and Other Determinants of First-Onset Myocardial Infarction in Malaysia: Protocol for the Malaysian Acute Vascular Events Risk Study

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Abstract

Background: Although the burden of premature myocardial infarction (MI) is high in Malaysia, direct evidence on the determinants of MI in this multi-ethnic population remains sparse.

Objective: The Malaysian Acute Vascular Events Risk (MAVERIK) study is a retrospective case-control study established to investigate the genomic, lipid-related, and other determinants of acute MI in Malaysia. In this paper, we report the study protocol and early results.

Methods: By June 2019, we had enrolled approximately 2500 patients with their first MI and 2500 controls without cardiovascular disease, who were frequency-matched by age, sex, and ethnicity, from 17 hospitals in Malaysia. For each participant, serum and whole blood have been collected and stored. Clinical, demographic, and behavioral information has been obtained using a 200-item questionnaire.

Results: Tobacco consumption, a history of diabetes, hypertension, markers of visceral adiposity, indicators of lower socioeconomic status, and a family history of coronary disease were more prevalent in cases than in controls. Adjusted (age and sex) logistic regression models for traditional risk factors indicated that current smoking (odds ratio [OR] 4.11, 95% CI 3.56-4.75; *P*<.001), previous smoking (OR 1.34, 95% CI 1.12-1.60; *P*=.001), a history of high blood pressure (OR 2.13, 95% CI 1.86-2.44; *P*<.001), a history of diabetes mellitus (OR 2.72, 95% CI 2.34-3.17; *P*<.001), a family history of coronary heart disease (OR 1.28, 95% CI 1.07-1.55; *P*=.009), and obesity (BMI >30 kg/m^2; OR 1.19, 95% CI 1.05-1.34; *P*=.009) were associated with MI in age- and sex-adjusted models.

Conclusions: The MAVERIK study can serve as a useful platform to investigate genetic and other risk factors for MI in an understudied Southeast Asian population. It should help to hasten the discovery of disease-causing pathways and inform regionally appropriate strategies that optimize public health action.

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KEYWORDS

myocardial infarction; cardiovascular disease; case-control study; Malaysia

Introduction

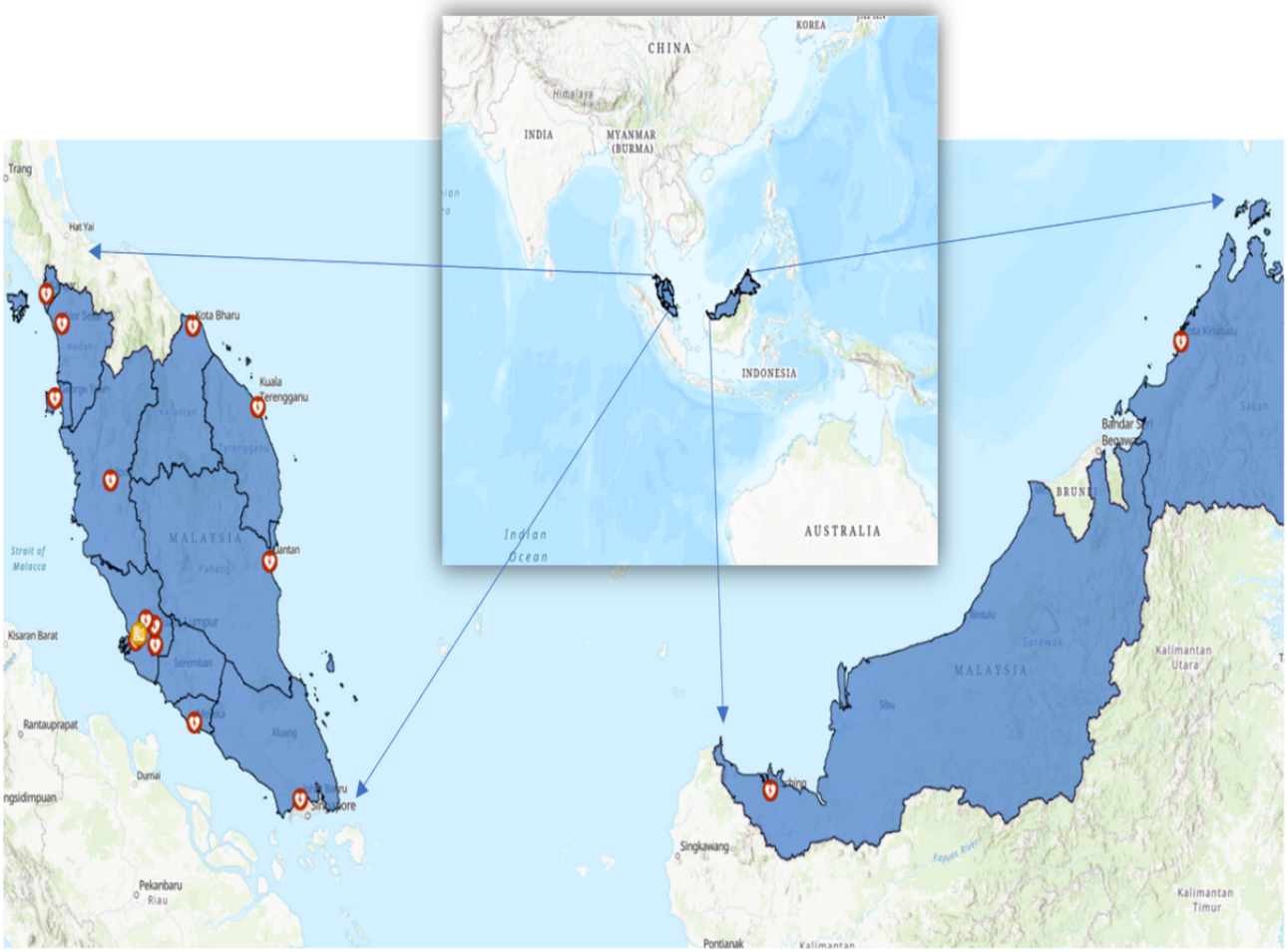
Coronary heart disease (CHD), with myocardial infarction (MI) as a key clinical manifestation, is the leading cause of death in Malaysia and elsewhere in Southeast Asia [1,2]. In recent decades, Malaysia has experienced a sustained increase in the incidence of CHD [3]. According to World Health Organization estimates, the age-adjusted death rates of CHD are approximately twice as high in Malaysia compared with the United States or the United Kingdom [4]. Furthermore, studies in Malaysia and other Southeast Asian countries indicate that CHD events tend to occur at younger ages and are characterized by more severe clinical features than in Western populations [5,6], resulting in substantial losses in productive working years owing to death and disability. Indeed, CHD in Malaysia is characterized by high rates of short-term post-MI mortality [7]. However, there is limited direct evidence regarding the determinants of CHD in Malaysia [2]. Therefore, we have established the Malaysian Acute Vascular Events Risk (MAVERIK) retrospective case-control study of MI to investigate genomic, lipid-related, and other determinants of acute MI in Malaysia. In this paper, we describe the rationale, protocol, and early baseline results of this study.

Methods

The MAVERIK study was established in 2017 in collaboration with the British Heart Foundation Cardiovascular Epidemiology Unit at the University of Cambridge, United Kingdom (the study's international coordinating center); the Institute for

Medical Research (IMR), Malaysia (the study's National Collaborating center); and 17 national collaborating cardiology referral hospitals in Malaysia serving as the study's recruitment centers (encompassing nearly all states and federal territories in Malaysia; Figure 1).

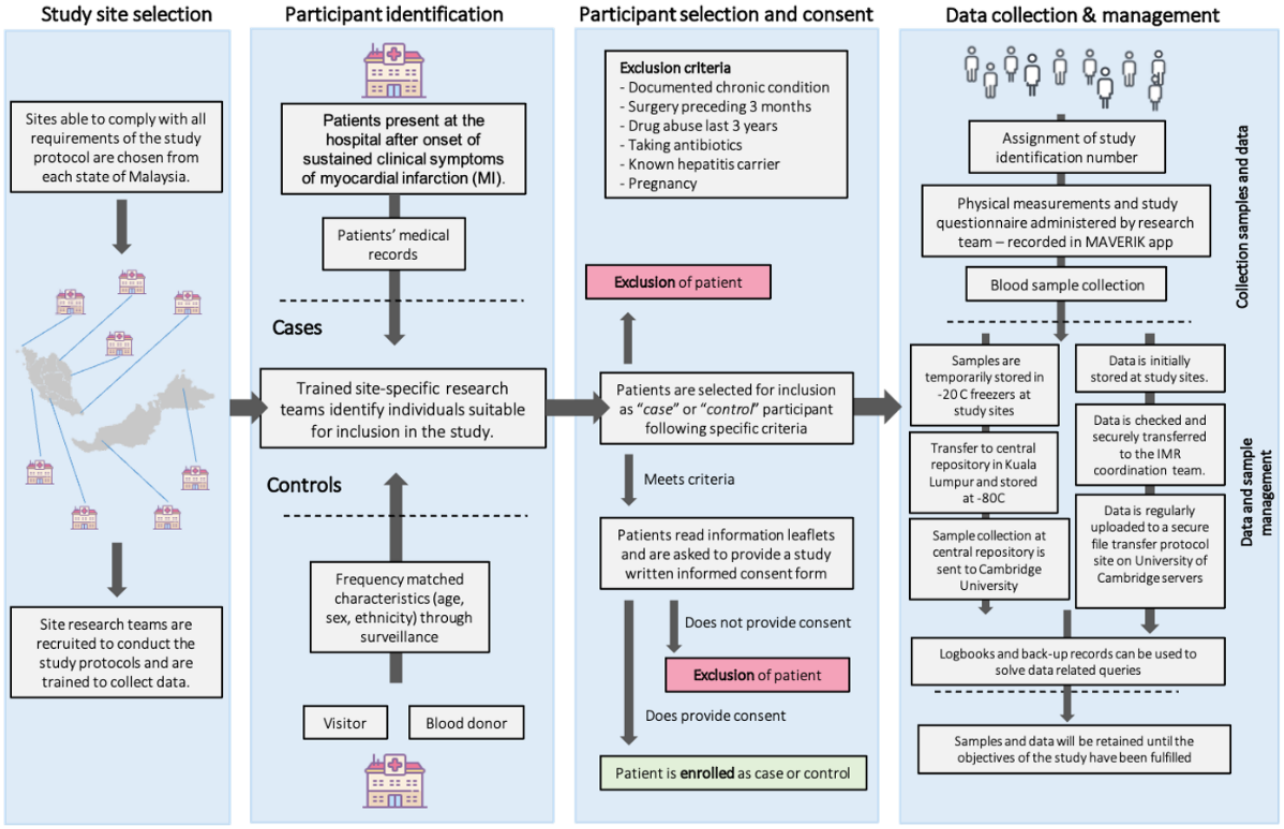
Figure 1. Location of the Malaysian Acute Vascular Events Risk (MAVERIK) study hospital sites. The sites in red denote the recruitment centers: Hospital Tuanku Fauziah Kangar, Hospital Sultanah Bahiyah Alor Setar, Hospital Pulau Pinang, Hospital Raja Permaisuri Bainun Ipoh, Hospital Serdang, Hospital Kuala Lumpur, Hospital Shah Alam, Hospital Tengku Ampuan Rahimah Klang, Hospital Sungai Buloh, Hospital Melaka, Hospital Sultanah Aminah Johor Bharu, Hospital Tengku Ampuan Afzan Kuantan, Hospital Sultanah Nur Zahirah Kuala Terengganu, Hospital Raja Perempuan Zainab II Kota Bharu, Hospital Queen Elizabeth II Kota Kinabalu, Hospital Umum Sarawak, and Pusat Jantung Sarawak Kota Samarahan. Sites in yellow denote the local coordinating center and national sample repository of the Institute for Medical Research, Malaysia. This figure has been made using Esri ArcGIS Online with the Topographic Basemap.



Study Design and Participants

The MAVERIK study is a retrospective case-control study of acute MI (Figure 2). By August 2019, the study had recruited 2547 confirmed first-ever MI cases and 2500 healthy controls without cardiovascular disease (CVD). Patients admitted to the cardiology unit or wards, general medical wards, or coronary care units of the participating hospitals have been screened by study research assistants trained to identify all relevant cases of acute MI. Cases were eligible for inclusion in the study if they (1) were Malaysians residing in Malaysia; (2) were adults aged ≥18 years; (3) were present at the hospital after the onset of clinical symptoms suggestive of MI, with symptoms lasting longer than 20 minutes; (4) had a confirmed diagnosis of acute MI based on the Malaysian Clinical Practise Guidelines [8-10], which included levels of cardiac troponins above the 99th percentile of the upper reference limits, accompanied with at least one of the following: clinical history consistent with chest pain of ischemic origin, new ischemic electrocardiogram changes or development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography; (5) had no previous CVD, defined as self-reported history of MI, coronary revascularization, transient ischemic attack, stroke, other CVDs or evidence of CHD on a prior electrocardiogram, or in other medical records; and (6) were not concurrently hospitalized for any MI or CVD events.

Figure 2. The Malaysian Acute Vascular Events Risk (MAVERIK) Study flow diagram for activities.



Control participants were recruited within 3 months of recruiting the index cases and were frequency-matched to cases by age (in 5-year age bands), sex, and self-reported ethnicity (Malay, Chinese, Indian, Sabah and Sarawak Bumiputera, Orang Asli, and others). The control participants had no previous self-reported history of CVD and were identified in the same hospitals as the index cases or collaborating hospitals in the same region and were recruited in the following order of priority: (1) visitors who were accompanying patients attending the outpatient department; (2) visitors of inpatients who were not part of the MAVERIK study; (3) visitors of index MI cases who were not their blood relatives; and (4) healthy blood donors in the same hospital. The selected cases and controls were excluded if they met any of the following criteria: (1) had documented chronic conditions on past medical history, such as malignancy, kidney (estimated glomerular filtration rate [eGFR] of <60 mL/min/1.73 m^2), thyroid or inflammatory disorders, or any chronic infection on past medical history; (2) had a recent history of surgery in the last 3 months; (3) were taking antibiotics; (4) were known to abuse drugs in the last 3 years; (5) were pregnant; or (6) were unwilling or unable to provide consent.

Before adopting the approach for the selection of controls, we carefully assessed several other options, such as choosing control groups who had an unrelated disease, population-based community controls, and controls from occupational settings or health-check clinics. Our chosen approach was considered desirable because it achieved a balance between feasibility and scientific rigor and because it was scalable in Malaysia. By contrast, even though the use of population-based community controls may be desirable in principle, it is considerably more labor-intensive and expensive. Furthermore, in agreement with the Wellcome Trust Case-Control Consortium [11], the MAVERIK study controls can be efficiently and validly used, at least in genetic studies, for patients with other cardiometabolic conditions owing to the broad geographic and ethnic scope of the MAVERIK study.

Questionnaire Administration and Physical Measurements

The MAVERIK study questionnaires used are adapted to the Malaysian context based on questionnaires used in previous case-control studies of acute MI in Southeast Asian populations (eg, the Bangladesh Risk of Acute Vascular Events study in Bangladesh) and were piloted in Malaysia before implementation in the MAVERIK study [12,13]. Trained personnel administered a prepiloted epidemiological questionnaire seeking information on >200 items related to demographic characteristics, consanguinity, behavior (eg, tobacco and alcohol consumption, dietary intake, and physical activity), personal and family medical history, and medication use (Table 1). A copy of the study questionnaire is available in the Multimedia Appendix 1. Paper-free data collection involved a bespoke Android interface (*MAVERIK app*) and operated through handheld touchscreen tablet devices. For a subset of the cases and controls, data were collected using both electronic and paper questionnaires for quality comparison purposes. To assess local dietary patterns, an 83-item food-frequency questionnaire, with an estimated standard portion size assigned to each food item, was adapted from a validated Malaysian national survey questionnaire (Multimedia Appendix 1, Table S1) [14]. We used standardized procedures and equipment to

assess height, weight, waist and hip circumference, systolic and diastolic blood pressure, and heart rate. Waist circumference was assessed over the abdomen at the widest diameter between the costal margin and the iliac crest, and hip circumference at the level of the greater trochanters (ie, the widest diameter around the buttocks). For both index cases and controls, anthropometric measurements were performed in a standing position (a copy of the anthropometric measurement protocol is available in the Multimedia Appendix 1).

Table 1. Summary of questionnaire-based information, physical measurements, and coronary assessments collected in the Malaysian Acute Vascular Events Risk study.

Characteristics	Availability of information
Demographic and behavioral	Age at onset, gender, use of tobacco for smoking or chewing, use of tobacco alternatives (vaping and e-cigarettes), levels of physical activity (sedentary, moderate, and vigorous), detailed dietary habits
Sociodemographic	Education, occupation, income (participant and household), marital status, consanguinity (of parents or with own spouse), residence (urban and rural)
Signs and symptoms	Time thrombolysis initiated, type of MI[a], outcome for the current event, onset of symptoms, hospital arrival, health care contact
Personal and family medical history (self-reported)	High blood pressure, high blood cholesterol, diabetes mellitus and family history of CHD[b], stroke, and sudden cardiac death
Sleep patterns and cell phone use	Hours of sleep, napping, time spent receiving or making phone calls and other purposes
Physical measurements	Blood pressure (systolic and diastolic), heart rate, height, weight, waist, and hip circumferences

[a]MI: myocardial infarction.

[b]CHD: coronary heart disease.

General Quality Control Approaches

To ensure effective surveillance for eligible MI cases and controls, the research staff received training and supervision by a study medical coordinator designated for that center. We aimed to reduce variation in the collection of data through extensive training, the use of standardized approaches, validated instruments, and paper-free methods with built-in validity checks and queries. For example, our paper-free data collection tool involved extensive computerized checks to restrict missing values, duplications, inconsistencies, and outliers. Information from the study app was transferred daily in a secure manner to the central database at the IMR, with a copy also kept at the UK coordinating center for additional checks and queries.

Collection and Storage of Biological Samples

A total of 20 mL of nonfasting whole blood was collected from each participant (with the time of their last meal recorded) in 2×5 mL designated serum tubes and 2×5 mL designated EDTA tubes. For MI cases, we recorded the time passed since the onset of pain and the administration of thrombolytic medication. Samples are centrifuged (2500 g for 15 minutes) within 45 minutes of venipuncture. Isolated serum, EDTA plasma, and whole blood samples were stored in cryogenic vials at the local recruiting centers in −80 °C freezers or temporarily in −20 °C freezers until transfer to −80 °C freezers (Multimedia Appendix 1, Figure S1). Samples have been transferred to the central repository at the IMR in Kuala Lumpur, typically within 2 weeks. To enable the measurement of additional potential risk factors (eg, metal contaminants), since October 2018, we have also collected finger- and toe-nail clippings, kept separately in plastic bottles, stored at room temperature, and transferred regularly to the IMR to be weighed and cataloged. Biological samples are stored long-term at both the IMR and the UK coordinating center.

Ethical Approval and Informed Consent

The MAVERIK study has received approval from the Malaysian Medical Research and Ethics Committee (reference (11)KKM/NIHSEC/P17-103). Written informed consent has been obtained from each participant before recruitment, including for future use of data and stored samples for genetic, biochemical, recall-by-genotype or -phenotype, and other analyses. The data collected in this research are subject to the core data protection principles and requirements of the United Kingdom Data Protection Act 1998 [15]. The investigators and institutional review boards are committed to ensure that research is conducted according to the latest version of the Declaration of Helsinki [16], Universal Declaration on the Human Genome and Human Rights adopted by the United Nations Educational, Scientific and Cultural Organization (UNESCO) [17], and other legislations.

Statistical Analysis

Sample size considerations were guided by a combination of pragmatic constraints (eg, the availability of resources) and statistical power calculations. For the association with early-onset MI, the study of approximately 2500 cases and 2500 controls should provide 80% power to detect an odds ratio (OR) of 1.08 per 1 SD increase at a 5% significance level. This report includes an initial descriptive analysis in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for case-control studies (Multimedia Appendix 1, Table S4) [18].

Continuous variables were summarized using mean (SD) or median and IQR, and categorical variables were summarized using frequencies. Extreme or implausible values for height, weight, waist circumference, hip circumference, BMI, and waist-to-hip ratio were excluded (eg, height<110 cm or >200 cm; weight<25 kg and >450 kg). Variables were compared

using the *t* test or Mann-Whitney *U* test for continuous variables and the chi-square test or Fisher exact (n≤5 in any cell) test for categorical variables. All statistical tests were 2-sided, and the significance level was set at $P<.05$. To evaluate the association between MI and selected risk factors, crude and adjusted (sex and age) OR with 95% CIs were calculated using unconditional logistic regression, in keeping with our study's frequency-matched controls rather than individually matched controls. Analyses were performed using STATA (version 16, StataCorp) and R (version 4.0.1, R Foundation for Statistical Computing). Future statistical analyses will be developed following relevant guidelines for case-control data (eg, Strengthening the Reporting of Observational Studies [18] and National Cancer Institute/National Human Genome Research Institute (NCI/NHGR) working group [19]) and will be presented elsewhere.

Results

Complete information on age, sex, and ethnicity was available for 2547 MI cases and 2500 controls (Table 2). Missingness for other variables ranged between 2.2% (history of high blood pressure in controls) and 11.6% (monthly income level in cases). Complete case analysis was used (ie, participants with missing values were excluded from the analysis). The mean (SD) age of MI cases was 50.3 (9.4) years, with 91.2% (2324/2547) of participants being male. In total, 60.7% (1548/2547) of cases self-identified as being of Malay ancestry, 19.1% (487/2547) were of Indian ancestry, 13.5% (346/2547) were of Chinese ancestry, and 5.8% (150/2547) as Sabah and Sarawak Bumiputera (including Iban, Kadazan, Dusun, Bidayuh, Melanau, Bumiputera of Sabah, and other Bumiputera of Sarawak ethnicities). As expected, the age, sex, and ethnicity of the cases and controls were similar owing to the frequency matching (standardized mean difference [SMD] age=0.1443 years; SMD female sex=0.0008; SMD Malay ethnicity=0.0001, and SMD Chinese ethnicity=0.0009).

Table 2. General characteristics of myocardial infarction cases and controls.

Variable	Cases (n=2547)		Controls (n=2500)		Unadjusted *P* value
Demography					
Age (years), mean (SD)	50.3 (9.4)		48.9 (10)		Frequency-matched
Female sex, n (%)	223 (8.76)		222 (8.88)		Frequency-matched
Major ethnicities, n (%)					Frequency-matched
Malay	1548	(60.77)	1536	(61.44)	
Chinese	346	(13.58)	347	(13.88)	
Indian	487	(19.12)	455	(18.20)	
Sabah and Sarawak Bumiputera[a]	150	(5.89)	150	(6.00)	
Orang Asli	2	(0.08)	1	(0.04)	
Others	14	(0.55)	11	(0.44)	
Tobacco use and tobacco alternatives, n (%)					
Smoking[b]					<.001[c]
Never	604 (25)		1120 (45.94)		
Ex	325 (13.45)		501 (20.55)		
Current	1487 (61.55)		817 (33.51)		
Chewing tobacco					.52
Never	2328 (97.90)		2386 (98.31)		
Ex	9 (0.38)		9 (0.37)		
Current	41 (1.72)		32 (1.32)		
Vaping[b], n (%)					.21
Yes	28 (1.18)		39 (1.61)		
No	2343 (98.82)		2386 (98.39)		
Number of cigarettes per day in current smokers	1475	20 (10-20)	806	10 (5-20)	<.001[c]
Number of chewing tobacco products per day in current users	38	2 (2-4)	31	2 (2-4)	.73
Number of times vaping per day in current users	23	3.5 (1-10)	36	5 (1.5-10)	.77
Consanguinity, n (%)					
Parents first cousins (yes)[b]	68 (2.86)		66 (2.72)		0.96
Spouse first cousin (yes)[b]	41 (1.76)		34 (1.43)		0.37
Conventional risk factors, n (%)					
History of high blood pressure—self-report *(Yes)*[b]	872 (35.68)		500 (20.44)		<.001[c]
History of diabetes mellitus—self-report *(Yes)*[b]	691 (28.40)		308 (12.59)		<.001[b]
Family history of CHD[d]—self-report *(Yes)*[b]	270 (11.36)		220 (9.02)		.007[c]
Waist-to-hip ratio	2108	0.96 (0.93-0.98)	2285	0.94 (0.90-0.97)	<.001[c]
BMI (kg/m^2)	2258	26.4 (23.9-29.5)	2399	26.9 (24.0-30.0)	.013[c]
Sociodemographic, n (%)					
Monthly personal income (Malaysian ringgit)[b]					<.001[c]
<1500 (US $ 357)	846 (37.58)		700 (30.24)		
1500 to <3000 (US $ 357 to <714)	795 (35.32)		740 (31.96)		
3000 to <4500 (US $ 714 to 1071)	342 (15.19)		440 (19.01)		

Variable	Cases (n=2547)	Controls (n=2500)	Unadjusted *P* value
4500 to <6000 (US $ 1071 to <1428)	159 (7.06)	226 (9.76)	
6000 and above (US $ 1428 and above)	109 (4.84)	209 (9.03)	
Education level[b]			<.001[c]
None	63 (2.76)	34 (1.47)	
Primary	358 (15.67)	234 (10.15)	
Secondary	1260 (55.16)	1160 (50.30)	
Higher secondary	284 (12.44)	276 (11.97)	
Bachelors or diploma	275 (12.04)	517 (22.42)	
Masters or higher	44 (1.93)	85 (3.69)	
Occupational group[b]			<.001[c]
Business or self-employed	516 (21.74)	483 (20.00)	
Professional	526 (22.16)	785 (32.51)	
Skilled labor	324 (13.65)	257 (10.64)	
General labor	202 (8.51)	165 (6.83)	
Farmer	70 (2.95)	53 (2.20)	
Student	4 (0.17)	5 (0.22)	
Housewife/house husband	84 (3.54)	77 (3.19)	
Unemployed	111 (4.68)	109 (4.51)	
Retired	219 (9.22)	273 (11.30)	
Other	318 (13.40)	208 (8.61)	

[a]Sabah and Sarawak Bumiputera include Iban: Kadazan Dusun; Bidayuh: Melanau, other Bumiputera of Sabah, and other Bumiputera of Sarawak ethnicities.

[b]Smoking: information for smoking was available (missing %) in 2416 cases (5.1%) and 2438 controls (2.5%); chewing tobacco in 2378 cases (6.6%) and 2427 controls (2.9%); vaping in 2371 cases (6.9%) and 2386 controls (4.6%); marriage of a parent to a first cousin in 2376 cases (6.7%) and 2430 controls (2.8%); marriage to a spouse that is a first cousin in 2330 cases (8.5%) and 2385 controls (4.6%); history of high blood pressure in 2444 cases (4%) and 2446 controls (2.2%); history of diabetes in 2433 cases (4.5%) and 2446 controls (2.2%); family history of CHD in 2376 cases (6.7%) and 2440 controls (2.4%); monthly income level in 2251 cases (11.6%) and 2315 controls (7.4%); education level in 2284 cases (10.3%) and 2306 controls (7.8%); occupation in 2374 cases (6.8%) and 2415 controls (3.4%). Normally distributed variables are presented as mean (SD), and nonnormally distributed variables are presented as median (IQR), and categorical variables are presented as n (%).

[c]*P*<.05 was calculated from the unadjusted χ^2 test of independence or Fisher exact test (n≤5 in any cell) for categorical variables and from *t* test for equalities of the means or Mann-Whitney *U* test (nonnormally distributed data) for continuous variables.

[d]CHD: coronary heart disease.

Approximately 61.55% (1487/2416) of MI cases were current smokers, compared with only 33.51% (817/2438) of controls (*P*<.001; Table 2). Cigarette consumption in smokers was higher among cases than in controls (median, IQR daily consumption for cases vs controls 20, 10-20 *v*s 10, 5-20) cigarettes per day; *P*<.001). However, the prevalence of tobacco consumption by chewing and vaping was low and did not materially differ among cases and controls. Other risk factors that had a higher prevalence in MI cases than controls included high blood pressure (872/2444, 35.68% vs 500/2446, 20.44%; *P*<.001; Table 2), diabetes mellitus (691/2433, 28.4% vs 308/2446, 12.59%; *P*<.001), and family history of CHD (70/2376, 11.36% vs 220/2440, 9.02%; *P*=.007). MI cases also had higher median levels of waist-to-hip ratio than controls (0.96 vs. 0.94; *P*<.001), but median levels of BMI were not materially different.

Indicators of lower socioeconomic status were more common among MI cases than controls, including higher percentages with a monthly income below MYR1500 (US $357; 846/2251, 37.58% cases vs 700/2315, 30.24% controls; *P*<.001), and educational attainment to primary school level or lower (421/2284, 18.43% vs 268/2306, 11.62%; *P*<.001). The prevalence of participants reporting being the offspring of a first cousin marriage (68/2376, 2.86% vs 66/2430, 2.72%) or having a first cousin as a spouse (41/2330, 1.76% vs 34/2385, 1.43%) was not materially higher in cases than in controls. Additional details about the baseline distribution of characteristics, subdivided by age group and sex, are outlined in Multimedia Appendix 1, Tables S2 and S3.

Crude and adjusted (age and sex) logistic regression models for traditional risk factors are summarized in Table 3. Current smoking (OR 4.11, 95% CI 3.56-4.75; *P*<.001), previous smoking (OR 1.34, 95% CI 1.12-1.60; *P*=.001), history of high blood pressure (OR 2.13, 95% CI 1.86-2.44; *P*<.001), history of diabetes mellitus (OR 2.72, 95% CI 2.34-3.17; *P*<.001),

family history of CHD (OR 1.28, 95% CI 1.07-1.55; *P*=.009), and obesity (BMI >30 kg/m^2; OR 1.19, 95% CI 1.05-1.34; *P*<.01) were associated with MI in age- and sex-adjusted models.

Table 3. Odds ratios for established myocardial infarction risk factors.

Risk factor	Crude odds ratio (95% CI)	Adjusted odds ratio for age and sex (95% CI)
Smoking cigarettes		
Ex	1.19 (1.00-1.41)[a]	1.34 (1.12-1.60)[a]
Current	3.33 (2.93-3.79)[b]	4.11 (3.56-4.75)[b]
History of high blood pressure	2.17 (1.91-2.46)[b]	2.13 (1.86-2.44)[b]
History of diabetes mellitus	2.74 (2.37-3.19)[b]	2.72 (2.34-3.17)[b]
Family history of CHD[c]	1.28 (1.06-1.54)[d]	1.28 (1.07-1.55)[d]
Obesity (BMI >30 kg/m^2)	1.16 (1.03-1.31)[a]	1.19 (1.05-1.34)[d]

[a]*P*<.05.

[b]*P*<.001.

[c]CHD: coronary heart disease.

[d]*P*<.01.

Discussion

Although Malaysia is experiencing a substantial increase in the burden of CVD, the risk factors for CHD in this population have been relatively little studied. We established the MAVERIK study, an epidemiological bioresource comprising over 2500 confirmed cases of acute MI and 2500 controls, and confirmed the importance of several known risk factors for MI (eg, tobacco consumption, history of diabetes, and hypertension). To our knowledge, this represents the largest case-control study of MI and related traits in Malaysia. Our long-term objective is to enable direct investigation of genetic and other determinants of MI in this multi-ethnic population. In this paper, we report the design and initial results of this study, which suggest several conclusions.

First, our study has demonstrated the ability to use modern and standardized epidemiological methods in a national study in Malaysia encompassing 17 hospitals. For example, the study used electronic data collection, including apps with *intelligent* study forms, and collected several types of biological samples, including serum, plasma, DNA, and nails.

Second, the mean age at first confirmed MI was only 50 years in Malaysia, suggesting that premature CHD is highly prevalent in this population.

Third, this study's multi-ethnic population broadly mirrors the overall ethnic composition of the Malaysian national population, which is approximately 61.8% Malay, 21.4% Chinese, 6.4% Indian, and 0.9% others and 9.6% non-Malaysian resident [20]. Malaysia's complex genetic ancestry is distinct from the commonly studied East Asian populations (eg, Chinese and Japanese) and other Southeast Asian populations (eg, Thai and Filipino) [21]. In contrast, most existing genetic studies of MI and cardiometabolic risk factors involve European or East Asian (eg, Chinese and Japanese) descent populations. The distinctive genetic architecture of the Malaysian population suggests that, with the use of genome sequencing technologies, the MAVERIK study should help identify population-specific genetic risk factors, leveraging transethnic differences. For example, variants in the myosin binding protein C3 (*MYBPC3*) gene region, which are common (2%-8%) in South Asian ancestry populations but rare (<0.1%) in European ancestry populations, are associated with an increased risk of hypertrophic cardiomyopathies [22].

Fourth, an analysis of initial baseline data supports the validity of the MI outcomes recorded, suggested by the observation of expected associations of MI risk with a panel of conventional risk factors, including high blood pressure, diabetes mellitus, family history of coronary disease, and higher waist-to-hip ratio (a marker of visceral adiposity). Finally, the study's initial data suggest that in Malaysia, a middle-income country with a population of 32 million people in the midst of economic and epidemiological transition, there are inverse associations of indicators of socioeconomic status (such as income and educational attainment) with MI risk, a pattern similar to that observed in many high-income populations in Western countries.

The strengths and potential limitations of the MAVERIK study merit consideration. Retrospective case-control studies of MI can usefully complement prospective studies because the former involves the ascertainment of exposure information and the blood sampling of people who have already developed MI and a comparable group of controls without MI, enabling the rapid and cost-effective accrual of large numbers of relevant cases. By contrast, prospective studies require many tens of thousands of people to be screened (with all of their blood samples kept in frozen storage) and followed for several years to accrue a sizable number of MI cases. Retrospective studies are also often able to include large numbers of individuals who have developed the disease at younger ages, when associations with risk factors are often stronger, providing particularly sensitive tests of certain hypotheses. Furthermore, owing to the richness of data collected, the MAVERIK study allows for the use of a range of analytical techniques, including machine learning approaches [23,24].

As demonstrated by the Wellcome Trust Case-Control Consortium [11], Myocardial Infarction Genetics Consortium [25], Pakistan Risk of Myocardial Infarction Study [26], and Bangladesh Risk of Acute Cardiovascular Events study [13], case-control studies can powerfully and efficiently facilitate genetic discovery and can use genomic data to quantify and robustly correct for any population structure. Furthermore, the International Study of Infarct Survival (ISIS) (United Kingdom–based) [27] and INTERHEART (conducted across 52 countries) studies [28] have demonstrated that appropriately conducted, large case-control studies can usefully address some nongenetic hypotheses in MI, such as tobacco and alcohol consumption, and serological evidence of infection. However, INTERHEART did not focus extensively on Malaysia; INTERHEART-Malaysia involved approximately only 100 MI cases [29].

Nevertheless, particularly regarding nongenetic hypotheses, retrospective case-control studies may be liable to potential biases, such as selection and recall biases. To minimize such biases, standardized questioning approaches were used for all study participants, and both cases and controls were selected from the same population. Furthermore, there may be less scope for recall bias in a study of acute MI than in a study of chronic stable CHD, as hours rather than months or years may have elapsed since the index event. As noted earlier, the selection of controls in case-control studies invariably involves trade-offs between scientific rigor and feasibility. Following the examples of INTERHEART [28], Pakistan Risk of Myocardial Infarction Study [26], and Bangladesh Risk of Acute Cardiovascular Events study [13], we chose to recruit controls drawn from attendants of people visiting outpatient clinics or (nonblood-related) attendants of cardiac patients. Studies of plasma components may be affected by case-control studies of acute MI because certain circulating markers may be altered by the sampling of blood within 24 hours of MI symptoms. If, as in MAVERIK, the time since the onset of symptoms has been recorded, any material bias can be quantified and at least partially corrected for. Similar considerations apply to fasting status and the recording of the time since the last meal. We seek to evaluate the findings of the MAVERIK study with reference to prospective cohort studies in Malaysia (eg, the Malaysian Cohort project) [30]. Finally, it is important to recognize that we were unable to screen controls for silent MI and that the external generalizability of the MAVERIK study may be limited as the study comprises 91.18% of male participants.

In conclusion, the MAVERIK study is a large, multi-ethnic epidemiological resource for CHD that should help identify and evaluate genetic and other determinants of MI in Malaysia. It should help to hasten the discovery of disease-causing pathways and inform regionally appropriate strategies that optimize public health action.

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Authors' Contributions

RC and MFBMN contributed equally as first authors. SRI and KvD contributed equally as second authors. EDA, NSS, JD and ASB contributed equally as last authors. RC conceptualized the study, supported by MFBN, JD, and ASB. SRI and KRD drafted the manuscript, conducted the analyses, and created the figures. All authors contributed to the design, implementation, and coordination of the research, the analysis of the results, and the writing of the manuscript.

Conflicts of Interest

JD has served on the International Cardiovascular and Metabolic Advisory Board for Novartis (since 2010), the Steering Committee of the UK Biobank (since 2011), the International Cardiovascular and Metabolism Research and Development Portfolio Committee

for Novartis, and the Astra Zeneca Genomics Advisory Board (2018). ASB received grants outside of this work from AstraZeneca, Bayer, Biogen, BioMarin, Bioverativ, Merck, Novartis, and Sanofi, and personal fees from Novartis.

Multimedia Appendix 1
Malaysian Acute Vascular Events Risk, a resource to study genetic and other determinants of first-ever myocardial infarction in Malaysia.
[DOCX File , 581 KB - resprot_v11i2e31885_app1.docx]

References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016 Oct 08;388(10053):1459-1544 [FREE Full text] [doi: 10.1016/S0140-6736(16)31012-1] [Medline: 27733281]
2. Noncommunicable Diseases Country Profiles 2014. World Health Organization. 2014. URL: http://apps.who.int/iris/bitstream/handle/10665/128038/9789241507509_eng.pdf;jsessionid=3632C396FDAE474DABCC631204EAD1A6?sequence=1 [accessed 2021-11-25]
3. Global Burden of Disease Study 2016 (GBD 2016) Incidence, Prevalence, and Years Lived with Disability 1990-2016. Global Health Data Exchange. URL: http://ghdx.healthdata.org/record/ihme-data/gbd-2016-incidence-prevalence-and-ylds-1990-2016 [accessed 2021-11-25]
4. WHO Mortality Database. World Health Organization. URL: https://www.who.int/data/data-collection-tools/who-mortality-database [accessed 2021-11-25]
5. National Health and Morbidity Survey (NHMS) 2017: key findings from the adolescent health and nutrition surveys. NHMS 2017. 2018. URL: https://www.researchgate.net/publication/331033418_NATIONAL_HEALTH_AND_MORBIDITY_SURVEY_NHMS_2017_Key_Findings_from_the_Adolescent_Health_and_Nutrition_Surveys [accessed 2021-11-25]
6. Lam CS. Heart failure in Southeast Asia: facts and numbers. ESC Heart Fail 2015 Jun;2(2):46-49 [FREE Full text] [doi: 10.1002/ehf2.12036] [Medline: 28834655]
7. Chan MY, Du X, Eccleston D, Ma C, Mohanan PP, Ogita M, et al. Acute coronary syndrome in the Asia-Pacific region. Int J Cardiol 2016 Jan 01;202:861-869 [FREE Full text] [doi: 10.1016/j.ijcard.2015.04.073] [Medline: 26476044]
8. Clinical Practice Guidelines: UA/NSTEMI. Ministry of Health Malaysia. 2011. URL: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/CARDIOVASCULAR/12.pdf [accessed 2021-11-25]
9. Management of acute ST Segment Elevation Myocardial Infarction (STEMI). Ministry of Health Malaysia. 2014. URL: https://www.moh.gov.my/moh/resources/penerbitan/CPG/CPG%20STEMI%202019.pdf [accessed 2021-11-25]
10. Ministry of Health Malaysia (MOH). Clinical Practice Guidelines: Management of Acute ST Segment Elevation Myocardial Infarction. (STEMI) 4th edition 2021:2019.
11. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007 Jun 07;447(7145):661-678 [FREE Full text] [doi: 10.1038/nature05911] [Medline: 17554300]
12. Saleheen D, Zaidi M, Rasheed A, Ahmad U, Hakeem A, Murtaza M, Fazal-ur-Rehman, et al. The Pakistan Risk of Myocardial Infarction Study: a resource for the study of genetic, lifestyle and other determinants of myocardial infarction in South Asia. Eur J Epidemiol 2009;24(6):329-338 [FREE Full text] [doi: 10.1007/s10654-009-9334-y] [Medline: 19404752]
13. Chowdhury R, Alam DS, Fakir II, Adnan SD, Naheed A, Tasmin I, Cardiology Research Group, et al. The Bangladesh Risk of Acute Vascular Events (BRAVE) Study: objectives and design. Eur J Epidemiol 2015 May 01;30(7):577-587 [FREE Full text] [doi: 10.1007/s10654-015-0037-2] [Medline: 25930055]
14. Zainuddin AA, Jai A, Baharuddin A, Naidu B, Chan YY, Siew Man CEA. National Health and Morbidity Survey 2014: Malaysian Adult Nutrition Survey. Vol. 1: Methodology and General Findings. 2016. URL: https://www.researchgate.net/publication/301203877_National_Health_and_Morbidity_Survey_2014_Malaysian_Adult_Nutrition_Survey_Vol_1_Methodology_and_General_Findings [accessed 2021-11-25]
15. 16 UKG. UK Data Protection Act. UK Government 2021:1998.
16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-2194. [doi: 10.1001/jama.2013.281053] [Medline: 24141714]
17. Mayor F. The Universal Declaration on the human genome and human rights. C R Biol 2003;326(10-11):1121-1125 [FREE Full text] [doi: 10.1016/j.crvi.2003.09.017] [Medline: 14744123]
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007 Oct 16;147(8):573-577 [FREE Full text] [doi: 10.7326/0003-4819-147-8-200710160-00010] [Medline: 17938396]

19. NCI-NHGRI Working Group on Replication in Association Studies, Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, et al. Replicating genotype-phenotype associations. Nature 2007 Jun 07;447(7145):655-660. [doi: 10.1038/447655a] [Medline: 17554299]
20. Demography of population. Malaysia Information. URL: https://www.malaysia.gov.my/portal/content/30114 [accessed 2021-12-07]
21. Deng L, Hoh B, Lu D, Saw W, Twee-Hee Ong R, Kasturiratne A, et al. Dissecting the genetic structure and admixture of four geographical Malay populations. Sci Rep 2015 Sep 23;5:14375 [FREE Full text] [doi: 10.1038/srep14375] [Medline: 26395220]
22. Harper AR, Bowman M, Hayesmoore JB, Sage H, Salatino S, Blair E, HCMR Investigators. Reevaluation of the South Asian intronic deletion in hypertrophic cardiomyopathy. Circ Genom Precis Med 2020 Jun;13(3):e002783 [FREE Full text] [doi: 10.1161/CIRCGEN.119.002783] [Medline: 32163302]
23. Sarajlic P, Simonsson M, Jernberg T, Bäck M, Hofmann R. Incidence, associated outcomes, and predictors of upper gastrointestinal bleeding following acute myocardial infarction: a SWEDEHEART-based nationwide cohort study. Eur Heart J Cardiovasc Pharmacother 2021 Aug 23:pvab059. [doi: 10.1093/ehjcvp/pvab059] [Medline: 34423350]
24. Sarajlic P, Plunde O, Franco-Cereceda A, Bäck M. Artificial intelligence models reveal sex-specific gene expression in aortic valve calcification. JACC Basic Transl Sci 2021 May;6(5):403-412 [FREE Full text] [doi: 10.1016/j.jacbts.2021.02.005] [Medline: 34095631]
25. Myocardial Infarction Genetics Consortium Investigators, Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, et al. Inactivating mutations in NPC1L1 and protection from coronary heart disease. N Engl J Med 2014 Nov 27;371(22):2072-2082 [FREE Full text] [doi: 10.1056/NEJMoa1405386] [Medline: 25390462]
26. Saleheen D, Zaidi M, Rasheed A, Ahmad U, Hakeem A, Murtaza M, Fazal-ur-Rehman, et al. The Pakistan Risk of Myocardial Infarction Study: a resource for the study of genetic, lifestyle and other determinants of myocardial infarction in South Asia. Eur J Epidemiol 2009 Apr 30;24(6):329-338. [doi: 10.1007/s10654-009-9334-y]
27. Clarke R, Xu P, Bennett D, Lewington S, Zondervan K, Parish S, International Study of Infarct Survival (ISIS) Collaborators. Lymphotoxin-alpha gene and risk of myocardial infarction in 6,928 cases and 2,712 controls in the ISIS case-control study. PLoS Genet 2006 Jul;2(7):e107 [FREE Full text] [doi: 10.1371/journal.pgen.0020107] [Medline: 16839190]
28. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004 Sep;364(9438):937-952. [doi: 10.1016/S0140-6736(04)17018-9] [Medline: 15364185]
29. Noor Hassim I, Norazman MR, Diana M, Khairul Hazdi Y, Rosnah I. Cardiovascular risk assessment between urban and rural population in Malaysia. Med J Malaysia 2016 Dec;71(6):331-337 [FREE Full text] [Medline: 28087957]
30. Jamal R, Syed Zakaria SZ, Kamaruddin MA, Abd Jalal N, Ismail N, Mohd Kamil N, Malaysian Cohort Study Group. Cohort Profile: The Malaysian Cohort (TMC) project: a prospective study of non-communicable diseases in a multi-ethnic population. Int J Epidemiol 2015 Apr;44(2):423-431 [FREE Full text] [doi: 10.1093/ije/dyu089] [Medline: 24729425]

Abbreviations

CHD: coronary heart disease
CVD: cardiovascular disease
IMR: Institute for Medical Research
MAVERIK: Malaysian Acute Vascular Events Risk
MI: myocardial infarction
OR: odds ratio
SMD: standardized mean difference

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Protocol

Digital Interventions to Reduce Distress Among Health Care Providers at the Frontline: Protocol for a Feasibility Trial

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Abstract

Background: Stress, anxiety, distress, and depression are high among health care workers during the COVID-19 pandemic, and they have reported acting in ways that are contrary to their moral values and professional commitments that degrade their integrity. This creates moral distress and injury due to constraints they have encountered, such as limited resources.

Objective: The purpose of this study is to develop and show the feasibility of digital platforms (a virtual reality and a mobile platform) to understand the causes and ultimately reduce the moral distress of health care providers during the COVID-19 pandemic.

Methods: This will be a prospective, single cohort, pre- and posttest study examining the effect of a brief informative video describing moral distress on perceptual, psychological, and physiological indicators of stress and decision-making during a scenario known to potentially elicit moral distress. To accomplish this, we have developed a virtual reality simulation that will be used before and after the digital intervention for monitoring short-term impacts. The simulation involves an intensive care unit setting during the COVID-19 pandemic, and participants will be placed in morally challenging situations. The participants will be engaged in an educational intervention at the individual, team, and organizational levels. During each test, data will be collected for (1) physiological measures of stress and after each test, data will be collected regarding (2) thoughts, feelings and behaviors during a morally challenging situation, and (3) perceptual estimates of psychological stress. In addition, participants will continue to be monitored for moral distress and other psychological stresses for 8 weeks through our Digital intervention/intelligence

Group mobile platform. Finally, a comparison will be conducted using machine learning and biostatistical techniques to analyze the short- and long-term impacts of the virtual reality intervention.

Results: The study was funded in November 2020 and received research ethics board approval in March 2021. The study is ongoing.

Conclusions: This project is a proof-of-concept integration to demonstrate viability over 6 months and guide future studies to develop these state-of-the-art technologies to help frontline health care workers work in complex moral contexts. In addition, the project will develop innovations that can be used for future pandemics and in other contexts prone to producing moral distress and injury. This project aims to demonstrate the feasibility of using digital platforms to understand the continuum of moral distress that can lead to moral injury. Demonstration of feasibility will lead to future studies to examine the efficacy of digital platforms to reduce moral distress.

Trial Registration: ClinicalTrials.gov NCT05001542; https://clinicaltrials.gov/ct2/show/NCT05001542

International Registered Report Identifier (IRRID): DERR1-10.2196/32240

(JMIR Res Protoc 2022;11(2):e32240) doi:10.2196/32240

KEYWORDS

virtual reality; mobile app; moral distress; simulation; moral injury; COVID-19

Introduction

Background

Health care providers, particularly during the COVID-19 crisis, have reported acting in ways that are contrary to their moral values, integrity, and professional commitments because of constraints in their work environments [1,2]. Moral suffering can ensue when a health care provider's moral foundation is threatened or violated by witnessing or participating in decisions or actions that degrade their integrity [3]. Moral distress might arise when health care providers are unable to translate their moral choices into action because of internal or external constraints [4].

Moral injury, a more extreme form of moral distress, arises in high-stakes situations wherein integrity and conscience have been violated or one's moral core is eroded [5]. As these events and other workplace stressors accumulate, health care providers' capacities to provide the level of care they desire can be diminished. There has been a growing attempt to conceptualize moral distress and injury in different health care professions, but the numerous definitions can confuse the issue [6,7]. The concept of moral injury has existed for much longer than its first conceptualization by Shay [7] concerning the military, where it was defined as a betrayal of moral character, usually as a result of the actions of a person in a position of authority. There is a large body of literature within the military context, and moral injury has conceptually evolved to include betrayal of one's moral values, and furthermore, as a spiritual, psychological, and somatic response to a series of morally injurious events [5]. While some may contend that actions by military members during a war require forethought based on training, others suggest that actions are made on rapid and subconscious decision-making and that moral injury occurs only when individuals question their actions after the fact [8].

However, moral injury is not well defined in health care professions. Cartolovini et al [9] argue that moral injury occurs in health care providers when they encounter traumatic events that involve high-stakes situations beyond their control in which they perpetuate, fail to prevent, or bear witness to actions that transgress deeply held moral beliefs [10]. A related concept, moral distress, was first described within the nursing context by Jameton [11] as "… when one knows the right thing to do, but institutional constraints make it nearly impossible to pursue the right course of action." Additional studies [12] have provided more context to this definition and have described causes of moral distress as beyond the organization to specific clinical situations and internal caregiver dynamics. Moral distress and injury likely occur along a continuum, with moral injury at the extreme end [13].

The COVID-19 pandemic has necessitated fundamental changes to health care provision. As we continue to learn about the virus and differing courses of disease, health care providers have often willingly accepted inherent risks during the pandemic to care for their patients. However, the need for rapid and changing contingency planning, shortages in personal protective equipment, resource shortages, and the inability to provide the ethical caring called for by professional codes of ethics have placed health care providers in what has been described as a "war zone [14]." The sudden and unprecedented similarities between civilian health care and military scenarios have potentially resulted in moral distress and possibly moral injury. It is nearly impossible to anticipate the course of the virus and make predictions about its physiological outcomes; it is also challenging to predict the course of mental health needs of health care providers, but it is known that there will be needs.

Research has concentrated on treatment for moral injury, either in the military realm or the civilian realm. Gilligan [15] discussed moral injury as "a shattering of trust that compromised our ability to love" and would seem to suggest the health care providers who suffer moral injury during extreme circumstances such as a pandemic may lose the ability for empathy that is required by professional values. Moral injury has been found to not generally respond to typical treatment of posttraumatic stress disorder, even though most treatment focuses on the posttraumatic stress disorder symptomatology [5]. Being able to preserve or restore integrity requires that health care providers have the opportunity for moral repair by strengthening their moral compass and restoring their integrity. Having a moral

compass has been identified as a modifiable factor effective in healing from trauma [16]. When one's moral foundation is clear and accessible, health care providers have a potential opportunity to heal the wounds caused by the COVID-19 crisis and an additional resource that they can leverage when ethical challenges arise.

In this paper, we propose using digital platforms, specifically virtual reality and mobile apps, to develop an understanding of the continuum of moral distress that leads to moral injury in health care workers. Virtual reality technology will be used as a digital platform to simulate an intensive care unit during the pandemic. Our aim is to determine the feasibility of creating a digital environment and implementing digital interventions to better understand the phenomenon of moral distress by developing platforms to examine moral distress and monitor participants over time in order to develop a better understanding of the continuum of moral distress to moral injury.

Methods

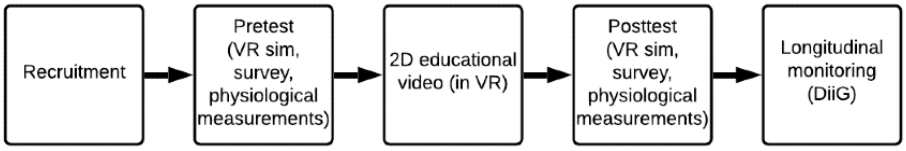
Ethics

As of March 20, 2021, the research ethics board at St. Michael's Hospital, Unity Health Toronto has approved the study, and the reference number is UHTDTS25377. The clinical trial is registered with ClinicalTrial.gov with the Registration/identifier number NCT05001542.

Overview

We will recruit health care workers to participate in our feasibility trial that will be composed of pretesting, 2D educational video, posttesting, and longitudinal monitoring (Figure 1). During pre- and posttest components, we will pilot unique digital technology platforms (virtual reality environments) to identify circumstances that have the potential to cause moral distress; examine interactions at the individual, team, and organizational levels; perform detailed concept mapping to understand features of moral distress and injury and to aid the design of potential interventions. The educational video will be in 2D; however, the rest of the study components will be 3D virtual reality. The video will be presented on the virtual reality headset after the pretest and before the posttest, and is a brief educational video about moral injury. After the posttest, for 2 months, we will longitudinally monitor participants through the collection of active and passive data through our novel mobile platform.

Figure 1. Flow diagram of feasibility trial design. VR sim: virtual reality simulation. DiiG: digital intervention/intelligence group.



The expected outcomes of our protocol include (1) using virtual reality technology to design a virtual reality environment to simulate intensive care unit settings during the pandemic and determine the feasibility of understanding moral distress and injury for potential future implementations of digital interventions and (2) using acute physiological monitoring within a virtual reality for simulation of a hospital environment where health care workers have to make challenging moral decisions in complex moral simulated situations, and using a novel mobile platform for longitudinal monitoring by collecting passive and active data to understand the contribution of moral distress to the experience in real-time. The information from these digital platforms will influence each other and aid in the development of models to predict and respond to risks associated with moral distress and injury.

Experimental Flow

Participant Recruitment

Eligible participants include health care providers at 3 affiliated hospitals at Unity Health Toronto, who are 18 years of age or older and who own a mobile phone (Android phones with OS version 6.0 and above, iPhone 6 with OS 11 and above). Since this is a feasibility study conducted among health care providers during a pandemic, we require participants to be currently providing health care at the respective hospitals.

We aim to recruit 15 health care providers (minimum of 10 participants including physicians, nursing, and allied staff) from St. Michael's, St. Joseph, and Providence hospitals by posting study notices on Unity Health Toronto microsites (eg, Twice a Week newsletters, MD matters, Leadership links), posting flyers at the hospital sites, and by sending email notices. Interested participants will email the study coordinator indicating their interest to participate in the study. The study coordinator will send the participant the consent and demographics forms to sign and complete, and the available time slots to participate in the virtual reality and wearable component of the study. (The demographic survey will include questions regarding age, sex, type of work at Unity Health Toronto, COVID-19 clinical status). Participants will be required to email back their choice for their preferred time slot, the signed consent form, and the completed demographics form.

Introduction and Prebrief

The session begins with an introduction of our feasibility trial, goals, and objectives. The session will prepare the participant for the virtual reality simulation in which they take on the role of a health care provider during the COVID-19 pandemic. We will utilize virtual reality simulation to understand the decision-making and emotional response of health care professionals in morally challenging environments, and we will use physiological sensors to monitor the responses. This

information will allow us to develop a better understanding of moral distress and create an appropriate intervention.

Pretest: Virtual Reality Scenario

After the introduction, participants take on the role of health care providers. The scenario will take place in a hospital setting and will include a physician and nurse, all of whom will be computer-controlled nonplayable characters. There will be an ongoing discussion among them in a scenario that involves decision-making in a morally challenging context.

The virtual reality scenario was created with a particular focus on 2 situations and modified iteratively based on the concepts and research related to moral distress and injury—not having the power to decide which patient to provide life-saving care to when resources are limited and not being able to provide optimum care to all patients.

This pretest virtual reality scenario will initially include all the suggested interventions at the individual, team, and organizational levels and examine the efficacy of these suggested interventions. Additional interventions will be added based on user experience.

Intervention (2D Educational Video)

Participants will watch an educational video that effectively summarizes the causes and symptoms of moral distress and injury and the potential interventions at the individual, team, and organizational levels.

Posttest: Virtual Reality Scenario

For the posttest, the virtual reality scenario with moral distress and injury knowledge and its respective interventions are repeated.

Debrief

After completing the pre- and posttest, participants will engage in a debrief led by the researchers. The debrief includes open-ended questions that will encourage the participants to speak about their experience in the virtual reality setting, followed by an exit survey. If needed, participants will be able to speak with a psychotherapist at the Center for Depression and Suicide Studies at St. Michael's Hospital.

Longitudinal Monitoring

After completing the session, participants will use the app for longitudinal monitoring by collecting passive and active data to understand the distress experienced in real-time.

Compound Intervention

The compound intervention is composed of the virtual reality simulation-based educational intervention and data collection of mental health and moral injury surveys. The virtual reality simulation-based educational intervention contains a moral injury educational video based on the Moral Injury Guide developed by the Ottawa PTSD Center for Excellence [17].

The latter component of the compound intervention evaluates the effectiveness of the virtual reality simulation-based educational intervention through mental health surveys. These surveys include the Perceived Stress Scale (PSS), Moral Injury Outcome Scale (MIOS), Igroup presence questionnaire (IPQ), and Adapted Moral Injury Symptom Scale: Health care Professionals Version (MISS-HP). PSS is a self-report instrument that evaluates level of stress. MIOS and MISS-HP are tools that evaluate the effect of moral injury, and the IPQ is a questionnaire that evaluates the experience of presence during virtual reality simulations. We will use this information to improve our compounded intervention for use on digital platforms iteratively.

Trial Design

This is a multilayer feasibility trial (Figure 2). The in-person session (Figure 3), begins with participant arrival at St. Michael's Hospital Simulation Centre. This is followed by experimental set-up and prebrief. The prebrief is held to inform the participant of the purpose of the session, to collect presurvey data, and obtain written consent. The experimental set-up involves the attachment of the virtual reality equipment and physiological sensors. The debrief is hosted after the experiment and is composed of a semistructured interview, open-ended questions, and an exit survey. The purpose of the debrief is to obtain qualitative feedback on the session to better understand the participant experience.

The virtual reality session will be used for short-term monitoring of participants for acute distress. After the intervention, participants will use a mobile app (developed by the Digital intervention/intelligence Group) for long-term distress monitoring.

Figure 2. Overview of the virtual reality experimental set-up and data collection.

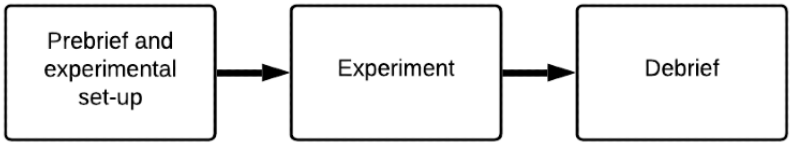
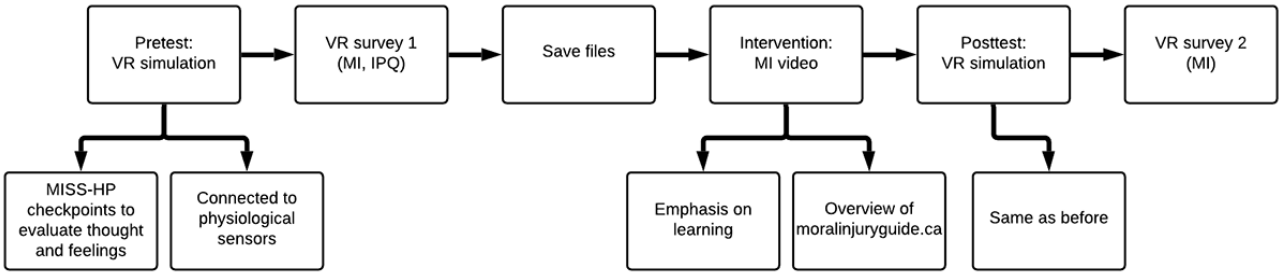


Figure 3. Diagram of experiment components. VR: virtual reality. MI: moral injury. IPQ: igroup presence questionnaire. MISS-HP: moral injury symptom scale: healthcare professionals version.



Security and Privacy of the Study Data

During the session hosted at St. Michael's Hospital Simulation Centre, data (CSV files, text files, audio, and video files from the session) will be securely uploaded to a password-protected drive. Only specific members of the project have access to the data. Responses on paper questionnaires will be input to a spreadsheet and stored on the encrypted drive. During the longitudinal monitoring part of the study, all active and passive data will be stored on the participant's phone (if storage space is available) until those data are synced back to the back-end server. Data are transferred over a TLS layer; hence, it is encrypted by RSA Asymmetric Encryption Algorithm.

Study data will be stored for 10 years. No personal information will be collected through the mobile component of the study. Demographic data (ie, age, sex, type of job at Unity Health Toronto, diagnosis, and COVID-19 status) will be collected separately from data collected by the app. A study participant ID will link these data for final analysis.

The server and the dashboard will be hosted on the same virtual machine server, and the database will be hosted on a different database server (Multimedia Appendix 1).

Virtual Reality Development

The first stage of the development involved defining the context of the scenario, with the support of a subject-matter expert, and determining how it connects to the domains *betrayal of the team*, *transgression of moral values*, *emotional response*, and *support and reframing in relation to guilt and loss of trust in colleagues and shame*.

An overview of the scenario was then outlined, describing the location, main characters, key points (eg, the removal of the ventilator), and the actions and reactions of each character. Based on this document, 2 activities were performed in parallel: the definition of the scenario script with the lines and actions of all characters and the development of the 3D assets (characters, objects, and environment) of the virtual reality scenario. Both activities were developed iteratively, with discussions and demonstrations during weekly meetings. The final version of the script includes 7 nonplayable characters (Table 1) and 4 conversations (Table 2), not including the initial tutorial.

For the virtual environment (Figure 4 and Figure 5), royalty-free models and scenarios were purchased and used as a starting point. They were combined and modified to fit the project's needs. Subject-matter experts provided feedback on key elements to make the environment appear closer to the reality of a Canadian hospital environment. The goal was to represent a standard intensive care unit with individual rooms for patients and a nursing station.

Table 1. List of nonplayable characters.

Character	Description
Administrator	Intensive care unit team lead
Nurse	Intensive care unit nurse
Mr. Adam	Mr. Adam, a 65-year-old man who has multiple comorbidities with COVID on a ventilator
Mr. Adam's partner	Distraught, accusing the participant of cruelty, mismanagement, and malpractice
Ms. Betty	A 56-year-old woman has a more favorable prognosis
Medical Doctor 2	Another intensive care unit physician, not aware of the situation
Medical Doctor X	Highly experienced and respected intensivist whose advice and counsel are often sought

Table 2. List of conversations.

Scene	Nonplayable characters	Description
Intensive care unit hallway	Administrator, nurse	Conversation between the participant, administrator, and nurse about the lack of ventilators. It is decided to move the ventilator from Mr. Adam to Ms. Betty.
Mr. Adam's room	Mr. Adam, Mr. Adam's partner	The participant must inform Mr. Adam's partner about the decision to remove the ventilator.
Intensive care unit hallway 2	Medical doctor 2	A medical doctor questions the participant about what happened, and they witness Mr. Adam (now without the ventilator) going into cardiac arrest
Nursing station	Medical doctor X	An experienced medical doctor reaches out to the participant to provide counsel and provide support.

Figure 4. Patient's room with a patient connected to a ventilator.

Figure 5. Nursing station, monitor station, and intensive care unit corridor.

To represent the nonplayable characters and the participant, royalty-free models were purchased as starting points. Based on these models, a customizable character system was implemented that allowed us to quickly modify external elements (such as clothing or masks) or the character's characteristics, such as height and weight (Figure 6).

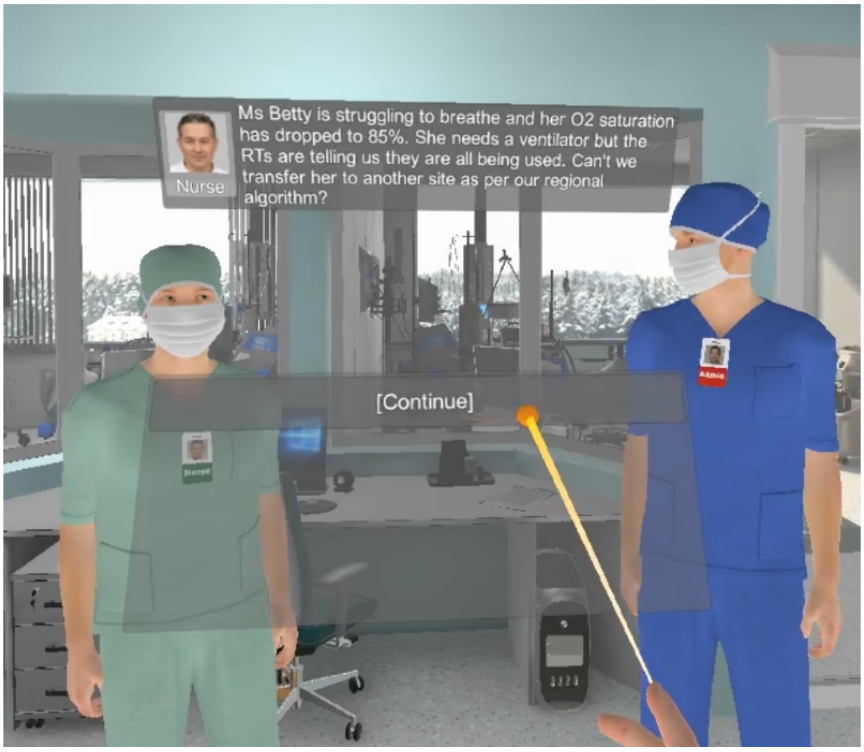
For the user interface, 2 semitranslucent panels are displayed as spatial elements in the virtual reality environment (Figure 7). The dialogue panel shows current nonplayable character's photograph, name, and the text version of the dialogue being spoken. The interaction panel displays available choices (for example, the option *Continue* to advance to the following dialogue or a list of choices).

To interact with the panel, participants need to move one of the controllers, point to the desired choice, and click any buttons under the index finger or thumb. The participant can see a blue ray being casted from their index finger tip within the virtual reality environment, which turns yellow when hovering over the interactive panel (Figure 7). As additional visual feedback,

dialogue choices include a highlight effect when the ray hovers over each.

Figure 6. Testing 2 characters with different clothing and body parameters.

Figure 7. User interface displaying the dialog and interaction panels, and the interaction ray from the right-hand index finger.



Software and Hardware

The virtual reality scenarios were created using a cross-platform game engine (Unity 3D, Unity Technologies) that has been adopted, not only by the game industry, but also by film, architecture, and education industries [18]. The virtual reality scenario is played using a consumer-grade head-mounted display (Oculus Quest 2, MetaQuest) (Figure 8) that can track the user's head movements with 6 degrees of freedom and track the user's movements either in stationary mode (sitting in a chair) or in room mode (recommended room size is up to 2 m × 2 m), allowing the user to physically walk around within the defined boundaries. In addition, the system includes 2 handheld motion-tracked controllers that allow the user to interact with the environment and with virtual reality interface components. Our virtual reality scenarios will adopt stationary-mode tracking

and use the handheld motion-tracked controllers for more accurate tracking.

Figure 8. Oculus Quest 2 components.

Currently, Oculus Quest and Oculus Quest 2 are not Health Insurance Portability and Accountability Act–compliant. However, no data will be stored in the virtual reality device, and the Oculus framework is not used to develop our virtual reality app. The Oculus Quest 2 is connected to a virtual reality-capable PC laptop using a USB-C cable.

Subjective Data Collection

We plan to collect subjective data such as qualitative data from surveys and open-ended feedback. As mentioned in the previous sections, the MISS-HP, IPQ, PSS, and MIOS will be answered throughout the experiment. At the end of the virtual reality session, an exit survey composed of open-ended and 3 multiple choice questions for general feedback.

Overall, the MIOS and PSS are evaluated at the beginning and end of the study for a global assessment of distress (Multimedia Appendix 2), whereas the MISS-HP is collected for a local assessment of distress (Multimedia Appendix 3).

Objective Data Collection

During the virtual reality session, electrocardiogram, electrodermal activity, photoplethysmography, and respiration impedance sensors will be attached to the participant (Figure 9), and these data will be collected with an acquisition and analysis system (MP160, Biopac).

Figure 9. Example of the physical set-up: researcher wearing the head-mounted display, controllers, and Biopac sensors during the virtual reality simulation.

Virtual Reality Data Analysis

We will create a personalized digital phenotype profile, an objective parameter which will help track individual trends over time which will assist in identifying the efficacy of digital interventions and exposure to immersive virtual reality environments, for each participant using primarily heart rate, respiratory rate, oxygen saturation, and skin conductance (BioNomadix, Biopac) (Table 3). These signal features will be paired with reported psychological measures (scales) for a holistic understanding. Both cardiovascular and cerebrovascular dynamics can be captured with these data by deriving features such as heart rate, respiratory rate, and heart rate variability (which is related to the autonomic nervous system and affect states [19]). The autonomic nervous system is the control system that acts largely unconsciously and regulates bodily functions,

including heart rate and respiratory rate. This system is the primary mechanism in control of the fight-or-flight response [19]. We expect that participants in stressful situations will have specific personalized digital phenotype profiles.

Table 3. Description of sensors used and physiological signals collected.

Sensor	Description
Galvanic skin response (electrodermal activity)	Galvanic skin response, also known as electrodermal activity, is a sensor that collects the change in the sweat glands. It measures the electrical conduction of the skin. This sensor is commonly reflective of emotional state and arousal such as anxiety
Electrocardiogram	Electrocardiogram is a physiological signal electrocardiogram collects the electrical activity of the heart. We will measure the heart rate using electrocardiogram features that can be extracted can include heart rate variability and R-R intervals
Respiratory impedance	respiration impedance is a physiological signal that collects the respiration of a participant. It can be defined as the mechanical load of the respiratory system to ventilation. We will collect the number of breaths a participant takes
Photoplethysmography	A noninvasive sensor that uses a pulse oximeter to illuminate a light on the skin. By doing so, it measures the blood volume changes respiratory impedance

Mobile Platform

Customized Digital intervention/intelligence Group Platform

We will use the app, which is based on an open-source mobile-based platform, LAMP (Learn, Assess, Manage, Prevent [20,21]), which is fully compliant with patient and participant confidentiality standards and is currently in use at various US, Canadian, and international hospitals [20]. Applicable privacy legislation include the Personal Health Information Protection Act of Ontario and The Personal Information Protection and Electronic Documents Act.

Learn: This module offers health tips and accurate health news from sources the participant can trust [20].

Assess: This module infers the participant's mood and cognitive status (eg, depression, anxiety, etc) by asking the participant to complete surveys. In addition, this module collects the participant's phone data (eg, geolocation, phone usage).

Manage: In this module, participants can maintain a journal by writing in a diary or have personalized interventions. However, only the participant can write or read the material in this module since all data collected here is personal and available only to the participant.

Prevent: This module uses a dashboard to post figures and curves summarizing the participant's mood, cognitive status, and phone data, such as how fast the participant is moving.

The app is compatible with both iOS and Android platforms. It will be available for free download and for use by approved participants (log-in information will be provided after obtaining informed consent), and deidentified data will be stored at Unity Health Toronto. Furthermore, the platform will be tailored to collect information pertinent to the COVID-19 context. The platform collects various forms of active data (while the participant is using the app) and passive data (whether or not the user is actively using the app) [20]. Study participants will have the option of full access to their active and passive data in real time on the phone or web-based dashboard.

Participant Anonymity

Since participants are required to come to the St. Michael's Hospital Simulation Centre to complete the virtual reality and wearable components of the study, the study will not be anonymous. Participants will only start using the mobile app after they participate in the virtual reality simulation component of the study. The study coordinator will provide an ID and password by email after participants provide written consent, logistical information (preferred time slot), and demographic information to the study coordinator by email.

Mobile Data Collection

Active Data

The surveys will pop up on fixed days of the week for active data collection (ie, Monday, Wednesday, and Friday), as reminders. The participants are then free to complete the surveys (Table 4). These surveys will allow for monitoring of stress-related symptoms using validated scales—Daily surveys using 15 items taken from the UCLA Loneliness Scale [22] (3 items), PSS [23] (4 items), Generalized Anxiety Disorder [24] scale (2 items), Patient Health Questionnaire [25] (2 items), and MIOS [26] (4 items). Each week, on the weekend, the complete versions of the PSS [23] (10 items), Generalized Anxiety Disorder [24] scale (7 items), Patient Health Questionnaire [25] (9 items), MIOS [26] (10 items). Once during the study, the App Experience Survey (6 items) will be administered.

The content of the Moral Injury Outcome Scale is more specific to reflect the virtual reality scenario, unlike in the mobile study, where the survey is more generalized. The cognitive tests appear similar to electronic games wherein participants have to complete a trail or pattern. We will collect the time and number of errors made by the participants.

Passive Data

Passive data (GPS and accelerometer data) are collected automatically while the phone is on, even when the participant is not using the phone (Table 4). The app will access information collected and stored on the phone. Participants can opt out of this feature if they choose.

GPS collects data of the participant's location data with 3-meter accuracy; however, the participant's specific location will not be used as data in the study. The app collects GPS data constantly, and data are immediately converted into broad summary metrics, such as the distance per day and or unique locations visited. These data are not monitored in real time, and will not be reviewed by and party.

The accelerometer records triaxial acceleration, which can be used to indicate if the participant is running or walking. These data are not monitored in real time.

Participants may receive an automated alert based on established survey cut-offs at the beginning of the study. After some time, these alerts may be based on the participant's change in scores compared to their own baseline. The alerts will be simple, for example, "your score today suggests mild anxiety, we suggest exercise, mindfulness practice, etc." If more than 1 alert is required because more than 1 scale has reached the cut-off, the alert will be given once for all the scales.

For active data, we will use visual analog scales (Figure 10). The scale is linear and continuous for the participant to slide on. The scale is subdivided into varying Likert items according to the questionnaire (eg, a scale with 4 items).

We will use predetermined cut-offs (Table 4) to establish the score for each assessment.

Passive data (eg, GPS, accelerometer) will be collected for the first 2 weeks at the beginning of the study to establish a baseline. Members of the research team will be monitoring the in-person data collection for safety concerns. In addition, participants who are inactive will be contacted to remind them of data collection and patients who are having problems will be contact to give technical support.

Figure 10. Visual analog scale with a sliding bar for participants to score on the screen of their phones.

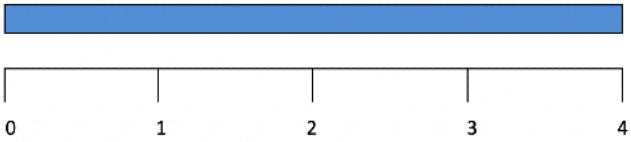


Table 4. Cut-off values and example notifications.

Assessment and classification	Cut-off values	Example of notification
Surveys		
General Anxiety Disorder -7		
Mild anxiety	5≤score<10	"Based on your scores during the past week, you do not appear clinically anxious/depressed, which is mild/moderate; recommendations include Bibliotherapy, mindfulness, exercise, sleep management"
Moderate anxiety	10≤score<15	"Based on your scores during the past week, you do not appear clinically anxious/depressed, which is mild/moderate; recommendations include Bibliotherapy, mindfulness, exercise, sleep management"
Severe anxiety	score≥15	"Based on your scores during the past week, you appear clinically anxious/depressed, which is severe; In addition to continued Bibliotherapy, mindfulness, exercise, sleep management"
Perceived Stress Scale		
Low	0≤score<14	"Based on your scores during the past week, you do not appear to have increased stress which is mild/moderate; recommendations include Bibliotherapy, mindfulness, exercise, sleep management"
Moderate	14≤score<27	"Based on your scores during the past week, you do not appear to have increased stress which is mild/moderate; recommendations include Bibliotherapy, mindfulness, exercise, sleep management"
High	score≥27	"Based on your scores during the past 2 week, you appear clinically stressed which is severe; In addition to continued Bibliotherapy, mindfulness, exercise, sleep management"
Patient Health Questionnaire -9		
Mild depression	5≤score<10	"Based on your scores during the past week, you do not appear clinically anxious/depressed, which is mild/moderate; recommendations include Bibliotherapy, mindfulness, exercise, sleep management"
Moderate depression	10≤score<15	"Based on your scores during the past week, you do not appear clinically anxious/depressed, which is mild/moderate; recommendations include Bibliotherapy, mindfulness, exercise, sleep management"
Moderately severe depression	15≤score<20	"Based on your scores during the past week, you appear clinically anxious/depressed, which is severe; In addition to continued Bibliotherapy, mindfulness, exercise, sleep management"
Severe depression	score≥20	"Based on your scores during the past week, you appear clinically anxious/depressed, which is severe; In addition to continued Bibliotherapy, mindfulness, exercise, sleep management"
Cognitive test: Trails B	>3 minutes or 3 errors	"Your cognition score today is reduced, potential interventions: A) Mindfulness, B) Exercise, C) Sleep habits"
Passive data		
GPS mobility metrics, call-test logs, latency of response, phone pattern of use, sleep, activity		
Moderate change	1 SD to 2 SD from baseline	"Based on your (specify item) scores during the last 2 weeks, you appear to have moderately increased or decreased (specify item); If increased: recommendations include continued exercise; If decreased: recommendations include Bibliotherapy and more exercise"
Large change	>2 SD from baseline; direction of change is important	"Based on your (specify item) scores during the last 2 weeks, you appear to have severely increased or decreased (specify item); If increased: recommendations include continued exercise; If decreased: recommendations include Bibliotherapy and more exercise. Also link provided for further help."

Mobile Data Analysis

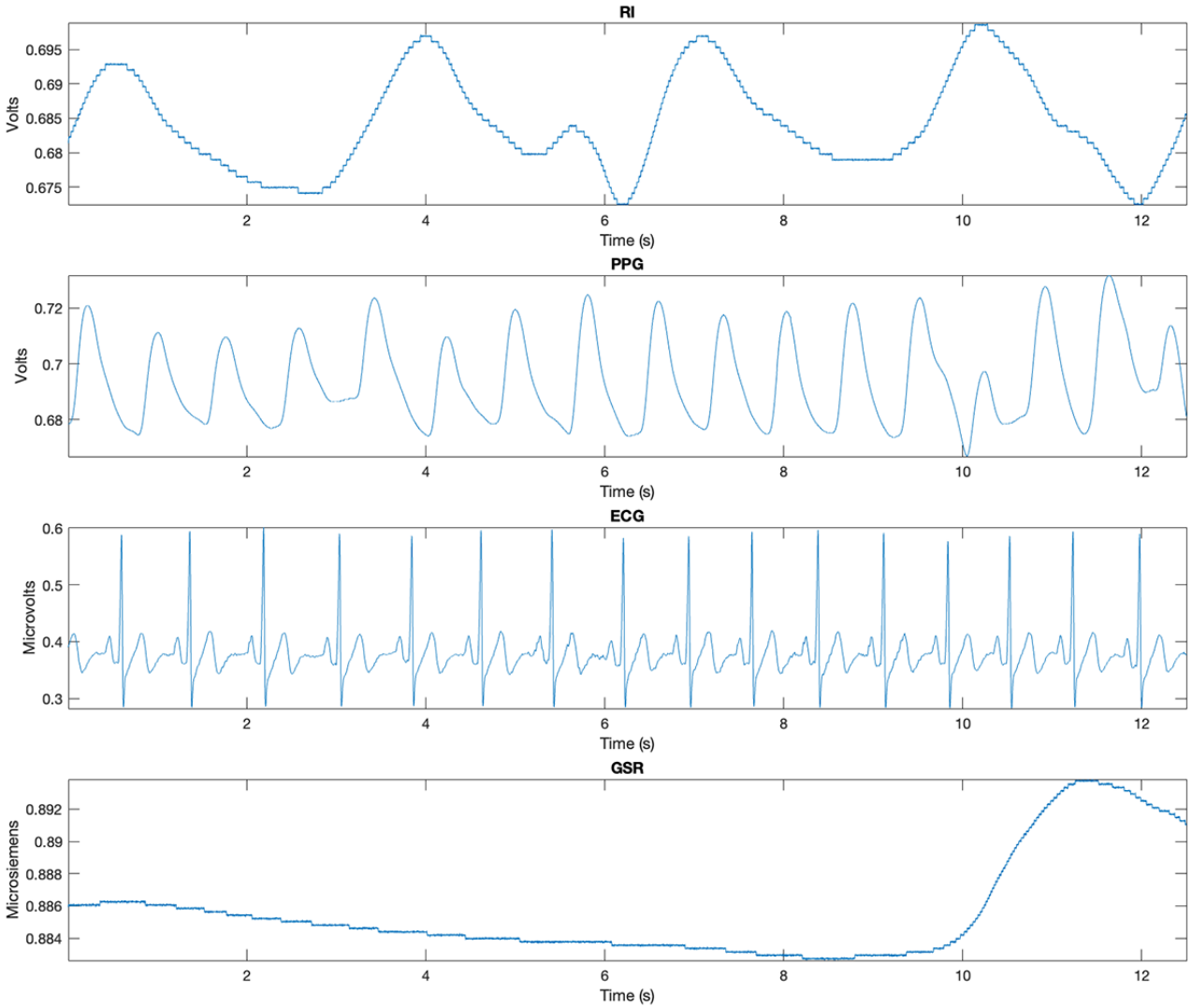
Smartphones are ubiquitous in our daily lives and incorporate a suite of sensors, such as accelerometer and GPS. In addition, digital platforms can be used to collect active data. This results in a multimodal system on a smartphone device. To objectively analyze the data, preprocessing will include Kalman filtering, GPS data cleaning, and Wavelet transforms, and feature extraction techniques, such as multiview biclustering [27] and statistical and structural features from time-series signals [28],

will be used for machine learning (decision tree, logistic regression, and support vector machine) to find associations between passive and active data. These models are simple, consume low power, and have the capability of explainable artificial intelligence to understand our machine learning models better [29]. We plan to extend the machine learning models to long short-term memory and convolutional neural networks due to the popularity and effectiveness of the models in mobile data analysis [28].

Analysis Approach

Signals (Figure 11; Multimedia Appendix 4) will be collected with a sampling frequency of 2000 Hz. The software used to collect the data from Biopac performs all internal calculations to the accuracy defined by the IEEE format for double-precision floating-point numbers and stores the results of those calculations in double-precision floating-point format; this format assigns 8 bytes to all numbers in calculations or resulting from calculations [30]. Biopac equipment has an interface to interact with the virtual reality scenario; thus, we have markers for the sessions, such as the start and end of the session and when the user answers a question.

Figure 11. Physiological signal examples: respiration impedance (RI), photoplethysmography (PPG), electrocardiogram (ECG), and galvanic skin response (GSR).



Numeric programming computing software will be used to conduct the analysis. The signals will be collected in a raw format. Preprocessing, feature extraction, and machine learning will be applied to the data. Preprocessing involves techniques such as low-pass filters, high-pass filters, and notch filters to remove noise. The filtered signal will then be passed along to extract features. Feature extraction will involve extracting attributes of the signals to be better represented. Techniques for feature extraction include handcrafted features, such as statistical values. Lastly, machine learning techniques such as decision tree, random forest, and logistic regression will be used for classification. These techniques are chosen due to their ability to manage small sample sizes. Once familiar with the newly acquired data set, we will reflect on a new approach for analysis.

Results

As of March 20, 2021, the research ethics board at St. Michael's Hospital has approved the study (UHTDTS25377). This project was funded on November 20, 2020.

Discussion

As previously explored, this research will develop and validate the use of digital platforms, specifically virtual reality and mobile apps to understand the continuum of moral distress that leads to moral. Demonstration of feasibility will lead to future studies to examine the efficacy of these digital interventions.

We hypothesize that features of the physiological data will help to identify mental health disorders and distress within users. For example, many studies [31,32] have looked at the impact of stress and burnout in health care workers due to the COVID-19 pandemic.

Modern signal processing and classification tools will be used to find associations between the data and mental health surveys. We expect to discover identifiers within physiological signals that reflect distress and other psychological disorders in the short- and long-term fluctuations of the passive data response related to mental health.

Given the pilot project's aims, the number of participants (10-15 health care providers) was chosen with a view toward demonstrating feasibility while taking into consideration the availability of participants during the COVID-19 pandemic.

Determining the feasibility and utility of virtual reality environments to aid health care workers in reducing distress and becoming resilient in morally challenging and complex environments, by using physiological data in a personalized digital phenotype profile with mobile platforms will lead to future work on the implementation of a larger scale study.

Acknowledgments

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Authors' Contributions

The study was conceptualized by VB, SK, EP, and AD. BN and AT were involved in software design, virtual reality set-up, and physiological sensors. SK,VB, BP, and AD provided supervision. EP and DK were involved with scenario development and qualitative research. DC and LB provided input and direction for study coordination. All authors have read and approved the final manuscript.

Conflicts of Interest

VB is supported by an Academic Scholar Award from the UofT Dept of Psychiatry and has received research support from CIHR, BBRF, MOH Innovation Funds, RCPSC, DND, Canada, and an investigator-initiated trial from Roche Canada. All other authors have no conflicts to declare.

Multimedia Appendix 1
Requirements for LAMP (Learn, Assess, Manage, Prevent) mobile app servers.
[PDF File (Adobe PDF File), 119 KB - resprot_v11i2e32240_app1.pdf]

Multimedia Appendix 2
Moral Injury Outcome Scale and Perceived Stress Scale.
[PDF File (Adobe PDF File), 597 KB - resprot_v11i2e32240_app2.pdf]

Multimedia Appendix 3
Adapted Moral Injury Symptom Scale: Healthcare Professionals version.
[PDF File (Adobe PDF File), 143 KB - resprot_v11i2e32240_app3.pdf]

Multimedia Appendix 4
Additional physiological signals.
[PDF File (Adobe PDF File), 307 KB - resprot_v11i2e32240_app4.pdf]

References

1. Travers M. COVID-19 poses a major quandary for the field of moral psychology. Forbes. URL: https://www.forbes.com/sites/traversmark/2020/04/15/covid-19-poses-a-major-quandary-for-the-field-of-moral-psychology/ [accessed 2021-06-21]
2. Asken MJ. Medical Economics. Now it is moral injury: the COVID-19 pandemic and moral distress. URL: https://www.medicaleconomics.com/view/now-it-moral-injury-covid-19-pandemic-and-moral-distress [accessed 2021-06-21]

3. Holtz H, Heinze K, Rushton C. Interprofessionals' definitions of moral resilience. J Clin Nurs 2018 Feb;27(3-4):e488-e494. [doi: 10.1111/jocn.13989] [Medline: 28771909]
4. Brémault-Phillips S, Pike A, Scarcella F, Cherwick T. Spirituality and moral injury among military personnel: a mini-review. Front Psychiatry 2019;10:276 [FREE Full text] [doi: 10.3389/fpsyt.2019.00276] [Medline: 31110483]
5. Litz BT, Stein N, Delaney E, Lebowitz L, Nash WP, Silva C, et al. Moral injury and moral repair in war veterans: a preliminary model and intervention strategy. Clin Psychol Rev 2009 Dec;29(8):695-706. [doi: 10.1016/j.cpr.2009.07.003] [Medline: 19683376]
6. Corley MC. Nurse moral distress: a proposed theory and research agenda. Nurs Ethics 2002 Nov;9(6):636-650. [doi: 10.1191/0969733002ne557oa] [Medline: 12450000]
7. Shay J. Achilles in Vietnam: Combat Trauma and the Undoing of Character. New York: Simon and Schuster; 2010.
8. Doris JM, Murphy D. From My Lai to Abu Ghraib: the moral psychology of atrocity. Midwest Stud Philos 2007 Sep;31(1):25-55. [doi: 10.1111/j.1475-4975.2007.00149.x]
9. Čartolovni A, Stolt M, Scott PA, Suhonen R. Moral injury in healthcare professionals: a scoping review and discussion. Nurs Ethics 2021 Aug;28(5):590-602 [FREE Full text] [doi: 10.1177/0969733020966776] [Medline: 33427020]
10. Epstein E, Whitehead P, Prompahakul C, Thacker L, Hamric A. Enhancing understanding of moral distress: the measure of moral distress for health care professionals. AJOB Empir Bioeth 2019;10(2):113-124. [doi: 10.1080/23294515.2019.1586008] [Medline: 31002584]
11. Jameton A. Nursing Practice: The Ethical Issues. Englewood Cliffs, N.J: Prentice-Hall; 1984:978.
12. Hamric AB. Empirical research on moral distress: issues, challenges, and opportunities. HEC Forum 2012 Mar;24(1):39-49. [doi: 10.1007/s10730-012-9177-x] [Medline: 22476738]
13. Rushton C. Mapping the path of moral adversity. In: Moral Resilience: Transforming Moral Suffering in Health Care. Oxford: Oxford University Press; 2018.
14. Dishman L. Describing a coronavirus 'war zone,' nurses sue New York and two hospitals over safety issues. Fast Company. 2020 Apr 20. URL: https://www.fastcompany.com/90493806/describing-a-coronavirus-war-zone-nurses-sue-new-york-and-two-hospitals-over-safety-issues [accessed 2021-06-21]
15. Gilligan C. Moral injury and the ethic of care: Reframing the conversation about differences. J Soc Philos 2014 Mar 18;45(1):89-106. [doi: 10.1111/josp.12050]
16. Southwick S, Charney D. The science of resilience: implications for the prevention and treatment of depression. Science 2012 Oct 05;338(6103):79-82. [doi: 10.1126/science.1222942] [Medline: 23042887]
17. A guide to moral injury. Moral Injury Guide. 2020. URL: https://www.moralinjuryguide.ca/ [accessed 2021-10-11]
18. Unity. Unity Technologies. URL: https://unity.com/ [accessed 2021-06-21]
19. Baig M, Kavakli M. A Survey on Psycho-Physiological Analysis & Measurement Methods in Multimodal Systems. MTI 2019 May 28;3(2):37. [doi: 10.3390/mti3020037]
20. Torous J, Wisniewski H, Bird B, Carpenter E, David G, Elejalde E, et al. Creating a digital health smartphone app and digital phenotyping platform for mental health and diverse health care needs: An interdisciplinary and collaborative approach. J Technol Behav Sci 2019 Apr 27;4(2):73-85 [FREE Full text] [doi: 10.1007/s41347-019-00095-w]
21. LAMP. Division of Digital Psychiatry at Beth Israel Deaconess Medical Center. URL: https://www.digitalpsych.org/lamp.html [accessed 2021-10-22]
22. Russell D, Peplau LA, Cutrona CE. The revised UCLA loneliness scale: concurrent and discriminant validity evidence. J Pers Soc Psychol 1980 Sep;39(3):472-480. [doi: 10.1037//0022-3514.39.3.472] [Medline: 7431205]
23. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [Medline: 6668417]
24. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
25. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. Psychiatric Annals 2002 Sep 01;32(9):509-515. [doi: 10.3928/0048-5713-20020901-06]
26. Yeterian JD, Berke DS, Carney JR, McIntyre-Smith A, St Cyr K, King L, Members of the Moral Injury Outcomes Project Consortium. Defining and measuring moral injury: rationale, design, and preliminary findings from the moral injury outcome scale consortium. J Trauma Stress 2019 Jun;32(3):363-372. [doi: 10.1002/jts.22380] [Medline: 30947372]
27. Nguyen B, Kolappan S, Bhat V, Krishnan S. Clustering and feature analysis of smartphone data for depression monitoring. 2021 Presented at: 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society; Nov 1-5; Guadalajara, Mexico p. 113-116. [doi: 10.1109/embc46164.2021.9629737]
28. Nguyen B, Coelho Y, Bastos T, Krishnan S. Trends in human activity recognition with focus on machine learning and power requirements. Mach Learn Appl 2021 Sep;5:100072. [doi: 10.1016/j.mlwa.2021.100072]
29. Barredo Arrieta A, Díaz-Rodríguez N, Del Ser J, Bennetot A, Tabik S, Barbado A, et al. Explainable artificial intelligence (XAI): concepts, taxonomies, opportunities and challenges toward responsible AI. Information Fusion 2020 Jun;58:82-115. [doi: 10.1016/j.inffus.2019.12.012]
30. AcqKnowledge accuracy. BIOPAC. URL: https://www.biopac.com/knowledge-base/acqknowledge-accuracy/ [accessed 2021-10-20]

31. Zhou Q, Lai X, Wan Z, Zhang X, Tan L. Impact of burnout, secondary traumatic stress and compassion satisfaction on hand hygiene of healthcare workers during the COVID-19 pandemic. Nurs Open 2021 Sep;8(5):2551-2557 [FREE Full text] [doi: 10.1002/nop2.786] [Medline: 33605557]
32. Geng S, Zhou Y, Zhang W, Lou A, Cai Y, Xie J, et al. The influence of risk perception for COVID-19 pandemic on posttraumatic stress disorder in healthcare workers: A survey from four designated hospitals. Clin Psychol Psychother 2021 Sep;28(5):1146-1159 [FREE Full text] [doi: 10.1002/cpp.2564] [Medline: 33592682]

Abbreviations

IPQ: Igroup presence questionnaire
MIOS: Moral Injury Outcome Scale
MISS-HP: Moral Injury Symptom Scale: Healthcare Professional version
PSS: Perceived Stress Scale

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Protocol

Investigating Adolescents' Video Gaming and Gambling Activities, and Their Relationship With Behavioral, Emotional, and Social Difficulties: Protocol for a Multi-Informant Study

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Abstract

Background: Growing empirical evidence suggests that adolescents have a relatively greater propensity to develop problematic video gaming or gambling habits.

Objective: The main objectives of this study are to estimate the prevalence of potential pathological gambling and video game use among adolescent students and to evaluate their risk factors.

Methods: This is a cross-sectional multi-informant study based on an online survey. It will include a sample of adolescents attending secondary schools located in Brescia, northern Italy, their schoolteachers, and parents. The survey includes extensive data on adolescents' (1) demographic, social, economic, and environmental characteristics; (2) behavioral, emotional, and social problems and adaptive functioning; (3) emotional and social loneliness; (4) perception of the reasons to use social networks; (5) video game habits and pathological use of video gaming; and (6) gambling behaviors.

Results: This protocol was approved by the Institutional Ethics Board of the Spedali Civili of Brescia (Italy). We expect to collect data from 793 or more adolescent students, as determined by our sample size calculation.

Conclusions: This multisite project will make a substantial contribution to (1) the implementation of a system for identifying pathological gambling and pathological video game use among adolescents, allowing for interventions aimed at improving adolescents' financial, emotional, and social well-being; and (2) the identification of distinct profiles of gamblers and pathological video gamers that will contribute to setting up effective targeted prevention measures. Understanding the causes and impact of gambling and pathological video gaming on adolescents is a public health issue.

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KEYWORDS

adolescents; gaming disorder; gambling disorder; pathological video gaming; pathological gambling

Introduction

Background

Adolescence is characterized by increased risk-taking behaviors [1]. Consequent to these behavioral alterations is the adolescents' relatively greater propensity to develop problematic video gaming or gambling habits, which in recent years has become a serious social and public health policy issue [2-4]. In Europe, where a legalization and liberalization of gambling markets has taken place over the past few decades [5], adolescent gambling prevalence rates range from 0.2% to 12.3% [2], whereas the prevalence of internet gaming disorder rates range from 1.2% to 5.0% [6]. Such large variances reflect the difficulties in obtaining accurate measurements of this phenomenon.

Video gaming is very popular among adolescents [7] and can be associated with many positive aspects of youth development [8,9]. However, during recent years, an increasing number of adolescents are overusing video games that could lead to a gaming disorder, defined as "a pattern of persistent or recurrent gaming behavior ('digital gaming' or 'video gaming') […] manifested by: 1) impaired control over gaming […]; 2) increasing priority given to gaming to the extent that gaming takes precedence over other life interests and daily activities; and 3) continuation or escalation of gaming despite the occurrence of negative consequences" [10]. Indeed, a recent review found that the prevalence of internet gaming disorder [11] ranges from 1.2% to 5.0% in the European Union [6].

Growing empirical evidence suggests that gaming disorder is associated with internalized (such as anxiety and depression) and externalized (such as attention deficit hyperactivity disorder) symptoms [12-14], substance use [15,16], and physical violence including weapon carrying and use [17]. Furthermore, video gaming problems seem to be a gateway to problematic gambling behavior [18]. This is not, however, surprising when you consider that 7 out of 9 Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) [14] criteria for internet gaming disorder are identical to those used for diagnosing gambling disorder [19].

Although the majority of adolescents who have had experience of gambling maintain recreational and controlled activities, some of them develop a gambling disorder. This latter is characterized by "a pattern of persistent or recurrent gambling behavior, which may be online [...] or offline, manifested by: 1) impaired control over gambling […]; 2) increasing priority given to gambling to the extent that gambling takes precedence over other life interests and daily activities; and 3) continuation or escalation of gambling despite the occurrence of negative consequences" [10]. Like gaming disorders, gambling disorder is associated with various mental health issues, such as high levels of impulsivity, anxiety, depression, and stress [20-22] as well as substance use [23].

Few empirical research studies have explored both problematic gaming and gambling habits, the relationship between them, and their effects on adolescents' well-being, often considering a limited number of characteristics of adolescents' psychological, interpersonal, and environmental lives [24,25].

Italian studies have shown that being male, poor parental monitoring, having an anomic view of the social environment [26], using more than 1 game (especially strategy games), having a gambler father or both parents who used to gamble [27], living with nonbirth parents, and having a higher perception of the family's financial status [28] are factors that increase the possibility of becoming at risk of problem gamblers. These studies investigate the Italian profile of adolescent and young adult gamblers.

Objectives

The main aims of this study are to:

- estimate the prevalence of potential pathological gambling and pathological video game use among a sample of adolescent students attending upper-secondary schools;
- estimate the prevalence of emotional/behavioral problems in a sample of adolescent students attending upper-secondary schools, evaluating the correlation between data obtained from different informants (adolescents, parents, and teachers);
- identify distinct profiles of gamblers and pathological video gamers based on their self-reported gambling/gaming behaviors;
- explore risk factors of pathological gambling and pathological video game use among adolescent students attending upper-secondary schools;
- develop a model for identifying adolescents' pathological gambling and pathological video game use.

Methods

Study Design and Setting

This is a cross-sectional multi-informant study conducted in the province of Brescia, the second most populous city in Lombardy (northern Italy), among adolescent students attending secondary schools, their schoolteachers, and parents. The study will involve a total of 5 first-grade secondary schools ("middle school"; aged 11-14 years) and 5 second-grade secondary schools ("high school"; aged 14-19 years).

Pretest

A pretest will be performed to validate the feasibility of the study before beginning data collection. Specifically, we recruited a convenience sample of 28 students to test the comprehensibility of the survey questionnaires and the correct functioning of the online survey system.

Recruitment

We will recruit participants from 10 schools (5 middle schools and 5 high schools). We will present information about the research study both orally and in written form to the schoolteachers of each school. Subsequently, the research team members will visit each participating school to provide a seminar with the aim of presenting the study to students, and then contact the parents or guardians to obtain informed consent for their

children to participate in the study. The final enrollment is expected to be 793 adolescents.

Eligibility Criteria

Inclusion criteria are that the participants are attending the third year of middle school or any of the 5 years of high school. Furthermore, the participation in the study of both a parent (or guardian) and a schoolteacher is required for each student. Students are also required to have adequate knowledge in Italian language to be able to complete the questionnaire.

Typically Developing Reference Sample

Adolescents are eligible to participate in the reference sample if they are students aged between 13 and 19 years, have acquired Italian language skills, and do not have an intellectual disability.

Data Collection

The participants will complete a 1-time online survey between February and October 2020. We will collect data from multiple informants, including students' self-report questionnaires and parents' (or guardians') and schoolteachers' questionnaires on their child/pupil (Table 1). Each participant will complete questionnaires using an online survey tool (LimeSurvey) [29].

Data will be collected from students at the schools during school hours; this activity will take approximately 1 hour. Within 1 month, both parents and schoolteachers will complete a set of questionnaires on their children/pupils; each adolescent will be evaluated by a single schoolteacher. The parent questionnaire takes 25-30 minutes to complete, whereas the schoolteacher questionnaire takes 20-25 minutes.

Table 1. Measurement tools.

Categories and measures	Source
Exposure variables	
Gambling Behavior Scale for Adolescents	Student
Real-Money Games	Student
Video-Gaming Scale for Adolescents	Student
External perception of the adolescent's gambling behavior and money availability	Parent/teacher
Psychodiagnostic assessment	
Child Behavior Checklist	Parent
Strength and Difficulties Questionnaire	Student/parent/teacher
Teacher's Report Form	Teacher
Youth Self-Report	Student
Social factors	
Loneliness Scale	Student
Social Network	Student
Personal factors	
Demographic, social, and environmental information	Student/parent
Economic resources	Student

Measurement

Demographic, Social, and Environmental Information

We will obtain information on the student's sex, age, place of residence and its characteristics, family composition, parental education level, and parental job from the student assessment. We will obtain information on the student's infancy from both student and parent assessments.

Strength and Difficulties Questionnaire

The Strength and Difficulties Questionnaire (SDQ) [30] is a 25-item questionnaire developed with reference to the main nosological categories recognized by the DSM-IV (also valid for the DSM-5) and describing positive and negative attributes of adolescents. Each item is scored on a 3-point scale: "Not true," "Somewhat true," or "Certainly true." The items are divided into 5 subscales each with 5 items: emotional symptoms, behavioral problems, hyperactivity inattention, peer relationship problems, and prosocial behavior. It is also possible to assess chronicity, distress, burden to others, and social impairment. The SDQ provides scores for 3 dimensions of impact: perceived difficulties, impact score, and a burden rating. There are 3 versions of the SDQ: self-report, parent report, and teacher report version. The Italian version of the SDQ has good psychometric properties, with Cronbach α ranging from .73 to .89 [31].

Achenbach System of Empirically Based Assessment School-Age Forms

The Achenbach System of Empirically Based Assessment (ASEBA) [32,33] is an integrated system of multi-informant assessment of behavioral, emotional, and social problems and adaptive functioning in youth aged 11-18. Adolescents complete the *Youth Self-Report* (YSR; 119 items), parents complete the *Child Behavior Checklist* (CBCL; 120 items), and schoolteachers complete the *Teacher's Report Form* (TRF; 120

items). Each questionnaire consists of a problem section with items rated as "Not True" (0), "Somewhat or Sometimes True" (1), or "Very or Often True" (2).

Each of these 3 questionnaires provides 8 syndrome scales: anxious/depressed, withdrawn/depressed, and somatic complaints (together: internalizing or emotional problems); rule-breaking behavior and aggressive behavior (together: externalizing or behavioral problems); and social problems, thought problems, and attention problems. Internalizing score, externalizing score, and total problems score can be calculated by summing up the problem items. Additionally, items from the YSR, CBCL, and TRF can be grouped into the following DSM-IV–oriented scales (still valid for the DSM-5): affective problems, anxiety problems, somatic problems, attention deficit/hyperactivity problems, oppositional defiant problems, and conduct problems [34]. The YSR shows good internal validity (Cronbach α=.71-.95) [35]. Cronbach α was high for the Broadband and the Total Problem scales, ranging from .83 to .91 for the CBCL [33]. The Internalizing scale can be derived from the first 3 syndrome scales (Cronbach α=.86), and the Externalizing scale from the last 2 (Cronbach α=.85). The Total Problems scale was determined by adding up the individual item scores (Cronbach α=.84) [36]. The TRF ranged from 0.86 to 0.94 [33].

Loneliness Scale

The Loneliness Scale (LS) [37] consists of 6 statements (rated as "yes," "more or less," or "no") designed to measure emotional, social, and overall loneliness. Cronbach α was .92 [38].

Economic Resources

Three self-report questions about how often the adolescent receives money, how much, and from whom.

Social Network

Three self-report questions on the adolescent's subjective perception of the reasons to use social networks.

Video-Gaming Scale for Adolescents

The Video-Gaming Scale for Adolescents (VGS-A) [39] is a self-report questionnaire that evaluates adolescents' video game habits and pathological use of video gaming. The first section consists of 3 unscored items investigating video game habits: the frequency with which they have played each of the various video game genres during the last year, the devices used to game and the time spent on each of them, and preferences about the use of online or offline gaming. The second section is composed of 9 items rated on a 3-point scale: "never" (0), "sometimes" (1), or "often" (2), which were developed to relieve the 9 DSM-5 diagnostic criteria of pathological gaming among adolescents. Pathological gaming is measured by taking into account the severity of each symptom described by the 9 items. Cronbach α for VGS-A was .71 [40].

Gambling Behavior Scale for Adolescents

The Gambling Behavior Scale for Adolescents (GBS-A) [41] is a self-report questionnaire that assesses gambling behavior among adolescents. The first section consists of 4 unscored items investigating the frequency of participation in each of the different gambling activities (eg, card games, bets on sports games, lotteries) during the last year, the age at which gambling started, the existence of any gambling partners and the relative frequency of gambling with each of them, and the amount of money spent on each of the various gambling activities. The second section is composed of 9 items rated on a 3-point scale: "never" (0), "sometimes" (1), or "often" (2), which were developed to relieve the 9 DSM-5 diagnostic criteria of gambling disorder among adolescents. The GBS-A classifies the respondents as nonproblem gamblers, at-risk gamblers, or disordered gamblers. Cronbach α for GBS-A was .77 [42].

Real Money Games

A total of 16 self-report questions were developed to assess the frequency of and time spent in real money games (both online and offline) during the last year. These provide information on where money games are played, which devices are used to play money games, and the amount of money played.

Adults' Perception of the Adolescent's Gambling Behavior and Money Availability

Adults' (both parents and schoolteachers) perceptions of their adolescent child/pupil's involvement or noninvolvement in gambling behaviors and his/her money availability will be evaluated.

Sample Size Estimation

The primary endpoint of the study is the prevalence of pathological gambling, pathological video game use, and emotional/behavioral problems in a sample of adolescent students attending upper-secondary schools. A sample size of 750 students produces a 2-sided 95% CI of 1.5%, 2%, and 2.5% when the prevalence is equal to 5%, 10%, and 15%, respectively.

Little is known from previous literature about risk factors for pathological gambling, pathological video game use, and emotional/behavioral problems in adolescent students attending upper-secondary schools. Assuming a prevalence of 15% [43] and considering a power (1-β) of 0.80 and a type I error (α) of .05, a sample of 750 students would allow the detection of an odds ratio of 2.2 for a binary risk factor present in 30% of the students. An adjustment was made because a multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an R^2=0.5. According to the "one in ten" rule of thumb, the proposed sample size ensures to fit a multivariate logistic regression model with up to 12 independent variables.

Statistical Analysis Plan

The main characteristics of the sample will be summarized using absolute and relative frequencies for categorical variables and through mean or median and range, interquartile range, and standard deviation for continuous variables.

The prevalence of pathological gambling, pathological video game use, and emotional/behavioral problems will be quantified in terms of proportion (relative frequency) and its 95% CI.

We will use the chi-square test for categorical variables, or the Fisher exact test when expected frequencies are lower than 5,

to assess differences among categorical variables. The normality of continuous variables will be assessed graphically using the quantile–quantile plot and through a nonparametric test (eg, the Shapiro–Wilk test). We will compare continuous variables among groups defined by a categorical variable using the *t* test when the normality assumption is met, or otherwise using the nonparametric rank-based Wilcoxon–Mann–Whitney *U* test. The strength of the correlation among continuous variables obtained from different informants (ie, students, parents, and teachers) will be evaluated using the Pearson linear correlation coefficient or the Spearman rank correlation coefficient. The Cohen kappa statistic and the Bland–Altman plot will be used to test concordance among categorical and continuous variables, respectively.

Multivariate clustering techniques (principal component analysis, multiple correspondence analysis, hierarchical clustering) will be used to identify distinct gambler and pathological video gamer profiles according to their gambling/gaming behaviors based on data collected through the questionnaires. We will use these advanced multivariate statistical techniques to reduce the size of the data by identifying a small number of underlying main components without losing too much information.

A multivariate logistic regression model combined with variable selection techniques will be used to identify risk factors associated with pathological gambling and pathological video gaming. The results will be presented in terms of odds ratios with their 95% CI.

We will consider a *P* value less than .05 as statistically significant.

Patient and Public Involvement

Adolescent students, parents, or the teachers were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics Approval

Our protocol was reviewed and approved by the Institutional Ethics Board of the Spedali Civili of Brescia, Italy (resolution n. NP3662 f 28-01-2020). All procedures performed in this study are in accordance with the ethical standards of the Institutional Ethics Board of the Spedali Civili of Brescia and with the 1964 Declaration of Helsinki and its later amendments. We will obtain written consent from the parents, on their own behalf and on behalf of their children under 18, the schoolteachers, and from the adolescents of legal age. Students under 18 will be also asked for their consent.

Availability of Data and Materials

Data sharing does not apply to this article as data sets will not be generated or analyzed in this article.

Dissemination

We will publish all results in peer-reviewed international journals indexed in Web of Science or Scopus databases and present them at national and international conferences.

Results

According to our sample size calculation, we expect that at least 793 adolescent students from 10 schools (5 middle schools and 5 high schools) located in Brescia, northern Italy, will participate in the study.

Discussion

This study will quantify the prevalence of pathological gambling, pathological video game use, and emotional/behavioral problems in a sample of adolescent students attending upper-secondary schools in Brescia and its province, the second most populous province in Lombardy (northern Italy). This study will contribute to the implementation of a system for identifying pathological gambling and pathological video game use among adolescents, allowing for interventions aimed at improving adolescents' financial, emotional, and social well-being. Furthermore, findings from this study will allow us to identify distinct profiles of gamblers and pathological video gamers that will contribute to setting up effective targeted prevention measures. Understanding the causes and impact of gambling and pathological video gaming on adolescents is a public health issue. We will present a report with the study results to the Osservatorio Provinciale del contrasto alle ludopatie e al gioco d'azzardo di Brescia [Provincial Observatory for the Prevention of Compulsive Gambling Disorders and Betting of the Lombardy region] and the Ufficio scolastico regionale per la Lombardia Ufficio IV Ambito Territoriale di Brescia [Regional School Office for Lombardy, IV District of Brescia], and the teaching staff of the schools and educational institutions involved. Additionally, a public conference will be organized as the project's final step to inform students, parents, and the general population.

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Authors' Contributions

LC was the chief investigator and, together with AS, designed this study protocol. MR was responsible for the statistical analysis plan. AS drafted the first version of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Galván A. Risky behavior in adolescents: The role of the developing brain. In: Reyna VF, Chapman SB, Dougherty MR, editors. The Adolescent Brain: Learning, Reasoning, and Decision Making. Washington, DC: American Psychological Association; 2012:267-289.
2. Calado F, Alexandre J, Griffiths MD. Prevalence of adolescent problem gambling: a systematic review of recent research. J Gambl Stud 2017 Jun 2;33(2):397-424 [FREE Full text] [doi: 10.1007/s10899-016-9627-5] [Medline: 27372832]
3. Ferrara P, Franceschini G, Corsello G. Gambling disorder in adolescents: what do we know about this social problem and its consequences? Ital J Pediatr 2018 Dec 04;44(1):146 [FREE Full text] [doi: 10.1186/s13052-018-0592-8] [Medline: 30514334]
4. Andrie EK, Tzavara CK, Tzavela E, Richardson C, Greydanus D, Tsolia M, et al. Gambling involvement and problem gambling correlates among European adolescents: results from the European Network for Addictive Behavior study. Soc Psychiatry Psychiatr Epidemiol 2019 Nov 6;54(11):1429-1441. [doi: 10.1007/s00127-019-01706-w] [Medline: 31062040]
5. Kingma S. The liberalization and (re) regulation of Dutch gambling markets: National consequences of the changing European context. Regulation & Governance 2008;2(4):445 [FREE Full text] [doi: 10.1111/j.1748-5991.2008.00045.x]
6. Mihara S, Higuchi S. Cross-sectional and longitudinal epidemiological studies of Internet gaming disorder: A systematic review of the literature. Psychiatry Clin Neurosci 2017 Jul 31;71(7):425-444 [FREE Full text] [doi: 10.1111/pcn.12532] [Medline: 28436212]
7. Lenhart A, Smith A, Anderson M, Duggan M, Perrin A. Teens, technology and friendships. Pew Research Center. 2015 Aug. URL: https://www.pewresearch.org/internet/2015/08/06/teens-technology-and-friendships/ [accessed 2022-02-18]
8. Bavelier D, Green CS, Han DH, Renshaw PF, Merzenich MM, Gentile DA. Brains on video games. Nat Rev Neurosci 2011 Nov 18;12(12):763-768 [FREE Full text] [doi: 10.1038/nrn3135] [Medline: 22095065]
9. Lim J, Lee J, Jung H, Sohn B, Choi S, Kim Y, et al. Changes of quality of life and cognitive function in individuals with Internet Gaming Disorder: A 6-month follow-up. Medicine 2016;95(50):e5695. [doi: 10.1097/md.0000000000005695]
10. World Health Organization. International Statistical Classification of Diseases and Related Health Problems (11th ed). WHO. 2019. URL: https://icd.who.int/ [accessed 2022-02-18]
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Arlington, VA: American Psychiatric Publishing; 2013.
12. Lobel A, Engels RCME, Stone LL, Burk WJ, Granic I. Video gaming and children's psychosocial wellbeing: a longitudinal study. J Youth Adolesc 2017 Apr 21;46(4):884-897 [FREE Full text] [doi: 10.1007/s10964-017-0646-z] [Medline: 28224404]
13. González-Bueso V, Santamaría JJ, Fernández D, Merino L, Montero E, Ribas J. Association between Internet Gaming Disorder or pathological video-game use and comorbid psychopathology: a comprehensive review. Int J Environ Res Public Health 2018 Apr 03;15(4):668 [FREE Full text] [doi: 10.3390/ijerph15040668] [Medline: 29614059]
14. Lau C, Stewart S, Sarmiento C, Saklofske D, Tremblay P. Who is at risk for problematic video gaming? Risk factors in Problematic video gaming in clinically referred Canadian children and adolescents. MTI 2018 Apr 26;2(2):19. [doi: 10.3390/mti2020019]
15. van Rooij AJ, Kuss DJ, Griffiths MD, Shorter GW, Schoenmakers TM, van de Mheen D. The (co-)occurrence of problematic video gaming, substance use, and psychosocial problems in adolescents. Journal of Behavioral Addictions 2014 Sep;3(3):157-165. [doi: 10.1556/jba.3.2014.013]
16. Turel O, Bechara A. Little video-gaming in adolescents can be protective, but too much is associated with increased substance use. Subst Use Misuse 2019 Jan 17;54(3):384-395. [doi: 10.1080/10826084.2018.1496455] [Medline: 30654698]
17. Zhai ZW, Hoff RA, Howell JC, Wampler J, Krishnan-Sarin S, Potenza MN. Differences in associations between problematic video-gaming, video-gaming duration, and weapon-related and physically violent behaviors in adolescents. J Psychiatr Res 2020 Feb;121:47-55 [FREE Full text] [doi: 10.1016/j.jpsychires.2019.11.005] [Medline: 31765836]
18. Molde H, Holmøy B, Merkesdal AG, Torsheim T, Mentzoni RA, Hanns D, et al. Are video games a gateway to gambling? A longitudinal study based on a representative Norwegian sample. J Gambl Stud 2019 Jun 5;35(2):545-557 [FREE Full text] [doi: 10.1007/s10899-018-9781-z] [Medline: 29869768]
19. Petry NM, Rehbein F, Gentile DA, Lemmens JS, Rumpf H, Mößle T, et al. An international consensus for assessing internet gaming disorder using the new DSM-5 approach. Addiction 2014 Sep 23;109(9):1399-1406. [doi: 10.1111/add.12457] [Medline: 24456155]
20. Nigro G, Cosenza M, Ciccarelli M. The blurred future of adolescent gamblers: impulsivity, time horizon, and emotional distress. Front Psychol 2017 Apr 03;8:486 [FREE Full text] [doi: 10.3389/fpsyg.2017.00486] [Medline: 28421013]
21. Adams BLM, Stavropoulos V, Burleigh TL, Liew LWL, Beard CL, Griffiths MD. Internet gaming disorder behaviors in emergent adulthood: a pilot study examining the interplay between anxiety and family cohesion. Int J Ment Health Addiction 2018 Jan 30;17(4):828-844. [doi: 10.1007/s11469-018-9873-0]

22. Cosenza M, Ciccarelli M, Nigro G. Decision-making styles, negative affectivity, and cognitive distortions in adolescent gambling. J Gambl Stud 2019 Jun 29;35(2):517-531. [doi: 10.1007/s10899-018-9790-y] [Medline: 29959691]
23. Ko C, Yen J, Yen C, Chen C, Weng C, Chen C. The association between Internet addiction and problematic alcohol use in adolescents: the problem behavior model. Cyberpsychol Behav 2008 Oct;11(5):571-576. [doi: 10.1089/cpb.2007.0199] [Medline: 18785835]
24. Delfabbro P, King DL. Gaming-gambling convergence: evaluating evidence for the 'gateway' hypothesis. International Gambling Studies 2020 Jun 02;20(3):380-392. [doi: 10.1080/14459795.2020.1768430]
25. van Holst RJ, Lemmens JS, Valkenburg PM, Peter J, Veltman DJ, Goudriaan AE. Attentional bias and disinhibition toward gaming cues are related to problem gaming in male adolescents. J Adolesc Health 2012 Jun;50(6):541-546. [doi: 10.1016/j.jadohealth.2011.07.006] [Medline: 22626478]
26. Marinaci T, Venuleo C, Ferrante L, Della Bona S. What game we are playing: the psychosocial context of problem gambling, problem gaming and poor well-being among Italian high school students. Heliyon 2021 Aug;7(8):e07872 [FREE Full text] [doi: 10.1016/j.heliyon.2021.e07872] [Medline: 34485746]
27. Cavalera C, Bastiani L, Gusmeroli P, Fiocchi A, Pagnini F, Molinari E, et al. Italian adult gambling behavior: at risk and problem gambler profiles. J Gambl Stud 2018 Sep 13;34(3):647-657. [doi: 10.1007/s10899-017-9729-8] [Medline: 29134497]
28. Canale N, Griffiths MD, Vieno A, Siciliano V, Molinaro S. Impact of Internet gambling on problem gambling among adolescents in Italy: Findings from a large-scale nationally representative survey. Computers in Human Behavior 2016 Apr;57:99-106. [doi: 10.1016/j.chb.2015.12.020]
29. LimeSurvey. LimeSurvey GmbH. URL: https://www.limesurvey.org/ [accessed 2022-02-19]
30. Tobia V, Gabriele MA, Marzocchi GM. The Italian version of the Strengths and Difficulties Questionnaire (SDQ)—Teacher. Journal of Psychoeducational Assessment 2013 Feb 07;31(5):493-505. [doi: 10.1177/0734282912473456]
31. Cusinato M, Iannattone S, Spoto A, Poli M, Moretti C, Gatta M, et al. Stress, resilience, and well-being in Italian children and their parents during the COVID-19 pandemic. Int J Environ Res Public Health 2020 Nov 10;17(22):8297. [doi: 10.3390/ijerph17228297] [Medline: 33182661]
32. Achenbach T. Achenbach System of Empirically Based Assessment: School Age Forms and Profiles, Child Behavior Checklist for Ages 6-18. Burlington, VT: ASEBA; 2001.
33. Frigerio A, Cattaneo C, Cataldo M, Schiatti A, Molteni M, Battaglia M. Behavioral and emotional problems among Italian children and adolescents aged 4 to 18 years as reported by parents and teachers. European Journal of Psychological Assessment 2004 Jan;20(2):124-133. [doi: 10.1027/1015-5759.20.2.124]
34. Achenbach TM, Dumenci L, Rescorla LA. DSM-oriented and empirically based approaches to constructing scales from the same item pools. Journal of Clinical Child & Adolescent Psychology 2010 Jun 07;32(3):328-340. [doi: 10.1207/s15374424jccp3203_02]
35. Pace CS, Muzi S. Binge-eating symptoms, emotional-behavioral problems and gender differences among adolescents: a brief report. Mediterr J Clin Psychol 2019;7(2):1-9. [doi: 10.6092/2282-1619/2019.7.2161]
36. Thommessen S, Laghi F, Cerrone C, Baiocco R, Todd B. Internalizing and externalizing symptoms among unaccompanied refugee and Italian adolescents. Children and Youth Services Review 2013 Jan;35(1):7-10. [doi: 10.1016/j.childyouth.2012.10.007]
37. Gierveld JDJ, Tilburg TV. A 6-item scale for overall, emotional, and social loneliness. Res Aging 2016 Aug 18;28(5):582-598. [doi: 10.1177/0164027506289723]
38. Primi C, Fioravanti G, Casale S, Donati MA. Measuring problematic Facebook use among adolescents and young adults with the Bergen Facebook Addiction Scale: a psychometric analysis by applying item response theory. Int J Environ Res Public Health 2021 Mar 14;18(6):2979 [FREE Full text] [doi: 10.3390/ijerph18062979] [Medline: 33799401]
39. Primi C, Donati MA, Chiesi F. Scala per la Misura dell'Uso dei Videogiochi negli Adolescenti [Video-Gaming Scale for Adolescents, VGS-A. A Scale to Assess Video-Gaming among Adolescents]. Florence, Italy: Hogrefe Editore; 2017.
40. Milani L, La Torre G, Fiore M, Grumi S, Gentile DA, Ferrante M, et al. Internet gaming addiction in adolescence: risk factors and maladjustment correlates. Int J Ment Health Addiction 2017 Mar 20;16(4):888-904. [doi: 10.1007/s11469-017-9750-2]
41. Primi C, Donati M, Chiesi F. Scala per la Misura del Comportamento di Gioco D'azzardo Negli Adolescenti Gambling Behavior Scale for Adolescents [A Scale to Assess Gambling Behavior among Adolescents]. Florence, Italy: Hogrefe Editore; 2015.
42. Donati MA, Weller J, Primi C. Using the risk-return model to explain gambling disorder symptoms in youth: an empirical investigation with Italian adolescents. J Gambl Stud 2021 Sep 03;37(3):779-794. [doi: 10.1007/s10899-020-09992-9] [Medline: 33389431]
43. Colasante E, Gori M, Bastiani L, Scalese M, Siciliano V, Molinaro S. Italian adolescent gambling behaviour: psychometric evaluation of the South Oaks Gambling Screen: Revised for Adolescents (SOGS-RA) among a sample of Italian students. J Gambl Stud 2014 Dec;30(4):789-801. [doi: 10.1007/s10899-013-9385-6] [Medline: 23740346]

Abbreviations

ASEBA: Achenbach System of Empirically Based Assessment
CBCL: Child Behavior Checklist
DSM: Diagnostic and Statistical Manual of Mental Disorders
GBS-A: Gambling Behavior Scale for Adolescents
SDQ: Strength and Difficulties Questionnaire
TRF: Teacher's Report Form
VGS-A: Video-Gaming Scale for Adolescents
YSR: Youth Self-Report

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Protocol

The Shishu Pushti Trial–Extended Peer Counseling for Improving Feeding Practices and Reducing Undernutrition in Children Aged 0-48 Months in Urban Bangladesh: Protocol for a Cluster-Randomized Controlled Trial

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Abstract

Background: The aim of this study is to assess if peer counseling of women improves breastfeeding, complementary feeding practices, and child growth, and thus reduces the prevalence of undernutrition in children up to 4 years of age.

Objective: Lack of exclusive breastfeeding and inappropriate complementary feeding are critical factors in reducing child undernutrition, morbidity, and mortality. There are reported trials of peer counseling to improve breastfeeding; however, they did not examine the efficacy of peer counseling to improve complementary feeding or the long-term impacts on child growth and development.

Methods: This study has used a community-based, cluster-randomized controlled trial with a superiority design and 2 parallel treatment arms. It is assessing the impact of peer counseling, starting in late pregnancy up to 1 year after delivery, on child feeding practices, growth, and development with follow-up until 48 months of age. The study site was Mirpur, a densely populated area in Dhaka. Using satellite maps and geographic information system mapping, we constructed 36 clusters with an average population of 5000 people. We recruited pregnant women in the third trimester aged 16-40 years, with no more than 3 living children. Trained peer counselors visited women at home twice before delivery, 4 times in the first month, monthly from 2 to 6 months, and again at 9 and 12 months. Trained research assistants collected anthropometric measurements. The primary outcome will be differences in child stunting and mean length for age at 6, 12, 15, and 18 months. Secondary outcomes will be differences in the percentage of women exclusively breastfeeding in the mean duration of any breastfeeding and in the percentage of children at 6 and 9 months of age who receive solid, semisolid, or soft foods; and the percentage of children consuming foods from 4 or more food groups at 9, 12, 15, and 18 months. We will assess the mean cognitive function scores from the Ages and Stages Questionnaire (9 and 18 months) and Bayley tests (24 and 36 months).

Results: We identified 65,535 people in mapped residences, from which we defined 36 clusters and randomly allocated them equally to intervention or control groups stratified by cluster socioeconomic status. From July 2011 to May 2013, we identified 1056 pregnant women and 993 births in the intervention group and 994 pregnancies and 890 births in the control group. At 18 months, 692 children remained in the intervention group and 551 in the control group. From January 2015 to February 2017, we conducted the long-term follow-up of the cohort. We have now completed the data collection and processing and have started analyses.

Conclusions: This study will help fill the evidence gap about the short- and long-term impact of peer counseling on improving infant feeding, preventing childhood undernutrition, and enhancing child cognitive development.

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International Registered Report Identifier (IRRID): DERR1-10.2196/31475

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KEYWORDS

child stunting; prevention; nutrition behavior change; breastfeeding: infant and young child feeding; peer counseling, child development

Introduction

Although progress has been made in reducing child undernutrition [1], it remains a highly prevalent condition in low- and middle-income countries [2]. South Asia has a major portion of the global burden of childhood undernutrition, with an estimated 59 million (or 33.3%) of children under 5 years living with stunted growth in this region [3]. Undernutrition contributes to 45% of deaths in children under 5 years old [4], and effective interventions are needed to reduce its prevalence, particularly in countries with high prevalence. In Bangladesh, child undernutrition is an important public health problem, with 36% of children younger than 5 years being stunted, 33% being underweight, and 14% being wasted in 2014 [5].

Suboptimal breastfeeding increases the risks of childhood morbidity, which potentially contributes to the development of undernutrition and mortality, particularly in the first 2 years of life [2]. The World Health Organization (WHO) recommends exclusively breastfeeding children until 6 months of age, and after that, continuing breastfeeding with appropriately diverse and frequent complementary foods [6,7]. The complementary feeding period from 6 to 24 months also provides a window of opportunity for preventing undernutrition [8] as most postnatal growth faltering occurs during the first 2 years of life. Studies have shown that even with optimum breastfeeding, growth faltering will occur if children do not receive an adequate quantity and quality of complementary foods after 6 months [9].

A study from 2016 has shown that most stunting occurs in the first 2 years [10]. This growth retardation happens because children have a higher demand for nutrients and a higher rate of infectious diseases such as diarrhea, which adversely affects growth and nutritional status [11]. A lack of diversity of foods given to young children also contributes to undernutrition. For example, animal-source foods are an important source of protein and micronutrients, such as zinc, and low intakes of these foods are associated with stunting in children [8]. Improved breastfeeding practices and more diverse foods, and increased frequency of complementary feeds can help protect infants from childhood undernutrition and improve their developmental potential.

Growth faltering, in turn, has effects on a child's developmental potential [12,13]. The South Asian region also harbors a very high proportion of children with low cognitive and socioemotional Early Childhood Development Index scores [14]. Few studies have examined the relationship between undernutrition and cognitive development in Bangladeshi children. The evidence available comes mainly from 5 trials of psychosocial stimulation [15-19]. In all these studies, malnourished children had very low developmental scores, which were significantly lower than those of better-nourished children. In micronutrient supplementation trials, children's height-for-age and weight-for-age *z* scores were significantly correlated with their developmental levels, indicating a close association of nutritional status and child development [20-25].

A systematic review and meta-analysis of 110 studies for breastfeeding promotion found statistically significant increases in exclusive breastfeeding (EBF) rates: 43% at day 1, 30% at <1 month, and 90% at 1-5 months. Rates of “no breastfeeding” reduced by 32% at 1 day, 30% at <1 month, and 18% at 1-5 months [26]. An established approach to promoting appropriate breastfeeding practices in low- and middle-income countries involves local peer counselors providing information and support to mothers feeding young children [27,28]. A systematic review showed that in low- and middle-income countries, compared to usual care, community-based peer support increased EBF in the first 6 months and initiation of breastfeeding within the first hour of life, and decreased the risk of prelacteal feeding [29]. There is research demonstrating the feasibility of implementing a peer-counseling intervention in urban Bangladesh with evidence of changed feeding behaviors [28]. To date, there have been few reports of using peer counseling to educate, support, and build a mother's skills regarding both breastfeeding and appropriate complementary feeding. A before-and-after study conducted in a lower socioeconomic population in the Lalitpur district of Uttar Pradesh, India, suggests that peer counselors can improve infant feeding practices by increasing EBF and appropriate complementary feeds [30]. However, there is a need

to examine the impact of peer counseling interventions on long-term child undernutrition, growth, and development.

We used the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline [31] to prepare this protocol. It was peer reviewed by the Australian National Health and Medical Research Council (NHMRC) grant review panels in 2009 (GNT63329) and 2013 (GNT1071005) and by the Research Review Committee of the International Centre for Diarrheal Disease Research-Bangladesh (icddr,b). The University of Sydney Human Ethics committee and the Ethics Review Committee of ICDDR-B approved the protocols. This report combines the 2 approved protocols.

We aim to implement a community-based, cluster -randomized controlled trial to collect evidence of whether peer counseling of women to promote appropriate infant feeding can improve breastfeeding, complementary feeding, and child growth, and thus reduce the prevalence of stunting (low height-for-age) in their children up to 18 months of age. In addition, the proposed study will examine the long-term impact of peer counseling for appropriate infant feeding on child anthropometry and cognitive development at 36 and 48 months.

Our primary hypothesis is that in a community-based, cluster-randomized controlled trial of peer counseling to support infant feeding starting from the third trimester of pregnancy to 1 year after delivery will reduce the prevalence of stunting (length-for-age < –2 z score) in children at 18 months of age by 10% compared to the control group with no peer counseling.

The short-term outcomes (secondary hypotheses) are the following:

1. The percentage of children with low length-for-age, low weight-for-height, and low weight-for-age between 6 and 18 months of age will be lower in the peer counseling group than in the control group.

2. The mean length-for-age, weight-for-height, and weight-for-age in children between 6 and 18 months of age will be higher in the peer counseling group than in the control group.

3. The children's height and weight velocity from birth to 18 months of age will be higher in the peer counseling group than in the control group.

4. The percentage of women EBF (breast milk and no other foods or milk-based liquids) their infants at 3 and 6 months will be higher in the peer counseling group than in the control group.

5. The mean duration of any breastfeeding will be longer in the peer counseling group than in the control group.

6. The percentage of women bottle feeding (any liquid or semisolid food from a bottle with a nipple or teat) their infants at 12 months will be lower in the peer counseling group than in the control group.

7.The percentage of children at 6 and 9 months of age who receive solid, semisolid, or soft foods will be higher in the peer counseling group than in the control group.

8. The percentage of children consuming >4 food groups at 9, 12, 15, and 18 months will be higher in the peer counseling group than in the control group.

9. Mean intake of children’s food energy, protein, carbohydrate, fat, and selected micronutrients (eg, zinc, iron, phytate vitamin A) from complementary feeds at 9, 12, 15, and 18 months will increase more in the peer counseling group than in the control group.

10. The mean days ill with diarrhea, acute respiratory illness, and fever at each monthly recall period from 1 to 18 months will be lower in the peer counseling group than in the control group.

The longer-term outcomes (secondary hypotheses) are the following:

1. The percentage of children with low length-for-age, low weight-for-length, and low weight-for-age in children between 18 and 48 months of age will be lower in the peer counseling group than in the control group.

2. The mean length-for-age, weight-for-length, and weight-for-age of children between 18 and 48 months of age will be higher in the peer counseling group than in the control group.

3. The children's length and weight velocity from 18 to 48 months of age will be higher in the peer counseling group than in the control group.

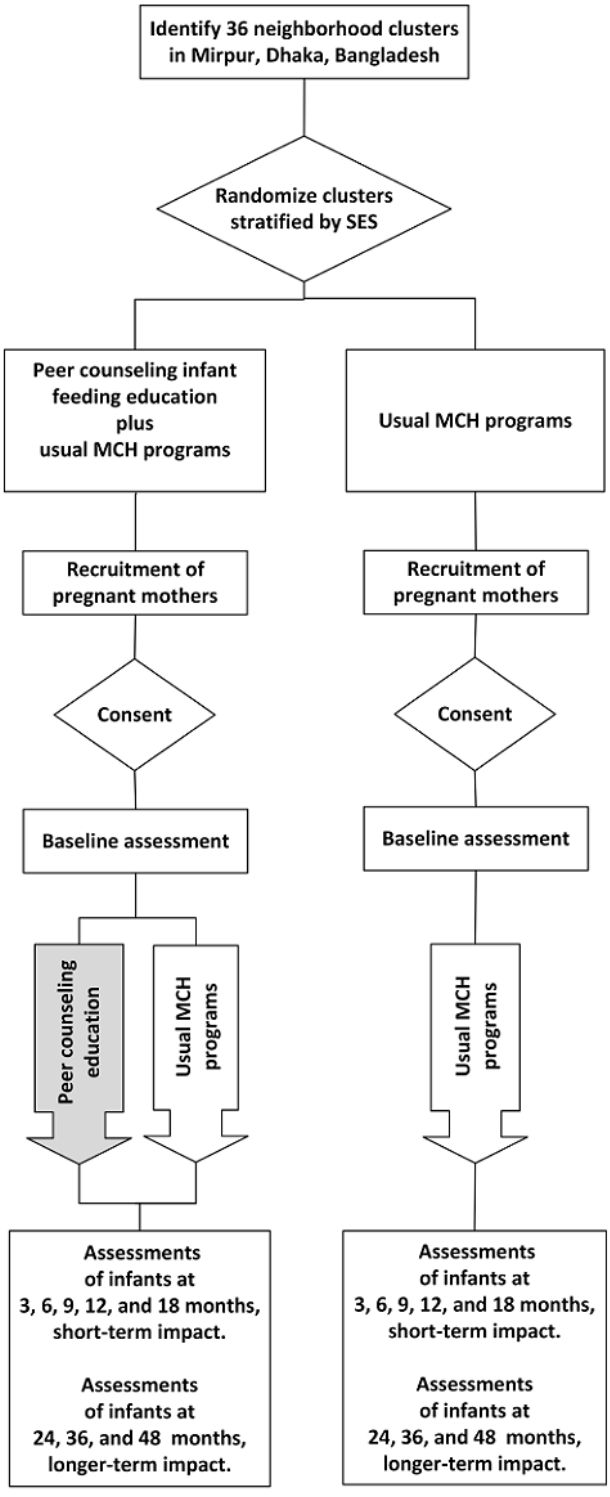
4. Mean cognitive, language, and motor composite scores as measured by the Ages and Stages Questionnaire and Bayley Scales of Infant and Toddler Development at 48 months of age will be higher in the peer counseling group than in the control group.

Methods

Study Design

The study is a community-based, cluster-randomized controlled trial with a superiority design and 2 parallel treatment arms with a 1:1 allocation ratio. It examines the impact of a peer-counseling infant-feeding education program starting in the third trimester of pregnancy to 1 year after delivery on child feeding practices, growth, and development (Figure 1). We followed the cohort of the mother-child dyads from recruitment until the children were 48 months of age.

Figure 1. The Shishu Pushti study design. MCH: mother and child health; SES: socioeconomic status.



Study Setting

We conducted the trial in Mirpur, an area of approximately 39 square kilometers located in the northwest of Dhaka City, Bangladesh. It has 16 wards (administrative regions), of which 4 wards were selected for the trial where there were no other major health or nutrition studies ongoing. Mirpur is a middle-to-lower socioeconomic area in Dhaka, but it includes very disadvantaged slum areas.

Identification of Clusters

The study site is a very densely populated and includes areas of slum housing where there are no established addresses and houses are very close to each other against each other along narrow paths. In this setting, there were no administrative or natural boundaries to define clusters. For the trial, we used satellite maps of the study areas in Mirpur to define clusters with buffer areas. We digitalized all structures, buildings, roads, and water bodies from satellite maps of the study area and gave

each structure an identification number. Our field census team visited all the structures and buildings in the study area and identified if it was a residence or was used for other purposes. After obtaining written informed consent, we conducted a brief household census and screened for pregnant women in all residential buildings. We used the census data to create a population database linked to the mapped structures. Using geographic information system mapping techniques, we constructed 36 clusters from the population maps to cover an average population of 5000 people with a surrounding 200-meter buffer zone between clusters. We classified each cluster as low socioeconomic status or not based on the census data. Figure 2 shows a map of the study site.

Figure 2. Map of the study site [32].

Assignment of Treatments

We randomly allocated the 36 clusters in an equal ratio to intervention or control groups but with stratification by socioeconomic status of the clusters. We generated the random allocation sequence using SAS software (SAS Institute).

Recruitment, Inclusion and Exclusion Criteria, and Consent of Mothers and Their Families

We visited the pregnant women identified in the census, and recruited eligible women in their third trimester of pregnancy into the trial. We updated the census data, including the

pregnancy screening, every 3 months to identify and recruit potentially eligible women once they reached their third trimester. We included pregnant women who were 16 to 40 years of age and who had no more than 3 living children. We excluded women who planned to migrate from the Mirpur area after delivery and women with medical records of heart disease, tuberculosis, gestational diabetes, or eclampsia in previous pregnancies, from the trial. In addition, we excluded mother-infant pairs where the child had congenital abnormalities, had a very low birth weight below 1.5 kg, or were admitted to a neonatal intensive care unit. We used the same approach to recruitment in both intervention and control clusters. Trained project staff obtained written informed consent from the eligible women and their husbands. Based on experience with similar projects in Bangladesh [33,34], we expected at least 95% of the mothers would consent to participate. We anticipated excluding up to 30% of the women mainly related to their desire to migrate back to their home village after the delivery [34].

Intervention Plan

We selected the trial intervention due to its feasibility, previous testing in urban populations in Dhaka [34], and likely future sustainability. We expect the proposed individual peer counseling education will have sufficient intensity to alter infant and young child feeding practices and improve young children's growth. After 1 year of preparation for the trial, we delivered the interventions to recruited pregnant women until their children reached 1 year of age.

This approach promoted appropriate infant and young child feeding through a program of home-based peer counseling by trained local women from the mothers' community. The peer counselors reached mothers who delivered at home and allowed the messages to reach other key family members who played a role in supporting breastfeeding and influenced the choice of foods for the infant. The main messages encouraged early initiation of breastfeeding, promoting EBF during the first 6 months of life, promoting appropriate timing of the introduction of complementary feeds, and ensuring an adequate frequency of feeds and diversity of foods used in their preparation.

Selection and Training of Peer Counselors

Women with personal breastfeeding experience and at least 6 years of schooling who resided in the same area and who were motivated to work to become peer counselors were selected. We trained the peer counselors using the joint WHO/UNICEF (United Nations International Children's Emergency Fund) breastfeeding counseling course adapted to the local language and culture and validated in a previous study [34]. They were trained for 40 hours (4 hours daily for 10 days). Counseling skills were taught mainly by demonstrations and role-play. The topics included listening to mothers, learning about their difficulties, assessing the position and attachment of infants during breastfeeding, building mother's confidence, giving support, and providing relevant information and practical help when required. During the course, the trainee counselors practiced antenatal and postpartum counseling at the field site with pregnant women, mothers with newborns, and infants aged 1-12 months. We trained counselors in how to use locally available foods for complementary feeding of infants and young children and how best to demonstrate these food preparation skills to mothers.

We anticipated that each peer counselor would support up to approximately 50-60 mothers and thus provide support to about 1000 women receiving the intervention. We recruited and trained 18 peer counselors (one in each cluster). Senior infant feeding counselors monitored the performance of the peer counselors at least 4 times during the study.

Counseling Schedules

We scheduled 13 visits by the peer counselors: 2 before delivery, 4 during the first month, 5 monthly visits from age 2 to 6 months, and 3 monthly visits at age 9 and 12 months. The counselors were free to make additional visits if the mother's circumstances required them. The counseling took place at home to include key family members (eg, mother-in-law and fathers) in the counseling sessions. The duration of each visit was from 20 to 40 minutes.

Antenatal Visits

During the 2 antenatal visits, peer counselors prepared and informed the mothers and other family members who supported the mothers at delivery about the importance of holding the infant within a few minutes of delivery and breastfeeding initiation within 1 hour of delivery. They discouraged prelacteal feeds and encouraged the mothers to eat more foods and rest during the third trimester. These meetings also covered problems with breastfeeding that the mothers might have encountered and provided strategies to deal with them.

Visits in the First Month of Life

The mothers were contacted 4 times by the peer counselors (within 48 hours of delivery, at 5-7 days, at 10-14 days, and at 24-28 days). During these visits, EBF was encouraged, and any barriers to EBF, such as sore nipples, problems with attachment and position of the baby during feeds, family pressure to introduce other foods, and mothers' doubts about the adequacy of their breastmilk, were resolved. If the counselor could not resolve these issues, the mothers were referred to the senior infant-feeding counselors.

Visits From 2 to 6 Months of Life

The mothers were contacted monthly by the peer counselors, who addressed any specific problems and continued to provide support for EBF, especially how to deal with family pressures, the introduction of other foods, and concerns about the adequacy of the infants' growth. From 5 months of age, specific messages covered the importance of complementary feeding and demonstrations and preparation of complementary foods from homemade, regular family food. Mothers were given measuring bowls (250 ml) and spoons to promote the age-specific frequency of complementary feeding. According to the UNICEF guidelines, mothers received hands-on training on the frequency and amount of complementary feeding [35]. For the average healthy breastfed infant, meals of complementary food are needed 2-3 times (half a bowl of 250 ml) per day at 6-8 months of age and 3-4 times per day at 9-11 months and 12-23 months

of age with additional nutritious snacks. Mothers were discouraged from using bottles for complementary feeding.

Visits From 6 to 12 Months of Life

The mothers were contacted twice at 3-month intervals by the peer counselors. They were encouraged to continue breastfeeding and supported to give an adequate frequency of complementary feeds and appropriate diversity of foods. There were further demonstrations on the preparation of complementary feeds as needed.

Management of Interventions

We recruited 3 breastfeeding counselors who trained the peer counselors under the supervision of 1 of the investigators (RH) and the research investigator (GA). The breastfeeding counselor provided technical support to the peer counselors and helped them resolve problems encountered during the implementation of the trial interventions by regular meetings with them in the field. The research officer supervised, monitored, and provided the necessary support for troubleshooting for breastfeeding complementary feeding. To facilitate the overall implementation process, we established an advisory committee consisting of local health officers, local government officials, representatives of mothers' groups from the community, representatives of the Bangladesh Breastfeeding Foundation, other relevant nongovernmental organizations, and project staff.

Evaluation Plan

We applied a range of quantitative data collection methods to assess the primary and secondary outcomes, including pretested structured questionnaires and anthropometric measurements. Figure 3 presents a timeline depicting the schedule of data collection.

Figure 3. Schedule of enrollment, interventions, and assessments. IYCF: Infant and Young Child Feeding.

	Study period														
	Cluster Allocation	Enrollment						Postallocation follow-up visits								Close out
Time point		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q12	Q15	Q17	Q21	Q21
Life cycle stage		*Third trimester*						*0-3 mo*	*4-6 mo*	*7-9 mo*	*10-12 mo*	*13-15 mo*	*16-18 mo*	*24 mo*	*36 mo*	*48 mo*
Allocation & enrollment																
Allocation	X															
Eligibility screening		→	→	→	→	→	→									
Informed consent		→	→	→	→	→	→									
Other procedures		→	→	→	→	→	→									
Intervention																
Peer counselling on IYCF			→	→	→	→	→	→	→	→	→					
Assessments																
Baseline variables																
Maternal characteristics		X	X	X	X	X	X									
Socioeconomic status		X	X	X	X	X	X									
Food security		X	X	X	X	X	X			X						
Maternal depression		X	X	X	X	X	X	X		X						
Maternal anthropometry		X	X	X	X	X	X									
Maternal reproductive history		X	X	X	X	X	X									
Feeding of previous child		X	X	X	X	X	X									
List of outcome variables																
Child feeding history								X	X	X	X	X	X	X	X	
Child morbidity								X	X	X	X	X	X	X	X	
24-hour dietary recall										X			X			
Child anthropometry								X	X	X	X	X	X	X	X	
Responsive feeding										X	X					
Family care indicator										X			X			
Ages and Stages Questionnaire											X		X			
Bayley Scale-III													X	X	X	
Movement Assessment (MABC)																X
Wechsler Intelligence Scale (WPPSI)																X
Strengths & Difficulties Questionnaire																X
Hand washing											X					
Immunization											X					
Social network								X	X							
List of other variables																
Peer counselling monitoring data								X	X	X	X	X	X			

Primary Outcomes to be Measured

The primary outcome measured was the differences in the percentage of stunted infants (length-for-age <–2 *z* score) of children at 6, 12, 15, and 18 months. We also measured changes in mean length-for-age *z* scores from birth until 48 months.

Secondary Outcomes to be Measured

We measured changes in the percentage of women EBF (breast milk and no other foods or milk-based liquids) their infants from 1 to 6 months. We also measured changes in the mean duration of any breastfeeding. We calculated the changes in the percentage of children at 6 and 9 months of age who received solid, semisolid, or soft foods; and the percentage of children consuming foods from 4 or more food groups at 9, 12, 15, and 18 months. We assessed bottle feeding (any liquid or semisolid food from a bottle with a nipple or teat) in infants at 7, 9, and 12 months. We measured the changes in mean cognitive function scores with the Ages and Stages Questionnaire (9 and 18 months) and Bayley tests (24 and 36 months).

Measurements

Anthropometry

Trained research assistants collected the anthropometric measurements (weight and height) using established methods [36] and recorded these measurements on both the research instruments and an infant growth chart for the mother to keep.

We standardized these measurements before and during the data collection. Anthropometry was collected soon after birth and every month up to 12 months, at 3-month intervals up to 18 months (15 and 18 months), and then at 24, 36, and 48 months. We used the 2006 WHO growth standards to construct anthropometric indices. We calculated the standard WHO-recommended indicators to assess stunting (height-for-age <–2 *z* score), wasting (weight-for-height <–2 *z* score), and being underweight (weight-for-age <–2 *z* score).

Infant Feeding Practices

We collected infant feeding data every month from birth to 6 months, and then at 3-month intervals between 6 and 18 months. We applied the standard Bangladesh Demographic Health Survey (DHS) questions about infant-feeding practices [37] and monitored these patterns at the 3 monthly data collection periods from birth until 18 months of age. These include questions about current breastfeeding status, current use of other liquids and solid foods, the timing of introduction of other liquids or solid foods, use of bottles for feeding, and information about who was providing advice about infant feeding among family and friends.

A senior research assistant monitored about 10% of the interviewer's scheduled visits. The supervisors checked questionnaires daily, and if the information was incomplete or not clear, they returned to the home on the next day to complete the data form. Senior research assistants verified the mother's reports of infant feeding practices through a 4-hour observation period in an unscheduled visit.

Dietary Intake

Trained interviewers collected 24-hour dietary recalls using standard methods starting at 6 months of age until 18 months. They recorded all the foods consumed 24 hours before the interview and measured the portion sizes in local utensils. They also recorded the recipes used to prepare foods, including the amounts of raw food used and the preparation methods. Research assistants analyzed and presented the nutrient intakes and food groups consumed. In a subsample of 10% of respondents, we took duplicate 24-hour recalls to assess within-person variability and to allow adjustment of the prevalence of low intake nutrients.

Birth Weight and Gestational Age

Trained field research assistants measured the birth weight of the neonate within 72 hours of birth. In the intervention clusters, the peer counselors provided delivery information to the research team in timely fashion. In the case of control clusters, we recruited volunteers responsible for the timely reporting of the delivery information.

Child Morbidity

The interviewers obtained illness histories, such as diarrhea, dysentery (blood and mucus), fever and cough, and ear infection (purulent discharge), every month until 12 months, and at 3-month intervals until 18 months using the 2-weeks' recall method. The questions asked were based on the standard DHS infant morbidity recall questions but were expanded to include questions about ear discharge.

Diarrhea was defined as an episode of the passage of 3 or more loose or watery stools within 24 hours. The presence of blood in the stool was defined as invasive diarrhea. When a single episode of diarrhea lasted for more than 2 weeks, it was be classified as persistent diarrhea. Acute respiratory illnesses were defined as an episode of cough with reported fast and rapid breathing or difficulty breathing with or without fever.

Child Development

We collected a variety of child development measures at 9, 18, 24, 36, and 48 months. The Ages and Stages Questionnaire [38] was used to collect data on problem-solving, socioemotional, communication, and fine and gross motor functions at 9 and 18 months of age. The Bayley Scales of Infant and Toddler development-III (Bayley-III) [39] was used to assess children's cognitive, language, and motor development at 24 and 36 months of age. The test is not standardized in Bangladesh but has been culturally adapted and used in several studies on Bangladeshi children [40,41]. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) [42] will be used on a subsample of children at 48 months to assess their full scale, verbal, and performance IQs. The children's behavior during the Bayley test was rated using 5 behavior ratings developed by Wolke et al [43], each of which has ratings from 1 to 9, with 1 being the poorest behavior and 9 being the best. We interviewed mothers on child behaviors using the Strengths and Difficulties Questionnaire [44] at 48 months after the WPPSI test.

The Movement Assessment Battery for Children [45] will be administered along with WPPSI at 48 months of age on the same subsample.

Information on quality of home stimulation was assessed by a family care indicators questionnaire [46] at 9, 18, and 24 months. An early childhood version of the home observation for measurement of the environment [47] was administered at 24 and 36 months to collect information on approaches that the family employs, such as availability of toys, books, musical instruments, play activities with the child, and other learning opportunities at home.

Maternal Depression

We assumed that the mother's mental well-being or depression condition could affect the child's nutrition and caring practices, which can mediate child development. We collected information regarding the mothers' mental status and depression conditions in the third trimester of pregnancy and at 1 and 10 months postpartum from all participants using the Center for Epidemiological Studies-Depression questionnaire [48].

Maternal IQ was measured using the Raven Coloured Progressive Matrices [49].

Socioeconomic Status

Information on religion, pregnant women's and her husband's levels of education, their occupations, number of family members, ownership of the number of dwelling rooms, household construction materials, toilet facilities, drinking water sources, household assets, and land ownership were collected as the key indicators of socioeconomic status.

Household Food Security

As household food security plays a vital role in complementary feeding practices and child nutrition, we assessed the family's food security from all participants (during enrolment and at 10 months).

Information on Social Network

Family members, friends, neighbors, peers, and people around caregivers play important roles in feeding and caring for young infants. Therefore, we collected information on the social networks of caregivers at different times of follow-up from 100 families in 4 clusters.

Schedule of Data Collection

We carried out a pilot study in the first year of the trial in a single cluster to test the recruitment methods, implementation of the intervention, the evaluation of instruments, and field methods before commencing the trial.

For the assessment of trial outcomes, we collected basic sociodemographic information about the family and maternal characteristics in a baseline survey at enrolment. We recorded the details of the birth and pregnancy shortly after delivery. We assessed the trial outcomes by measurements at monthly intervals from birth until 12 months, at 3-month intervals until 18 months, and annually until 48 months. These included anthropometric measurements, the recording of dietary patterns, dietary intake, and morbidity. The schedule of data collection is given in Figure 3.

Process Evaluation

We conducted a mixed methods process evaluation within the Mirpur Shishu Pushti Trial to answer the primary question of how and why or why no impacts were achieved [50,51]. The specific aims included the assessment of fidelity, dose, reach, and intensity of the peer counseling intervention; the response of the beneficiaries to the intervention; experience of the peer counselors of counseling the women; and the barriers and challenges encountered by the project staff to implement the trial.

We further aimed to synchronize the process evaluation data collection with the timeline of program implementation. Data collection has been planned to occur in 2 stages: (1) ongoing throughout the intervention delivery and (2) at a time point near the end of the intervention. This approach will enable us to use the process evaluation data for both providing feedback to keep the program on track (formative use) and to interpret and explain intervention outcomes (summative use) [52].

We collected the data for the process evaluation through regular project monitoring on the participation of mothers in peer counseling sessions, surveys of self-reported adherence to counseling guidelines by the peer counselors, unscheduled direct observations of the peer counseling at-home visits, in-depth interviews of mothers, semistructured interviews with the project managers (GA) and the project field staff, and focus group discussion with peer counselors. We collected the data in a purposively selected sample of intervention clusters to cover the variations within the households.

Sampling Design and Sample Size

The sample size required was 1950 mother-infant dyads (975 in each treatment group) from 50 clusters with 39 mother-infant dyads per community cluster recruited over 3 months. The sample size calculation was estimated with the following assumptions: Each community cluster had an average population of 70,000 and an expected crude birth rate of 4.3 per 1000 total population over 6 months (based on the crude birth rate for urban Bangladesh of 25.8/1000 population over 36 months from the 2004 Bangladesh DHS]) thus giving an average expected number of births of 150 over 3 months per cluster. Previous research [34] indicated that appropriately 33% of pregnant women returned to their home village following delivery, leaving an expected number of eligible births of 200 over 6 months per cluster. We anticipated having 39 mother-infant dyads per cluster, assuming 95% participation but 22% loss to follow-up based on earlier research [34] from the approximately 200 mother-infant dyads available in each cluster over 6 months. We also assumed 90% power and a 5% two-sided α and intracluster correlation coefficient of 0.015 (based on analyses of the child anthropometric measurements from the 2004 Bangladesh DHS survey data for urban child populations [53]). We also expect the difference in the prevalence of stunting between the treatment groups of 10% (35% in control to 25% in the intervention group), which is similar to the change reported in an earlier education intervention for young child feeding in Peru [54].

Statistical Analyses

Data analysis will be by intention to treat. Analyses will be conducted at the mother-infant dyad level but will be adjusted for the community-cluster randomization [55]. The primary analyses will compare the prevalence of stunting (length-for-age < -2 *z* score) in children at 18 months of age using Pearson chi-square tests and 95% CIs for the group difference, with adjustments for clustering. We will report the results for 2-sided 5% tests.

Secondary analyses will examine each outcome variable (length-for-age, percentage EBF, duration of breastfeeding, percentage doing bottle feeding, percentage giving complementary feeds, percentage receiving diverse food groups, and mean nutrient intakes), taking account of the repeated measurements within children by using separate mixed models. We will use linear mixed models for the continuous outcomes (eg, height for age *z* score, duration of breastfeeding, Ages and Stages Questionnaire, Bayley, and Wechsler scales) and generalized linear mixed models for noncontinuous outcomes (eg, logistic mixed models for binary outcomes, such as percentage stunted or percentage exclusively breastfeeding). Models will include the treatment group as a fixed effect and infants as a random effect to account for the repeated measurements, and community cluster as a random effect to account for the cluster effect. The models will evaluate the impact of the interventions over time by testing for an interaction between time and the intervention group.

We will conduct analyses to identify the baseline characteristics of the mother-infant dyads who may benefit most from the intervention. Model assumptions will be checked, and

appropriate adjustments to the analysis will be made where necessary. We will use Stata software (Stata Corp) for all analyses, with the "mixed" command to fit linear mixed models, the "melogit" command to fit mixed-effects models for binary outcomes, and the "mepoisson" command to fit mixed-effects models for event count data.

Research Ethics

We obtained ethical approval for the study from the research ethics committee of icddr,b (#PR-10001) and The University of Sydney (#12900). Trained field staff carefully explained the background and objectives of the study to the women and gave a written information sheet to all women contacted. We obtained written informed consent from those women who agreed to participate in the study. We will maintain the privacy, anonymity, and confidentiality of the information provided by respondents during all phases of the trial. We will store all information in an encrypted database with the participant's study identifier instead of with personal identifiers. Only the investigators and an authorized data management team will have access to collected data.

Data Access

All data collected will be accessible by the study investigators, who will have the right to analyze and publish data. We will make the relevant anonymized individual-level data available upon reasonable request.

Results

Using satellite maps, we digitized all structures in the study areas, and from a brief census of all mapped residences, we identified a population of 65,535 people. We created a population database linked to the map structure and applied this information to define 36 clusters with 500-meter buffer zones. We randomly allocated the 36 clusters in an equal ratio to intervention or control groups but stratified by the socioeconomic status of the clusters. We screened for pregnant women in all residences and identified 5377 eligible pregnant women.

From July 2011 to May 2013, we carried out a baseline survey. In the third trimester, we examined 2050 pregnant women, including 1056 women in the intervention group and 994 women in the control group. The women participating in the trial had 1883 birth outcomes, with 993 in the intervention group and 890 in the control group. The study followed up the women who delivered the infants until 18 months of life. In December 2012, we began assessing the original cohort and completed 18 months of study follow-up in October 2014 for participants. Among them, 692 in the intervention group and 551 in the control group remained in the study until 18 months follow-up, with 301dropouts in the intervention and 339 dropouts in the control group. We continued evaluating the cohort until the children were 36 months of age, with child growth and development outcomes measured at 24 and 36 months. The long-term follow-up began in January 2015 and ended in February 2017. We have now completed the data cleaning and processing and have started analyses of the data.

Discussion

The 2008 Lancet Maternal and Child Undernutrition series called for high quality "how-to" research to become a priority [9,56]. It is now widely accepted that the lack of EBF and inappropriate complementary feeding are critical factors contributing to undernutrition, morbidity, and mortality in children. However, interventions to improve these critical factors have had mixed success. Ascertaining what works and what does not work is important for continuing progress on alleviating undernutrition in children. We describe the protocol and processes for implementing a randomized controlled trial in urban Dhaka, Bangladesh. The trial aims to test the efficacy of peer counseling to improve breastfeeding and complementary feeding practices and reduce undernutrition in children under 4 years of age. Breastfeeding is almost universal in Bangladesh, and the rates of EBF have increased in recent years; however, the prevalence of appropriate complementary feeding remains low. The latest available representative data (from 2017 to 2018) show that 65% of children aged under 6 months are exclusively breastfed, and only 34% of children aged 6 to 23 months are fed appropriately according to recommended infant and young child feeding practices [5,57]. Previous studies conducted in urban areas of Bangladesh using individual peer counseling have shown significant increases in EBF rates [34]. Our research will build on this work and evaluate extended peer counseling supporting both breastfeeding and complementary feeding.

There are several limitations and challenges to the implementation of our study. One challenge will be recruiting peer counselors from a highly mobile urban mobile population and working effectively in urban slum communities. Another challenge will be training peer counselors drawn from the same disadvantaged neighborhoods to provide support to mothers and information about appropriate breastfeeding and complementary feeding. Recruiting and retaining working women with many competing demands will also be a major challenge, potentially contributing to loss to follow-up in the trial.

There is an urgent need to develop and disseminate effective interventions to improve complementary feeding, and this project will help resolve this information gap. There have been no interventions that include peer counseling to improve infant feeding practices implemented over the critical window of the first 1000 days and beyond to 36 months of life. This study will help fill the evidence gap regarding the long-term impact of peer counseling on improving infant feeding, preventing childhood undernutrition, and enhancing child cognitive development. The intensity and duration of this intervention are likely to result in a reduced rate of undernutrition. They can be adapted for various contexts and used by public health planners in other developing countries. The publications expected to arise from this research will contribute substantially to the evidence base. They will help with the development of public health nutrition policies for children in South Asia.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the National Health and Medical Research Council of Australia, and International Centre for Diarrhoeal Disease Research, Bangladesh.
[PDF File (Adobe PDF File), 22 KB - resprot_v11i2e31475_app1.pdf]

References

1. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018 Nov 10:1923-1994. [doi: 10.1016/S0140-6736(18)32225-6]
2. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet 2013 Aug;382(9890):427-451. [doi: 10.1016/s0140-6736(13)60937-x]
3. Levels and Trend in Child Nutrition. UNICEF/WHO/The World Bank: joint child malnutrition estimates – 2018 edition. Unicef Data.: UNICEF/WHO/The World Bank Group; 2018. URL: https://data.unicef.org/resources/levels-and-trends-in-child-malnutrition-2018/ [accessed 2021-10-01]
4. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. The Lancet 2012 Jun;379(9832):2151-2161. [doi: 10.1016/s0140-6736(12)60560-1]
5. National Institute of Population Research and Training (NIPORT). Bangladesh Demographic and Health Survey 2014. Dhaka, Bangladesh & Rockville, Maryland, USA: National Institute of Population Research and Training (NIPORT); 2016.
6. Victora CG, Christian P, Vidaletti LP, Gatica-Domínguez G, Menon P, Black RE. Revisiting maternal and child undernutrition in low-income and middle-income countries: variable progress towards an unfinished agenda. The Lancet 2021 Apr;397(10282):1388-1399. [doi: 10.1016/s0140-6736(21)00394-9]
7. World Health Organization/ UNICEF. Global Strategy on Infant and Young Child Feeding. Geneva: World Health Organization; 2003.
8. Michaelsen KF, Grummer-Strawn L, Bégin F. Emerging issues in complementary feeding: Global aspects. Matern Child Nutr 2017 Oct 15;13:e12444. [doi: 10.1111/mcn.12444]
9. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. The Lancet 2008 Jan;371(9608):243-260. [doi: 10.1016/s0140-6736(07)61690-0]
10. Svefors P, Rahman A, Ekström EC, Khan AI, Lindström E, Persson, et al. Stunted at 10 years. Linear growth trajectories and stunting from birth to pre-adolescence in a rural Bangladeshi cohort. PLoS One 2016;11(3):e0149700 [FREE Full text] [doi: 10.1371/journal.pone.0149700] [Medline: 26934484]
11. Dewey KG, Brown KH. Update on technical issues concerning complementary feeding of young children in developing countries and implications for intervention programs. Food Nutr Bull 2003 Mar;24(1):5-28. [doi: 10.1177/156482650302400102] [Medline: 12664525]
12. Engle PL, Black MM, Behrman JR, Cabral de Mello M, Gertler PJ, Kapiriri L, et al. Strategies to avoid the loss of developmental potential in more than 200 million children in the developing world. The Lancet 2007 Jan;369(9557):229-242. [doi: 10.1016/s0140-6736(07)60112-3]
13. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. The Lancet 2007 Jan;369(9555):60-70. [doi: 10.1016/s0140-6736(07)60032-4]
14. McCoy DC, Peet ED, Ezzati M, Danaei G, Black MM, Sudfeld CR, et al. Early childhood developmental status in low-and middle-income countries: national, regional, and global prevalence estimates using predictive modeling. PLoS Med 2016 Jun 7;13(6):e1002034. [doi: 10.1371/journal.pmed.1002034]

15. Tofail F, Hamadani J, Mehrin F, Ridout D, Huda S, Grantham-McGregor S. Psychosocial stimulation benefits development in nonanemic children but not in anemic, iron-deficient children. J Nutr 2013 Jun;143(6):885-893. [doi: 10.3945/jn.112.160473] [Medline: 23616511]
16. Hamadani JD, Mehrin SF, Tofail F, Hasan MI, Huda SN, Baker-Henningham H, et al. Integrating an early childhood development programme into Bangladeshi primary health-care services: an open-label, cluster-randomised controlled trial. The Lancet Global Health 2019 Mar;7(3):e366-e375. [doi: 10.1016/s2214-109x(18)30535-7]
17. Hamadani J, Huda S, Khatun F, Grantham-McGregor S. Psychosocial stimulation improves the development of undernourished children in rural Bangladesh. J Nutr 2006 Oct;136(10):2645-2652. [doi: 10.1093/jn/136.10.2645] [Medline: 16988140]
18. Nahar B, Hamadani JD, Ahmed T, Tofail F, Rahman A, Huda SN, et al. Effects of psychosocial stimulation on growth and development of severely malnourished children in a nutrition unit in Bangladesh. Eur J Clin Nutr 2009 Jun;63(6):725-731. [doi: 10.1038/ejcn.2008.44] [Medline: 18772893]
19. Nahar B, Hossain MI, Hamadani JD, Ahmed T, Huda SN, Grantham-McGregor SM, et al. Effects of a community-based approach of food and psychosocial stimulation on growth and development of severely malnourished children in Bangladesh: a randomised trial. Eur J Clin Nutr 2012 Jun;66(6):701-709. [doi: 10.1038/ejcn.2012.13] [Medline: 22353925]
20. Black M, Baqui A, Zaman K, Ake Persson L, El Arifeen S, Le K, et al. Iron and zinc supplementation promote motor development and exploratory behavior among Bangladeshi infants. Am J Clin Nutr 2004 Oct;80(4):903-910. [doi: 10.1093/ajcn/80.4.903] [Medline: 15447897]
21. Hamadani JD, Baker-Henningham H, Tofail F, Mehrin F, Huda SN, Grantham-McGregor SM. Validity and reliability of mothers' reports of language development in 1-year-old children in a large-scale survey in Bangladesh. Food Nutr Bull 2010 Jun 15;31(2_suppl2):S198-S206. [doi: 10.1177/15648265100312s212]
22. Hamadani JD, Fuchs GJ, Osendarp SJ, Huda SN, Grantham-McGregor SM. Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study. The Lancet 2002 Jul;360(9329):290-294. [doi: 10.1016/s0140-6736(02)09551-x]
23. Hamadani J, Fuchs G, Osendarp S, Khatun F, Huda S, Grantham-McGregor S. Randomized controlled trial of the effect of zinc supplementation on the mental development of Bangladeshi infants. Am J Clin Nutr 2001 Sep;74(3):381-386. [doi: 10.1093/ajcn/74.3.381] [Medline: 11522564]
24. Hamadani JD, Tofail F, Cole T, Grantham-McGregor S. The relation between age of attainment of motor milestones and future cognitive and motor development in Bangladeshi children. Matern Child Nutr 2012 Nov 20;9:89-104. [doi: 10.1111/mcn.12020]
25. Tofail F, Hamadani JD, Ahmed AZT, Mehrin F, Hakim M, Huda SN. The mental development and behavior of low-birth-weight Bangladeshi infants from an urban low-income community. Eur J Clin Nutr 2012 Feb;66(2):237-243. [doi: 10.1038/ejcn.2011.165] [Medline: 21952697]
26. Haroon S, Das JK, Salam RA, Imdad A, Bhutta ZA. Breastfeeding promotion interventions and breastfeeding practices: a systematic review. BMC Public Health 2013 Sep 17;13(S3):1471-2458. [doi: 10.1186/1471-2458-13-s3-s20]
27. Chapman DJ, Morel K, Anderson AK, Damio G, Pérez-Escamilla R. Breastfeeding peer counseling: from efficacy through scale-up. J Hum Lact 2010 Aug;26(3):314-326 [FREE Full text] [doi: 10.1177/0890334410369481] [Medline: 20715336]
28. Haider R, Kabir I, Huttly SRA, Ashworth A. Training peer counselors to promote and support exclusive breastfeeding in Bangladesh. J Hum Lact 2002 Feb;18(1):7-12. [doi: 10.1177/089033440201800102] [Medline: 11845742]
29. Shakya P, Kunieda MK, Koyama M, Rai SS, Miyaguchi M, Dhakal S, et al. Effectiveness of community-based peer support for mothers to improve their breastfeeding practices: A systematic review and meta-analysis. PLoS One 2017;12(5):e0177434 [FREE Full text] [doi: 10.1371/journal.pone.0177434] [Medline: 28510603]
30. Kushwaha KP, Sankar J, Sankar MJ, Gupta A, Dadhich JP, Gupta YP, et al. Effect of peer counselling by mother support groups on infant and young child feeding practices: the Lalitpur experience. PLoS ONE 2014;9(11):e109181 [FREE Full text] [doi: 10.1371/journal.pone.0109181] [Medline: 25369452]
31. Chan A, Tetzlaff J, Altman D, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Mar 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
32. Chowdhury S, Islam S. Banglapedia: National Encyclopedia of Bangladesh. In: Bengali and English combined CD edition Copyright by Asiatic Society of Bangladesh. Dhaka: Asiatic Society of Bangladesh; 2006.
33. Arifeen S, Black RE, Antelman G, Baqui A, Caulfield L, Becker S. Exclusive breastfeeding reduces acute respiratory infection and diarrhea deaths among infants in Dhaka slums. Pediatrics 2001 Oct;108(4):E67. [doi: 10.1542/peds.108.4.e67] [Medline: 11581475]
34. Haider R, Ashworth A, Kabir I, Huttly SR. Effect of community-based peer counsellors on exclusive breastfeeding practices in Dhaka, Bangladesh: a randomised controlled trial. The Lancet 2000 Nov;356(9242):1643-1647. [doi: 10.1016/s0140-6736(00)03159-7]
35. Kabir AKMI, Roy S, Khatoon S. Development of a complementary feeding manual for Bangladesh. In: A Study Conducted by the Bangladesh Breastfeeding Foundation. Dhaka: Bangladesh Breastfeeding Foundation; 2013.

36. Lohman T, Roche A, Martorell R. Anthropometric standardization reference manual. In: Human Kinetics Books. Champaign: Human kinetics books; 1988.
37. NIPORT. Bangladesh Demographic and Health Survey. Dhaka, Bangladesh & Rockville, Maryland, USA: National Institute of Population Research and Training (NIPORT); 2005.
38. Squires JT, Twombly E, Bricker D, Potter L. ASQ-3 User's Guide. Baltimore, MD: Brookes Publishing Co., Inc; 2009.
39. Bayley N. Bayley Scales of Infant and Toddler Development. In: 3rd Edition (BAYLEY-III). San Antonio, TX: Pearson; 2005.
40. Jiang NM, Tofail F, Moonah SN, Scharf RJ, Taniuchi M, Ma JZ, et al. Febrile illness and pro-inflammatory cytokines are associated with lower neurodevelopmental scores in Bangladeshi infants living in poverty. BMC Pediatr 2014 Feb 18;14:50 [FREE Full text] [doi: 10.1186/1471-2431-14-50] [Medline: 24548288]
41. Yesmin S, Rahman N, Khatun R, Begum T, Tahmid T, Afrin S. Community based psychosocial intervention in reducing maternal depression and improving infant's development in bangladesh: a randomized control trial. IOSR Journal of Nursing and Health Science 2016;5(3):11-20. [doi: 10.9790/1959]
42. Wechsler D. Wechsler Preschoolprimary Scale of Intelligence. Third Edition. San Antonio, TX: Harcourt Assessment, Inc; 2002.
43. Wolke D, Skuse D, Mathisen B. Behavioral style in failure-to-thrive infants: a preliminary communication. J Pediatr Psychol 1990 Apr;15(2):237-254. [doi: 10.1093/jpepsy/15.2.237] [Medline: 2374078]
44. Goodman R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 1997 Jul;38(5):581-586. [doi: 10.1111/j.1469-7610.1997.tb01545.x] [Medline: 9255702]
45. Henderson S, Sugden D. Movement assessment battery for children. London, The Psychological Corporation Ltd 1992:62. [doi: 10.1037/t55281-000]
46. Hamadani JD, Tofail F, Hilaly A, Huda SN, Engle P, Grantham-McGregor SM. Use of family care indicators and their relationship with child development in Bangladesh. J Health Popul Nutr 2010 Feb;28(1):23-33 [FREE Full text] [doi: 10.3329/jhpn.v28i1.4520] [Medline: 20214083]
47. Caldwell BM. Descriptive evaluations of child development and of developmental settings. Pediatrics 1967 Jul;40(1):46-54. [Medline: 6028898]
48. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 2016 Jul 26;1(3):385-401. [doi: 10.1177/014662167700100306]
49. Raven J. Raven's Progressive Matrices and Vocabulary Scales. Oxford, UK: Oxford Psychologists Press; 1998.
50. Menon P, Rawat R, Ruel M. Bringing Rigor to Evaluations of Large-Scale Programs to Improve Infant and Young Child Feeding and Nutrition: The Evaluation Designs for the Alive & Thrive Initiative. Food Nutr Bull 2013 Sep 04;34(3_suppl2):S195-S211. [doi: 10.1177/15648265130343s206]
51. Rawat R, Nguyen PH, Ali D, Saha K, Alayon S, Kim SS, et al. Learning How Programs Achieve their Impact: Embedding Theory-Driven Process Evaluation and Other Program Learning Mechanisms in Alive & Thrive. Food Nutr Bull 2013 Sep 04;34(3_suppl2):S212-S225. [doi: 10.1177/15648265130343s207]
52. Saunders RP, Evans MH, Joshi P. Developing a process-evaluation plan for assessing health promotion program implementation: a how-to guide. Health Promot Pract 2005 Apr;6(2):134-147. [doi: 10.1177/1524839904273387] [Medline: 15855283]
53. National Institute of Population Research and Training Mitra and Associates, ORC Macro. Bangladesh Demographic and Health Survey 2004. Dhaka, Bangladesh & Calverton, MD, USA: NIPORT; 2005.
54. Penny ME, Creed-Kanashiro HM, Robert RC, Narro MR, Caulfield LE, Black RE. Effectiveness of an educational intervention delivered through the health services to improve nutrition in young children: a cluster-randomised controlled trial. Lancet 2005;365(9474):1863-1872. [doi: 10.1016/S0140-6736(05)66426-4] [Medline: 15924983]
55. Murray D. Design and Analysis of Group-Randomized Trials. New York: Oxford University Press, USA; 1998.
56. Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, MaternalChild Undernutrition Study Group. What works? Interventions for maternal and child undernutrition and survival. Lancet 2008 Feb 02;371(9610):417-440. [doi: 10.1016/S0140-6736(07)61693-6] [Medline: 18206226]
57. National Institute of Population Research and Training (NIPORT). Bangladesh Demographic and Health Survey 2017-18. Dhaka, Bangladesh, & Rockville, MD, USA: NIPORT and ICF; 2019.

Abbreviations

DHS: Demographic Health Survey
EBF: exclusive breastfeeding
icddr,b: International Centre for Diarrhoeal Disease Research, Bangladesh
NHMRC: National Health and Medical Research Council
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial
UNICEF: The United Nations Children's Emergency Fund
WHO: World Health Organization

WPPSI: Wechsler Preschool and Primary Scale of Intelligence

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Protocol

Integrating and Disseminating Pre-Exposure Prophylaxis (PrEP) Screening and Dispensing for Black Men Who Have Sex With Men in Atlanta, Georgia: Protocol for Community Pharmacies

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Abstract

Background: Black men who have sex with men (BMSM) suffer from alarmingly high rates of HIV in the United States. Pre-exposure prophylaxis (PrEP) can reduce the risk of HIV infection by 99% among men who have sex with men, yet profound racial disparities in the uptake of PrEP persist. Low PrEP uptake in BMSM is driven by poor access to PrEP, including inconvenient locations of PrEP-prescribing physicians, distrust of physicians, and stigma, which limit communication about PrEP and its side effects. Previous work indicates that offering HIV prevention services in pharmacies located in low-income, underserved neighborhoods is feasible and can reduce stigma because pharmacies offer a host of less stigmatized health services (eg, vaccinations). We present a protocol for a pharmacy PrEP model that seeks to address challenges and barriers to pharmacy-based PrEP specifically for BMSM.

Objective: We aim to develop a sustainable pharmacy PrEP delivery model for BMSM that can be implemented to increase PrEP access in low-income, underserved neighborhoods.

Methods: This study design is a pilot intervention to test a pharmacy PrEP delivery model among pharmacy staff and BMSM. We will examine the PrEP delivery model's feasibility, acceptability, and safety and gather early evidence of its impact and cost with respect to PrEP uptake. A mixed-methods approach will be performed, including three study phases: (1) a completed formative phase with qualitative interviews from key stakeholders; (2) a completed transitional pilot phase to assess customer eligibility and willingness to receive PrEP in pharmacies during COVID-19; and (3) a planned pilot intervention phase which will test the delivery model in 2 Atlanta pharmacies in low-income, underserved neighborhoods.

Results: Data from the formative phase showed strong support of pharmacy-based PrEP delivery among BMSM, pharmacists, and pharmacy staff. Important factors were identified to facilitate the implementation of PrEP screening and dissemination in pharmacies. During the transitional pilot phase, we identified 81 individuals who would have been eligible for the pilot phase.

Conclusions: Pharmacies have proven to be a feasible source for offering PrEP for White men who have sex with men but have failed to reach the most at-risk, vulnerable population (ie, BMSM). Increasing PrEP access and uptake will reduce HIV incidence

and racial inequities in HIV. Translational studies are required to build further evidence and scale pharmacy-based PrEP services specifically for populations that are disconnected from HIV prevention resources.

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KEYWORDS

PrEP; MSM; HIV; prevention; pharmacy; implementation; pre-exposure prophylaxis; men who have sex with men; protocol; integration; dissemination; prophylaxis; screening; race; demographic; sex; sexuality; development; access

Introduction

Black men who have sex with men (BMSM) bear the highest burden of HIV in the US. Between 2015 and 2019, HIV diagnoses decreased by 18% for White men who have sex with men (WMSM) but decreased only by 5% for BMSM [1,2]. In Georgia—where the proposed study will take place—Black individuals make up less than 40% of the population but represent 71% of new HIV diagnoses [3]. Pre-exposure prophylaxis (PrEP) is the single most effective HIV prevention strategy, yet it is underutilized among BMSM. When taken every day, PrEP reduces the risk of HIV infection by approximately 99% among MSM, yet profound racial disparities in the uptake of PrEP persist [4-6]. Studies estimate that 48-70% of BMSM are willing to use PrEP [7,8]. Yet, uptake among Black individuals is only about 10% [9]. Lower insurance rates among Black compared to White individuals [10] may be a barrier to PrEP uptake. But, evidence of comparable insurance rates among BMSM and WMSM [11], federal legislation mandating PrEP coverage by insurance companies, and supplementary PrEP prescription payment programs do not completely explain significant inequities in PrEP uptake [12]. Indeed, limited access to PrEP, including inconvenient locations of PrEP-prescribing physicians [8,13-17], distrust of physicians, and stigma, which limit communication about PrEP and its side effects [13,17], are noted as critical barriers to PrEP that must be improved to reduce HIV [7,8].

There is a strong scientific premise for increasing PrEP delivery in pharmacies to improve PrEP uptake among BMSM. About 95% of Americans live within 5 miles of a pharmacy; pharmacies have flexible hours, and pharmacists have high credibility with community members [18]. Studies have shown pharmacies can engage with high-risk populations to reduce HIV risk behaviors [19-22] and provide primary prevention services, including immunizations [23], blood pressure screenings [24], and HIV testing [25-28]. PrEP has also been sustainably offered in some pharmacies. In one Seattle pharmacy, almost 100% of mostly WMSM patients initiated PrEP, and 75% followed up for continued PrEP [5]. Following this, 188 Walgreens across the US have offered PrEP through their existing in-pharmacy clinics [29,30]. Existing pharmacy PrEP models, however, have not been tailored for BMSM and are critically needed to reduce HIV transmission and ultimately end the HIV epidemic [31]. Prior work indicates that offering HIV prevention services in pharmacies located in low-income, underserved neighborhoods is feasible [25] and can reduce stigma because pharmacies offer a host of less stigmatized health services (eg, vaccinations) [29]. Further, both MSM and pharmacists have expressed strong support for PrEP screening and dispensing via pharmacies, given their convenience and accessibility [32]. Thus, pharmacy-based HIV prevention services could help overcome stigma and access barriers such as travel.

This protocol describes the development of a culturally appropriate pharmacy PrEP delivery model for BMSM who live in low-income, underserved neighborhoods. This study aims to (1) develop a pharmacy PrEP delivery model by evaluating the barriers to and facilitators of integrating PrEP into existing pharmacy practice among key stakeholders (eg, pharmacists, technicians, PrEP-prescribing physicians, and BMSM); (2) evaluate eligibility and willingness to receive PrEP in pharmacies among BMSM and collect data on customer engagement with PrEP delivery information from pharmacy staff during COVID-19; and (3) pilot test the pharmacy PrEP delivery model and examine its feasibility, acceptability, and safety with respect to PrEP uptake at baseline and at 3-months (the clinically suggested follow-up period) among BMSM.

Methods

Design and Evaluation

This pilot intervention tests a pharmacy PrEP delivery model among pharmacy staff and BMSM. We will examine the PrEP delivery model's feasibility, acceptability, and safety. A mixed-methods approach will be performed, including three study phases: (1) a completed formative phase with qualitative interviews from 30 key stakeholders including BMSM, pharmacists and pharmacy technicians, and PrEP prescribing clinicians; (2) a completed transitional pilot phase to assess customer eligibility and willingness to receive PrEP in pharmacies during COVID-19; and (3) a planned pilot intervention phase which will test delivery of a pharmacy-based PrEP model provided to 60 BMSM in 2 pharmacies in low-income, underserved neighborhoods. We will describe the recruitment, data collection, and planned analyses for each phase.

Ethics Approval

Ethics approval was obtained from the Emory University Institutional Review Board (IRB00106370).

Recruitment

Formative Phase

A detailed description of the recruitment strategy can be found elsewhere [32]. In brief, participant recruitment during the formative phase varied by key informant group. For pharmacists

(n=10) and technicians (n=10), all pharmacies in the highest HIV zip code in Atlanta, as shown by AIDSVu, were identified. AIDSVu is an online, interactive display of HIV prevalence across the US [33]. Using an existing list of all pharmacies in the state of Georgia obtained from the Georgia Board of Pharmacy, we generated a list of pharmacies from high HIV zip codes and then randomly called each pharmacy to determine whether pharmacists or technicians were interested in participating in the study. When we were unable to reach a pharmacy staff person via phone, we visited the pharmacy during normal business hours.

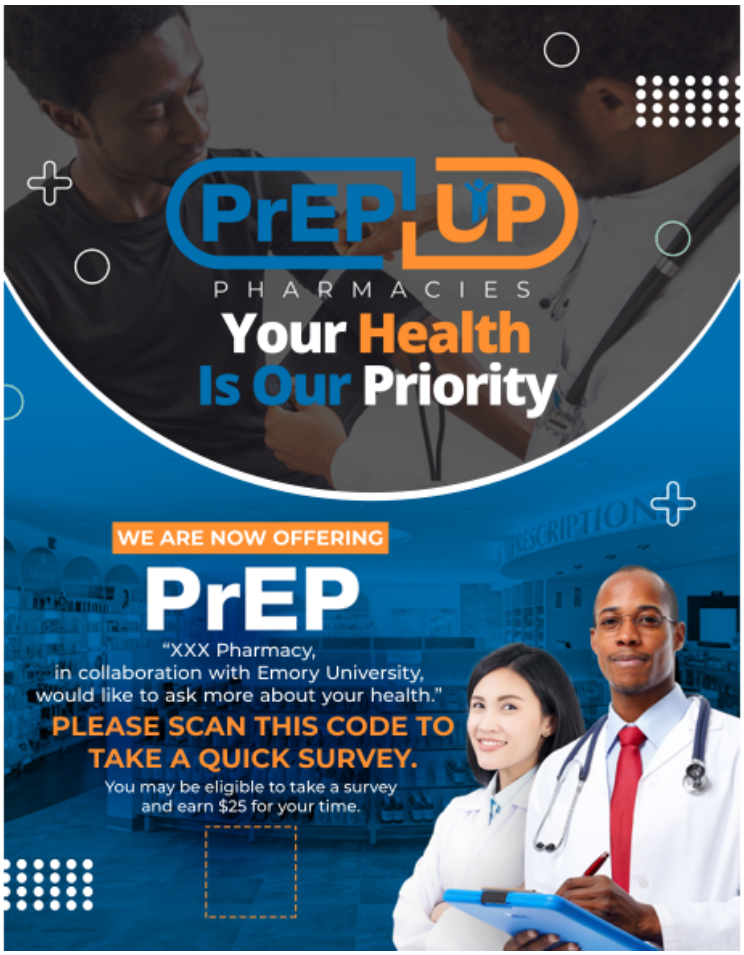
To recruit BMSM, we relied on referrals from our community partners who advertised our study during business hours for MSM seeking HIV prevention services. We also attended weekly social events hosted by our community partner for recruitment. Participants were eligible to participate if they were 18 years of age or older and identified as gay, bisexual, or same-gender-loving.

Transitional Pilot Phase

We enrolled 2 pharmacies located in low-income, underserved Atlanta neighborhoods. We obtained consent from at least 1 pharmacist and 2 to 3 technicians at each pharmacy to participate in the study (n=4 per pharmacy).

Posters and flyers were placed in the pharmacy advertising a study about their health to enroll pharmacy customers (Figure 1). Pharmacy staff also placed flyers in customers' medication delivery packages. The posters and flyers included a QR code that directed customers to an online consent and a 10-question screener survey. Customers who completed the eligibility screener received a US $1 pharmacy coupon regardless of their eligibility in the social behavioral survey. Customers were eligible for the social and behavioral survey if they were: (1) male or trans male, and (2) had any type of sex in the past 6 months, (3) engaged in unprotective sex in the past 6 months, (4) had protected and/or unprotected sex with HIV positive partners in the past 6 months, or (5) injected any drugs in the past 6 months. Eligible customers who completed the social and behavioral survey were compensated US $25 for their time.

Figure 1. Sample flyers and posters used for participant recruitment. PrEP: pre-exposure prophylaxis.



Pilot Phase

Two pharmacies from the final sampling frame developed during the formative phase will be recruited for the pilot intervention. Eligible pharmacies must have at least two pharmacy staff that are willing to perform study activities which include pharmacy training on the study protocol and methods, informing male customers about the study, and communicating with study staff during the customer recruitment period. Pharmacy customers will be considered eligible and offered pharmacy PrEP access if they are: (1) male or trans male, and (2) had any type of sex in the past 6 months, (3) engaged in unprotective sex in the past

6 months, (4) had protected or unprotected sex with HIV positive partners in the past 6 months, or (5) injected any drugs in the past 6 months. Although this PrEP delivery model is being developed for BMSM, Black race is not included in the eligibility criteria to avoid profiling and potentially stigmatizing one racial group. However, since the pharmacies selected to be a part of the study are located in underserved neighborhoods, we anticipate that most customers will be racial minorities.

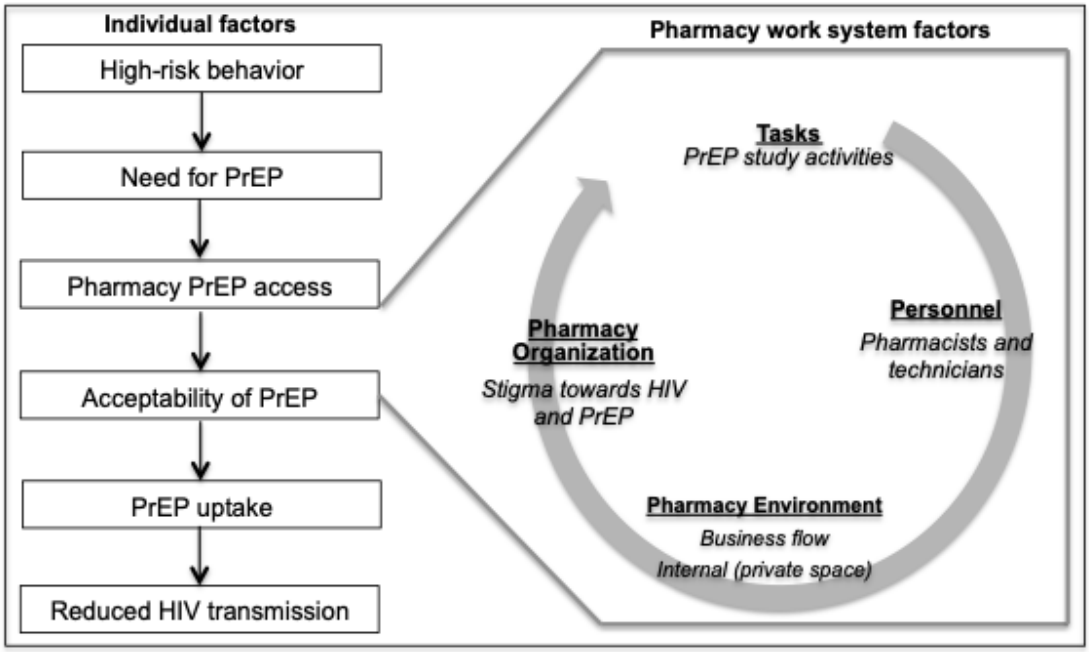
Data Collection

Formative Phase

Measures included in the study will be guided by the systems engineering initiative for patient safety (SEIPS) multilevel model [34] in order to evaluate whether pharmacy PrEP delivery is organizationally feasible and compatible with pharmacy systems. The conceptual application of SEIPS on pharmacy-based PrEP delivery is shown in Figure 2. The first line of entry to improving pharmacy-based PrEP access relies on implementable study activities. In turn, study activities are completed by the pharmacists and technicians with support from distal organizational structures that enable or prohibit tasks in the pharmacy environment relating to workflow or space. These include but are not limited to time constraints, compensation models, and the ability to complete the required activities for both BMSM and pharmacy staff. Given that pharmacy organizational factors may also underpin stigma towards HIV and HIV prevention services, stigma perceptions among each key stakeholder as well as cultural stigma within the pharmacy organization will also be assessed. Specific questions for pharmacy staff included: support for PrEP screening; policies influencing PrEP delivery; referral and monitoring in pharmacies; potential barriers to the delivery of an intervention in a pharmacy; knowledge of epidemiologic data on HIV; sexual behavior; drug use and PrEP; and sustainability through pharmacy-physician collaboration. In the interviews, we described a preliminary pharmacy-based PrEP screening and delivery model for specific feedback on each step with respect to advertising, engagement of BMSM, costs, and other concerns.

For pharmacists and technicians, we also performed direct observation of the pharmacy to understand routine and nonroutine activities. The door-to-door patient experience of obtaining a prescription and the process implemented behind the counter for filling a prescription were characterized using workflow diagrams for the pharmacy. Patterns were examined across the pharmacy environment to create an overall description that best represents a typical prescription dispensing encounter [35].

Figure 2. Conceptual framework integrating pharmacy work system influencing PrEP. PrEP: pre-exposure prophylaxis.



Transitional Pilot Phase

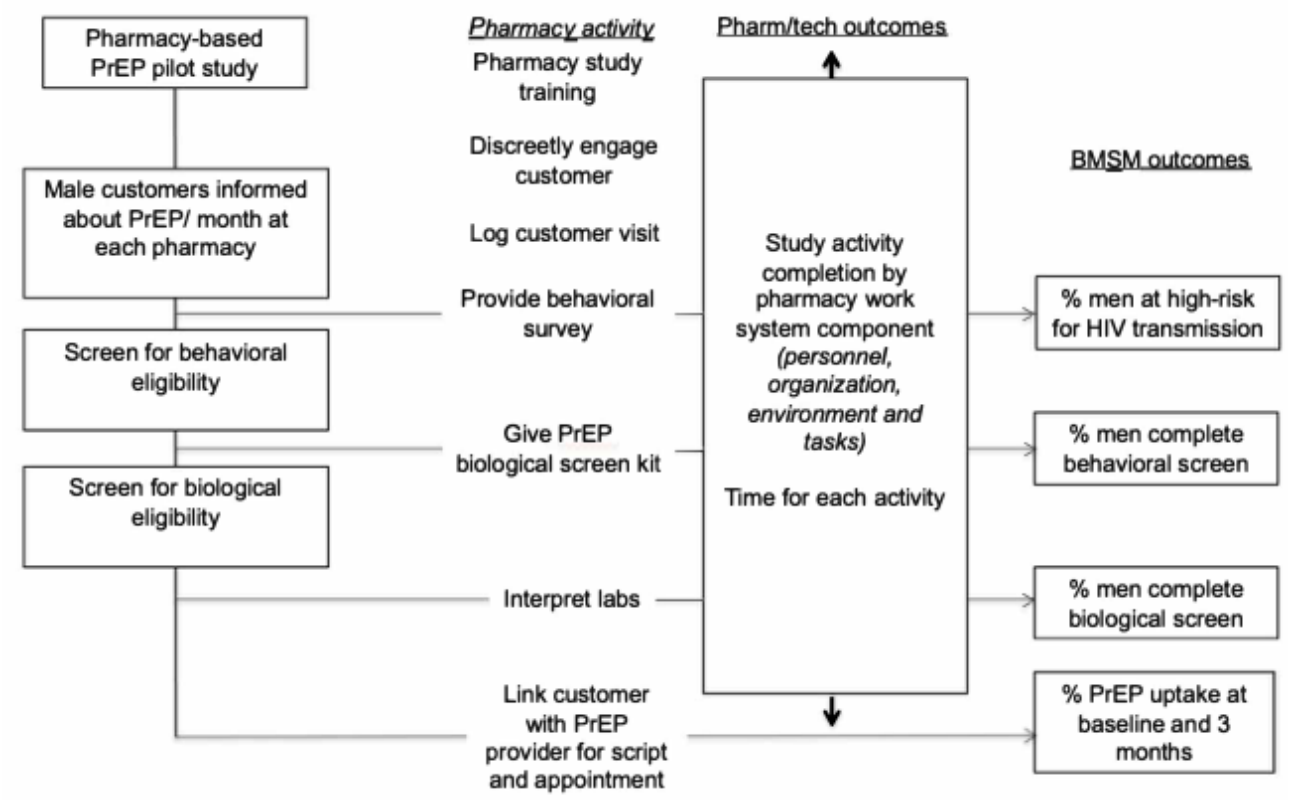
Two pharmacies were chosen to estimate how many customers would be eligible for the pilot phase. Among those who would be eligible, we assessed their willingness to receive PrEP in pharmacies through an electronic social and behavioral survey. The 20-minute social and behavioral survey included questions on demographics, sex and drug use risk behaviors, mental health, social exposures, and the feasibility, acceptability, and safety of the intervention.

Pilot Phase

Pharmacy staff will discreetly inform men (n=60) about the study and determine their willingness to complete an electronic 20-minute social and behavioral screener immediately or schedule an appointment to do so (Figure 3). Pharmacy staff will keep a record of those they approach about the study using an electronic log. Men who agree to participate will be directed to an area where they can privately provide electronic informed consent and complete the survey. If they are willing to participate at a later time, they will be scheduled, and their customer visit will be logged. To circumvent potential literacy

issues, the participant will listen to questions via headphones and mark their answers using the touchscreen computer.

Figure 3. Pilot study activities flow chart. BMSM: Black men who have sex with men; PrEP: pre-exposure prophylaxis.



The survey will ascertain demographics, sex and drug use risk behaviors, mental health, social exposures, and the feasibility, acceptability, and safety of the intervention. Individuals who report behavioral eligibility for PrEP according to Centers for Disease Control and Prevention guidelines [6] will be offered the opportunity to participate in clinical screening tests by pharmacy staff. The CDC defines PrEP behaviorally appropriate individuals as those who report: (1) having an HIV positive partner or (2) being a gay or bisexual male who engages in unprotected anal intercourse or has had a sexually transmitted infection (STI) in the past 6 months or (3) being a heterosexual male who engages in unprotected intercourse with partners of unknown HIV status who are at substantial risk of HIV infection [6]. We will program the surveys to automatically identify individuals who are behaviorally appropriate for PrEP, and at the end of each survey, a password-protected document will be automatically created that informs the pharmacists or technician if the individual is eligible for the clinical PrEP screening. The pharmacist/technician will only have information on whether the person is eligible or not. They will not know the specific reason that person is eligible as this information will be included in the individuals' specific data that the pharmacist/technician does not have access to.

Men who are behaviorally eligible for PrEP and agree to the clinical screening tests will be provided with a prepackaged kit of self-administered tests for HIV, rectal chlamydia, syphilis, and gonorrhea and directed back to the private area of the pharmacy to perform their screenings. Video and visual instructions will be provided on a tablet and paper to guide men through the process of each test. Men will also be able to reach a study staff member via phone or videoconference for questions about specimen collection. Those who are not comfortable being screened in the pharmacy will be counseled on the importance of PrEP and HIV prevention and will be given a referral to our community partner. The pharmacist or technician will interpret the results of a rapid HIV OraQuick, rapid rectal chlamydia, syphilis, and gonorrhea tests. Given the sensitivity of the HIV-testing results, the pharmacist will examine those results first in case an individual tests positive. Pharmacy technicians will be trained to deliver HIV negative results, STI results, and creatinine results. The pharmacy will be provided with a documentation system for maintaining the participants' results in a locked file cabinet. Individuals who have an inconclusive HIV test will be told that their test is inconclusive and will be referred to our community partner for a confirmatory HIV test. If a customer tests positive for HIV during the PrEP screening, he will be immediately sent for confirmatory testing and linkage to treatment. Pharmacists will dispense a 7-day starter PrEP prescription for customers who test negative for HIV. They will also be given an appointment with a PrEP-prescribing clinician within the 7-day period. We will complete a 3-month follow-up phone call with men prescribed PrEP to determine whether they continued PrEP use.

Planned Analyses

Formative Phase

All interviews were audio-recorded for verbatim transcription and data analysis. Audio data was immediately transferred to a secure server following every interview. Interviews were transcribed by research assistants with masters-level training

in public health and qualitative methods. The research team used a thematic approach [36] using code lists developed inductively from the literature and deductively from the research objective. The code lists were organized by listing codes, definitions, and example quotes from the transcripts. To enhance intercoder reliability, 2 researchers recoded the same transcripts, refined the code lists, and recoded the transcripts. Once coded, all texts were reviewed to conceptualize the inter-relationship between themes and how they related to the research questions. The research team used MAXQDA Analytics Pro (VERBI Software) for data analysis.

Transitional Pilot Phase

Exploratory data analysis (EDA) was conducted through data editing using SAS to (1) describe the population of pharmacy patients screened and eligible for PrEP, and (2) examine correlates of willingness to obtain HIV prevention services in the pharmacy. Differences between two means (or medians) were tested using *t* tests or rank tests, and categorical variables will be compared between groups using chi-square tests.

Pilot Phase

Formation of new variables and collapsing variables will be done when exploring the proportion and correlates of feasibility, acceptance, safety, and PrEP use at baseline and at 3-months among BMSM. EDA will be conducted through data editing using SAS. EDA will include calculation of means, medians, percentages, proportions, standard deviations, and skewness/kurtosis as appropriate. If outliers or nonstandard distributions exist, variable transformations or standardized cut-points in the data will guide the recoding of continuous variables. Externally validated standards will be used to recode the data if possible. The influence of outliers will be assessed and medians (or rank tests) used if required. Differences between two means (or medians) will be tested using *t* tests or rank tests, and categorical variables will be compared between groups using chi-square tests, exact tests, and with 95% confidence intervals to guide interpretation. Correlates of interest include health insurance, sexual behavior, substance use, and HIV testing behavior. Other relevant mediators and confounders will include variables such as previous or consistent access to health care. We plan to separately examine the relationship between each confounder and outcome of interest using *t* tests or rank tests on continuous measures and exact tests on categorized values if categorizations are used. Initial unadjusted comparisons will be made using exact tests. If significant bivariate associations are found, we will incorporate these exposures as covariates using linear regression for continuous variables and logistic regression for binary variables where sample size allows.

Results

Formative Phase

Textbox 1 describes the major findings of the formative interviews for each key stakeholder group. Overall, BMSM, pharmacists, and pharmacy technicians show strong support for pharmacy PrEP delivery. We found important differences between the pharmacist and technician reports that would impact the integration of PrEP into pharmacies. Specifically, pharmacists strongly suggested pharmacy staff training to better support PrEP screening for and dispensing PrEP to patients at high HIV risk, whereas pharmacy technicians highlighted privacy concerns and community support of a pharmacy-based PrEP model.

In the BMSM interviews, we created vignettes to elicit support for pharmacy-based PrEP and asked open-ended questions. The use of the vignette method facilitated increased discussion of sensitive topics and allowed participants to actively participate and place themselves in the hypothetical scenario, which provided greater depth in their responses. For example, participant responses spoke directly to how they would interact with the pharmacist or pharmacy technician and how the pharmacy's physical space would impact their comfort and perceived privacy. In fact, participants highlighted additional features that would enhance their experience and comfort in this setting, such as a PrEP expert who was on staff wearing a pin to highlight that they were the person to speak to if a customer needed more information.

During the BMSM interviews, we also pilot tested the self-administration of an open-source, electronic social network data collection software, Network Canvas. We used the think aloud method, which is a robust and flexible research technique used to perform usability testing by gathering qualitative information from participants on their cognitive process while completing the interview. Our results suggest that participants were willing to use Network Canvas and found it to be feasible and generally easy to use. However, the sociogram feature, which captures data on the complete social network, required the most instruction for participants. While participants believed that the design of Network Canvas was easy to understand, they had suggestions for improvement, including more intuitive forward buttons with labels noting which was the next step. They suggested the inclusion of a brief tutorial before allowing participants to complete the social network inventory on their own. They also noted a need for features and tools to be consistent on each data collection page to improve the application's intuitiveness.

Textbox 1. Data collection from BMSM, pharmacists, and pharmacy technicians. BMSM: Black men who have sex with men; PrEP: pre-exposure prophylaxis.

BMSM:

- Strong support of pharmacy PrEP delivery model.
- Men frequently made frequent purchases and obtained prescriptions and some health services at pharmacies.
- Some men had pre-existing relationships and trust for pharmacy staff.
- Men found pharmacies to be conveniently located and more accessible in their neighborhoods.
- Privacy, confidentiality, and specialized training in HIV and PrEP were important for being comfortable engaging in HIV prevention services.

Pharmacists:

- Strong support of pharmacy PrEP delivery model.
- High levels of comfort providing HIV prevention services, including HIV and STI testing, were reported.
- Increased training for pharmacists and pharmacy staff is needed to help counsel patients.
- Existing infrastructure (eg, relationships with physicians and HIV community organizations, ability to work through payment programs) would support pharmacy PrEP delivery.
- High willingness to make additional structural changes (eg, signage, electronic tablets, off-site training) to promote PrEP delivery.

Pharmacy technicians:

- Strong support of pharmacy PrEP delivery model.
- Strong willingness to obtain HIV prevention and PrEP training, including HIV testing training.
- Increased training for pharmacists and pharmacy staff is needed to help counsel patients.
- Pharmacy technicians are responsible for a number of tasks that could also support PrEP delivery (ie, provision of health and payment information to the patient, prescription and vaccination preparation, etc).
- There are important limitations on the scope of services technicians are allowed to perform (eg, vaccination administration).

Transitional Pilot Phase

During the transitional pilot phase, 406 individuals completed a 10-question screening survey. Of those, we identified 81 (19.9%) individuals who would have been eligible for the pilot phase based on engaging in high-risk behaviors that would deem them eligible for PrEP. Among this group, 34 (42%) were eligible based upon reported injection drug use with or without risky sexual behaviors, and 47 (58%) were eligible based upon sex risk behaviors alone (Table 1). Most individuals in the sample (50/81, 63%) made US $20,000 or fewer in the past 12 months. Almost half (35/81, 43%) reported ever being homeless, with 17 (20.9%) individuals reporting being homeless in the past 6 months.

Table 1. Socio-demographics of the transitional pilot phase study population by injection drug use with or without risky sexual behaviors.

	Total (N=81)	Injection drug use with or without sex risk (N=34)	Sex risk only (N=47)
Age (years), median (IQR)	31 (28-32)	30 (27-32)	31 (2-33)
Sex, n (%)			
Male	79 (97.5)	32 (94.1)	47 (100.0)
Female	2 (2.5)	2 (5.9)	0 (0.0)
Race/ethnicity, n (%)			
Hispanic, Latino, or Spanish	34 (42.0)	24 (70.6)	10 (21.3)
Black or African American	17 (21.0)	12 (35.3)	5 (10.6)
White	47 (58.0)	15 (44.1)	32 (68.1)
Marital status, n (%)			
Single, never married	39 (48.1)	16 (47.1)	23 (48.9)
Married, or in a domestic partnership	16 (19.8)	7 (20.6)	9 (19.1)
Divorced, separated, or widowed	12 (14.8)	10 (29.4)	2 (4.3)
Prefer not to answer	14 (17.3)	1 (2.9)	13 (27.7)
Highest level of school completed, n (%)			
Less than a college degree	24 (29.6)	15 (44.1)	9 (19.1)
College degree or greater	57 (70.4)	19 (55.9)	38 (80.9)
Total legal income in past 12 months (USD), n (%)			
≤$20,000	50 (63.3)	18 (52.9)	32 (71.1)
>$20,000	29 (36.7)	16 (47.1)	13 (28.9)
Housing history, n (%)			
Ever been homeless	35 (43.2)	13 (38.2)	22 (46.8)
Homeless in past 6 months	17 (48.6)	4 (30.8)	13 (59.1)

Pilot Phase

No preliminary results are available.

Discussion

Pharmacies have proven to be a feasible source for offering PrEP for WMSM [5,29] but have failed to reach the most at-risk, vulnerable population—BMSM [5]. Our preliminary data indicate that directing pharmacy-based services to communities with a high baseline HIV prevalence could reach individuals at high risk for HIV transmission. State regulations limit pharmacists' ability to screen and prescribe PrEP in 21 states, so many pharmacies use nurse practitioners (NPs) to administer PrEP programs [29]. But pharmacies in low-income, underserved neighborhoods often lack NPs. Thus, we have designed a multilevel intervention that does not solely rely on pharmacists or NPs to screen BMSM for PrEP. The pilot test of this model will determine the feasibility and acceptability of these procedures in the pharmacy environment. Our ability to increase PrEP access and uptake with pharmacy-delivered services could substantially reduce HIV incidence and racial inequities in HIV.

This study will shift the current paradigm of HIV prevention service delivery for BMSM in three critical ways. First, the proposed model will be developed such that pharmacy PrEP delivery could be achievable for most pharmacists in the US who currently lack the pharmacy-level resources to screen men for PrEP. Second, the proposed research employs a multilevel approach to pharmacy PrEP delivery that assesses not only the population receiving PrEP (BMSM) but also the pharmacy staff who are critical to disseminating PrEP. Evaluation of this model from the targeted population and pharmacy perspective is critical as many pharmacy-based studies have already shown important effects on HIV prevention outcomes among the targeted population, but none have been sustained beyond the study time frame [5,19,21,22,25-28]. Evaluation of each of the pharmacy factors will be guided by SEIPS, a model that is anchored in the industrial engineering subspecialty of human factors but new to public health and behavioral sciences. Given that the model is designed to optimize the system around a given individual (here, BMSM), it can help to identify key barriers and processes that care impair their ability to access PrEP. Hence, the study findings will provide a much-needed understanding of how to incorporate and sustain expanded services by characterizing specific breaks within the pharmacy work system that promote or weaken pharmacy PrEP delivery. Third, to efficiently screen for PrEP eligibility, we will use HIV and STI self-testing kits in a pharmacy—rather than a clinical or home setting [37,38]. This has the secondary benefit of increasing HIV testing.

We acknowledge that this study is subject to a number of limitations. First, selection bias may occur if a customer refuses to enter the study, potentially limiting the generalizability of the MSM sample. Given that this study's purpose is to test the feasibility of the intervention, we are not concerned about the lack of generalizability of the sample. However, to roughly assess the potential for this bias for a future efficacy trial, pharmacies will record general demographic data on each customer they engage so that those who refuse materials and study information can be compared to those who enroll in the study. These data will be based on observation of race and age (as opposed to inquiry) so that customers will not be discouraged from pharmacy use. Second, the drawback with targeted neighborhood samples is that they may not be representative of the entire target population (BMSM). Although the study may be limited in external validity, it is a prudent first step in examining this population in terms of determining risk for HIV, willingness to be screened and linked to PrEP, and the feasibility, acceptability, and safety of pharmacies as sites to provide PrEP. Third, social desirability bias may occur in the proposed study, as customer sex and drug risk behaviors will be ascertained through self-report. The use of electronic surveys has been shown to improve validity by minimizing invalid reports, such as socially desirable answers, and by ordering questions in a manner that will aid in recall. Additionally, including logic checks in the survey that prevent a respondent from proceeding on the electronic system if their responses are inconsistent can reduce invalid reporting [39]. Participants who consistently contradict themselves in survey responses will be excluded from these analyses. Fourth, we may have insufficient power to adequately detect differences in our primary outcome, given these differences exist. Due to the lack of published (or preliminary) data available to provide evidence of expanded pharmacy services for BMSM, this study will provide preliminary estimates for future efficacy studies. So, it is critical to note that the main goal of this protocol is to first determine if pharmacies can manage a PrEP delivery system for this vulnerable population. This will provide critical information as to whether or not this program can be scaled up, translated, and sustained at a community level.

The contribution of the proposed research is expected to be a sustainable, pharmacy PrEP delivery model that can be implemented without regulatory barriers to increase PrEP access in low-income, underserved neighborhoods for BMSM who have the highest need. This contribution will be significant because it will lay the foundation for making PrEP available in pharmacies specifically for populations that are disconnected from HIV prevention resources.

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Conflicts of Interest

AJS consults for Merck. The other authors have no conflicts to declare.

Multimedia Appendix 1
Peer review summary from the National Institute of Health.
[PDF File (Adobe PDF File), 156 KB - resprot_v11i2e35590_app1.pdf]

References

1. Centers FDC. HIV Surveillance Report. Vol 32. URL: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html [accessed 2021-09-15]
2. Hall HI, Song R, Tang T, An Q, Prejean J, Dietz P, et al. HIV Trends in the United States: Diagnoses and Estimated Incidence. JMIR Public Health Surveill 2017 Feb 03;3(1):e8 [FREE Full text] [doi: 10.2196/publichealth.7051] [Medline: 28159730]
3. The Georgia Department of Public Health HIV/AIDS Epidemiology Section. HIV Surveillance Summary, Georgia 2019. URL: https://dph.georgia.gov/data-fact-sheet-summaries [accessed 2021-09-15]
4. Paltiel A, Freedberg K, Scott C, Schackman B, Losina E, Wang B, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clin Infect Dis 2009 Mar 15;48(6):806-815 [FREE Full text] [doi: 10.1086/597095] [Medline: 19193111]
5. Tung E, Thomas A, Eichner A, Shalit P. Feasibility of a pharmacist-run HIV PrEP clinic in a community pharmacy setting. 2017 Presented at: Conference on Retroviruses and Opportunistic Infections; February 13-16, 2017; Seattle, Washington URL: https://www.croiconference.org/abstract/feasibility-pharmacist-run-hiv-prep-clinic-community-pharmacy-setting/
6. Centers FDCAP. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2017 Update: A Clinical Practice Guideline. Atlanta, Georgia: US Public Health Service; Mar 2018:1-77.
7. Fallon SA, Park JN, Ogbue CP, Flynn C, German D. Awareness and Acceptability of Pre-exposure HIV Prophylaxis Among Men Who have Sex with Men in Baltimore. AIDS Behav 2016 Nov 21;21(5):1268-1277. [doi: 10.1007/s10461-016-1619-z] [Medline: 27873081]

8. Lelutiu-Weinberger C, Golub SA. Enhancing PrEP Access for Black and Latino Men Who Have Sex With Men. J Acquir Immune Defic Syndr 2016 Dec 15;73(5):547-555 [FREE Full text] [doi: 10.1097/QAI.0000000000001140] [Medline: 27454250]
9. Bush S, Magnuson D, Rawlings M, Hawkins T, McCallister S, Mera GR. Racial Characteristics of FTC/TDF for Pre-exposure Prophylaxis (PrEP) Users in the US. 2016 Presented at: ASM Microbe / ICAAC; June 16-20, 2016; Boston, Massachusetts URL: https://www.natap.org/2016/HIV/062216_02.htm
10. Roemer M. The Uninsured in America, First Part of 2012: Estimates for the US Civilian Noninstitutionalized Population under Age 65. Statistical Brief (Medical Expenditure Panel Survey (US)). Rockville, Maryland: Agency for Healthcare Research and Quality URL: https://www.meps.ahrq.gov/data_files/publications/st422/stat422.shtml [accessed 2021-09-09]
11. Kass N, Flynn C, Jacobson L, Chmiel JS, Bing EG. Effect of Race on Insurance Coverage and Health Service Use for HIV-Infected Gay Men. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 1999;20(1):85-92. [doi: 10.1097/00042560-199901010-00013]
12. Gilead Sciences Incorporated. How can you get help paying for TRUVADA for PrEP?. 2017. URL: https://www.truvada.com/how-to-get-truvada-for-prep/truvada-cost [accessed 2021-09-15]
13. Cahill S, Taylor SW, Elsesser SA, Mena L, Hickson D, Mayer KH. Stigma, medical mistrust, and perceived racism may affect PrEP awareness and uptake in black compared to white gay and bisexual men in Jackson, Mississippi and Boston, Massachusetts. AIDS Care 2017 Nov;29(11):1351-1358 [FREE Full text] [doi: 10.1080/09540121.2017.1300633] [Medline: 28286983]
14. Eaton LA, Kalichman SC, Price D, Finneran S, Allen A, Maksut J. Stigma and Conspiracy Beliefs Related to Pre-exposure Prophylaxis (PrEP) and Interest in Using PrEP Among Black and White Men and Transgender Women Who Have Sex with Men. AIDS Behav 2017 Jan 20;21(5):1236-1246. [doi: 10.1007/s10461-017-1690-0]
15. Buot MG, Docena JP, Ratemo BK, Bittner MJ, Burlew JT, Nuritdinov AR, et al. Beyond Race and Place: Distal Sociological Determinants of HIV Disparities. PLoS ONE 2014 Apr 17;9(4):e91711. [doi: 10.1371/journal.pone.0091711]
16. Vaughan AS, Rosenberg E, Shouse RL, Sullivan PS. Connecting Race and Place: A County-Level Analysis of White, Black, and Hispanic HIV Prevalence, Poverty, and Level of Urbanization. Am J Public Health 2014 Jul;104(7):e77-e84. [doi: 10.2105/ajph.2014.301997]
17. Dasgupta S, Kramer MR, Rosenberg ES, Sanchez TH, Sullivan PS. Spatial Accessibility to HIV Providers in Atlanta, Georgia. AIDS Res Hum Retroviruses 2015 May;31(5):473-474. [doi: 10.1089/aid.2014.0365] [Medline: 25844663]
18. Gebhart F. Provider status: Keep the pressure on lawmakers and push for payment. Drug Topics. 2016. URL: http://drugtopics.modernmedicine.com/drug-topics/news/provider-status [accessed 2021-09-15]
19. Lewis CF, Rivera AV, Crawford ND, DeCuir J, Amesty S. Pharmacy-randomized intervention delivering HIV prevention services during the syringe sale to people who inject drugs in New York City. Drug and Alcohol Dependence 2015 Aug;153:72-77. [doi: 10.1016/j.drugalcdep.2015.06.006]
20. Fuller CM, Galea S, Caceres W, Blaney S, Sisco S, Vlahov D. Multilevel Community-Based Intervention to Increase Access to Sterile Syringes Among Injection Drug Users Through Pharmacy Sales in New York City. Am J Public Health 2007 Jan;97(1):117-124. [doi: 10.2105/ajph.2005.069591]
21. Crawford ND, Amesty S, Rivera AV, Harripersaud K, Turner A, Fuller CM. Randomized, Community-Based Pharmacy Intervention to Expand Services Beyond Sale of Sterile Syringes to Injection Drug Users in Pharmacies in New York City. Am J Public Health 2013 Sep;103(9):1579-1582. [doi: 10.2105/ajph.2012.301178]
22. Crawford ND, Amesty S, Rivera AV, Harripersaud K, Turner A, Fuller CM. Community Impact of Pharmacy-Randomized Intervention to Improve Access to Syringes and Services for Injection Drug Users. Health Educ Behav 2014 Apr 10;41(4):397-405. [doi: 10.1177/1090198114529131]
23. Rosenbluth SA, Madhavan SS, Borker RD, Maine LL. Experience: Pharmacy Immunization Partnerships: A Rural Model. J Am Pharm Assoc 2001 Jan;41(1):100-107. [doi: 10.1016/s1086-5802(16)31210-4]
24. Joyce A, Berbatis C, Sunderland V, Dhaliwal S. Analysis of primary prevention services for cardiovascular disease in Australia's community pharmacies. Aust N Z J Public Health 2007;31(6):516-519. [doi: 10.1111/j.1753-6405.2007.00135.x]
25. Amesty S, Crawford ND, Nandi V, Perez-Figueroa R, Rivera A, Sutton M, et al. Evaluation of Pharmacy-Based HIV Testing in a High-Risk New York City Community. AIDS Patient Care and STDs 2015 Aug;29(8):437-444. [doi: 10.1089/apc.2015.0017]
26. Crawford ND, Dean T, Rivera AV, Guffey T, Amesty S, Rudolph A, et al. Pharmacy Intervention to Improve HIV Testing Uptake Using a Comprehensive Health Screening Approach. Public Health Rep 2016 Jan 01;131(1_suppl):139-146. [doi: 10.1177/00333549161310s116]
27. Darin KM, Klepser ME, Klepser DE, Klepser SA, Reeves A, Young M, et al. Pharmacist-provided rapid HIV testing in two community pharmacies. J Am Pharm Assoc 2015;55(1):81-88. [doi: 10.1331/JAPhA.2015.14070] [Medline: 25415222]
28. Lecher SL, Shrestha RK, Botts LW, Alvarez J, Moore JH, Thomas V, et al. Cost analysis of a novel HIV testing strategy in community pharmacies and retail clinics. J Am Pharm Assoc 2015 Sep;55(5):488-492. [doi: 10.1331/japha.2015.150630]
29. Deam J. Walgreens STD tests will "expand our troops" in battle against infections. Chron. 2017 Apr 18. URL: https://www.chron.com/business/medical/article/Houston-Walgreens-will-begin-testing-for-STDS-11080632.php, [accessed 2021-09-15]

30. National HIV Community Partnership. Greater Than AIDS. URL: https://www.greaterthan.org/get-tested-with-greater-than-aids-walgreens/ [accessed 2021-09-13]
31. Zhao A, Dangerfield DT, Nunn A, Patel R, Farley JE, Ugoji CC, et al. Pharmacy-Based Interventions to Increase Use of HIV Pre-exposure Prophylaxis in the United States: A Scoping Review. AIDS Behav 2021 Oct 20:1-16. [doi: 10.1007/s10461-021-03494-4] [Medline: 34669062]
32. Crawford ND, Josma D, Morris J, Hopkins R, Young HN. Pharmacy-based pre-exposure prophylaxis support among pharmacists and men who have sex with men. J Am Pharm Assoc 2020 Jul;60(4):602-608. [doi: 10.1016/j.japh.2019.12.003]
33. Sullivan PS, Woodyatt C, Koski C, Pembleton E, McGuinness P, Taussig J, et al. A Data Visualization and Dissemination Resource to Support HIV Prevention and Care at the Local Level: Analysis and Uses of the AIDSVu Public Data Resource. J Med Internet Res 2020 Oct 23;22(10):e23173. [doi: 10.2196/23173]
34. Carayon P, Wooldridge A, Hoonakker P, Hundt AS, Kelly MM. SEIPS 3.0: Human-centered design of the patient journey for patient safety. Applied Ergonomics 2020 Apr;84:103033. [doi: 10.1016/j.apergo.2019.103033] [Medline: 31987516]
35. Unertl KM, Weinger MB, Johnson KB, Lorenzi NM. Describing and modeling workflow and information flow in chronic disease care. J Am Med Inform Assoc 2009;16(6):826-836 [FREE Full text] [doi: 10.1197/jamia.M3000] [Medline: 19717802]
36. Maguire M, Delahunt B. Doing a thematic analysis: A practical, step-by-step guide for learning and teaching scholars. All Irel J High Educ 2017;9(3).
37. Guerry SL, Bauer HM, Packel L, Samuel M, Chow J, Rhew M, et al. Chlamydia screening and management practices of primary care physicians and nurse practitioners in California. J Gen Intern Med 2005 Dec;20(12):1102-1107. [doi: 10.1111/j.1525-1497.2005.00240.x]
38. Wayal S, Llewellyn C, Smith H, Hankins M, Phillips A, Richardson D, et al. Self-sampling for oropharyngeal and rectal specimens to screen for sexually transmitted infections: acceptability among men who have sex with men. Sex Transm Infect 2009 Feb 01;85(1):60-64. [doi: 10.1136/sti.2008.032193]
39. Guest JL, Adam E, Lucas IL, Chandler CJ, Filipowicz R, Luisi N, et al. Methods for Authenticating Participants in Fully Web-Based Mobile App Trials from the iReach Project: Cross-sectional Study. JMIR mHealth uHealth 2021 Aug 31;9(8):e28232 [FREE Full text] [doi: 10.2196/28232] [Medline: 34463631]

Abbreviations

BMSM: Black men who have sex with men
CDC: Centers for Disease Control and Prevention
EDA: exploratory data analysis
MSM: men who have sex with men
NP: nurse practitioners
PrEP: pre-exposure prophylaxis
SEIPS: systems engineering initiative for patient safety
STI: sexually transmitted infections
WMSM: White men who have sex with men

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Protocol

Investigation of Prenatal Pesticide Exposure and Neurodevelopmental Deficits in Northern Thailand: Protocol for a Longitudinal Birth Cohort Study

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Abstract

Background: Prenatal exposure to pesticides has been linked to adverse neurodevelopmental outcomes. Gaps exist in the current literature about the timing and magnitude of exposures that result in these adverse outcomes.

Objective: The Study of Asian Women and their Offspring's Development and Environmental Exposures (SAWASDEE) cohort was established to investigate the impact of prenatal exposure to pesticides on early indicators of cognitive and motor skills, inhibitory control, emotion regulation, and memory that have been found to be important in the development of subsequent neurobehavioral and neurodevelopmental diseases. The overarching goal is to find earlier predictors of potential adverse neurologic outcomes in order to enable earlier interventions that could result in better outcome prognoses.

Methods: Recruitment of this prospective, longitudinal birth cohort began in July 2017 and was completed in June 2019 in Chom Thong and Fang, 2 farming districts in Chiang Mai Province in northern Thailand. Follow-up of the study participants is ongoing. During pregnancy, 7 questionnaires were administered. Time-resolved biospecimen samples were collected monthly (for urine) and during each trimester (for blood) during antenatal care visits. Medical records were abstracted. Infants were administered the NICU Network Neurobehavioral Scale (NNNS) test at 1 month of age. A total of 322 mother-child pairs completed the NNNS test. All children will be followed until 3 years of age and undergo a series of neurodevelopmental tests. We will complete several additional exposure related analyses.

Results: A total of 1298 women were screened, and of those, 394 (30.35%) women were enrolled. The mean gestational age at enrollment was 9.9 weeks (SD 2.6). Differences in literacy were observed between Chom Thong and Fang participants. In Fang, about 54 of 105 (51.4%) participants reported being able to read in Thai compared to about 206 of 217 (94.9%) participants in Chom Thong. The percentages were comparable for reporting to be able to write in Thai.

Conclusions: This longitudinal birth cohort study will inform risk assessment standards for pregnant women in Thailand and other countries. Building awareness of how insecticide exposure during specific windows of pregnancy affects the neurodevelopmental trajectories of children in developing countries is a specific need recognized by the World Health Organization.

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KEYWORDS

birth cohort; farmworker; neurodevelopment; organophosphate; pesticide; pregnant women; Thailand

Introduction

Prenatal exposure to mixtures of neurotoxic pesticides is prevalent worldwide and has the potential to disrupt and irreversibly alter neurologic development [1-3]. In 2017, approximately 8.8 billion pounds of pesticides were used worldwide [4]. Agricultural workers with occupational exposure to pesticides, on average, have greater exposure than the general population [5]. The agricultural sector comprises approximately 30% of the total workforce in Thailand, and an estimated 70% of the Thai population lives in rural areas [6,7]. Because of their widespread use in Thailand, exposure to pesticides is common [7,8]. The most abundantly used pesticides in Thailand include insecticides, such as pyrethroids and organophosphates (OPs) [8,9], despite their known acute human neurotoxic effects. After exposure to these pesticides via the diet (low background exposure) or dermal absorption and inhalation (primary occupational exposure routes), they are distributed throughout the body or quickly metabolized and excreted [10]. Urinary dialkylphosphates (DAPs), 3,5,6-trichloropyridinol (TCPY), and 3-phenoxybenzoic acid (3PBA) have all been commonly used as biomarkers of OPs and pyrethroid exposure [10].

Previous human and animal studies have reported that following exposure, neurotoxic insecticides, including pyrethroids and OPs, are able to cross the placental barrier and enter the fetal blood stream [11]. Until now, most studies evaluating prenatal pesticide exposure and birth outcomes or neurodevelopment have estimated exposure at only 1 or 2 time points during pregnancy [5]. The literature consistently reports that pesticide exposure is associated with adverse health outcomes; however, the actual outcome measure, exposure measures, and even susceptibility measures vary [5].

The Study of Asian Women and their Offspring's Development and Environmental Exposures (SAWASDEE) study was conceived to fill some of these knowledge gaps preventing effective policy implementation. The SAWASDEE study is a prospective, longitudinal birth cohort study evaluating pesticide exposure in farmworker women in northern Thailand enrolled during their first trimester of pregnancy and evaluating neurodevelopment in their children at multiple time points until 3 years of age. Our study was designed to collect uniquely refined pesticide exposure data to define critical windows of effect during pregnancy and to evaluate novel neurological testing parameters that could predict a child's neurodevelopmental trajectory. The study is a multi-institute initiative and builds upon an existing structure of collaboration and capacity building between Emory (Atlanta, GA, USA), Rutgers (Piscataway, NJ, USA), Chiang Mai (Chiang Mai, TH), and Chulalongkorn (Bangkok, TH) Universities. Our cohort includes the collection of robust prenatal and postnatal exposure assessment data; extensive biospecimens, including monthly maternal urine samples and trimester-specific maternal blood; and questionnaire data to enable identification of sensitive windows of exposure to pesticides on development. Children born as part of the birth cohort are followed longitudinally until the age of approximately 3 years to test the hypothesis that prenatal exposure may alter neurodevelopment and that the neurodevelopmental trajectory can be estimated by first-year testing parameters.

Because pesticides are not expected to selectively impact a specific brain region, the study is designed to assess neurodevelopmental trajectories using behavioral measures of infant and early childhood function that reflect underlying neural substrates of visual attention, regulation of emotion, memory, and inhibitory control. This approach integrates the measurement of cognitive and emotional development, recognizing that the regulation of biologically based emotional reactivity, such as anger or fear, is necessary for successful cognitive development. Moreover, the child must develop the ability to delay or inhibit immediate responses in order to achieve higher-level cognitive skills [12].

The purpose of this paper is to provide a comprehensive overview of the SAWASDEE cohort profile as a research resource for potential collaborations, including a description of the data collected, a description of baseline characteristics, and a summary of the future plans for the cohort.

Methods

Cohort Development

The SAWASDEE study is based on a longitudinal birth cohort of women residing in northern Thailand who are agricultural workers or live on a working farm. The exposures of interest are pyrethroids and OPs, while the outcomes of interest are birth outcome and child neurodevelopment. All study procedures were reviewed and approved by the institutional review board at Emory University (with Rutgers reliance) and the ethics review committee at the Research Institute for Health Sciences, Chiang Mai University (with Chulalongkorn reliance). Informed consent was obtained from all study participants prior to enrollment.

Recruitment occurred in Chiang Mai Province in northern Thailand because of its robust agricultural sector and its generalizability to other low-/middle-income countries (LMICs) that are similarly reliant on agriculture. The primary crops in

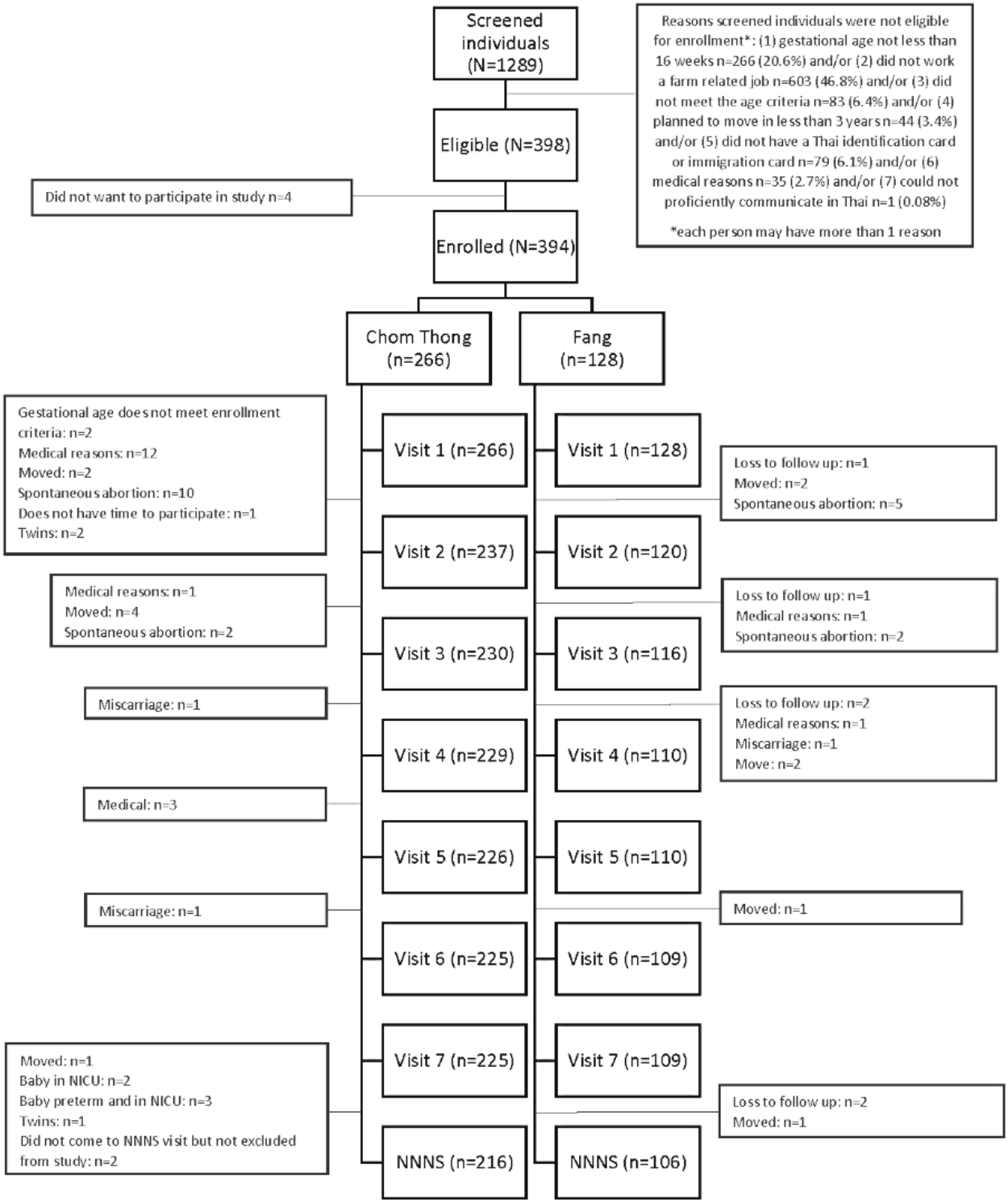
Chiang Mai include rice, tangerines, longans, lychee, and ornamental flowers, with their use of pesticides varying greatly with the crop grown. For example, fruits trees require a larger application amount in a shorter application period. Conversely, rice crops require insecticide application more regularly during the growing season but at lower quantities. These 2 types of pesticide application scenarios (ie, high application, short duration, and low application, longer duration) can be easily studied in Chiang Mai Province by focusing on 2 of its distinct districts: (1) Chom Thong and (2) Fang. Chom Thong and Fang are both agricultural communities located about 60 and 150 km, respectively, outside of Chiang Mai City. Chom Thong crops include longans, cut flowers, vegetables, and rice, while in Fang, located in the mountainous region near the Myanmar border, tangerines are the predominant crop. The differences in crops grown in the corresponding districts create a sort of natural experiment of exposure, allowing us to evaluate the differences in these scenarios.

Prior to recruitment, we developed and culturally validated, where appropriate, a detailed set of standard operating procedures (SOPs) and questionnaires. SOPs were developed for sample identification numbers and label generation, biospecimen collection and processing, laboratory testing, and quality assurance and control (QA/QC) procedures, including field blank sample collection, bench-level QC and blank samples, sample compositing, sample randomization for analysis, and neurological testing. In addition, to facilitate sample processing and efficient transfer of samples to Chiang Mai University, we scoped and rented apartments that we outfitted as satellite laboratories we called “SAWASDEE houses” located in each of the districts.

Recruitment began in July 2017 and was completed in June 2019. Women were recruited at community and district hospitals in both districts by trained study nurses. Nurses administered an initial screening questionnaire to determine eligibility of the pregnant women. Women were eligible for participation if they (1) were an agricultural worker or lived within 50 m of an agricultural field, (2) had a Thai identification card permitting hospital and antenatal clinic access, (3) resided in their regional district for ≥6 months and planned residence at least 3 years after delivery, (4) spoke Thai at home, (5) were in good general health (ie, no major medical conditions, such as hypertension, diabetes, thyroid disease, or HIV), (6) consumed fewer than 2 alcoholic beverages per day and did not use illegal drugs [13], (7) and were at <16 weeks’ gestation. Expectant mothers with nonsingleton pregnancies or major pregnancy complications that could affect fetal growth and development were excluded from further participation at the time of diagnosis.

We screened 1289 women, and of those, 398 (30.88%) met our enrollment criteria and of which 394 (98.9%) were enrolled. Of these 394 participants, 322 (81.7%) completed all data collection (Figure 1) through their child’s neurological visit at 1 month. Of these 322 participants, 217 (67.4%) were from Chom Thong and 105 (32.6%) were from Fang, with the proportion of total participants reflecting their relative population sizes. Most of the participants who were not retained in the study were excluded due to pregnancy complications (eg, miscarriage, blighted ovum) or because they moved away from the study area.

Figure 1. Participant selection and enrollment in the SAWASDEE Birth Cohort Study, Thailand 2017.



Questionnaires

Trained research assistants (RAs) and nurses administered each questionnaire in Thai. These questionnaires included a recruitment survey to determine eligibility (screening questionnaire); an intake questionnaire to collect baseline descriptive statistics; an extensive exposure questionnaire administered during early, middle, and late pregnancy that roughly corresponded to trimesters; and a Knowledge, Attitude, and Practices (KAP) survey of pesticides, collected during the first and third trimesters. The exposure questionnaires, which were validated and used in our pilot study [14], included questions on work-related tasks, household and occupational use of pesticides, personal habits of parents, food consumption, household characteristics and cleanliness, medical histories, maternal nutritional status during pregnancy, and demographics. These questionnaires include detailed information about the population characteristics, including information about medical conditions, medications, weight gain during pregnancy, education, family assets, supplements taken during pregnancy, parity, and more. By administering the exposure questionnaire 3 times, we were able to capture any changes that occurred that

might have altered exposures. The KAP survey was used to evaluate the participants' understanding of the toxicity and potential effects of pesticides and their routine practice related to pesticides and how those practices changed as pregnancy progressed. After delivery, an additional 9 questionnaires were completed over the course of 36 months to ascertain developmental milestones, maternal intelligence quotient (IQ), family assets and the home environment, and anthropometrics of the children to evaluate their nutritional status.

Case Records

The following information was extracted from medical records: early pregnancy weight and weight gain, parity, past obstetric history, planned pregnancy, smoking and alcohol consumption, marital status, occupation, history of illness, and prenatal visit history, which included gestational age at first visit, subsequent visit dates, doctor-assessed nutritional status, and compliance with micronutrient supplementation regimens. These data were updated at each of the visits to track a variety of indicators, including maternal nutritional status (using weight gain as a surrogate) and significant stressors that could complicate the exposure-effect evaluation. Data extracted from participant birth records included sex, birth weight, length, gestational age, and head circumference; appearance, pulse, grimace, activity, and respiration (APGAR) scores; type and route of delivery; anesthesia; and information about maternal and neonatal complications.

Biospecimen Collection

Biospecimens collected from enrolled participants are shown in Table 1. Most of these samples were processed and archived for planned future analysis or novel research questions.

Blood, serum, urine, and hair were used for exposure assessment, with urine being the primary matrix used. Blood was used for susceptibility biomarker analysis (ie, paraoxonase 1 [PON1] phenotyping), and placenta tissue was used for transcriptomics analysis.

Table 1. Questionnaire, biological sample collection, and neurotesting, SAWASDEE[a] study, Thailand, 2017-2019.

Time point	Visit, n	Questionnaire	Biological sample collection (M=maternal, C=child)								Neurological testing[b]
			Urine	Swabs[c]	Blood	Cord blood	Meconium	Breast milk[d]	Placenta	Hair[e]	
Enrollment <12 weeks	1	Intake, KAP[f]	M	M	M	N/A[g]	N/A	N/A	N/A	M	N/A
16 weeks	2	Maternal exposure (ME) baseline	M	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20 or 22 weeks	3	N/A	M	M	M	N/A	N/A	N/A	N/A	N/A	N/A
28 weeks	4	ME 2nd trimester	M	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
32 weeks	5	KAP	M	M	M	N/A	N/A	N/A	N/A	N/A	N/A
36 weeks	6	ME 3rd trimester	M	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Delivery	7	Medical chart abstraction	N/A	N/A	N/A	M	N/A	N/A	M	N/A	N/A
1-3 days post-delivery	8	DASS[h]	C	N/A	N/A	N/A	C	N/A	N/A	N/A	NNNS[i]
4 months	10	DASS	C	N/A	N/A	N/A	N/A	M	N/A	N/A	Visual habituation
7 months	11	DASS	C	N/A	N/A	N/A	N/A	M	N/A	N/A	Visual habituation, Bayley's Scales of Infant Development (BSID) motor, visual paired comparison (VPC), visual expectation (VEP), continuous familiarization (CFT), A not B test (AB)
12 months	12	Child exposure (CE)	C	N/A	N/A	N/A	N/A	M	N/A	N/A	VPC, VEP, CFT, AB, delayed recall, deferred imitation, cross-modal, Labtab subtests
12 months	12	Infant Behavior Questionnaire (IBQ), DASS	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
12 months	12	HOME[j]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
18 months	13	BDI, TONI[k]-IV	C	N/A	N/A	N/A	N/A	N/A	N/A	N/A	VPC, VEP, CFT, AB, delayed recall, deferred imitation, cross-modal
24 months	14	DASS, CE, HOME, Language Development Survey	C	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Delayed recognition, deferred imitation, cross-modal, inhibitory control
36 months	15	DASS, Child Behavior Checklist (CBCL), Early Child Behavior Questionnaire (ECBQ), CE	C	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Bayley III

[a]SAWASDEE: Study of Asian Women and their Offspring's Development and Environmental Exposures.

[b]A neurological test for this time point is scheduled for 2 sessions, 2 weeks apart, but only 1 sample will be collected from either session.

[c]Swabs: oral, vaginal, and gut.

[d]If breastfeeding at visit time.

[e]Need 5 g of hair.

[f]KAP: Knowledge, Attitude, and Practices.

[g]N/A: not applicable.

[h]DASS: Depression Anxiety Stress Scale.

[i]NNNS: NICU Network Neurobehavioral Scale.

[j]HOME: Home Observation for the Measurement of the Environment.

[k]TONI: Test of Nonverbal Intelligence.

Exposure Assessment

To provide trimester-specific exposure measures during pregnancy, while still keeping the study costs reasonable, we created trimester-specific urine composites from each participant but still retained the original discrete samples for later use. DAPs, TCPY, and 3PBA were measured in these maternal composited urine samples (Table 2) using established analytical methods [15-17]. PON1 enzyme activity, a measure of OP insecticide susceptibility, was measured in maternal serum using previously established procedures [14]. Other samples were archived for future use.

Table 2. Measurements to be made in biological matrices or matrices to be archived for future analysis, SAWASDEE[a] study, Thailand, 2017-2019.

	Analytes	Matrix	Laboratory
Insecticide or measure			
OP[b]	DAP[c] metabolites	Maternal urine	Chiang Mai University (CMU)
OP	Chlorpyrifos (TCPY[d])	Maternal urine	Emory
Pyrethroid	3PBA[e]	Maternal urine	Emory
OP	PON1[f] enzyme activity	Maternal blood	CMU
mRNA	N/A[g]	Placenta	Mount Sinai
Preserved samples			
Organochlorines/metals	Dichlorodiphenyldichloroethylene/dichloro-diphenyltrichloroethane (DDE/DDT), lead, mercury	Maternal blood	Emory
OP/pyrethroids	DAPs/3PBA	Child urine	CMU/Emory
OP/pyrethroids	Chlorpyrifos, permethrin, cypermethrin	Meconium, breast milk, blood/plasma	CMU/Emory
DNA methylation	N/A	Preserved DNA	To be determined (TBD)
Microbiome (maternal vaginal and gut and child gut)	N/A	Vaginal/rectal swabs	TBD

[a]SAWASDEE: Study of Asian Women and their Offspring's Development and Environmental Exposures.

[b]OP: organophosphate.

[c]DAP: dialkylphosphate.

[d]TCPY: 3,5,6-trichloropyridinol.

[e]3PBA: 3-phenoxybenzoic acid.

[f]PON1: paraoxonase 1.

[g]N/A: not applicable.

Assessment of Neurological Outcomes

Extensive neurodevelopment examination of each child was conducted by trained neuropsychologists at the following time points: 1, 4, 7, 12, 18, 24, and 36 months (Table 3).

Assessment at these intervals represents a significant departure from previous studies of pesticide exposure and will allow examination of how pesticides may alter the neurodevelopmental trajectory of children. For tests administered at more than 1 developmental period, age-appropriate adjustments were made to increase the difficulty of the test. Infant and child responses were either scored in real time in the case of visual habituation tests or scored from digital recordings when testing was complete. Interrater reliabilities were conducted monthly for all tests using different videos each month and independent scoring by psychologists to maintain reliability among testers. All tests were routinely recorded to allow recheck procedures and scoring. The neurodevelopmental measures used in our study included those traditionally used in other birth cohort studies (eg, Bayley Scales of Infant and Toddler Development at age 3 years) but also included tests of visual habituation at 4 and 7 months as indicators of visual attention and information processing, followed by tests of infant memory and executive function (Tables 1 and 3). The NNNS was used within the first week of delivery and is a comprehensive assessment of both neurological integrity and behavioral function. Additionally, tests of emotion regulation and inhibitory control were administered to determine how not only cognitive skills but also emotional development may be altered by exposures to pesticides. This more comprehensive battery of tests will enhance our ability to determine whether and at what developmental period prenatal pesticide exposure alters the building blocks of later cognitive, motor, and emotional development.

Table 3. Description of neurological test, the domain of function assessed by the test, and age of administration, SAWASDEE[a] study, Thailand, 2017-2019.

Domain/test	Age (months)	Task description	Measure
Newborn neurological state regulation			
Behavioral Assessment Scale	Newborn	Interactive assessment of physiologic and motor organization arousal and ability with stimulation; ability to attend and remain alert	Habituation, orientation/attention, motor control, range of state, regulation of state, autonomic stability, reflexes
NNNS[b]	1	N/A[c]	N/A
Visual attention			
Visual habituation	4, 7, 10	Familiarization with a visual stimulus followed by pairing with a novel stimulus	Visual habituation, duration of first look, novelty preference
Visual paired comparison (VPC)	18, 30	5 faces and 4 abstract figure patterns during familiarization with 2 identical images; tested by pairing with a novel stimulus	Look duration, shift rate, novelty preference
Processing speed			
Visual expectation paradigm	18, 30	Orientation to target stimuli presented to L and R of midline with 10 baseline and 60 predictable trials	Mean reaction time
Encoding speed			
Continuous familiarization (CFT) task	18, 30	Paired faces presented, 1 of which changes from trial to trial while the other remains constant	Trials to criterion (consistent preference for novel target), look duration, shift rate
Memory			
Immediate recognition	18, 30	Derived from VPC	Mean novelty preference score (percentage time looking at novel stimulus), look duration, shift rate
Delayed recognition	18, 30	Familiarization with 3D object followed by visual identification when paired with new object	Mean novelty preference score
Deferred imitation	10, 18, 24, 30	Modeling series of events with objects with immediate and delayed reproduction of sequence	Mean percentage of target actions reproduced in correct order
Representational competence			
Tactual-visual cross-modal transfer	18, 30	Tactile familiarization with 3D object followed by visual identification when paired with new object	Mean novelty preference score, look duration, shift rate
Executive function			
A not B test (AB), looking version	10, 24	Toy hidden in counterbalanced hiding locations based on performance	Percentage correct trials
Language and overall development			
Bayley Scales of Infant and Toddler Development-III	36	Sensorimotor development, exploration and manipulation, concept formation, memory, receptive/expressive communication, perceptual motor integration, motor speed, planning, locomotion, coordination	Cognitive scaled score, gross motor scaled score, fine motor scaled score, receptive language scaled score, expressive language scaled score
Language Development Survey	24	Parent report of child's individual word and phrase expressions	Number of words, length of phrases
HOME[d]	12, 24	Structured, observational interview of parental interaction with child and overall environment	Responsivity, acceptance, organization, learning materials, involvement, variety
Emotion regulation and adjustment			

Domain/test	Age (months)	Task description	Measure
Labtab subtests: 1. Fear (a) spider, (b) masks; 2. Anger (c) maternal separation, (d) toy behind barrier; 3. Joy (e) puppets	12	Remote-controlled spider approaches child; masks displayed 1 at a time; mom leaves room for 30 seconds; toy that child has been playing with placed behind barrier; standardized dialogue between puppets presented by examiner	Occurrence and intensity of behaviors coded from tape (latency to response, eg, fear); intensity of physical and verbal responses (eg, facial, vocal, body)
Early Childhood Behavior Questionnaire (ECBQ)	12	Parent report checklist to survey child behavior	Parent rating of child behavior: negative affect, surgency-exhaust, effort control
Child Behavior Checklist (CBCL)	36	Primary caregiver report of behaviors during past 2 months	Emotionally reactive, anxious/depressed, somatic complaints, withdrawn, attention problems, aggressive behavior, sleep problems
Inhibitory control			
Snack delay	24	Child waits until instructed to retrieve a snack	Ability to delay in seconds
Crayon delay	24	Child gives crayons to draw but must wait	Latency to touch crayons
Toy prohibition by mother	24	Child in room full of toys but told by mother not to play with the toys	Frequency and type of mother intervention, frequency of child attention to toy (eg, look, touch)

[a]SAWASDEE: Study of Asian Women and their Offspring's Development and Environmental Exposures.

[b]NNNS: NICU Network Neurobehavioral Scale.

[c]N/A: not applicable.

[d]HOME: Home Observation for the Measurement of the Environment.

The Home Observation for the Measurement of the Environment (HOME) is a structured interview conducted with the primary caretaker and child in the home of each participant to observe and assess the physical environment, family structure/relationships, and learning environment for the child [18]. HOME was administered at 12 and 24 months. HOME has been extensively used across the world, with adaptations for different cultures, and is predictive of child cognitive development [19]. Mothers were administered the Test of Nonverbal Intelligence (TONI)-I as a nonverbal measure of intelligence in recognition of the effects the mother's education and cognitive abilities have on child neurodevelopment. The Depression Anxiety Stress Scale 21 (DASS-21) is a measure of maternal depression and anxiety that has been used in cross-cultural settings, including Asia [20]. The DASS-21 was administered at the first antenatal visit (1 week after birth) and at every subsequent child assessment visit to assess the known effects of maternal depression and anxiety on development. Although we asked families to estimate their monthly income, in low- and middle-income agricultural settings, monthly income estimates are difficult to determine and may not fully capture the economic health of a family. Therefore, based on the Economic and Social Research Council (ESRC) Research Group on Wellbeing in Developing Countries [21], we developed a family assets questionnaire to augment income estimates [22].

Statistical Analysis

Calculation of Power

We assumed that differences in neurobehavioral estimates for infants of mothers working on fruit/vegetable farms and those with mothers working on rice farms will be similar to differences observed between infants from preterm versus full-term pregnancies. Thus, Rose et al [23] provided preliminary estimates, from measurements observed at 24 months, on which to determine sample sizes. Table 4 provides the outcomes and estimated total sample sizes (for 1 sample) needed to find a difference between groups with 80% power using a 2-sided 2-group *t* test at the .05 significance level. The longitudinal design of our study provides further power than estimated. Based on these calculations, 300 infants should provide enough power to detect differences between groups.

Table 4. Total sample sizes needed to detect differences in outcomes with 80% power.

Neurodevelopmental outcomes	Full-term/lower exposure, mean (SD)	Preterm/higher exposure, mean (SD)	n
Memory			
Immediate recognition Rose visual paired comparison (VPC) task percentage novelty	57.05 (5.38)	55.33 (4.36)	258
Immediate recognition Fagan VPC task percentage novelty	59.55 (4.82)	57.22 (3.65)	108
Recall: elicited imitation (percentage correct)	59.3 (18.65)	52.08 (21.19)	242
Processing speed			
Encoding speed (trails to criterion)	8.7 (4.12)	11.47 (8.5)	186
Attention			
Mean look duration (composite)	–0.1 (0.58)	0.19 (0.79)	182
Shift rate (composite)	0.07 (0.72)	–0.15 (0.7)	330

Cohort Characteristics

The baseline characteristics of the study participants were analyzed and reported by study location (Chom Thong and Fang). All analyses were performed using SAS V.9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Participant Characteristics

In total, 1289 pregnant women were administered the recruitment-screening questionnaire. The primary reasons screened individuals were not eligible were as follows: (1) their gestational age was more than 16 weeks (n=266, 20.64%) or (2) they were agricultural workers or lived within 50 m of an agricultural field (n=603, 46.78%). Of those individuals eligible for the study (n=398, 30.88%), 394 (98.9%) women provided consent to join the study and were enrolled (Figure 1). Among the participants, 322 (81.7%) completed the study through the first neurodevelopmental examination of their child, the NNNS.

Of the 322 (Chom Thong n=216, 67.1%; Fang n=106, 32.9%) mother-child pairs with a completed NNNS, the mean age of SAWASDEE study participants at enrollment was 25 years (SD 5.3); see Table 5. The mean gestational age at enrollment was 9.9 weeks (SD 2.6 weeks). In Chom Thong, 47 of 216 (21.8%) and 165 of 216 (76.4%) women reported being legally married or living as married, respectively, compared to 1 of 106 (0.9%) and 102 of 106 (96.2%) women in Fang. The mean gestational age at birth was 38.5 weeks (SD 1.2 weeks), with gestational age determined by ultrasound or last menstrual period differing by participant site (n=105/216, 48.6%, and n=106/106, 100%, determined by ultrasound at Chom Thong and Fang, respectively). The mean infant birth weight was 3 kg (range 1.7-4.2 kg) and was not statistically significant (P<.05) between participants from Chom Thong and Fang.

The median and range of exposure measures and PON1 activity categorizations are shown in Table 6. Overall, exposure to OPs was higher in Fang than in Chom Thong in keeping with their crop application rates. Levels of pyrethroids were similar across sites. Overall, about 29 (9%), 126 (39.1%), and 167 (51.8%) of 322 participants had low, normal, and high PON1 activity, with more participants in Fang having normal activity than in Chom Thong.

Table 5. Descriptive characteristics of the SAWASDEE[a] cohort, Thailand, 2017-2019.

Variable	SAWASDEE (N=322)	Chom Thong (n=216)	Fang (n=106)
Age of mother at enrollment (years), mean (SD)	25.0 (5.3)	25.5 (5.3)	23.9 (5.0)
Body mass index (BMI) of mother at visit 1 (kg/m^2), mean (SD)	22.9 (5.3)	22.7 (4.9)	23.3 (6.2)
Missing, n (%)	1 (0.03)	0	1 (0.9)
Ethnicity of the mother, n (%)			
Thai	204 (63.4)	196 (90.7)	8 (7.5)
Hmong	10 (3.1)	10 (4.6)	0
Thai Yai	25 (7.8)	1 (0.5)	24 (22.6)
Karen (Pagayo)	6 (1.9)	6 (2.8)	0
Burmese	4 (1.2)	2 (0.9)	2 (1.9)
Akha	5 (1.5)	0 (0.0)	5 (4.7)
Pa-Long (Dara-ang)	36 (11.2)	0 (0.0)	36 (34)
Lahu	31 (9.6)	0 (0.0)	31 (29.2)
Lawa	1 (0.3)	1 (0.5)	0
Mother, highest education level completed, n (%)			
None, never attended school	58 (18.4)	12 (5.6)	46 (43.1)
Primary 1-6	47 (14.4)	19 (8.9)	28 (26.1)
Junior high/high school	106 (32.4)	86 (39.6)	20 (18.3)
High school/did not graduate	70 (21.4)	63 (29.3)	7 (6.2)
Diploma/technical school equivalent	28 (8.4)	24 (11.4)	4 (3.8)
Attended college but did not graduate	1 (0.4)	1 (0.6)	1 (0.9)
College graduate or more	12 (3.4)	11 (5.5)	0
Mother able to read Thai, n (%)			
Yes	260 (80.4)	206 (95.1)	54 (50.9)
No	62 (19.4)	10 (4.9)	52 (49.1)
Mother able to write in Thai, n (%)			
Yes	262 (81.4)	205 (94.3)	57 (53.8)
No	60 (18.4)	11 (5.7)	49 (46.1)
Household income (Thai baht)[b], mean (SD)	10615.1 (8336.9)	11572.4 (9499.0)	8709.6 (4818.4)
Missing, n	11	9	2
Number of people living in households, mean (SD)	5.2 (2.5)	4.9 (2.2)	5.7 (3.0)
Missing, n	22	15	7
Marital status, n (%)			
Legally married	47 (14.4)	46 (21.9)	1 (0.9)
Living as married	268 (83.4)	166 (76.6)	102 (96.2)
Widowed	2 (0.4)	2 (0.2)	0
Divorced	2 (0.4)	2 (0.2)	0
Separated	3 (0.4)	0	3 (2.8)
Mother working in agriculture during pregnancy, n (%)[c]			
Yes	258 (80.4)	182 (84.3)	76 (72.4)
No	63 (19.6)	34 (15.7)	29 (27.6)
Missing, n	1	0	1

Variable	SAWASDEE (N=322)	Chom Thong (n=216)	Fang (n=106)
Maternal smoking during pregnancy, n (%)			
Yes	4 (1.3)	2 (0.9)	2 (1.9)
No	317 (98.7)	214 (99.1)	103 (98.1)
Missing, n	1	0	1
Gestational age (weeks), mean (SD)			
At enrollment	9.9 (2.6)	9.7 (2.6)	10.2 (2.5)
Missing, n	3	0	3
At birth	38.5 (1.2)	38.5 (1.1)	38.4 (1.2)
Missing, n	5	4	1
Infant birth weight (kg), mean (SD)	3.0 (0.4)	3.0 (0.4)	2.9 (0.4)
Missing, n	2	2	0
Infant's sex, n (%)			
Male	159 (49.5)	105 (48.8)	54 (50.4)
Female	162 (50.5)	110 (51.2)	52 (49.5)
Missing, n	1	1	0

[a]SAWASDEE: Study of Asian Women and their Offspring's Development and Environmental Exposures.

[b]A currency exchange rate of 1 Thai baht = US $0.03 is applicable.

[c]Ever/never variable, participants asked in each trimester, and if they ever responded yes, they were considered yes.

Table 6. Concentrations of exposure biomarkers in the SAWASDEE[a] study, 2017-2022 (N=322).

Biomarker	SAWASDEE (N=322)		Chom Thong (n=216)		Fang (n=106)	
	Frequency of detection (FOD), %	Median (range)	FOD, %	Median (range)	FOD, %	Median (range)
Exposure measures						
ΣDAP[b] (nmol/L)	100	86.6 (42.6-2852)	100	79.7 (42.6-2852)	100	150 (43.9-1942)
ΣDEAP[c] (nmol/L)	100	46.9 (7.3-1714)	100	40.4 (7.3-511)	100	98.3 (8.6-1714)
ΣDMAP[d] (nmol/L)	48	35.5 (35.31-2758)	67	35.5 (<35.3-2758)	47	<35.3 (<35.3-275)
TCPY[e] (ng/mL)	98	5.2 (<0.31-41.3)	100	5.1 (0.61-41.3)	94	5.36 (<0.31-40.1)
3PBA[f] (ng/mL)	84	0.58 (<0.31-19.8)	86	0.61 (<0.31-6.1)	80	0.51 (<0.31-19.8)
PON1[g] activity						
Low	9	N/A[h]	9	N/A	8	N/A
Normal	39	N/A	37	N/A	45	N/A
High	52	N/A	54	N/A	47	N/A

[a]SAWASDEE: Study of Asian Women and their Offspring's Development and Environmental Exposures.

[b]DAP: dialkylphosphate (ΣDAP=sum of all DAP metabolites).

[c]DEAP: diethyl alkylphosphate (ΣDEAP=sum of all DEAP metabolites).

[d]DMAP: dimethyl alkylphosphate (ΣDMAP=sum of all DMAPs).

[e]TCPY: 3,5,6-trichloropyridinol.

[f]3PBA: 3-phenoxybenzoic acid.

[g]PON1: paraoxonase 1.

[h]N/A: not applicable.

Discussion

Principal Findings

The SAWASDEE study was successfully established to fill critical gaps in the literature by measuring exposure multiple times during each trimester of pregnancy, while tracking neurodevelopmental trajectories in infancy and early childhood. By establishing the association between exposure biomarkers during early-to-late pregnancy and these neurodevelopmental trajectories, we will be able to examine windows of increased susceptibility to pesticide exposure. This information may result in specification of vulnerability, resulting in recommendations for reduction in adverse neurodevelopmental outcomes.

Our enrollment and participant rates were notable, provided the low population density and complexities of travel in these regions. The terrain is mountainous and winding; participants had to often rely on public transportation to make the study visits. We tried to align our study visits as closely as possible to their antenatal visits for convenience and reimbursed participants for travel. However, in some of the worst cases, participants traveled for up to 4 hours to attend these visits. Their loyalty to our study was largely a result of the close relationship our study nurses and RAs developed with the participants and the immense trust our participants had in them. Although we believe that the relationships that were established between field staff and study participants were essential in preserving study retention, it is also possible there were behavioral changes in pesticide practices over time due to unintentional influence by field staff or involvement in the study. Analysis of the KAP questionnaires from our pilot study revealed that there was an increase in pesticide-related knowledge among pregnant women and that influenced changes in pesticide practices [24]. In this study, we did observe that many women stop working in agricultural-related fields late in pregnancy; however, we were unable to discern whether this is a result of the physical challenges associated with pregnancy, especially in the third trimester of pregnancy; a natural shift in agricultural tasks required; or behavioral change from participating in our study. We hope to disentangle the reason(s) for a reduction in agricultural work late in pregnancy in future analyses using the longitudinal KAP data collected in our study.

Limitations

Our study is not without limitations. We may have some differential bias in gestational age among sites, which we described above. There is potential for exposure misclassification because of the contribution of preformed environmental metabolites to the measured urinary metabolite levels. However, given that our population is experiencing occupational exposures that occur after known pesticide application events, we expect this contribution to be smaller than if we were evaluating background dietary exposures. We also did not measure all pesticides to which participants may have been exposed. Although we have basic dietary information for mothers during pregnancy, we could not conduct a thorough assessment of dietary information, such as a food frequency questionnaire, largely because of funding issues. In addition, some of our neurological tests have no known cultural norms for comparison, but our pilot studies have provided insight into how this can be addressed in our data analyses [14].

Despite our study's limitations, this is still the first study to evaluate these neurodevelopmental outcomes in Thailand and to provide refined exposure measurements during pregnancy.

Strengths

Our study has several strengths. We have time-resolved and highly sensitive exposure measures from all trimesters of pregnancy in our participants. This includes 2 distinct exposure scenarios: long-term, lower-dose pesticide exposure, and high-dose, intermittent pesticide exposure. The robustness of exposure and outcome data will allow investigators to evaluate numerous scientific questions and ultimately improve the generalizability of associations between pesticide exposure and neurodevelopmental outcomes. The majority of previous studies have been conducted using cohorts from high-income countries and examination in LMICs is lacking. The success of our study recruitment and retention is largely attributed to the strong community-centered nature and the respect shown to the field research staff by study participants. We found this to be especially true within the Thai culture—individuals have a high level of respect for health care practitioners. The study also includes highly refined neurodevelopment assessment with sensitive measures of early neurointegrity that measure the basis of later cognitive and motor development. Previous studies have used clinical measures that are relatively less sensitive to subtle and early adverse effects. We can evaluate windows of vulnerability as they relate to specific neurodevelopmental processes and the trajectory of development. In addition, this study assesses not only cognitive and motor skills but also inhibitory control and emotion regulation, not previously studied with behavioral measures. The NNNS, in addition to the other neurodevelopmental assessments included in the study, creates a robust database of neurodevelopment, which can be used to evaluate several scientific questions related to neurodevelopment, including evaluating trajectories of neurodevelopment. The prospective longitudinal data in our study present a valuable resource for evaluating many scientific questions. The SAWASDEE study offers potential collaborators an opportunity to work with robust estimates of exposure and neurodevelopment. The number of supplemental studies that are part of the SAWASDEE study continues to increase, and thus, the database continues to grow, offering investigators an opportunity to test several hypotheses.

Conclusion

The SAWASDEE birth cohort study provides information essential for risk assessment paradigms addressing the risk of prenatal pesticide exposure and neurodevelopment. The cohort is unique in that it is designed with highly refined exposure and neurodevelopmental data with the ability to determine neurodevelopmental trajectories early in infancy with the hope of early intervention. Successful enrollment followed by high rates of retention and participation in the study provides a unique opportunity for evaluating maternal pesticide exposure and child neurodevelopmental outcomes.

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Authors' Contributions

Conception and design of study were performed by DBB, NF, TP, PS, PBR, and PP; funding acquisition was done by DBB, NF, CJM, and MMS; cohort development was performed by DBB, NF, TP, WN, and PP; exposure assessment was conducted by DBB, TP, PBR, BOB, and PP; field data collection was conducted by WN, TP, CD, and PS; neurodevelopmental assessments were performed by PS, SS, and CD; data cleaning and maintenance were conducted by BOB, WN, DBB, and NF; data analysis was performed by DBB, BOB, and NF; manuscript preparation was conducted by BOB, DBB, and NF; and manuscript review/editing was performed by all authors.

Conflicts of Interest

The authors have no competing financial or other interests that could interfere or be perceived to interfere with the study conduct and data evaluation.

References

1. Hertz-Picciotto I, Sass JB, Engel S, Bennett DH, Bradman A, Eskenazi B, et al. Organophosphate exposures during pregnancy and child neurodevelopment: recommendations for essential policy reforms. PLoS Med 2018 Oct 24;15(10):e1002671 [FREE Full text] [doi: 10.1371/journal.pmed.1002671] [Medline: 30356230]
2. Tessari L, Angriman M, Díaz-Román A, Zhang J, Conca A, Cortese S. Association between exposure to pesticides and ADHD or autism spectrum disorder: a systematic review of the literature. J Atten Disord 2022 Jan 22;26(1):48-71. [doi: 10.1177/1087054720940402] [Medline: 32697136]
3. Biosca-Brull J, Pérez-Fernández C, Mora S, Carrillo B, Pinos H, Conejo NM, et al. Relationship between autism spectrum disorder and pesticides: a systematic review of human and preclinical models. Int J Environ Res Public Health 2021 May 13;18(10):5190 [FREE Full text] [doi: 10.3390/ijerph18105190] [Medline: 34068255]
4. Food and Agricultural Organization. FAO Stat: Pesticides Use. 2021. URL: http://www.fao.org/faostat/en/#data/RP [accessed 2021-11-01]
5. Muñoz-Quezada MT, Lucero BA, Iglesias VP, Muñoz MP, Cornejo CA, Achu E, et al. Chronic exposure to organophosphate (OP) pesticides and neuropsychological functioning in farm workers: a review. Int J Occup Environ Health 2016 Jan 29;22(1):68-79 [FREE Full text] [doi: 10.1080/10773525.2015.1123848] [Medline: 27128815]
6. Sapbamrer R. Pesticide use, poisoning, and knowledge and unsafe occupational practices in Thailand. New Solut 2018 Aug 23;28(2):283-302. [doi: 10.1177/1048291118759311] [Medline: 29473443]
7. Laohaudomchok W, Nankongnab N, Siriruttanapruk S, Klaimala P, Lianchamroon W, Ousap P, et al. Pesticide use in Thailand: current situation, health risks, and gaps in research and policy. Hum Ecol Risk Assess 2021 Aug 27;27(5):1147-1169 [FREE Full text] [doi: 10.1080/10807039.2020.1808777] [Medline: 34290491]
8. Panuwet P, Siriwong W, Prapamontol T, Ryan PB, Fiedler N, Robson MG, et al. Agricultural pesticide management in Thailand: situation and population health risk. Environ Sci Policy 2012 Mar;17:72-81 [FREE Full text] [doi: 10.1016/j.envsci.2011.12.005] [Medline: 22308095]
9. Wongta A, Sawarng N, Tongchai P, Sutan K, Kerdnoi T, Prapamontol T, et al. The pesticide exposure of people living in agricultural community, northern Thailand. J Toxicol 2018 Nov 29;2018:4168034-4168037 [FREE Full text] [doi: 10.1155/2018/4168034] [Medline: 30631352]

10. Barr DB, Wong L, Bravo R, Weerasekera G, Odetokun M, Restrepo P, et al. Urinary concentrations of dialkylphosphate metabolites of organophosphorus pesticides: National Health and Nutrition Examination Survey 1999-2004. Int J Environ Res Public Health 2011 Aug 25;8(8):3063-3098 [FREE Full text] [doi: 10.3390/ijerph8083063] [Medline: 21909292]
11. Whyatt RM, Garfinkel R, Hoepner LA, Andrews H, Holmes D, Williams MK, et al. A biomarker validation study of prenatal chlorpyrifos exposure within an inner-city cohort during pregnancy. Environ Health Perspect 2009 Apr;117(4):559-567 [FREE Full text] [doi: 10.1289/ehp.0800041] [Medline: 19440494]
12. Kochanska G, Knaack A. Effortful control as a personality characteristic of young children: antecedents, correlates, and consequences. J Pers 2003 Dec;71(6):1087-1112. [doi: 10.1111/1467-6494.7106008] [Medline: 14633059]
13. Assanangkornchai S, Sam-Angsri N, Rerngpongpan S, Lertnakorn A. Patterns of alcohol consumption in the Thai population: results of the National Household Survey of 2007. Alcohol Alcohol 2010 Mar 26;45(3):278-285. [doi: 10.1093/alcalc/agq018] [Medline: 20348437]
14. Naksen W, Prapamontol T, Mangklabruks A, Chantara S, Thavornyutikarn P, Srinual N, et al. Associations of maternal organophosphate pesticide exposure and PON1 activity with birth outcomes in SAWASDEE birth cohort, Thailand. Environ Res 2015 Oct;142:288-296 [FREE Full text] [doi: 10.1016/j.envres.2015.06.035] [Medline: 26186137]
15. Prapamontol T, Sutan K, Laoyang S, Hongsibsong S, Lee G, Yano Y, et al. Cross validation of gas chromatography-flame photometric detection and gas chromatography-mass spectrometry methods for measuring dialkylphosphate metabolites of organophosphate pesticides in human urine. Int J Hyg Environ Health 2014 Apr;217(4-5):554-566. [doi: 10.1016/j.ijheh.2013.10.005] [Medline: 24280209]
16. Baker SE, Olsson AO, Barr DB. Isotope dilution high-performance liquid chromatography-tandem mass spectrometry method for quantifying urinary metabolites of synthetic pyrethroid insecticides. Arch Environ Contam Toxicol 2004 Apr;46(3):281-288. [doi: 10.1007/s00244-003-3044-3] [Medline: 15195798]
17. Olsson AO, Baker SE, Nguyen JV, Romanoff LC, Udunka SO, Walker RD, et al. A liquid chromatography-tandem mass spectrometry multiresidue method for quantification of specific metabolites of organophosphorus pesticides, synthetic pyrethroids, selected herbicides, and deet in human urine. Anal Chem 2004 May 01;76(9):2453-2461. [doi: 10.1021/ac0355404] [Medline: 15117183]
18. Caldwell BM, Bradley RH. Home Observation for Measurement of the Environment: Administration Manual. Tempe, AZ: Family & Human Dynamics Research Institute, Arizona University; 2003.
19. Bradley RH, Corwyn RF, Whiteside-Mansell L. Life at home: same time, different places; an examination of the HOME inventory in different cultures. Early Dev Parent 1996 Dec;5(4):251-269. [doi: 10.1002/(sici)1099-0917(199612)5:4<251::aid-edp137>3.0.co;2-i]
20. Oei TPS, Sawang S, Goh YW, Mukhtar F. Using the Depression Anxiety Stress Scale 21 (DASS-21) across cultures. Int J Psychol 2013 Dec;48(6):1018-1029. [doi: 10.1080/00207594.2012.755535] [Medline: 23425257]
21. Clarke R. Measuring Wealth Across Seven Thai Communities. 2006. URL: http://www.bath.ac.uk/soc-pol/welldev/research/workingpaperpdf/wed17.pdf [accessed 2020-11-01]
22. Howe LD, Galobardes B, Matijasevich A, Gordon D, Johnston D, Onwujekwe O, et al. Measuring socio-economic position for epidemiological studies in low- and middle-income countries: a methods of measurement in epidemiology paper. Int J Epidemiol 2012 Jun 21;41(3):871-886 [FREE Full text] [doi: 10.1093/ije/dys037] [Medline: 22438428]
23. Rose SA, Feldman JF, Jankowski JJ. Information processing in toddlers: continuity from infancy and persistence of preterm deficits. Intelligence 2009 May 01;37(3):311-320 [FREE Full text] [doi: 10.1016/j.intell.2009.02.002] [Medline: 20161244]
24. Lorenz AN, Prapamontol T, Narksen W, Srinual N, Barr DB, Riederer AM. Pilot study of pesticide knowledge, attitudes, and practices among pregnant women in northern Thailand. Int J Environ Res Public Health 2012 Sep 19;9(9):3365-3383 [FREE Full text] [doi: 10.3390/ijerph9093365] [Medline: 23202693]

Abbreviations

3PBA: 3-phenoxybenzoic acid
DAP: dialkylphosphate
HOME: Home Observation for the Measurement of the Environment
IQ: intelligence quotient
KAP: Knowledge, Attitude, and Practices
LMIC: low-/middle-income country
NNNS: NICU Network Neurobehavioral Scale
OP: organophosphate
PON1: paraoxonase 1
QA/QC: quality assurance and control
RA: research assistant
SAWASDEE: Study of Asian Women and their Offspring's Development and Environmental Exposures
SOP: standard operating procedures
TCPY: 3,5,6-trichloropyridinol

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Protocol

Defining the Pre-exposure Prophylaxis Care Continuum Among Recently Incarcerated Men at High Risk for HIV Infection: Protocol for a Prospective Cohort Study

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Abstract

Background: HIV disproportionately impacts criminal justice–involved individuals, including men who experience incarceration. Men make up the vast majority of those experiencing incarceration as well as those newly diagnosed with HIV infection. Pre-exposure prophylaxis (PrEP) is a highly effective biomedical intervention that significantly reduces the risk of HIV acquisition. However, implementation in criminal justice systems is limited. Little is known about effective PrEP implementation and use in this unique public health context.

Objective: The aim of this study is to characterize the experience of implementing PrEP clinical care in a criminal justice setting for men vulnerable to HIV acquisition.

Methods: This article describes a PrEP care continuum for men experiencing incarceration who are at increased risk of HIV acquisition, which can help conceptualize approaches to evaluating PrEP implementation.

Results: The outlined study will enroll 100 men experiencing incarceration at high risk for HIV acquisition prior to release into the community. The goal is to initiate PrEP prior to release and link individuals to PrEP providers in the community, capturing barriers and facilitators to PrEP use during this uniquely vulnerable time period for HIV acquisition.

Conclusions: Based on the proposed care continuum and what is known about HIV risk and prevention efforts in the criminal justice context, we outline key future research efforts to better understand effective approaches to preventing HIV infection among this vulnerable population. The described approach presents a powerful public health opportunity to help end the HIV epidemic.

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KEYWORDS

HIV; PrEP; criminal justice system; incarceration; criminal justice; pre-exposure prophylaxis; prison system

Introduction

There are approximately 38,000 new HIV diagnoses in the United States annually [1]. Men make up the vast majority of new diagnoses, accounting for over 80% of these cases [1]. The most frequent mechanisms of HIV acquisition are sexual contact and injection drug use [1]. Men who have sex with men (MSM), including men who participate in transactional sex with other men, have a high burden of HIV and comprise approximately 70% of all HIV diagnoses [1,2]. There are also significant racial disparities within the United States among incident cases of HIV annually, with racial and ethnic minorities comprising a

disproportionate number of new cases compared to White individuals. Black/African American men account for 39% of new HIV diagnoses, yet represent only 18% of the general male population, and Hispanic/Latino men accounted for 29% of new HIV diagnoses while only making up 13% of the general population [3]. Among MSM, Whites have a 1 in 11 lifetime risk of HIV acquisition, compared to Black/African American men, who have a 1 in 2 risk and Hispanic/Latino MSM, who have a 1 in 5 lifetime risk [4]. The most frequent mechanisms of HIV acquisition are sexual contact (88%) and injection drug use (7%-11%) [1].

Criminal justice–involved individuals in the United States are among the most vulnerable to and heavily impacted by HIV [5]. Individuals with a history of incarceration have a rate of HIV infection that is 3-5 times that of their nonincarcerated counterparts [6]. One in 7 people living with HIV pass through the criminal justice system each year [7]. The rate of incarceration for men is 10 times greater than that for women [8]. Black/African American men are also 6 times as likely and Hispanic/Latino men are more than twice as likely as White men to be incarcerated [9]. Criminal justice involvement is highly prevalent among people who inject drugs, with an estimated 72.2% reporting a history of incarceration [5]. Following release, criminal justice–involved individuals are more likely to participate in sexual and substance use behaviors, including injection drug use, that place them at increased risk of HIV infection and overdose [10-17]. Complex, intersecting social and structural forces place racial and ethnic minority populations in particular at increased vulnerability to both criminal justice involvement and HIV acquisition.

Although incarceration represents an opportunity to test criminal justice–involved individuals who are at risk for HIV and link them to HIV and/or pre-exposure prophylaxis (PrEP) care in the community as needed, surveys conducted in criminal justice settings show uneven uptake of HIV testing, preventive, and treatment services among criminal justice–involved individuals [18]. PrEP is currently available as an oral medication in two forms: tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) and tenofovir alafenamide and emtricitabine (TAF/FTC). Both medications are highly effective at preventing HIV transmission among MSM [19,20]. TDF/FTC has also been shown to be effective at preventing HIV transmission through receptive vaginal intercourse [21] as well as injection drug use [22]. Importantly, research has shown different concentrations of TDF/FTC in vaginal compared to anorectal tissue, leading to different approaches to initiate PrEP and measure adherence among men and women [23].

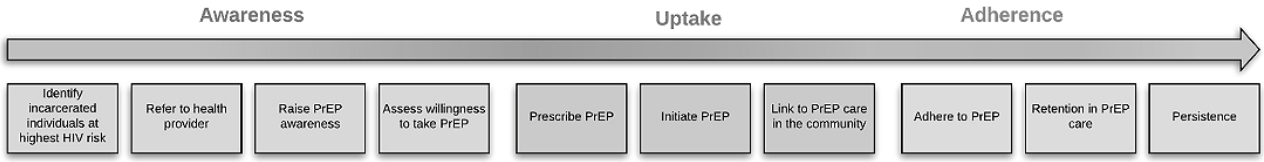
Despite its effectiveness, PrEP uptake in real-world settings among multiply marginalized populations, including criminal justice–involved individuals, remains low [24]. Although some research has demonstrated PrEP interest among criminal justice–involved individuals [25,26], little is known about the barriers to PrEP implementation during incarceration or the period immediately postrelease from incarceration [27,28]. What is known is that there are expressed reasons to decline PrEP initiation unique to the correctional setting such as institutional mistrust and the high degree of uncertainty in the postrelease period [29,30]. A PrEP care continuum is a useful conceptual tool for identifying facilitators and barriers to PrEP use, adherence, retention, and persistence in PrEP care [31]. In this article, we propose a modified PrEP care continuum for criminal justice–involved populations and then describe an approach to implementing and assessing PrEP care among criminal justice–involved men at high risk of HIV infection.

Methods

Defining the PrEP Care Continuum for Criminal Justice–Involved Populations

The PrEP care continuum can help to conceptualize and structure PrEP programming in the criminal justice system, including PrEP awareness, uptake, and adherence, and retention in PrEP care [31]. The PrEP care continuum has been used as a tool to better understand the barriers and facilitators to PrEP care for other vulnerable populations [32-34], but it has yet to be applied to or extensively studied in the criminal justice–involved population [35]. Adapting a PrEP continuum unique to criminal justice environments may help clinical providers and policy makers to identify gaps and barriers to uptake and develop specific programming to address them. Ideally, these efforts will enable successful identification of individuals who meet the clinical criteria for PrEP use, as well as frame the development of effective interventions to increase PrEP uptake, adherence, and retention in care, particularly during the postrelease period (Figure 1).

Figure 1. PrEP care continuum for incarcerated populations. PrEP: pre-exposure prophylaxis.



There are a number of elements to consider for the successful implementation of its use within the criminal justice setting. Although many individuals who pass through the criminal justice system are at increased risk for HIV, the Centers for Disease Control and Prevention (CDC) provides guidance for the clinical criteria for PrEP use that should be used when identifying individuals that are indicated for PrEP [36]. Additionally, for PrEP to be effective, adherence to the medication is crucial [22,37]. Finally, persistence in PrEP care is defined as maintaining all aspects of recommended PrEP

clinical care during a defined period (ie, attending care appointments, attending lab visits, taking medication as prescribed) [38]. For individuals with ongoing HIV risk, persistence in PrEP care should extend for as long as it is indicated.

Within the three phases of the continuum (PrEP awareness, uptake, and adherence), the steps are the following: (1) identify incarcerated individuals at highest risk for contracting HIV, (2) refer to health care provider within the criminal justice system, (3) increase PrEP awareness among those individuals, (4) assess willingness to take PrEP, (5) prescribe, and (6) initiate PrEP while still incarcerated, (7) link to PrEP care in the community, (8) support adherence to PrEP, (9) retain individuals in care, and (10) support persistence in PrEP care. This multistep process highlights the potential complexity of implementing a clinical intervention within a criminal justice context and then linking individuals to clinical care in the community upon release.

The challenges of successfully defining and implementing a care continuum have been more thoroughly studied among individuals who are living with HIV. Interventions to diagnose, initiate treatment for, and link people living with HIV to care in the community have become an important public health priority with a significant impact on the trajectory of the epidemic in the United States [5,39]. In order to broaden the public health impact of using the criminal justice system as a potential focal point for effective HIV prevention interventions, it is important to understand effective implementation strategies and interventions to promote PrEP uptake among the diverse populations that are both disproportionately impacted by HIV and criminal justice involvement.

The PrEP Care Continuum

Identify Incarcerated Individuals at Highest Risk for Contracting HIV

The variability in the availability of HIV screening and preventive services in the correctional setting presents one of the biggest challenges to successfully implementing PrEP care in the criminal justice system. This challenge is compounded in part by the potentially high volume of criminal justice–involved individuals who meet CDC criteria for PrEP initiation, but who may not self-identify as being at risk for HIV. There may be a number of reasons why individuals do not self-identify as being at risk for HIV acquisition including stigma, fear of legal repercussions for disclosing criminal behavior, or a lack of awareness of the risk of acquiring HIV from certain behaviors [40-42]. Perhaps the greatest public health benefit of PrEP use would be among pretrial individuals who are detained in the country's jail systems [43]. With a high volume of individuals who often spend a short period of time in confinement, quickly identifying individuals who are at increased risk of HIV acquisition and then linking them to HIV preventive care in the community poses significant challenges but could have a significant public health benefit. A different approach for identifying individuals who would benefit from HIV preventive care among the sentenced population, many of whom spend months or years incarcerated, warrants tailored clinical tools that acknowledge unique HIV acquisition risks not currently addressed by CDC guidelines, which focus on risk behaviors during the prior 6 months [43]. For individuals incarcerated for greater than 6 months, their risk for HIV acquisition is unlikely to be captured using this criterion, particularly as individuals prepare for reentry into the community postincarceration [18].

Refer to Health Care Provider Within the Criminal Justice System

For individuals at an increased risk of HIV acquisition, referral to a health care provider in the criminal justice setting who could order HIV, sexually transmitted infection, and other lab testing necessary to initiate PrEP is an important and often limiting step. Given the variability in access to medical providers in the criminal justice setting, particularly providers who are knowledgeable about PrEP, this may present a unique challenge to PrEP care implementation [44]. The identification and training of health care providers who could assess for PrEP eligibility and initiate the clinical care associated with its use will be important in this setting [43,44].

Increase PrEP Awareness Among Those Individuals

The little that is known about PrEP awareness in the criminal justice system has demonstrated a lack of knowledge but significant interest [24-26]. Encounters with health care providers and public health support staff in the criminal justice setting can serve as important opportunities to discuss the benefits of PrEP use and improve an individual's understanding of their own risk of HIV acquisition.

Assess Interest in, Willingness to, and Barriers to Taking PrEP

Although there is interest among incarcerated individuals in taking PrEP while in the criminal justice setting [45], it is important to characterize PrEP initiation patterns, hesitancy related to its use, and the influence of barriers both within the criminal justice system and upon reentry into the community. Components of this element of the PrEP care continuum are largely unknown and are likely to vary given the diverse makeup of those who experience incarceration, their socioeconomic context in the community, and the behaviors that put individuals at increased risk of HIV acquisition.

Prescribe PrEP

Many criminal justice–involved individuals experience barriers to accessing primary and preventive clinical care in the community [46]. Therefore, completing the clinical assessments and laboratory testing necessary to initiate PrEP during a period of detention provides significant advantages in promoting PrEP use. Ensuring individuals are HIV-negative, evaluating individuals for renal dysfunction, and assessing them for hepatitis B infection—disease processes that all disproportionately impact the criminal justice–involved population—facilitates identification of the few potential clinical limitations for PrEP use [47,48]. In addition to limited accessibility of PrEP providers and the clinical assessment needed to safely initiate PrEP, cost of the medication to criminal justice institutions may pose a barrier to its implementation. Onsite availability and prompt dispensation, particularly for

pretrial individuals who may be spending only a brief period in detention, may pose a logistical challenge to criminal justice institutions and their clinical service providers [43].

Initiate PrEP Care While Still Incarcerated

There is a well-documented risk of HIV infection among criminal justice–involved individuals during the period immediately following release [46]. Ideally, criminal justice–involved individuals at increased risk for HIV acquisition would initiate PrEP prior to release. This strategy would also allow for observation and evaluation of side effects, while providing an opportunity to initiate a protective biomedical intervention that can be continued in the community. Providing individuals with medication upon release may improve adherence in the crucial postrelease period, while reducing a potential barrier to HIV preventive care in this potentially chaotic period [29,37].

Link to PrEP Care in the Community

Linkage to care in the community poses another significant challenge to PrEP care among criminal justice–involved individuals. Currently, providing continuity of care for both pretrial individuals as well as those sentenced to a period of confinement poses a challenge, particularly for those who are HIV-positive, are impacted by substance use disorder, or have general medical needs [49,50]. The availability and accessibility of PrEP care providers is likely to vary significantly based on geographic region, an individual's insurance status, and the existence of other health linkage programs unrelated to PrEP care [51,52].

Support Adherence to PrEP

Although providing incarcerated individuals with a supply of medication upon release is likely to improve adherence by reducing a crucial barrier to PrEP access, adherence during the postrelease period is largely unknown and unstudied [43,53]. Given the importance of adherence to PrEP's effectiveness, adherence patterns during the postrelease period represent an important knowledge gap and one that is likely to require tailored interventions to improve. This study uses both biological markers of PrEP adherence through dried blood spot measurements of TDF/FTC concentrations as well as self-reported measures of PrEP adherence.

Support Retention and Persistence in PrEP Care

Retention and persistence in PrEP care pose a number of challenges in "real-world" community settings [31]. It is likely, although largely unknown, that retention and persistence in PrEP care will also pose a significant albeit unique challenge to those with criminal justice involvement given the barriers that have been well documented in retaining individuals with criminal justice involvement in HIV care [31], hepatitis C care, general primary care, and preventive care, to name a few [54]. By establishing a prospective cohort of individuals returning to the community postincarceration, the outlined methodological approach will allow for the monitoring of changes in HIV acquisition risk behaviors as well as indications for continued PrEP use.

Ethics Approval

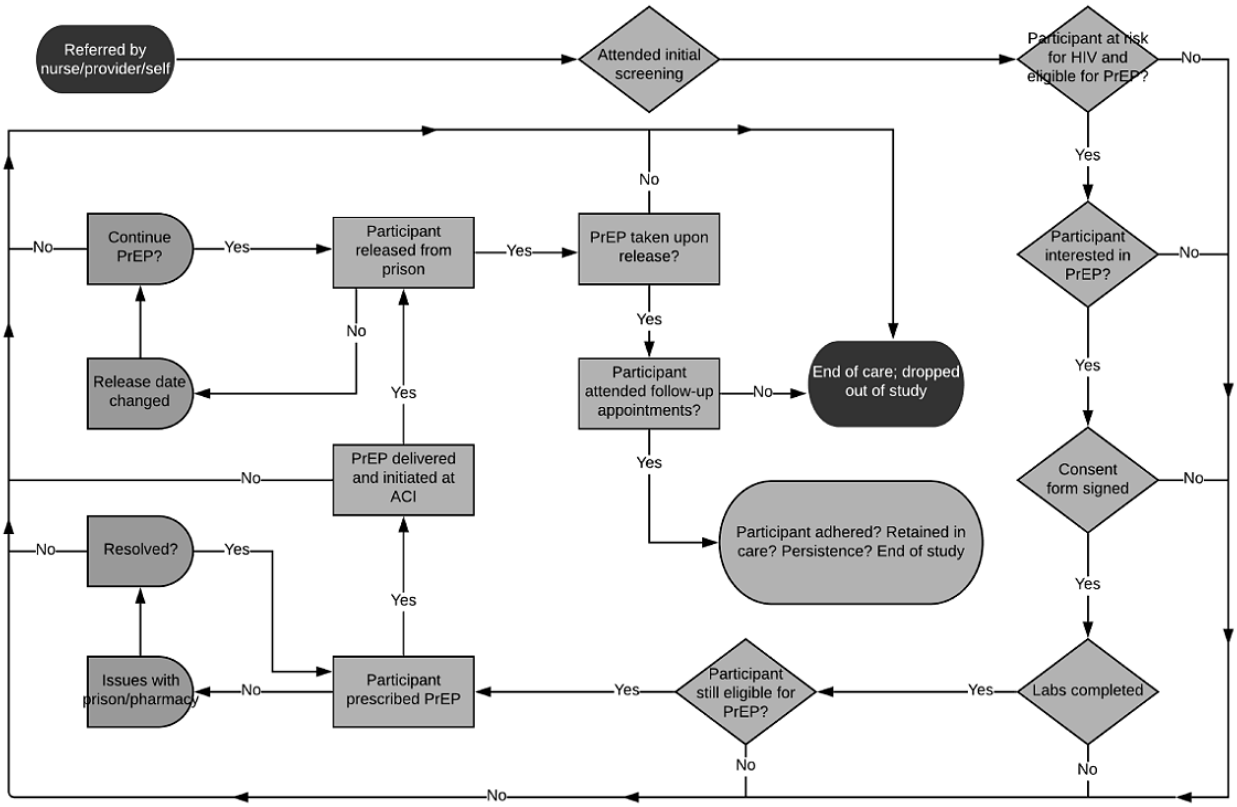
The study underwent review and approval by the Lifespan Institutional Review Board's special committee on research conducted among incarcerated populations. Additional review and approval was provided by the Rhode Island Department of Corrections' Ethical Review Advisory Group.

Results

Given that men make up more than 90% of individuals who are incarcerated, and also comprise a majority of new HIV cases, we have proposed a study that focuses on PrEP uptake among men currently experiencing incarceration. This includes all men experiencing incarceration, including those detained in pretrial facilities and those sentenced to a period of confinement. The study is an open, prospective cohort study of 100 men who are currently incarcerated at the Rhode Island Department of Corrections (RIDOC) and who are scheduled to be released within one month of being enrolled in the study. RIDOC is a unique study environment, as it is a unified correctional system with all statewide pretrial and sentenced individuals detained on one campus under a single administrative structure. Every individual processed at RIDOC undergoes a nurse-led medical evaluation at intake (Figure 2). Individuals who report behaviors that would place them at increased HIV risk (condomless sex with multiple sexual partners; sex work and/or transactional sex; or injection drug use) are then referred to a general medical provider for potential study enrollment and/or initiation of PrEP clinical care through standard medical screening procedures. The existing nurse evaluation is brief and not intended to be a comprehensive evaluation of HIV acquisition risk. Other staff and medical providers can also refer individuals to the PrEP provider and program if they determine an individual to be at increased risk of HIV acquisition.

During the meeting with the PrEP clinical provider, the provider and patient discuss HIV risk, the provider assesses the patient's baseline knowledge and interest in using PrEP, and the provider requisitions the necessary lab work and obtains the patient's medical history to determine whether the patient is a candidate for PrEP use per CDC guidelines. For those interested in participating in the study, written informed consent is obtained and clinical documentation is shared with the research team at a community partner site. A PrEP navigator then subsequently meets with the patient and helps to coordinate postrelease PrEP care including measures of adherence and ongoing HIV acquisition risk. PrEP clinical care and enrollment in this study are centered largely on the pretrial population housed in RIDOC's intake facility, which saw approximately 13,000 commitments during 2019 [55].

Figure 2. Implementing PrEP care continuum for criminal justice–involved populations. ACI: adult correctional institutions; PrEP: pre-exposure prophylaxis.



Once an interested individual is clinically screened and determined to be eligible for PrEP, TDF/FTC is prescribed, and the medication is delivered to the detention facility so that the individual may begin taking the medication prior to being released into the community; they are provided with a short-term supply upon release. Individuals are referred to a PrEP clinic in the community where they will continue their PrEP care postrelease. Enrolled individuals are provided with an appointment date and time prior to their release, which is facilitated by a patient navigator who also helps to ensure the communication of important clinical information between the criminal justice clinical providers and the community site. The patient navigator also helps individuals address barriers that arise postrelease to facilitate retention in postrelease PrEP clinical care [56]. The primary clinical outcomes are the following: (1) PrEP uptake (yes/no prescription), (2) adherence (measured by self-report and dried blood spot), and (3) attendance at 1 follow up visit (yes/no attendance). The goals of this study are to increase our knowledge of the characteristics and HIV risk of criminal justice–involved men, improve our understanding of the PrEP care continuum in a criminal justice setting to address these risks, and evaluate real-world barriers to PrEP care among this vulnerable population. This study is expected to conclude on November 30th, 2022.

Discussion

The results from this study will help to identify predictors for initiation, adherence, and retention in PrEP care among incarcerated and recently incarcerated men. This study will help characterize several key elements related to PrEP implementation that will need consideration in order for PrEP use to be implemented to scale in the criminal justice system in the United States. One important consideration for public health policy makers that work within the criminal justice system is the identification of individuals who meet clinical criteria for PrEP usage. Many individuals who pass through the criminal justice system are held for a brief period of time prior to sentencing (eg, pretrial). The study protocol presented here is designed to address gaps in the existing literature by documenting the number and type of individuals who meet the clinical criteria for PrEP, the organizational resources in the criminal justice setting, and the processes required to successfully implement PrEP care in this setting. For individuals who are detained for a significant period of time, particularly those who are sentenced to prolonged periods of detention, understanding how to incorporate HIV prevention into the criminal justice setting would be particularly helpful. Research on health-promoting interventions for HIV-negative criminal justice–involved individuals has generally focused on chronic care management during the period of transition from detention to community reentry [57]. This approach may benefit from incorporating HIV preventive care into the design of clinical linkage interventions.

Support from correctional leadership is key to the success of effective HIV prevention and PrEP programming. The commitment to effectively implement PrEP may vary

significantly between different correctional departments, particularly given the cost of medications as well as the clinical and support personnel that might be required. In RIDOC, support from administrative and medical leadership has been key to the feasibility of conducting this study. Moving forward, a greater understanding of this variability and its impact on effective PrEP implementation will be critical. This will be particularly true if an injectable version of PrEP becomes available. A long-acting version of PrEP may provide greater protection from HIV acquisition, particularly in the chaotic postrelease period when adhering to a daily pill may be difficult for this population.

Beyond the consideration of adapting PrEP clinical processes to the criminal justice context, encouraging PrEP uptake for individuals from multiply marginalized backgrounds, linking individuals to care in the community postrelease, and addressing HIV risk and PrEP use in the context of the complex health needs of criminal justice–involved individuals are likely to require different approaches than may have been successful in other populations. Importantly, the criminal justice system represents an opportunity to reach and intervene with MSM who may not be traditionally reached otherwise (eg, LGBTQ+ engaged in health care). This is because criminal justice–involved men may be less likely to seek medical care in the community and more likely to have risk behaviors that are more highly stigmatized (eg, having sex with men for money, for drugs, or to meet other needs). There are likely to be some important differences among different populations experiencing incarceration who are eligible for PrEP, and characterizing these nuances in clinical care will be important to fully understanding what is required to encourage PrEP uptake and engagement in care among criminal justice–involved individuals. Finally, this population experiences many challenges in being linked to care while also experiencing extremely high risk for HIV acquisition [10,17,58,59]. Successful implementation of PrEP care within the criminal justice system and linking criminal justice–involved individuals to PrEP care in the community has the potential to significantly reduce the spread of HIV both within the criminal justice setting and the broader community, and is an important step to ending the HIV epidemic in the United States [60,61].

Conflicts of Interest

BR receives funding from Gilead Sciences for a research project (number IN-US-276-5463).

References

1. Diagnoses of HIV Infection in the United States and Dependent Areas, 2018. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-31/index.html [accessed 2021-10-12]
2. HIV Infection, Risk, Prevention, and Testing Behaviors among Persons Who Inject Drugs. National HIV Behavioral Surveillance Injection Drug Use, 20 U.S. Cities, 2015. Centers for Disease Control and Prevention. 2018. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-special-report-number-18.pdf [accessed 2022-01-26]
3. Estimated HIV Incidence and Prevalence in the United States, 2014-2018. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-25-1.pdf [accessed 2021-08-15]
4. Hess KL, Hu X, Lansky A, Mermin J, Hall HI. Lifetime risk of a diagnosis of HIV infection in the United States. Ann Epidemiol 2017 Apr;27(4):238-243 [FREE Full text] [doi: 10.1016/j.annepidem.2017.02.003] [Medline: 28325538]
5. Rich JD, Beckwith CG, Macmadu A, Marshall BDL, Brinkley-Rubinstein L, Amon JJ, et al. Clinical care of incarcerated people with HIV, viral hepatitis, or tuberculosis. Lancet 2016 Sep 10;388(10049):1103-1114 [FREE Full text] [doi: 10.1016/S0140-6736(16)30379-8] [Medline: 27427452]
6. Maruschak L. HIV in Prisons, 2001-2010. Bureau of Justice Statistics. 2012. URL: https://bjs.ojp.gov/content/pub/pdf/hivp10.pdf [accessed 2022-01-26]
7. Westergaard RP, Spaulding AC, Flanigan TP. HIV among persons incarcerated in the USA. Current Opinion in Infectious Diseases 2013;26(1):10-16. [doi: 10.1097/qco.0b013e32835c1dd0]
8. Incarceration is not an equal opportunity punishment. Prison Policy Initiative. URL: https://www.prisonpolicy.org/articles/notequal.html [accessed 2020-12-30]
9. Bonczar T. Prevalence of Imprisonment in the US Population 1974-2001. Bureau of Justice Statistics. 2003. URL: https://bjs.ojp.gov/content/pub/pdf/piusp01.pdf [accessed 2022-01-26]
10. Adams J, Nowels C, Corsi K, Long J, Steiner J, Binswanger I. HIV risk after release from prison: a qualitative study of former inmates. J Acquir Immune Defic Syndr 1999 2011;57(5):1-7. [doi: 10.1097/qai.0b013e31821e9f41]
11. Binswanger IA, Nowels C, Corsi KF, Glanz J, Long J, Booth RE, et al. Return to drug use and overdose after release from prison: a qualitative study of risk and protective factors. Addict Sci Clin Pract 2012;7:3 [FREE Full text] [doi: 10.1186/1940-0640-7-3] [Medline: 22966409]
12. DeBeck K, Kerr T, Li K, Milloy M, Montaner J, Wood E. Incarceration and drug use patterns among a cohort of injection drug users. Addiction 2009 Jan;104(1):69-76 [FREE Full text] [doi: 10.1111/j.1360-0443.2008.02387.x] [Medline: 19133890]
13. Genberg B, Astemborski J, Vlahov D, Kirk G, Mehta S. Incarceration and injection drug use in Baltimore, Maryland. Addiction 2015 Jul;110(7):1152-1159 [FREE Full text] [doi: 10.1111/add.12938] [Medline: 25845621]

14. McKnight I, Maas B, Wood E, Tyndall MW, Small W, Lai C, et al. Factors associated with public injecting among users of Vancouver's supervised injection facility. Am J Drug Alcohol Abuse 2007 Jul 07;33(2):319-325. [doi: 10.1080/00952990601175102] [Medline: 17497555]
15. Scheim A, Rachlis B, Bardwell G, Mitra S, Kerr T. Public drug injecting in London, Ontario: a cross-sectional survey. CMAJ Open 2017 Apr 11;5(2):E290-E294. [doi: 10.9778/cmajo.20160163]
16. Merrall E, Kariminia A, Binswanger I, Hobbs MS, Farrell M, Marsden J, et al. Meta-analysis of drug-related deaths soon after release from prison. Addiction 2010 Sep;105(9):1545-1554 [FREE Full text] [doi: 10.1111/j.1360-0443.2010.02990.x] [Medline: 20579009]
17. Adams LM, Kendall S, Smith A, Quigley E, Stuewig JB, Tangney JP. HIV risk behaviors of male and female jail inmates prior to incarceration and one year post-release. AIDS Behav 2013 Oct 22;17(8):2685-2694 [FREE Full text] [doi: 10.1007/s10461-011-9990-2] [Medline: 21779954]
18. Solomon L, Montague BT, Beckwith CG, Baillargeon J, Costa M, Dumont D, et al. Survey finds that many prisons and jails have room to improve HIV testing and coordination of postrelease treatment. Health Aff (Millwood) 2014 Mar;33(3):434-442 [FREE Full text] [doi: 10.1377/hlthaff.2013.1115] [Medline: 24590942]
19. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016 Jan 02;387(10013):53-60 [FREE Full text] [doi: 10.1016/S0140-6736(15)00056-2] [Medline: 26364263]
20. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis 2014 Sep;14(9):820-829. [doi: 10.1016/S1473-3099(14)70847-3] [Medline: 25065857]
21. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, Partners PrEP Study Team. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS 2013 Aug 24;27(13):2155-2160 [FREE Full text] [doi: 10.1097/QAD.0b013e3283629037] [Medline: 24384592]
22. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2013 Jun 15;381(9883):2083-2090. [doi: 10.1016/S0140-6736(13)61127-7] [Medline: 23769234]
23. Dumond J, Yeh R, Patterson K. Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. AIDS 2007;21(14):1899-1907. [doi: 10.1097/qad.0b013e328270385a]
24. Siegler AJ, Mouhanna F, Giler RM, Weiss K, Pembleton E, Guest J, et al. The prevalence of pre-exposure prophylaxis use and the pre-exposure prophylaxis-to-need ratio in the fourth quarter of 2017, United States. Ann Epidemiol 2018 Dec;28(12):841-849 [FREE Full text] [doi: 10.1016/j.annepidem.2018.06.005] [Medline: 29983236]
25. Boys A, Farrell M, Bebbington P, Brugha T, Coid J, Jenkins R, et al. Drug use and initiation in prison: results from a national prison survey in England and Wales. Addiction 2002 Dec;97(12):1551-1560. [doi: 10.1046/j.1360-0443.2002.00229.x] [Medline: 12472639]
26. Calzavara L, Burchell A, Schlossberg J, Myers T, Escobar M, Wallace E, et al. Prior opiate injection and incarceration history predict injection drug use among inmates. Addiction 2003 Sep;98(9):1257-1265. [doi: 10.1046/j.1360-0443.2003.00466.x] [Medline: 12930213]
27. Kolind T, Duke K. Drugs in prisons: Exploring use, control, treatment and policy. Drugs: Education, Prevention and Policy 2016 May 23;23(2):89-92. [doi: 10.3109/09687637.2016.1153604]
28. Kinner SA, Jenkinson R, Gouillou M, Milloy M. High-risk drug-use practices among a large sample of Australian prisoners. Drug Alcohol Depend 2012 Nov 01;126(1-2):156-160. [doi: 10.1016/j.drugalcdep.2012.05.008] [Medline: 22658284]
29. Bunn R. Intersectional needs and reentry: Re-conceptualizing ‘multiple and complex needs’ post-release. Criminology & Criminal Justice 2018 Jan 02;19(3):328-345. [doi: 10.1177/1748895817751828]
30. Wallace D, Fahmy C, Cotton L, Jimmons C, McKay R, Stoffer S, et al. Examining the Role of Familial Support During Prison and After Release on Post-Incarceration Mental Health. Int J Offender Ther Comp Criminol 2014 Aug 25;60(1):3-20. [doi: 10.1177/0306624x14548023]
31. Nunn A, Brinkley-Rubinstein L, Oldenburg C, Mayer KH, Mimiaga M, Patel R, et al. Defining the HIV pre-exposure prophylaxis care continuum. AIDS 2017 Mar 13;31(5):731-734 [FREE Full text] [doi: 10.1097/QAD.0000000000001385] [Medline: 28060019]
32. Kelley CF, Kahle E, Siegler A, Sanchez T, Rio CD, Sullivan PS, et al. Applying a PrEP Continuum of Care for Men Who Have Sex With Men in Atlanta, Georgia. Clin Infect Dis 2015 Nov 15;61(10):1590-1597. [doi: 10.1093/cid/civ664] [Medline: 26270691]
33. Holloway IW, Krueger EA, Meyer IH, Lightfoot M, Frost DM, Hammack PL. Longitudinal trends in PrEP familiarity, attitudes, use and discontinuation among a national probability sample of gay and bisexual men, 2016-2018. PLoS One 2020 Dec 31;15(12):e0244448 [FREE Full text] [doi: 10.1371/journal.pone.0244448] [Medline: 33382743]
34. Chan PA, Goedel WC, Nunn AS, Sowemimo-Coker G, Galárraga O, Prosperi M, et al. Potential Impact of Interventions to Enhance Retention in Care During Real-World HIV Pre-Exposure Prophylaxis Implementation. AIDS Patient Care STDS 2019 Oct 01;33(10):434-439 [FREE Full text] [doi: 10.1089/apc.2019.0064] [Medline: 31584857]

35. Brinkley-Rubinstein L, Dauria E, Tolou-Shams M, Christopoulos K, Chan PA, Beckwith CG, et al. The Path to Implementation of HIV Pre-exposure Prophylaxis for People Involved in Criminal Justice Systems. Curr HIV/AIDS Rep 2018 Apr 8;15(2):93-95 [FREE Full text] [doi: 10.1007/s11904-018-0389-9] [Medline: 29516265]
36. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States, A Clinical Practice Guideline (Update). Centers for Disease Control and Prevention. 2017. URL: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf [accessed 2021-01-17]
37. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, Bangkok Tenofovir Study Group. The impact of adherence to preexposure prophylaxis on the risk of HIV infection among people who inject drugs. AIDS 2015 Apr 24;29(7):819-824. [doi: 10.1097/QAD.0000000000000613] [Medline: 25985403]
38. Coy KC, Hazen RJ, Kirkham HS, Delpino A, Siegler AJ. Persistence on HIV preexposure prophylaxis medication over a 2-year period among a national sample of 7148 PrEP users, United States, 2015 to 2017. J Int AIDS Soc 2019 Feb 18;22(2):e25252 [FREE Full text] [doi: 10.1002/jia2.25252] [Medline: 30775846]
39. Zaller ND, Holmes L, Dyl AC, Mitty JA, Beckwith CG, Flanigan TP, et al. Linkage to treatment and supportive services among HIV-positive ex-offenders in Project Bridge. J Health Care Poor Underserved 2008 May;19(2):522-531. [doi: 10.1353/hpu.0.0030] [Medline: 18469423]
40. Furukawa NW, Maksut JL, Zlotorzynska M, Sanchez TH, Smith DK, Baral SD. Sexuality Disclosure in U.S. Gay, Bisexual, and Other Men Who Have Sex With Men: Impact on Healthcare-Related Stigmas and HIV Pre-Exposure Prophylaxis Denial. Am J Prev Med 2020 Aug;59(2):e79-e87 [FREE Full text] [doi: 10.1016/j.amepre.2020.02.010] [Medline: 32376144]
41. Rubenstein LS, Amon JJ, McLemore M, Eba P, Dolan K, Lines R, et al. HIV, prisoners, and human rights. Lancet 2016 Sep 17;388(10050):1202-1214. [doi: 10.1016/S0140-6736(16)30663-8] [Medline: 27427457]
42. Ravlija J, Vasilj I, Marijanović I, Vasilj M. Risk behaviour of prison inmates in relation to HIV/STI. Psychiatr Danub 2014 Dec;26 Suppl 2:395-401. [Medline: 25433321]
43. Parsons J, Cox C. PrEP in Prisons: HIV prevention in incarcerated populations. IJPH 2019 Nov 26;16(2):199-206. [doi: 10.1108/ijph-09-2019-0053]
44. Grinstead O, Seal DW, Wolitski R, Flanigan T, Fitzgerald C, Nealey-Moore J, Project START Study Group. HIV and STD testing in prisons: perspectives of in-prison service providers. AIDS Educ Prev 2003 Dec;15(6):547-560. [doi: 10.1521/aeap.15.7.547.24045] [Medline: 14711167]
45. Brinkley-Rubinstein L, Peterson M, Arnold T, Nunn AS, Beckwith CG, Castonguay B, et al. Knowledge, interest, and anticipated barriers of pre-exposure prophylaxis uptake and adherence among gay, bisexual, and men who have sex with men who are incarcerated. PLoS One 2018 Dec 7;13(12):e0205593 [FREE Full text] [doi: 10.1371/journal.pone.0205593] [Medline: 30532275]
46. Shavit S, Aminawung JA, Birnbaum N, Greenberg S, Berthold T, Fishman A, et al. Transitions Clinic Network: Challenges And Lessons In Primary Care For People Released From Prison. Health Aff (Millwood) 2017 Jun 01;36(6):1006-1015. [doi: 10.1377/hlthaff.2017.0089] [Medline: 28583958]
47. Roth AM, Aumaier BL, Felsher MA, Welles SL, Martinez-Donate AP, Chavis M, et al. An Exploration of Factors Impacting Preexposure Prophylaxis Eligibility and Access Among Syringe Exchange Users. Sexual Trans Dis 2018;45(4):217-221. [doi: 10.1097/olq.0000000000000728]
48. Solomon M, Schechter M, Liu A, McMahan VM, Guanira JV, Hance RJ, iPrEx Study Team. The Safety of Tenofovir-Emtricitabine for HIV Pre-Exposure Prophylaxis (PrEP) in Individuals With Active Hepatitis B. J Acquir Immune Defic Syndr 2016 Mar 01;71(3):281-286 [FREE Full text] [doi: 10.1097/QAI.0000000000000857] [Medline: 26413853]
49. Ross M, Liebling A, Tait S. The Relationships of Prison Climate to Health Service in Correctional Environments: Inmate Health Care Measurement, Satisfaction and Access in Prisons: The Relationships of Prison Climate to Health Service in Correctional Environments. Howard J Crim Justice 2011;50(3):262-274. [doi: 10.1111/j.1468-2311.2011.00658.x]
50. Komalasari R, Wilson S, Haw S. A social ecological model (SEM) to exploring barriers of and facilitators to the implementation of opioid agonist treatment (OAT) programmes in prisons. IJPH 2021 Aug 07;17(4):477-496. [doi: 10.1108/ijph-04-2020-0020]
51. Kay ES, Pinto RM. Is Insurance a Barrier to HIV Preexposure Prophylaxis? Clarifying the Issue. Am J Public Health 2020 Jan;110(1):61-64. [doi: 10.2105/ajph.2019.305389]
52. Siegler AJ, Bratcher A, Weiss KM. Geographic Access to Preexposure Prophylaxis Clinics Among Men Who Have Sex With Men in the United States. Am J Public Health 2019 Sep;109(9):1216-1223. [doi: 10.2105/ajph.2019.305172]
53. LeMasters K, Oser C, Cowell M, Mollan K, Nowotny K, Brinkley-Rubinstein L. Longitudinal pre-exposure prophylaxis (PrEP) acceptability, initiation and adherence among criminal justice-involved adults in the USA: the Southern PrEP Cohort Study (SPECS) protocol. BMJ Open 2021 Jul 16;11(7):e047340 [FREE Full text] [doi: 10.1136/bmjopen-2020-047340] [Medline: 34272219]
54. Hariri S, Sharafi H, Sheikh M, Merat S, Hashemi F, Azimian F, et al. Continuum of hepatitis C care cascade in prison and following release in the direct-acting antivirals era. Harm Reduct J 2020 Oct 20;17(1):80-87 [FREE Full text] [doi: 10.1186/s12954-020-00431-x] [Medline: 33081794]
55. RIDOC, Fiscal Year 2019 Population Report. The Rhode Island Department of Corrections. 2020. URL: http://www.doc.ri.gov/docs/FY19%20Annual%20Population%20Report.pdf [accessed 2021-01-13]

56. Pinto RM, Berringer KR, Melendez R, Mmeje O. Improving PrEP Implementation Through Multilevel Interventions: A Synthesis of the Literature. AIDS Behav 2018 Jun 5;22(11):3681-3691. [doi: 10.1007/s10461-018-2184-4]
57. Wang EA, Hong CS, Shavit S, Sanders R, Kessell E, Kushel MB. Engaging Individuals Recently Released From Prison Into Primary Care: A Randomized Trial. Am J Public Health 2012 Sep;102(9):e22-e29. [doi: 10.2105/ajph.2012.300894]
58. Hu C, Jurgutis J, Edwards D, O'Shea T, Regenstreif L, Bodkin C, et al. "When you first walk out the gates…where do [you] go?": Barriers and opportunities to achieving continuity of health care at the time of release from a provincial jail in Ontario. PLoS One 2020;15(4):e0231211 [FREE Full text] [doi: 10.1371/journal.pone.0231211] [Medline: 32275680]
59. Carswell C, Noble H, Farrow D. Barriers between offenders and primary health care after release from prison: a case study. Practice Nursing 2017 Sep 02;28(9):386-389. [doi: 10.12968/pnur.2017.28.9.386]
60. Millett GA. New pathogen, same disparities: why COVID-19 and HIV remain prevalent in U.S. communities of colour and implications for ending the HIV epidemic. J Int AIDS Soc 2020 Nov 22;23(11):e25639 [FREE Full text] [doi: 10.1002/jia2.25639] [Medline: 33222424]
61. Beyrer C, Adimora AA, Hodder SL, Hopkins E, Millett G, Mon SHH, et al. Call to action: how can the US Ending the HIV Epidemic initiative succeed? Lancet 2021 Mar 20;397(10279):1151-1156 [FREE Full text] [doi: 10.1016/S0140-6736(21)00390-1] [Medline: 33617770]

Abbreviations

CDC: Centers for Disease Control and Prevention
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RIDOC: Rhode Island Department of Corrections
TAF/FTC: tenofovir alafenamide and emtricitabine
TDF/FTC: tenofovir disoproxil fumarate and emtricitabine

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Protocol

Predicting Real-world Hypoglycemia Risk in American Adults With Type 1 or 2 Diabetes Mellitus Prescribed Insulin and/or Secretagogues: Protocol for a Prospective, 12-Wave Internet-Based Panel Survey With Email Support (the iNPHORM [Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models] Study)

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Abstract

Background: Hypoglycemia prognostic models contingent on prospective, self-reported survey data offer a powerful avenue for determining real-world event susceptibility and interventional targets.

Objective: This protocol describes the design and implementation of the 1-year iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) study, which aims to measure real-world self-reported severe and nonsevere hypoglycemia incidence (daytime and nocturnal) in American adults with type 1 or 2 diabetes mellitus prescribed insulin and/or secretagogues, and develop and internally validate prognostic models for severe, nonsevere daytime, and nonsevere nocturnal hypoglycemia. As a secondary objective, iNPHORM aims to quantify the effects of different antihyperglycemics on hypoglycemia rates.

Methods: iNPHORM is a prospective, 12-wave internet-based panel survey that was conducted across the United States. Americans (aged 18-90 years) with self-reported type 1 or 2 diabetes mellitus prescribed insulin and/or secretagogues were conveniently sampled via the web from a pre-existing, closed, probability-based internet panel (sample frame). A sample size of 521 baseline responders was calculated for this study. Prospective data on hypoglycemia and potential prognostic factors were self-assessed across 14 closed, fully automated questionnaires (screening, baseline, and 12 monthly follow-ups) that were piloted using semistructured interviews (n=3) before fielding; no face-to-face contact was required as part of the data collection. Participant responses will be analyzed using multivariable count regression and machine learning techniques to develop and internally validate prognostic models for 1-year severe and 30-day nonsevere daytime and nocturnal hypoglycemia. The causal effects of different antihyperglycemics on hypoglycemia rates will also be investigated.

Results: Recruitment and data collection occurred between February 2020 and March 2021 (ethics approval was obtained on December 17, 2019). A total of 1694 participants completed the baseline questionnaire, of whom 1206 (71.19%) were followed

up for 12 months. Most follow-up waves (10,470/14,472, 72.35%) were completed, translating to a participation rate of 179% relative to our target sample size. Over 70.98% (856/1206) completed wave 12. Analyses of sample characteristics, quality metrics, and hypoglycemia incidence and prognostication are currently underway with published results anticipated by fall 2022.

Conclusions: iNPHORM is the first hypoglycemia prognostic study in the United States to leverage prospective, longitudinal self-reports. The results will contribute to improved real-world hypoglycemia risk estimation and potentially safer, more effective clinical diabetes management.

Trial Registration: ClinicalTrials.gov NCT04219514; https://clinicaltrials.gov/ct2/show/NCT04219514

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KEYWORDS

severe hypoglycemia; nonsevere hypoglycemia; type 1 diabetes mellitus; type 2 diabetes mellitus; real-world; risk model; risk prediction; hypoglycemia; symptom; diabetes; risk; model; protocol; survey; internet survey; adverse event; insulin; secretagogue

Introduction

Background

Although prognostic models can complement clinical decision-making and risk-tailored interventions [1-5], their performance depends heavily on the attributes of their underlying data sources [6]. The prognostic literature on diabetes-related hypoglycemia—a potentially lethal [7,8] and costly [9-11] side effect of insulin and/or secretagogues—has been dominated by analyses of pre-existing trial [12] or administrative databases [13]. However, these sources poorly represent high-risk diabetes populations [14-18], underestimate up to 95% of hypoglycemia events [14,19,20], and limit substantive evidence on potential predictors [21].

Prospective, web-based survey data, especially when collected anonymously [22], can reveal robust indications of hypoglycemia burden [23-26] routinely unmeasured or uncapturable by other research methods [20]. Such insight could help rectify extant evidence gaps, leading to more valid, real-world event prognostication [27] and, ultimately, targeted, cost-effective strategies that support hypoglycemia prevention in broad clinical contexts.

In 2020, our team launched iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models)—the first prospective (1-year) survey of hypoglycemia risk in the American public with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) prescribed insulin and/or secretagogues. The results of this study will culminate in real-world hypoglycemia prognostic models that are readily compatible with and complementary to routine practice. Here, we detail the design and implementation protocol of iNPHORM. The paper has been structured according to established guidelines [28,29] and the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) guidelines [30].

Objectives of the iNPHORM Study

Coprimary Objectives

The primary objectives are as follows:

1. To determine the real-world incidence of self-reported 1-year severe and 30-day nonsevere daytime and nocturnal hypoglycemia among American adults with T1DM or T2DM prescribed insulin and/or insulin secretagogues
2. To develop and internally validate real-world hypoglycemia risk prediction models for 1-year severe, 30-day nonsevere daytime, and 30-day nonsevere nocturnal hypoglycemia, which will be converted into a user-friendly, clinic-based tool

Secondary Objective

The secondary objective is to assess treatment-related causes of hypoglycemia among American adults with T1DM or T2DM prescribed insulin and/or insulin secretagogues.

Methods

Study Design and Setting

iNPHORM is an internet-based panel survey that was conducted across the United States. Repeated self-assessed measures were taken over 12 monthly interwave intervals via web-based questionnaires. Prospective longitudinality allowed us to (1) obtain data not reliably collected retrospectively or cross-sectionally (eg, variability in totals/averages or low-salience events), (2) assess within-person changes or stability masked by aggregate statistics, and (3) narrow the SE between measurements.

Participants and Sample Size

Participants were recruited via the web from an established, closed, probability-based internet panel. The internet panel comprised 5 vendor samples of the United States public consenting to receive survey notifications by email (sample frame). Vendor partners used random probability sampling and, when necessary, validity checks, quotas, and multidimensional calibration. These approaches helped maintain fair and representative (geodemographic, attitudinal, and behavioral) sampling within communities [31]. The internet panel comprised >65,000 Americans with self-reported T1DM (N=10,000 approximately) and T2DM (N=58,000 approximately).

Internet panelists could enroll if they were (1) aged 18 to 90 years, (2) living in the United States (past year), (3) self-reporting a diagnosis of T1DM or T2DM [32], and (4) using insulin, secretagogues, or both insulin and secretagogues (past year). Individuals were ineligible if they were unable to read

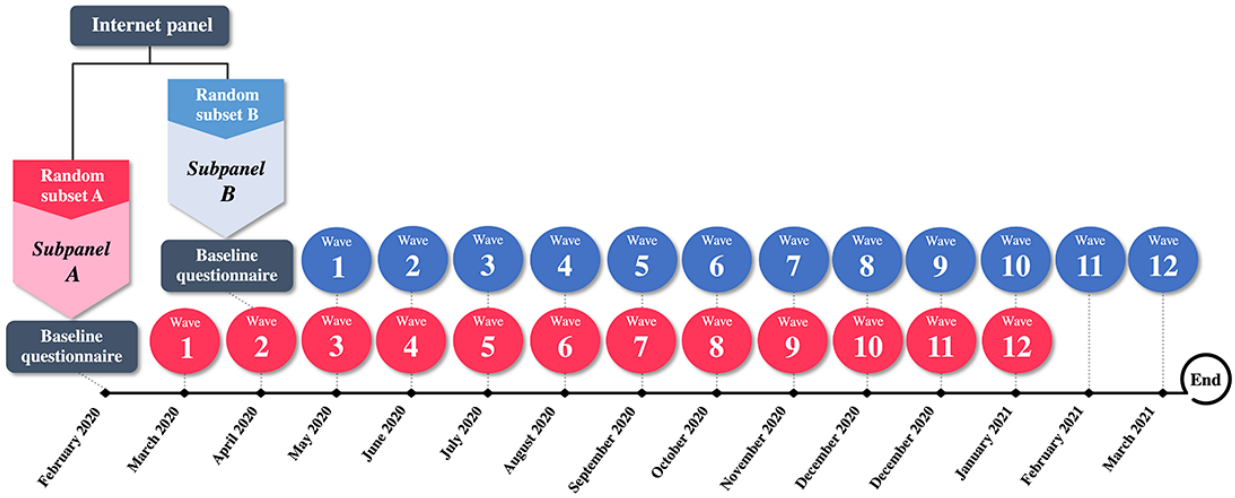
and understand English, possessed insufficient computer and internet literacy, or were participating in a concurrent trial. Those who were pregnant (at screening or in the prior year) and/or those with gestational diabetes were excluded, given their distinct pathogenesis and clinical management.

On the basis of recent conservative techniques [33,34], N≥521 respondents would be required to produce a 25-factor prognostic model for severe hypoglycemia (the rarest event type) with sufficient precision and minimal overfitting with ≤0.05 expected optimism [34,35]. Anticipating a degree of right censoring [35,36], we inflated our target sample to 1250 enrollees.

Sampling, Recruitment, and Data Collection

Figure 1 summarizes participant sampling, recruitment, and data collection.

Figure 1. Schematic of participant sampling, recruitment, and data collection.



A total of 2 subpanels (*A* and *B*) were recruited into the prospective, 12-wave iNPHORM study using convenience sampling. First, vendor partners emailed a generally worded study invitation to a randomly selected subset of the internet panel (subset A). Those interested were emailed a link to a screener. To enroll, eligible respondents were required to provide consent (see *Ethical Considerations* section), complete a baseline questionnaire (accessible by the emailed link), and register with iNPHORM using a confirmed, valid email address and unique username/password. Enrollees were hosted and monitored by Ipsos Interactive Services (IIS) [37], a global leader in diabetes insights and patient-centered, real-world survey conduct.

Links to the screener and baseline questionnaires remained active until we reached 1250 enrollees (ie, *subpanel A*). Participants in *subpanel A* who failed to complete the first wave follow-up questionnaire were withdrawn and systematically refreshed with new eligible recruits (ie, *subpanel B*). *Subpanel B* was sampled and enrolled in the same way as *subpanel A* but from a different, randomly selected subset (subset B) of the contemporaneous internet panel. Screener and baseline links remained active for approximately 2 weeks or until a 1:1 ratio of *subpanel B* to *subpanel A* wave 1 dropouts was achieved (whichever came first). Collectively, individuals in *subpanel A* who completed the first follow-up questionnaire and all those in *subpanel B* comprised the *iNPHORM longitudinal panel*.

Quota sampling ensured prespecified minimum parameters of the *iNPHORM longitudinal panel*. We required that ≥10% of participants report T1DM, ≥5% are aged ≥75 years, and ≥10% are female/male. Among T2DM respondents, we specified a ≥10% representation for insulin (without secretagogues), secretagogues (without insulin), and a combination of insulin and secretagogue users each.

We followed the *iNPHORM longitudinal panel* for 12 months. The calendar schedule between subpanels was identical; however, systematic refreshment caused follow-up waves to offset by 2 months (*subpanel A*: February 2020 to January 2021; *subpanel B*: April 2020 to March 2021). At each wave, IIS emailed participants an individualized link to a closed, fully automated questionnaire that involved no face-to-face contact. The link could only be accessed by the email recipient using their *iNPHORM longitudinal panel* username/password. Links were active for 7 days from distribution (activation window). The responses were synchronously stored on the IIS platform. Completed questionnaires could not be reaccessed or modified.

Notifications, Precontacts, and Reminders

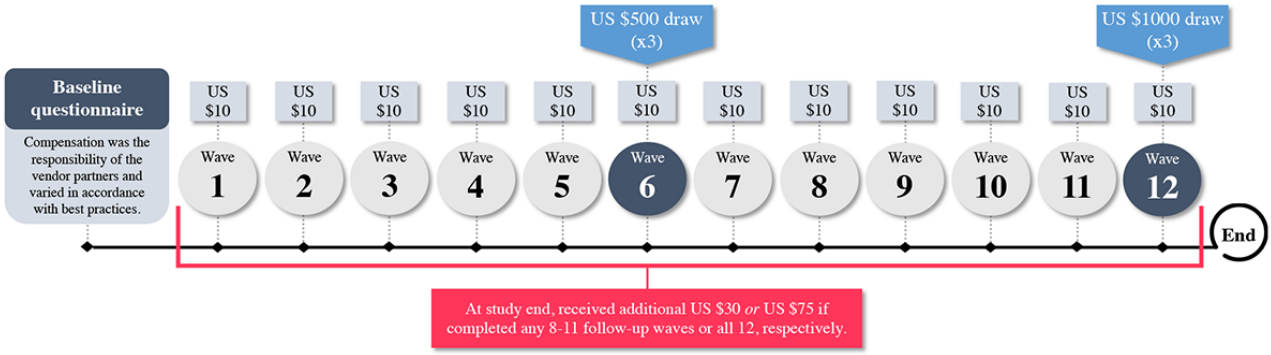
Personalized notifications, precontacts, and reminders were emailed automatically by IIS. Each notification contained the questionnaire link, the deadline for submission, and details on remuneration (see *Incentivization Scheme* section). Notifications also included the date of the participant's last completed questionnaire, as well as their last reported use/type of antihyperglycemic(s) and glucose monitoring device(s).

To boost completion rates [38,39], a precontact alerting participants of an upcoming questionnaire was emailed 7 days before the notification. After the notification, individuals were sent 2 reminder emails on days 4 and 6 of the 7-day activation window. Reminders contained the same information as the corresponding notification emails.

Incentivization Scheme

Figure 2 summarizes participant honoraria.

Figure 2. Incentivization scheme.



A thank you message and link to a US $10 e-gift card was emailed after each submitted follow-up. At the end of the study, participants received an additional e-gift card of US $30 if they completed any 8 to 11 waves or US $75 if they completed all 12 waves. Wave 6 and 12 responders were entered to win 1 of 3 randomly selected US $500 or US $1000 e-gift cards, respectively.

Incentive amounts balanced our desired response rates against ethical standards of reciprocity [40]. For internet-based surveys, monetary versus other inducements can decrease volunteer bias [35,36] and respondent refusals [41-43]. Lottery incentivization has been shown to act much like cash incentives with a value effect equal to the lottery prize divided by the sample size [44].

Questionnaire Development Procedures

Western University scientists (AR-L, BLR, and SBH) developed questionnaires in consultation with the literature and pre-existing surveys. Questionnaires were designed in English for use on diverse internet-equipped devices (eg, computers, phones, and tablets). The content was crafted parsimoniously to lessen panel fatigue, conditioning, satisficing, social desirability bias, and demand characteristics [38]. Double-barreled questions, clinical jargon, and value-laden or complex/ambiguous language were avoided. We also ensured that the items were mutually exclusive, exhaustive, and specified an appropriate and consistent level of detail. Key questions were prioritized early; conversely, all sensitive items—justified and respectfully crafted (eg, income was categorized)—were interspersed to encourage respondent honesty [45]. We did not randomize/alternate items within or between questionnaires or participants. When applicable, items addressed the causal ordering of sequence, timing, and duration [46]. Recall intervals balanced the observation probability against the timing of questionnaire completion.

Established design principles were adopted to minimize burden and sustain engagement. Clearly worded preambles signaled topic changes and explained the importance of respondent honesty and vigilance [39,47]. To mitigate comprehension bias, concise instructions and definitions were provided in text and on mouseover [47]. In addition, efforts were taken to enhance accessible visual appeal, navigation, and user convenience. Adaptive questioning streamlined transitions between items and decreased the complexity and length (ie, number of screens) of the web interface questionnaires. For ease of completion, straightforward response options (via radio buttons, checkboxes, drop-down lists, and open-text fields) were presented, and only 1 item appeared per screen. Questionnaires could be accessed, delayed, and/or paused ad libitum up until submission or the activation window closed (whichever came first). Percentage-based progress bars on each screen supplied visual feedback on completion.

Quality assurance methods were applied to reinforce data integrity. *Calibration* questions [48] were incorporated in the screener to detect straight lining, verify item comprehension, and avert nonsensical free text [49]; unsatisfactory answers precluded participant enrollment. In-built logic checks supported data accuracy [49]. For example, questions were prespecified with single- or multi-responses, and *not applicable*, *prefer not to say*, and *I don't know* were delimited as exclusive options. Missing responses were immediately flagged. To bypass a question, individuals had to type "OPT OUT" in a pop-up response box, helping discriminate intentional nonresponse from inadvertent omissions/straight lining. At the start of every questionnaire, respondents were reminded to retrieve any documents/materials that could facilitate response accuracy (eg, medication lists/containers and glucose monitoring logs/graphs).

During follow-up, IIS monitored bugs, downtimes, and other unexpected events that could have affected the study design. At any point, participants could email IIS Technical Support (email address was included in all iNPHORM communications).

Pretesting and Piloting

iNPHORM researchers and colleagues performed extensive pretesting of detailed mock-up and programmed study materials to redress issues of content, display, adaptive questioning, and implementation. Before their dissemination, programmed questionnaires, notifications, and reminders were piloted via in-depth semistructured interviews with 3 participants who were screened and sampled purposively from a subset different than subsets A and B of the internet panel. Of the 3 participants, 1 (33%) participant had T1DM; the other 2 (67%) had T2DM (1, 50%, was prescribed secretagogues without insulin, and 1, 50%, a combination of insulin and secretagogues). A trained IIS moderator (JDB) interviewed participants simultaneously by phone and a computer-assisted personal interview platform using an interview guide developed by the Western University research team.

Qualitative feedback was collected on content, formatting, flow, usability, and technical functionality. Pilot data were also gathered on sample variability, item response rate, and time to

completion. Behaviors signaling design issues were documented (eg, instances where the respondent hesitated or requested to change an answer) [38]. Interviews took 60 to 90 minutes. The study materials were emended based on respondents' feedback. Pilot participants were remunerated US $300 (e-gift card); they were not permitted to enroll in the panel survey.

Once finalized and in field, no changes were made to questionnaires except for the addition of a COVID-19 subquestionnaire (see the *COVID-19 Subquestionnaire* section). Dynamic components were obviated to preserve study replicability.

Prognostic Factors Related to Hypoglycemia and COVID-19

Overview

Across the screener, baseline, and follow-up questionnaires, web-based self-assessed data were collected on a broad scope of hypoglycemia-related anthropometric, demographic, situational or environmental, lifestyle (Multimedia Appendix 1), and clinical (Multimedia Appendix 2 [50-53]) prognostic factors. Follow-up questionnaires also contained items related to COVID-19 (Multimedia Appendix 3; see *Definitions and Measures of Hypoglycemia* section for methods of hypoglycemia-specific data capture).

Screener

The pilot screener took an average of 9.6 (SD 4.73; minimum 6 and maximum 15) minutes to complete. Data were collected on age, sex assigned at birth, self-identified gender, residence, concurrent trial involvement, diabetes type, pregnancy status, and insulin and/or secretagogue use (eg, administration mode [when applicable], dose, and duration). Response options for medication type were arranged by class, save second-generation basal insulin analogs, which were listed by brand (Toujeo SoloSTAR, Toujeo Max SoloStar, Tresiba FlexTouch U-100, and Tresiba FlexTouch U-200). Screener data were retained for all consenting individuals.

Baseline Questionnaire

On average, pilot respondents completed the baseline questionnaire in 47.3 (SD 13.65; minimum 38 and maximum 63) minutes. Information was elicited on anthropometric, demographic, situational or environmental, and lifestyle factors (eg, levels of aerobic/anaerobic activity and cigarette, alcohol, and recreational drug use). Numerous clinical data were also collected on diabetes duration, diabetes self-management behaviors, diabetes complications (eg, chronic kidney disease), general health status (eg, chronic multi-morbidities and use of dialysis), and health-related quality of life.

To simplify future population-based comparisons and statistical weighting, we devised items with reference to existing population-based surveys by the US Census Bureau (2020) [54] and the Centers for Disease Control and Prevention (ie, National Health and Nutrition Examination [2019-2020] [55], Behavioral Risk Factor Surveillance System [2020] [56], and National Health Interview Survey [2020] [57]). We also embedded several validated questionnaires (eg, Veterans RAND-12 [50,53], Self-Rated Health [51], and Brief Health Literacy Screening Tool [52]).

Follow-up Questionnaires

Follow-ups (except wave 6 see *Definitions and Measures of Hypoglycemia* section) were on average piloted in 10.8 (SD 5.30; minimum 7 and maximum 14.5) minutes. Items assessed mutable clinical variables (eg, medication regimen, hemoglobin A1c, and continuous/flash glucose monitoring). Employment status, household income, and health insurance were re-evaluated at waves 4, 8, and 12.

COVID-19 Subquestionnaire

Pandemic-related items were added after study commencement in response to the escalating severity of the COVID-19 pandemic. Beginning with *subpanel A* wave 2 (April 21 to April 28, 2020), each follow-up contained a 25-item COVID-19 subquestionnaire that assessed self-reported infection status (per Centers for Disease Control and Prevention's community case definitions [April 2020]; [58]) and the impact of the pandemic situation on socioeconomic, clinical, and psychosocial aspects of diabetes management [59].

Definitions and Measures of Hypoglycemia

At baseline and at each follow-up (Multimedia Appendix 4 [60-63]), web-based self-assessed data were collected on severe and nonsevere daytime and nocturnal hypoglycemia; definitions consistent with the 2019 American Diabetes Association Standards of Medical Care in Diabetes [64] were provided in all questionnaires (Textbox 1).

In line with past research [60,65-67], we specified interwaves of ≤1 year for severe and ≤30 days for nonsevere hypoglycemia. At baseline, participants were asked to report on their severe daytime/nocturnal hypoglycemia in the past year and nonsevere daytime/nocturnal hypoglycemia in the past 30 days. To prevent overlapping recall intervals during follow-up, data on nonsevere daytime and nocturnal hypoglycemia were captured *within the past 30 days* (if the last scheduled questionnaire was not completed) or *since the last time an iNPHORM survey was completed* (if the last scheduled questionnaire *was* completed). Given its relative infrequency and saliency, severe daytime and nocturnal hypoglycemia data were captured *since the last time an iNPHORM survey was completed*.

Besides hypoglycemia frequency, closed- and open-ended items assessed event detection methods (eg, symptoms and/or blood glucose), symptom severity (eg, unconsciousness), causes (eg, excess insulin and/or secretagogue use, insufficient carbohydrate intake, and excess physical activity), treatments, hypoglycemia-specific self-management behaviors/social support, and experiences with continuous/flash glucose monitoring. We also investigated the type of assistance required for severe hypoglycemia recovery (eg, treatment by family/friend and health care use). Each month, modified Clarke [61] and Gold [62] scores evaluated impaired hypoglycemia awareness. At wave 6, we administered the Hypoglycemia Fear Survey II [63] and the InHypo-DM Person with Diabetes Questionnaire [60].

Textbox 1. iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) hypoglycemia definitions provided to participants by severity and timing.

Severe

- "When you are *physically unable* to treat your hypoglycemia by yourself, it is considered a *Severe Hypoglycemia* event. You may be severely disorientated, unable to swallow, or unconscious. As a result, you are likely to need the help of another person to recover. This person may need to administer glucagon or a glucose injection to treat your severe hypoglycemia event. Emergency medical services may be called, and hospitalization may be required. Severe events can arise when your low blood glucose is left untreated and continues to drop. The early signs and symptoms of severe hypoglycemia typically include blurred vision, difficulty concentrating, confused thinking, slurred speech, numbness, and/or drowsiness. If your blood glucose stays low for too long, it can result in seizures, comas, and in rare cases, death. Consequently, severe hypoglycemia is a medical emergency."

Mild/moderate (also known as nonsevere)

- "When you are *physically able* to treat your hypoglycemia by yourself, it is considered a *Mild/Moderate Hypoglycemia* event. Treatment can include taking a glucose or sucrose tablet, drinking a glass of juice, or eating some food. Mild/moderate hypoglycemia events can be identified by symptoms such as shakiness, sweatiness or chills, irritability, feeling nervous or anxious, hunger, weakness, mild confusion, forgetfulness, fast heartbeat, feeling dizzy, and color draining from the skin. Mild/moderate hypoglycemia events can be identified from these symptoms or by a measured blood glucose level taken from a self-monitoring blood glucose (SMBG) meter or continuous/real-time glucose monitoring (CGM) device. You are still conscious and able to swallow."

Daytime

- "*Daytime events* (mild/moderate or severe) occur while you are awake."

Nocturnal

- "*Nocturnal events* (mild/moderate or severe) occur while you are sleeping or attempting to sleep. In addition to the symptoms described above, nocturnal hypoglycemia can be marked by symptoms such as vivid dreams/nightmares, restless sleep, morning headaches, night sweats, tiredness, irritability/confusion upon waking, convulsions, and talking/shouting while sleeping."

Ethical Considerations

iNPHORM was funded by an investigator-initiated grant from Sanofi Global (contract executed with Sanofi Canada, April 11, 2019). Before recruitment, we obtained ethics approval from the Western University health sciences research ethics board (December 17, 2019) and registered the study with ClinicalTrials.gov (NCT04219514; January 7, 2020). The COVID-19 subquestionnaire was approved as an ethics amendment before fielding.

A letter of information was emailed to all eligible respondents (Multimedia Appendices 5 and 6). The letter named Western University as the responsible academic institution and Sanofi Canada as the funding agency. It also outlined the study's purpose, nature and expectations of participation (eg, content of surveys, time commitment, follow-up frequency, and incentivization), risks and benefits, participant rights (eg, refusals/withdrawals), and confidentiality/privacy measures (eg, data storage, retention, sharing, and reporting). Contacts were provided for IIS, faculty coprincipal investigator (SBH), Western University research team, and the Office of Human Research Ethics at Western University. Conflicts of interest for SBH have been declared. Consent was obtained via the web. Individuals were advised to read the letter of information before clicking on *I agree to participate* or *I do not agree to participate*.

Participation was voluntary. Enrollees could withdraw at any time by informing the IIS interviewer (pilot participants only), clicking an unsubscribe button provided in each email, or by emailing IIS directly. Privacy breaches and technical problems were monitored by IIS. Personally identifiable data (eg, phone numbers [pilot participants only], email addresses, and full birthdates) were encrypted automatically by the IIS platform and kept confidential from IIS and research personnel. IIS transferred deidentified data files to the Western University research team using a secure file transfer protocol on a password-protected network drive. All deidentified data will be stored for 7 years on a password-protected network drive at the Department of Family Medicine at Western University and on encrypted password-protected external drives; storage devices will be erased after this time. The iNPHORM assessments and data are owned by Western University.

Complying with US Food and Drug Administration postmarket safety reporting regulations [68], we emailed Sanofi United States and Novo Nordisk United States monthly pharmacovigilance reports of severe adverse events among Toujeo and Tresiba users, respectively. The reports were anonymized.

Planned Statistical Analyses

Overview

Unique IDs, randomly assigned by IIS at the study outset, were used to tether the participants' data across waves. Closed-ended responses were directly precoded, and a data dictionary and map have been developed. Repair rules addressing impossible, implausible, and discordant values will be documented in iNPHORM's metadata (eg, erroneous responses will be classified as missing or cross-checked against valid responses). Both the raw and repaired data sets will be retained.

Describing the iNPHORM Sample

Recruitment and Completion Rate

The recruitment rate will be calculated as the ratio of consenting individuals to enrollees. The average total completion rates for the *iNPHORM longitudinal panel* will be computed as the ratio of the observed number of completed waves to the maximum expected number (12 waves per participant). To evaluate the success of our completion rate against our predetermined sample size (N=521; *Sample Size* section), the observed number of waves for which severe hypoglycemia information was available will be compared against the maximum expected number of completed follow-ups.

Completeness Rate

All data were stored in real time for analysis, even if the questionnaire was incomplete (eg, prematurely terminated). The completeness rate will be assessed after data cleaning and repair. Missing values will be coded as unit, block, item (because of skip logic), or residual (because of *not applicable*/*prefer not to say*/*I don't know* or opt out) nonresponses. Missing data will be handled using multiple imputation by chained equations [69].

Participant Characteristics

Categorical variables will be summarized as frequencies and percentages, and continuous variables as means and SDs (parametric) or medians and IQRs (nonparametric).

Hypoglycemia Incidence (Coprimary Objective 1)

Crude severe and nonsevere daytime and nocturnal hypoglycemia incidence proportions and densities with 95% CIs for overdispersed count data will be reported overall and by diabetes type, medication regimen, mode of detection (symptoms and/or blood glucose), symptom severity (unconsciousness), and health care use. Incidence density calculations will account for observation durations as an offset for zero-risk and/or unobserved periods.

Prognostic Model Construction (Coprimary Objective 2)

Overview

The following procedures comply with current guidelines [70,71] and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement [72,73]. Analyses will be performed on baseline respondents who submitted ≥1 follow-up questionnaire. To pre-empt statistical power loss and selection bias, all baseline and follow-up data on this cohort will be examined [74]. Iterative proportional fitting (raking) [38] to correct for nonresponse and unequal selection probability will be investigated.

Model Development

Prognostic models will be developed for severe, nonsevere daytime, and nonsevere nocturnal hypoglycemia. Daytime and nocturnal severe events will be combined, given their nonspecific relevance and to ensure sufficient precision. Severe hypoglycemia will be modeled over 1 year using the Andersen-Gill Cox proportional hazards regression for recurrent events [34]. Nonsevere daytime and nocturnal hypoglycemia will be modeled over 30 days using negative binomial regression. Observation duration will be included as an offset variable, and generalized estimating equations will account for within-person dependence.

Candidate prognostic factors will be selected a priori based on biological plausibility, previous literature, data quality, measurement reliability, and multicollinearity. Intrinsic, extrinsic, nonmodifiable, and modifiable predictors (including frequency of previous severe and nonsevere hypoglycemia) will be considered. To minimize overfitting [75,76] and improve parsimony, model parameters will be estimated using machine learning penalized regression with Lasso (least absolute shrinkage and selection operator) [77]. Regression splines and fractional polynomials will assess the potential for nonlinearity and nonmonotonicity [78]. Interaction and subgroup analyses will be performed where suggested by external evidence [2]; sensitivity analyses will test the robustness of the findings. Informative censoring will be explored using inverse probability of censoring weighted estimation [79,80].

Internal Validation

Bootstrapping will be used to determine the optimism-corrected performance of each final model [74,77,81]. Discrimination will be evaluated using receiver operating characteristic curves and c-statistics [82]. Calibration will be assessed visually (eg, via graphical plots) and quantified using the calibration slope, the Hosmer-Lemeshow goodness-of-fit test, and the Grønnesby and Borgan test for survival data [83-85].

Pragmatic Tool Creation

Models will be converted into a user-friendly, clinic-based tool to complement real-world practice. Back-end computations of patients' prognostic factors will provide point-of-care assessments for 1-year severe and/or 30-day nonsevere daytime/nocturnal hypoglycemia. To aid interpretation, risk estimates will also be categorized (eg, low, moderate, high, and very high).

The tool will be streamlined for easy integration in clinicians' existing electronic medical records (EMRs) and compatible with prepopulated EMRs and manually inputted data. A standalone internet application and paper-based nomogram will be developed for when EMR integration is not possible. Real-time imputation will be explored [86].

Treatment-Related Causes of Hypoglycemia (Secondary Objective)

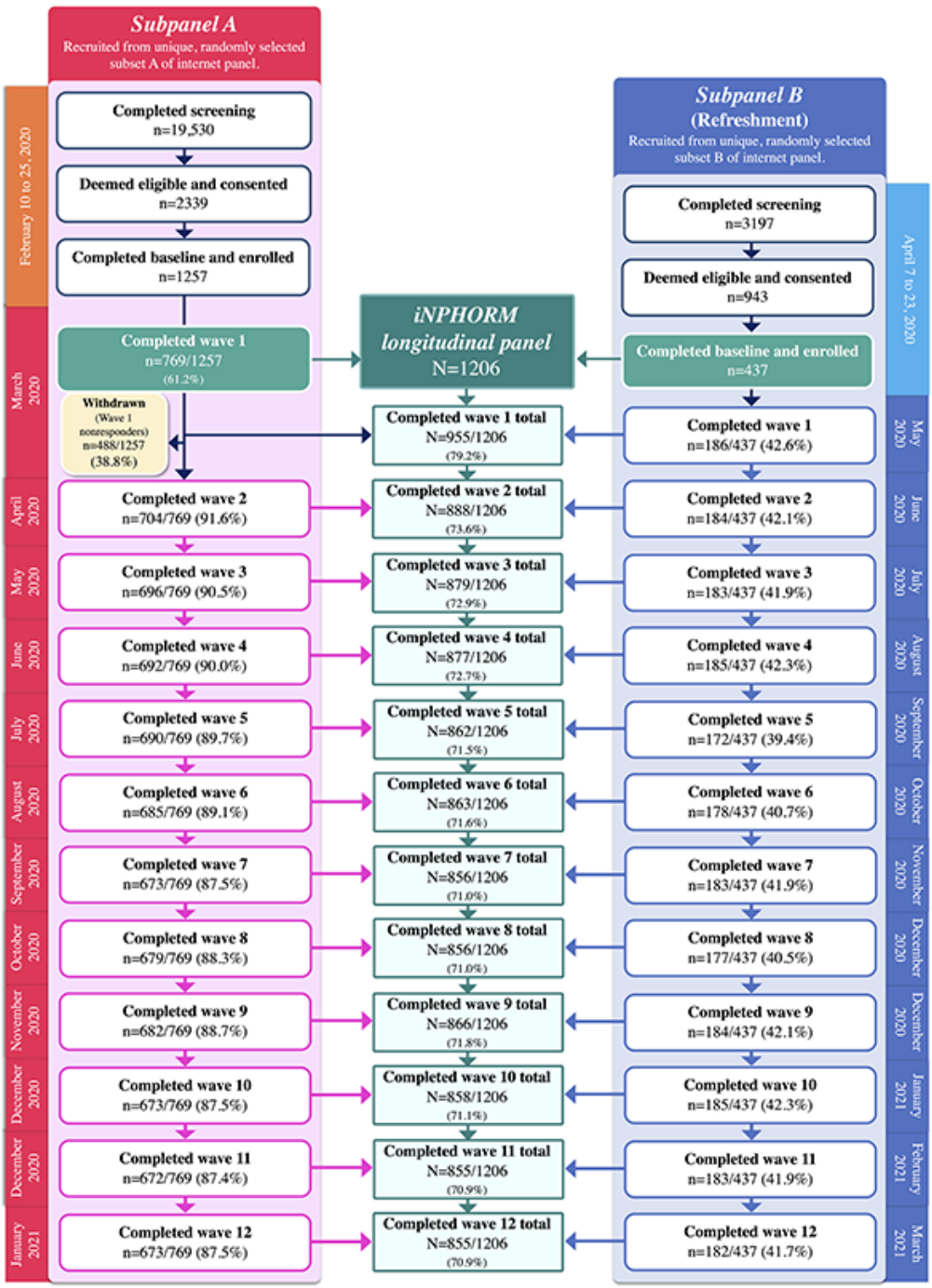
Differential effects of antihyperglycemic regimens on hypoglycemia rates will be tested using causal analytic techniques (eg, directed acyclic graphs, parallel and serial mediation, and time-dependent confounding). The results may help in identifying new and useful associations that can improve model performance or otherwise real-world event detection and management [87].

Results

Overview

iNPHORM commenced in February 2020 and concluded in March 2021. No bugs, downtimes, privacy breaches, or other unexpected events were reported/detected. Herein, we present the recruitment and completion rates (Figure 3). Analyses of participant characteristics and hypoglycemia incidence and prognostication are currently underway, with published results anticipated by fall 2022. Future studies will investigate the distributions of participant discontinuance [35] and systematically report on quality metrics, including missing values and data cleaning statistics, follow-up completeness [88], degree of coverage/sampling bias, and process outcomes (eg, average time-to-completion).

Figure 3. Recruitment and completion rates. iNPHORM: Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models.



Recruitment Rate

From February 10 to February 25, 2020, 2339 individuals consented to participate in iNPHORM; of these individuals, 1257 (53.74%) completed all actions to enroll (ie, *subpanel A*). Individuals in *subpanel A* who failed to complete wave 1 were withdrawn (488/1257, 38.82%) and systematically refreshed with *subpanel B*. From April 7 to April 23, 3197 individuals consented, of whom 437 (13.67%) were enrolled. Thus, as of April 2020, 1206 participants comprised the *iNPHORM longitudinal panel*.

Completion Rate

The average total completion rate across the *iNPHORM longitudinal panel* was 72.4% (Multimedia Appendix 7). Given our use of systematic refreshment, *subpanel A* exhibited a higher completion rate than *subpanel B* (89.8% vs 41.6%, respectively). Dropout was highest at wave 1, with completion rates stabilizing thereafter. Across respondents, 71.89% (867/1206) completed ≥8 follow-ups, with 55.22% (666/1206) completing all 12 (Table 1). We observed minimal loss to follow-up (ie, individuals who discontinued participation until the end of the study). Most (855/1206, 70.9%) completed wave 12 (Table 2). Compared with our target sample size (N=521), we calculated a completion rate of 179% (Multimedia Appendix 8).

Table 1. Number of questionnaires completed overall and by diabetes type (N=1206).

Number of questionnaires completed[a]	Respondents, n (%)		
	Total	T1DM[b] (n=194)	T2DM[c] (n=1012)
Baseline only[d]	193 (16)	29 (14.9)	164 (16.2)
1-7	146 (12.1)	20 (10.2)	126 (12.5)
8-11	201 (16.7)	35 (18.2)	166 (16.4)
All 12	666 (55.2)	110 (56.7)	556 (54.9)

[a]Questionnaires completed could be nonconsecutive.

[b]T1DM: type 1 diabetes mellitus.

[c]T2DM: type 2 diabetes mellitus.

[d]Only *subpanel B* respondents; *subpanel A* respondents were removed upon wave 1 noncompletion.

Table 2. Number of respondents lost to follow-up after each wave overall and by diabetes type (N=1206).

Wave[a]	Respondents lost to follow-up after each wave, n (%)		
	Total	T1DM[b] (n=194)	T2DM[c] (n=1012)
Baseline[d]	193 (16)	29 (14.9)	164 (16.2)
Wave 1	33 (2.7)	8 (4.1)	25 (2.5)
Wave 2	17 (1.4)	2 (1)	15 (1.5)
Wave 3	10 (0.8)	1 (0.5)	9 (0.9)
Wave 4	14 (1.2)	0 (0)	14 (1.4)
Wave 5	7 (0.6)	0 (0)	7 (0.7)
Wave 6	5 (0.4)	3 (1.6)	2 (0.2)
Wave 7	8 (0.7)	0 (0)	8 (0.8)
Wave 8	6 (0.5)	1 (0.5)	5 (0.5)
Wave 9	8 (0.7)	1 (0.5)	7 (0.7)
Wave 10	12 (1)	0 (0)	12 (1.2)
Wave 11	38 (3.2)	9 (4.6)	29 (2.9)
Wave 12[e]	855 (70.9)	140 (72.2)	715 (70.7)

[a]Last wave responded to; after this wave, the respondent was considered to be lost to follow-up.

[b]T1DM: type 1 diabetes mellitus.

[c]T2DM: type 2 diabetes mellitus.

[d]Only *subpanel B* respondents; *subpanel A* respondents were removed upon wave 1 noncompletion.

[e]No data were collected past wave 12.

Discussion

Principal Findings

The real-world iNPHORM study is the first primary research investigation focused on quantifying and predicting prospective self-reported hypoglycemia in the United States. A general cohort of adult Americans with self-reported insulin- and/or secretagogue-treated T1DM or T2DM was recruited between February and April 2020 and followed for 1 year. The sample size was achieved using a 1-time systematic refreshment and quota sampling. The use of an established probability-based internet panel, push factors (precontacts, reminders, and incentives), and easy-to-complete questionnaires shored up high participation rates. Sample characteristics, quality metrics, and hypoglycemia incidence and prognostication will be published by fall 2022.

Study Strengths

Poor generalizability has been an ongoing problem in prognostic hypoglycemia research [89]. To promote real-word representativeness and population inferencing, iNPHORM participants were recruited from random subsets of a well-established, probability-based internet panel. Community-based adults across a wide age range with either T1DM or T2DM, irrespective of past hypoglycemia, were eligible to enroll, as were people prescribed secretagogues, an often underappreciated cause of events [90]. Backstopped by quota sampling, our use of broad eligibility criteria stands in juxtaposition to most prognostic models [91], especially those based on pre-existing trial data, which focus on inpatient [18-21] or younger, healthier (eg, no severe hypoglycemia history or impaired awareness) [14,17] populations.

Data were collected over 12 one-month intervals, balancing the probability of observing events against participants' abilities to recall them accurately. Frequent and long-term data capture enabled us to obtain maximally valid self-reported information on not only hypoglycemia occurrence but also a range of important, preselected factors commonly unavailable in secondary sources [92]. The longitudinal, prospective nature of our study contrasts the typically short, retrospective follow-ups of other prediction models (mode duration 24 hours-3 months) [12,93-96]. Buttressed by a sufficiently large sample size and completion rate >70%, iNPHORM will facilitate assessments of time-varying predictors, lagged dependent variables, and low-salience events (eg, nonsevere hypoglycemia) with minimal false negatives, extrapolation bias, and statistical power loss [97].

Our self-report study yields pertinent insights into the routinely uncaptured burden of hypoglycemia. Past prognostic hypoglycemia research has relied heavily on administrative, insurance-based claims records; however, these sources poorly represent events occurring outside the health care system. Recent evidence suggests that only 5% of severe events require hospitalization, and as many as 50% are treated at home by family/friends [19,20]. Moreover, nonsevere hypoglycemia, by definition *self-treated*, [98] is scarcely, if ever, documented. Patient nondisclosure and provider underrecognition further constrain the real-world applicability of epidemiological data gleaned from clinical encounters. Studies indicate that 65% and 85% of people with diabetes deliberately underreport their severe [99] and nonsevere [100] events, respectively, whereas 57% are seldom asked about hypoglycemia by their providers [99]. Not surprisingly, anonymous versus onymous hypoglycemia reporting has been associated with 2- to 3-fold higher rates [22].

iNPHORM builds on the methodological and economic advantages of real-time, web-based self-report to acquire instantaneous and representative [25,26] data within large samples [101]. Indeed, web-based questionnaires have been lauded for democratizing and potentiating self-report research. Currently, >90% of Americans use the internet [102]. iNPHORM data were collected via user-friendly, self-administered questionnaires completable on diverse internet-equipped devices at the participants' convenience. Very little personal information was requested, and participants were made aware in the letter of information that their data would be deidentified before analysis. By forgoing dependence on health care codes and records, we could obtain real-world, granular information on severe (regardless of health care use) and nonsevere hypoglycemia—events rarely reported in the literature, despite their clinical significance.

Limitations and Strategies to Mitigate Them

Certain limitations and safeguards warrant elaboration. Notwithstanding efforts to promote generalizability, selection biases could have arisen because of the nonrepresentativeness of the internet panel demography and/or of respondents/responses [36,103,104]. This concern affects correlative estimates less; however, it could distort the validity of summary statistics [105]. For this reason, post hoc statistical weighting will be explored [105]. Biases resulting from English language restriction, lack of technological literacy, being limited to no internet access, and survivorship cannot be discounted. Furthermore, although volunteer bias will be assessed during follow-up, baseline self-selection is not calculable (it was unethical to retain data on otherwise eligible invited panelists who did not complete the screener).

Another related limitation is the risk of attrition bias. To mitigate loss to follow-up, ostensibly unmotivated respondents in *subpanel A* were identified and removed at wave 1 via logic testing and noncompletion. One-time systematic refreshment, especially during the first interwave when attrition is highest, has been shown to reduce panel stagnation while improving study feasibility and analytic validity [38]. To prevent further biases, *subpanel B* was recruited from a contemporaneous subgroup of the same frame population as *subpanel A*. Push factors were used to sustain participation [35]. Remuneration coincided with the widely recognized Tailored Design Method by Dillman [106]. Cash amounts were vetted and approved by the Western University health sciences research ethics board before study commencement and outlined in the letter of information. Token incentives were strategized to facilitate revenue-neutral participation (eg, reasonably compensate individuals for their time and help overcome access barriers), reducing volunteer bias [35,36] and respondent dropout [41-43].

Although web-based (vs postal or telephone) surveys have been shown to promote item completeness and accuracy [23,24], they are not immune to recall bias. Research indicates that 90% [63] of patients correctly recall past-year severe hypoglycemia; however, past-month nonsevere hypoglycemia recall ranges from 48% to 75% [67]. To reduce differential misclassification bias, standardized, accessibly worded instructions and definitions were provided in each questionnaire. Furthermore, sensitive items were carefully crafted and positioned to encourage respondent honesty [45]. Technical constraints on the IIS platform precluded participants from reviewing or changing the submitted items. In addition, as mechanisms for deterring multiple participant identities, individuals could not reaccess/resubmit questionnaires, and authentication by email plus log-in was required. To foster confident and accurate responses, we provided individuals as much time as needed to reflect on items and/or review personal clinical documentation/materials. Each notification also contained information on the participants' last completed questionnaire.

Before fielding, the assessments underwent pretesting and piloting to promote content usability and accuracy. A total of 3 individuals participated in the pilot process; this sample size aligned with established best practices at IIS while permitting parsimonious representativity and feasibility. Nevertheless, a larger pilot sample size may have yielded further meaningful feedback. Finally, despite the proven validity/reliability and/or widespread use of many iNPHORM items, no validated self-reported hypoglycemia measure exists yet. To attenuate instrumentation effects in our study [107], hypoglycemia definitions and classifications followed the 2019 American Diabetes Association standards [64], and recall periods echoed peer-reviewed conventions [60,65-67]. Frequent and recurrent hypoglycemia-related information was amassed across extensive, detailed, and standardized items formulated to promote scientific replicability and future outgrowth. The validity of iNPHORM is further fortified by high completion rates [108] and numerous design principles and quality assurance methods that reinforce data accuracy and integrity.

Conclusions

iNPHORM promises important forward strides in real-world hypoglycemia detection and prevention. This protocol highlights the powerful application of an internet-based panel survey to assess long-term hypoglycemia risk in a large, community-based cohort of adult Americans with insulin- and/or secretagogue-treated T1DM and T2DM. To date, descriptive and prognostic hypoglycemia estimates have stemmed mainly from cross-sectional and short-term retrospective analyses of pre-existing databases subject to untenable bias. Pairing the importance of longitudinal, prospective self-reported hypoglycemia data with the advantages of web-based survey modes, iNPHORM aims to clarify putative epidemiological understandings and reveal opportune insights into point-of-care decision-making, research priorities, and effective interventional precision [109-111].

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Neither Sanofi Global nor Sanofi Canada was involved in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the paper for publication. All authors confirm their independence from funders and that they had full access to the study data (including statistical reports and tables). They take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest

AR-L received grants from Sanofi and Eli Lilly, paid fees for presentations, and is a consultant at Novo Nordisk and Eli Lilly. SBH is a consultant at, received grants from, and is in the member advisory boards of Sanofi, Eli Lilly, Novo Nordisk, Janssen, AstraZeneca, Abbott, and Boehringer Ingelheim and is involved in clinical studies at Eli Lilly, Novo Nordisk, AstraZeneca, and Boehringer Ingelheim. SBH also received grants from Juvenile Diabetes Research Foundation, Lawson, and the Canadian Institutes of Health and Research.
The authors are distinct from the developers/sponsors of the iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) questionnaires.

Multimedia Appendix 1
Anthropometric, demographic, situational or environmental, and lifestyle variables.
[DOCX File , 29 KB - resprot_v11i2e33726_app1.docx]

Multimedia Appendix 2
Clinical variables.
[DOCX File , 33 KB - resprot_v11i2e33726_app2.docx]

Multimedia Appendix 3
COVID-19–related variables.

[DOCX File , 22 KB - resprot_v11i2e33726_app3.docx]

Multimedia Appendix 4
Hypoglycemia-related variables.
[DOCX File , 26 KB - resprot_v11i2e33726_app4.docx]

Multimedia Appendix 5
Letter of information and consent emailed to prospective participants of the iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) pilot study.
[DOCX File , 24 KB - resprot_v11i2e33726_app5.docx]

Multimedia Appendix 6
Letter of information and consent emailed to prospective participants of the iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) longitudinal study.
[DOCX File , 26 KB - resprot_v11i2e33726_app6.docx]

Multimedia Appendix 7
Calculation of average total completion rate.
[DOCX File , 16 KB - resprot_v11i2e33726_app7.docx]

Multimedia Appendix 8
Calculation of average total completion rate against estimated required sample size (N=521).
[DOCX File , 18 KB - resprot_v11i2e33726_app8.docx]

References

1. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. JAMA 1997;277(6):488-494. [Medline: 9020274]
2. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. New York: Springer; 2009.
3. Toll DB, Janssen KJ, Vergouwe Y, Moons KG. Validation, updating and impact of clinical prediction rules: a review. J Clin Epidemiol 2008;61(11):1085-1094. [doi: 10.1016/j.jclinepi.2008.04.008] [Medline: 19208371]
4. Riley RD, Hayden JA, Steyerberg EW, Moons KG, Abrams K, Kyzas PA, PROGRESS Group. Prognosis research strategy (PROGRESS) 2: prognostic factor research. PLoS Med 2013;10(2):e1001380 [FREE Full text] [doi: 10.1371/journal.pmed.1001380] [Medline: 23393429]
5. Sandhu S, Lin AL, Brajer N, Sperling J, Ratliff W, Bedoya AD, et al. Integrating a machine learning system into clinical workflows: qualitative study. J Med Internet Res 2020;22(11):e22421. [doi: 10.2196/22421] [Medline: 33211015]
6. Wynants L, Riley RD, Timmerman D, Van Calster B. Random-effects meta-analysis of the clinical utility of tests and prediction models. Stat Med 2018;37(12):2034-2052. [doi: 10.1002/sim.7653] [Medline: 29575170]
7. Terauchi Y, Ozaki A, Zhao X, Teoh C, Jaffe D, Tajima Y, et al. Humanistic and economic burden of cardiovascular disease related comorbidities and hypoglycaemia among patients with type 2 diabetes in Japan. Diabetes Res Clin Pract 2019;149:115-125 [FREE Full text] [doi: 10.1016/j.diabres.2019.01.019] [Medline: 30685348]
8. Cannon A, Handelsman Y, Heile M, Shannon M. Burden of illness in type 2 diabetes mellitus. J Manag Care Spec Pharm 2018;24(9-a Suppl):S5-13. [doi: 10.18553/jmcp.2018.24.9-a.s5] [Medline: 30156443]
9. Vigersky RA. The benefits, limitations, and cost-effectiveness of advanced technologies in the management of patients with diabetes mellitus. J Diabetes Sci Technol 2015;9(2):320-330 [FREE Full text] [doi: 10.1177/1932296814565661] [Medline: 25555391]
10. Shi L, Fonseca V, Childs B. Economic burden of diabetes-related hypoglycemia on patients, payors, and employers. J Diabetes Complications 2021;35(6):107916. [doi: 10.1016/j.jdiacomp.2021.107916] [Medline: 33836965]
11. Foos V, Varol N, Curtis BH, Boye KS, Grant D, Palmer JL, et al. Economic impact of severe and non-severe hypoglycemia in patients with type 1 and type 2 diabetes in the United States. J Med Econ 2015;18(6):420-432. [doi: 10.3111/13696998.2015.1006730] [Medline: 25629654]
12. Shao H, Fonseca V, Stoecker C, Liu S, Shi L. Novel risk engine for diabetes progression and mortality in USA: building, relating, assessing, and validating outcomes (BRAVO). Pharmacoeconomics 2018;36(9):1125-1134. [doi: 10.1007/s40273-018-0662-1] [Medline: 29725871]
13. Ruan Y, Bellot A, Moysova Z, Tan GD, Lumb A, Davies J, et al. Predicting the risk of inpatient hypoglycemia with machine learning using electronic health records. Diabetes Care 2020;43(7):1504-1511. [doi: 10.2337/dc19-1743] [Medline: 32350021]

14. Elliott L, Fidler C, Ditchfield A, Stissing T. Hypoglycemia event rates: a comparison between real-world data and randomized controlled trial populations in insulin-treated diabetes. Diabetes Ther 2016;7(1):45-60 [FREE Full text] [doi: 10.1007/s13300-016-0157-z] [Medline: 26886441]
15. Saunders C, Byrne CD, Guthrie B, Lindsay RS, McKnight JA, Philip S, Scottish Diabetes Research Network Epidemiology Group. External validity of randomized controlled trials of glycaemic control and vascular disease: how representative are participants? Diabet Med 2013 Mar;30(3):300-308. [doi: 10.1111/dme.12047] [Medline: 23075287]
16. McGovern A, Feher M, Munro N, de Lusignan S. Sodium-glucose co-transporter 2 (SGLT2) inhibitor: comparing trial data and real-world use. Diabetes Ther 2017;8(2):365-376 [FREE Full text] [doi: 10.1007/s13300-017-0254-7] [Medline: 28324484]
17. Pedersen-Bjergaard U, Thorsteinsson B. Reporting severe hypoglycemia in type 1 diabetes: facts and pitfalls. Curr Diab Rep 2017;17(12):131. [doi: 10.1007/s11892-017-0965-1] [Medline: 29080929]
18. Mauricio D, Westerbacka J, Nicholls C, Wu J, Gupta R, Menon AA, et al. 135-LB: the forgotten populations: real-world patients with T2DM not meeting eligibility criteria of the glargine 300 U/mL EDITION and BRIGHT RCTs. Diabetes 2019;68(Supplement 1):135-LB. [doi: 10.2337/db19-135-lb]
19. Sarkar U, Karter AJ, Liu JY, Moffet HH, Adler NE, Schillinger D. Hypoglycemia is more common among type 2 diabetes patients with limited health literacy: the diabetes study of Northern California (DISTANCE). J Gen Intern Med 2010;25(9):962-968 [FREE Full text] [doi: 10.1007/s11606-010-1389-7] [Medline: 20480249]
20. Ratzki-Leewing A, Harris S, Zou G, Ryan B. Real-world estimates of severe hypoglycaemia and associated healthcare utilisation in the US: baseline results of the iNPHORM study. Diabetologia 2020:750.
21. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J 2003;20(1):54-60 [FREE Full text] [doi: 10.1136/emj.20.1.54] [Medline: 12533370]
22. Pedersen-Bjergaard U, Færch L, Allingbjerg ML, Agesen R, Thorsteinsson B. The influence of new European Union driver's license legislation on reporting of severe hypoglycemia by patients with type 1 diabetes. Diabetes Care 2015;38(1):29-33. [doi: 10.2337/dc14-1417] [Medline: 25288675]
23. Warner CH, Appenzeller GN, Grieger T, Belenkiy S, Breitbach J, Parker J, et al. Importance of anonymity to encourage honest reporting in mental health screening after combat deployment. Arch Gen Psychiatry 2011;68(10):1065-1071. [doi: 10.1001/archgenpsychiatry.2011.112] [Medline: 21969463]
24. Gnambs T, Kaspar K. Disclosure of sensitive behaviors across self-administered survey modes: a meta-analysis. Behav Res Methods 2014;47(4):1237-1259. [doi: 10.3758/s13428-014-0533-4] [Medline: 25410404]
25. Loxton D, Powers J, Anderson AE, Townsend N, Harris ML, Tuckerman R, et al. Online and offline recruitment of young women for a longitudinal health survey: findings from the Australian Longitudinal Study on Women's Health 1989-95 Cohort. J Med Internet Res 2015;17(5):e109 [FREE Full text] [doi: 10.2196/jmir.4261] [Medline: 25940876]
26. McGee B, Leonte M, Wildenhaus K, Wilcox M, Reps J, LaCross L. Leveraging digital technology in conducting longitudinal research on mental health in pregnancy: longitudinal panel survey study. JMIR Pediatr Parent 2021;4(2):e16280. [doi: 10.2196/16280] [Medline: 33904826]
27. Henderson JT, Thompson JH, Burda BU, Cantor A, Beil T, Whitlock EP. Screening for preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force [Internet]. Rockville: Agency for Healthcare Research and Quality (US); 2017.
28. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61(4):344-349. [doi: 10.1016/j.jclinepi.2007.11.008] [Medline: 18313558]
29. Berger ML, Martin BC, Husereau D, Worley K, Allen JD, Yang W, et al. A questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health 2014;17(2):143-156 [FREE Full text] [doi: 10.1016/j.jval.2013.12.011] [Medline: 24636373]
30. Eysenbach G. Improving the quality of web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004;6(3):e34 [FREE Full text] [doi: 10.2196/jmir.6.3.e34] [Medline: 15471760]
31. Knowledge panel: a methodological overview. Ipsos. URL: https://www.ipsos.com/sites/default/files/ipsosknowledgepanelmethodology.pdf [accessed 2021-12-15]
32. Goldman N, Lin IF, Weinstein M, Lin YH. Evaluating the quality of self-reports of hypertension and diabetes. J Clin Epidemiol 2003;56(2):148-154. [doi: 10.1016/s0895-4356(02)00580-2] [Medline: 12654409]
33. Riley RD, Snell KI, Ensor J, Burke DL, Harrell Jr FE, Moons KG, et al. Minimum sample size for developing a multivariable prediction model: part I - continuous outcomes. Stat Med 2019;38(7):1262-1275. [doi: 10.1002/sim.7993] [Medline: 30347470]
34. Riley RD, Snell KI, Ensor J, Burke DL, Harrell Jr FE, Moons KG, et al. Minimum sample size for developing a multivariable prediction model: part II - binary and time-to-event outcomes. Stat Med 2019;38(7):1276-1296 [FREE Full text] [doi: 10.1002/sim.7992] [Medline: 30357870]
35. Eysenbach G. The law of attrition. J Med Internet Res 2005;7(1):e11 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]

36. Eysenbach G, Wyatt J. Using the Internet for surveys and health research. J Med Internet Res 2002;4(2):E13 [FREE Full text] [doi: 10.2196/jmir.4.2.e13] [Medline: 12554560]
37. Medical Devices & Diagnostics Centre of Expertise: 2020 Capabilities. Ipsos. URL: https://www.ipsos.com/sites/default/files/ipsos-mdd-global-capabilities.pdf [accessed 2021-12-15]
38. Stopher P. Collecting, managing, and assessing data using sample surveys. Cambridge: Cambridge University Press; 2012.
39. Dillman DA. Mail and telephone surveys: the total design method. New York: John Wiley; 1978.
40. Kalfs N, van Evert H. Nonresponse and travel surveys. In: Jones P, Stopher PR, editors. Transport survey quality and innovation. Bingley: Emerald Group Publishing; 2003:567-585.
41. Goyder J. The silent minority: nonresponse in sample surveys. Boulder: Westview Press; 1988.
42. Nederhof AJ. The effects of material incentives in mail surveys: two studies. Public Opin Q 1983;47(1):103-111. [doi: 10.1086/268770]
43. Sudman S, Bradburn NM. Response effects in surveys: a review and synthesis. London: Aldine Publishing Company; 1974.
44. Groves RM, Dillman DA, Eltinge JL, Little RJ. Survey nonresponse. Hoboken: Wiley; 2001.
45. Vinten G. The art of asking threatening questions. Manag Decis 1995;33(7):35-39. [doi: 10.1108/00251749510090566]
46. Raimond T, Hensher DA. Review of panel surveys and other longitudinal techniques: an annotated bibliographic review. University of Sydney. Sydney: Institute of Transport Studies, Graduate School of Business, the University of Sydney; 1992. URL: https://ses.library.usyd.edu.au/bitstream/handle/2123/19035/ITS-WP-92-19.pdf?sequence=1 [accessed 2021-08-11]
47. Bradburn NM, Sudman S, Wansink B. Asking questions: the definitive guide to questionnaire design: for market research, political polls, and social and health questionnaires. San Francisco: Wiley; 2004.
48. Wyatt JC. When to use web-based surveys. J Am Med Inform Assoc 2000;7(4):426-429 [FREE Full text] [doi: 10.1136/jamia.2000.0070426] [Medline: 10887170]
49. Liu H, Cella D, Gershon R, Shen J, Morales LS, Riley W, et al. Representativeness of the patient-reported outcomes measurement information system Internet panel. J Clin Epidemiol 2010;63(11):1169-1178 [FREE Full text] [doi: 10.1016/j.jclinepi.2009.11.021] [Medline: 20688473]
50. VR-36, VR-12 and VR-6d. Boston University School of Public Health. URL: https://www.bu.edu/sph/about/departments/health-law-policy-and-management/research/vr-36-vr-12-and-vr-6d/ [accessed 2021-12-15]
51. Bombak AE. Self-rated health and public health: a critical perspective. Front Public Health 2013;1:15. [doi: 10.3389/fpubh.2013.00015] [Medline: 24350184]
52. Haun J, Luther S, Dodd V, Donaldson P. Measurement variation across health literacy assessments: implications for assessment selection in research and practice. J Health Commun 2012;17 Suppl 3:141-159. [doi: 10.1080/10810730.2012.712615] [Medline: 23030567]
53. Selim AJ, Rogers W, Fleishman JA, Qian SX, Fincke BG, Rothendler JA, et al. Updated U.S. population standard for the veterans RAND 12-item health survey (VR-12). Qual Life Res 2009;18(1):43-52. [doi: 10.1007/s11136-008-9418-2] [Medline: 19051059]
54. American community survey 5-year data (2009-2019). United States Census Bureau. Washington D.C: Unites States Department of Commerce; 2020. URL: https://www.census.gov/data/developers/data-sets/acs-5year.html [accessed 2021-05-04]
55. NHANES 2019-2020 questionnaire instruments. Centers for Disease Control and Prevention. Hyattsville: National center for health statistics URL: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/questionnaires.aspx?BeginYear=2019 [accessed 2021-07-21]
56. 2020 BRFSS questionnaire. Centres for disease control and prevention. 2021. URL: https://www.cdc.gov/brfss/questionnaires/pdf-ques/2020-BRFSS-Questionnaire-508.pdf [accessed 2021-07-21]
57. 2020 National Health Interview Survey (NHIS) questionnaire. Centres for disease control and prevention. URL: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Survey_Questionnaires/NHIS/2020/EnglishQuest-508.pdf [accessed 2021-07-21]
58. Coronavirus disease 2019 (COVID-19): 2020 interim case definition, approved april 5, 2020. Centers for disease control and prevention. 2020. URL: https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2020-08-05/ [accessed 2020-12-24]
59. Ratzki-Leewing AA, Ryan BL, Buchenberger JD, Dickens JW, Black JE, Harris SB. COVID-19 hinterland: surveilling the self-reported impacts of the pandemic on diabetes management in the USA (cross-sectional results of the iNPHORM study). BMJ Open 2021;11(9):e049782 [FREE Full text] [doi: 10.1136/bmjopen-2021-049782] [Medline: 34475174]
60. Ratzki-Leewing A, Harris SB, Mequanint S, Reichert SM, Belle Brown J, Black JE, et al. Real-world crude incidence of hypoglycemia in adults with diabetes: results of the InHypo-DM Study, Canada. BMJ Open Diabetes Res Care 2018;6(1):e000503 [FREE Full text] [doi: 10.1136/bmjdrc-2017-000503] [Medline: 29713480]
61. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 1995;18(4):517-522. [doi: 10.2337/diacare.18.4.517] [Medline: 7497862]
62. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994;17(7):697-703. [doi: 10.2337/diacare.17.7.697] [Medline: 7924780]

63. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, et al. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. Diabetes Care 2011;34(4):801-806 [FREE Full text] [doi: 10.2337/dc10-1343] [Medline: 21346182]
64. American Diabetes Association. Standards of Medical Care in Diabetes-2019 abridged for primary care providers. Clin Diabetes 2019;37(1):11-34 [FREE Full text] [doi: 10.2337/cd18-0105] [Medline: 30705493]
65. Brod M, Christensen T, Bushnell DM. The impact of non-severe hypoglycemic events on daytime function and diabetes management among adults with type 1 and type 2 diabetes. J Med Econ 2012;15(5):869-877. [doi: 10.3111/13696998.2012.686465] [Medline: 22510017]
66. Kern W, Holstein A, Moenninghoff C, Kienhöfer J, Riedl M, Kulzer B. Self-reported hypoglycaemic events in 2 430 patients with insulin-treated diabetes in the German sub-population of the HAT study. Exp Clin Endocrinol Diabetes 2017;125(9):592-597 [FREE Full text] [doi: 10.1055/s-0043-112350] [Medline: 28750429]
67. Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes Metab Res Rev 2003;19(3):232-240. [doi: 10.1002/dmrr.377] [Medline: 12789657]
68. CFR - code of federal regulations title 21. United States Food and Drug Administration. 2021. URL: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32 [accessed 2021-12-15]
69. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393 [FREE Full text] [doi: 10.1136/bmj.b2393] [Medline: 19564179]
70. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. BMJ 2009;338:b604. [doi: 10.1136/bmj.b604] [Medline: 19336487]
71. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ 2009;338:b605. [doi: 10.1136/bmj.b605] [Medline: 19477892]
72. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. BMC Med 2015;13:1 [FREE Full text] [doi: 10.1186/s12916-014-0241-z] [Medline: 25563062]
73. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart 2012;98(9):683-690. [doi: 10.1136/heartjnl-2011-301246] [Medline: 22397945]
74. Steyerberg EW, Uno H, Ioannidis JP, van Calster B, Collaborators. Poor performance of clinical prediction models: the harm of commonly applied methods. J Clin Epidemiol 2018;98:133-143. [doi: 10.1016/j.jclinepi.2017.11.013] [Medline: 29174118]
75. Moons KG, Donders AR, Steyerberg EW, Harrell FE. Penalized maximum likelihood estimation to directly adjust diagnostic and prognostic prediction models for overoptimism: a clinical example. J Clin Epidemiol 2004;57(12):1262-1270. [doi: 10.1016/j.jclinepi.2004.01.020] [Medline: 15617952]
76. Pavlou M, Ambler G, Seaman SR, Guttmann O, Elliott P, King M, et al. How to develop a more accurate risk prediction model when there are few events. BMJ 2015;351:h3868 [FREE Full text] [doi: 10.1136/bmj.h3868] [Medline: 26264962]
77. Tibshirani R. Regression shrinkage and selection via the lasso. J R Stat Soc Series B Stat Methodol 1996;58(1):267-288. [doi: 10.1111/j.2517-6161.1996.tb02080.x]
78. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28(5):964-974. [doi: 10.1093/ije/28.5.964] [Medline: 10597998]
79. Howe CJ, Cole SR, Lau B, Napravnik S, Eron Jr JJ. Selection bias due to loss to follow up in cohort studies. Epidemiology 2016;27(1):91-97 [FREE Full text] [doi: 10.1097/EDE.0000000000000409] [Medline: 26484424]
80. Scharfstein D, Robins JM, Eddings W, Rotnitzky A. Inference in randomized studies with informative censoring and discrete time-to-event endpoints. Biometrics 2001;57(2):404-413. [doi: 10.1111/j.0006-341x.2001.00404.x] [Medline: 11414563]
81. Steyerberg EW, Harrell Jr FE. Prediction models need appropriate internal, internal-external, and external validation. J Clin Epidemiol 2016;69:245-247 [FREE Full text] [doi: 10.1016/j.jclinepi.2015.04.005] [Medline: 25981519]
82. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. Stat Med 2011;30(10):1105-1117 [FREE Full text] [doi: 10.1002/sim.4154] [Medline: 21484848]
83. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162(1):W1-73 [FREE Full text] [doi: 10.7326/M14-0698] [Medline: 25560730]
84. Grønnesby JK, Borgan O. A method for checking regression models in survival analysis based on the risk score. Lifetime Data Anal 1996;2(4):315-328. [doi: 10.1007/BF00127305] [Medline: 9384628]
85. May S, Hosmer DW. A cautionary note on the use of the Grønnesby and Borgan goodness-of-fit test for the Cox proportional hazards model. Lifetime Data Anal 2004;10(3):283-291. [doi: 10.1023/b:lida.0000036393.29224.1d] [Medline: 15456108]
86. Nijman SW, Groenhof TK, Hoogland J, Bots ML, Brandjes M, Jacobs JJ, et al. Real-time imputation of missing predictor values improved the application of prediction models in daily practice. J Clin Epidemiol 2021;134:22-34 [FREE Full text] [doi: 10.1016/j.jclinepi.2021.01.003] [Medline: 33482294]

87. Steyerberg EW, Borsboom GJ, van Houwelingen HC, Eijkemans MJ, Habbema JD. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. Stat Med 2004;23(16):2567-2586. [doi: 10.1002/sim.1844] [Medline: 15287085]
88. von Allmen RS, Weiss S, Tevaearai HT, Kuemmerli C, Tinner C, Carrel TP, et al. Completeness of follow-up determines validity of study findings: results of a prospective repeated measures cohort study. PLoS One 2015;10(10):e0140817 [FREE Full text] [doi: 10.1371/journal.pone.0140817] [Medline: 26469346]
89. Kimball AW. Errors of the third kind in statistical consulting. J Am Stat Assoc 1957;52(278):133-142. [doi: 10.1080/01621459.1957.10501374]
90. Edridge CL, Dunkley AJ, Bodicoat DH, Rose TC, Gray LJ, Davies MJ, et al. Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: a systematic review and meta-analysis of population based studies. PLoS One 2015;10(6):e0126427 [FREE Full text] [doi: 10.1371/journal.pone.0126427] [Medline: 26061690]
91. Kodama S, Fujihara K, Shiozaki H, Horikawa C, Yamada MH, Sato T, et al. Ability of current machine learning algorithms to predict and detect hypoglycemia in patients with diabetes mellitus: meta-analysis. JMIR Diabetes 2021;6(1):e22458 [FREE Full text] [doi: 10.2196/22458] [Medline: 33512324]
92. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research: an epidemiologic approach. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2001.
93. Han K, Yun JS, Park YM, Ahn YB, Cho JH, Cha SA, et al. Development and validation of a risk prediction model for severe hypoglycemia in adult patients with type 2 diabetes: a nationwide population-based cohort study. Clin Epidemiol 2018;10:1545-1559 [FREE Full text] [doi: 10.2147/CLEP.S169835] [Medline: 30425585]
94. Mathioudakis NN, Everett E, Routh S, Pronovost PJ, Yeh HC, Golden SH, et al. Development and validation of a prediction model for insulin-associated hypoglycemia in non-critically ill hospitalized adults. BMJ Open Diabetes Res Care 2018;6(1):e000499 [FREE Full text] [doi: 10.1136/bmjdrc-2017-000499] [Medline: 29527311]
95. Eren-Oruklu M, Cinar A, Quinn L. Hypoglycemia prediction with subject-specific recursive time-series models. J Diabetes Sci Technol 2010;4(1):25-33 [FREE Full text] [doi: 10.1177/193229681000400104] [Medline: 20167164]
96. Faruqui SH, Du Y, Meka R, Alaeddini A, Li C, Shirinkam S, et al. Development of a deep learning model for dynamic forecasting of blood glucose level for type 2 diabetes mellitus: secondary analysis of a randomized controlled trial. JMIR Mhealth Uhealth 2019;7(11):e14452 [FREE Full text] [doi: 10.2196/14452] [Medline: 31682586]
97. Frier BM, Ratzki-Leewing A, Harris SB. Reporting of hypoglycaemia in clinical trials of basal insulins: a need for consensus. Diabetes Obes Metab 2019;21(7):1529-1542 [FREE Full text] [doi: 10.1111/dom.13732] [Medline: 30924567]
98. Diabetes Canada Clinical Practice Guidelines Expert Committee, Yale JF, Paty B, Senior PA. Hypoglycemia. Can J Diabetes 2018;42 Suppl 1:S104-S108. [doi: 10.1016/j.jcjd.2017.10.010] [Medline: 29650081]
99. Mojdami D, Mitchell BD, Spaepen E, Syring K, Rabasa-Lhoret R, Punthakee Z, et al. Conversations and reactions around severe hypoglycemia study: results of hypoglycemia experiences in Canadian adults with insulin-treated diabetes and their caregivers. Can J Diabetes 2021;45(3):236-242. [doi: 10.1016/j.jcjd.2020.08.104] [Medline: 33087294]
100. Leiter LA, Boras D, Woo VC. Dosing irregularities and self-treated hypoglycemia in type 2 diabetes: results from the Canadian cohort of an international survey of patients and healthcare professionals. Can J Diabetes 2014;38(1):38-44. [doi: 10.1016/j.jcjd.2013.08.270] [Medline: 24485212]
101. Wasfi R, Poirier Stephens Z, Sones M, Laberee K, Pugh C, Fuller D, et al. Recruiting participants for population health intervention research: effectiveness and costs of recruitment methods for a cohort study. J Med Internet Res 2021;23(11):e21142 [FREE Full text] [doi: 10.2196/21142] [Medline: 34587586]
102. Demographics of internet and home broadband usage in the United States. Pew Research Center. 2021. URL: https://www.pewresearch.org/internet/fact-sheet/internet-broadband/ [accessed 2021-05-04]
103. Delgado-Rodríguez M, Llorca J. Bias. J Epidemiol Community Health 2004;58(8):635-641 [FREE Full text] [doi: 10.1136/jech.2003.008466] [Medline: 15252064]
104. Craig BM, Hays RD, Pickard AS, Cella D, Revicki DA, Reeve BB. Comparison of US panel vendors for online surveys. J Med Internet Res 2013;15(11):e260 [FREE Full text] [doi: 10.2196/jmir.2903] [Medline: 24292159]
105. Hays RD, Liu H, Kapteyn A. Use of Internet panels to conduct surveys. Behav Res Methods 2015;47(3):685-690 [FREE Full text] [doi: 10.3758/s13428-015-0617-9] [Medline: 26170052]
106. Dillman DA. Mail and internet surveys: the tailored design method - 2007 update with new internet, visual, and mixed-mode guide. Hoboken: John Wiley & Sons; 2007.
107. Tofthagen C. Threats to validity in retrospective studies. J Adv Pract Oncol 2012;3(3):181-183 [FREE Full text] [Medline: 25031944]
108. Schonlau M. Will web surveys ever become part of mainstream research? J Med Internet Res 2004;6(3):e31 [FREE Full text] [doi: 10.2196/jmir.6.3.e31] [Medline: 15471757]
109. Stewart MA. Effective physician-patient communication and health outcomes: a review. CMAJ 1995;152(9):1423-1433 [FREE Full text] [Medline: 7728691]
110. Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 2017;318(2):197-198 [FREE Full text] [doi: 10.1001/jama.2017.7156] [Medline: 28586821]

111. Little P, Everitt H, Williamson I, Warner G, Moore M, Gould C, et al. Observational study of effect of patient centredness and positive approach on outcomes of general practice consultations. BMJ 2001;323(7318):908-911 [FREE Full text] [doi: 10.1136/bmj.323.7318.908] [Medline: 11668137]

Abbreviations

EMR: electronic medical record
IIS: Ipsos Interactive Services
iNPHORM: Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models
Lasso: least absolute shrinkage and selection operator
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus

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Protocol

Cardiovascular Health Status And Genetic Risk In Survivors of Childhood Neuroblastoma and Nephroblastoma Treated With Doxorubicin: Protocol of the Pharmacogenetic Part of the LESS-Anthra Cross-Sectional Cohort Study

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Abstract

Background: In childhood cancer survivors (survival of 5 years or more after diagnosis), cardiac toxicity is the most common nonmalignant cause of death attributed to treatment-related consequences. Identifying patients at risk of developing late cardiac toxicity is therefore crucial to improving treatment outcomes. The use of genetic markers has been proposed, together with clinical risk factors, to predict individual risk of cardiac toxicity from cancer therapies, such as doxorubicin.

Objective: The primary aim of this study is to evaluate the value of multimarker genetic testing for RARG rs2229774, UGT1A6 rs17863783, and SLC28A3 rs7853758 for predicting doxorubicin-induced cardiotoxicity. The secondary aim is to replicate previously described associations of candidate genetic markers with doxorubicin-induced cardiotoxicity. Moreover, we will evaluate the prevalence of cardiovascular dysfunction in childhood cancer survivors after neuroblastoma or nephroblastoma.

Methods: This is the pharmacogenetic substudy of the research project Structural Optimization for Children With Cancer After Anthracycline Therapy (LESS-Anthra). We invited 2158 survivors of childhood neuroblastoma or nephroblastoma treated with doxorubicin according to the trial protocols of SIOP 9/GPOH, SIOP 93-01/GPOH, SIOP 2001/GPOH, NB 90, NB 97, or NB 2004 to participate in this prospective cross-sectional cohort study. The study participants underwent a cardiological examination and were asked to provide a blood or saliva sample for genotyping. The study participants' health statuses and cardiovascular diagnoses were recorded using a questionnaire completed by the cardiologist. Digital echocardiographic data were centrally evaluated to determine the contractile function parameters. Medical data on the tumor diagnosis and treatment protocol were taken from the study documentation. Survivors were screened for variants of several candidate genes by TaqMan genotyping.

Results: This study includes 657 survivors treated with doxorubicin for childhood cancer, the largest German cohort assembled to date to investigate cardiovascular late effects. Data analyses are yet to be completed.

Conclusions: This study will define the genetic risk related to 3 marker genes proposed in a pharmacogenetic guideline for risk assessment. Moreover, the results of this study will show the prevalence of cardiovascular dysfunction in survivors of pediatric neuroblastoma or nephroblastoma who were treated with doxorubicin. The results will help to improve primary treatment and follow-up care, thus reducing cardiovascular late effects in the growing population of childhood cancer survivors.

Trial Registration: German Clinical Trials Register DRKS00015084; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00015084

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KEYWORDS

cardiotoxicity; anthracyclines; childhood cancer survivors; genetics; polymorphisms; cardiology; cardiac health; cancer; survivors; childhood; children; risk monitoring; genetics; cardiovascular health; pediatrics

Introduction

Despite the emergence of new so-called targeted therapies, standard cytotoxic chemotherapies remain a cornerstone for treating various cancers. Anthracyclines, such as doxorubicin, daunorubicin, and epirubicin, are still among the most used chemotherapeutic agents. However, cardiotoxicity is a frequent complication with this class of anticancer drugs. In particular, childhood cancer survivors are at risk for cardiovascular complications, with a 15-fold increase in the relative risk of severe congestive heart failure compared to their noncancer siblings [1] and an 8-fold increase in mortality due to cardiovascular disease compared to the overall population [2,3]. Previous studies showed that 4.4%-42% of childhood survivors of acute lymphoblastic leukemia or nephroblastoma had progressive cardiac abnormalities several years after completing doxorubicin therapy [4-6].

Anthracycline-induced cardiomyopathy may develop during treatment or several years after completion of treatment and may include decreased left ventricular ejection fraction and signs and symptoms of congestive heart failure. Many risk factors for anthracycline-induced cardiotoxicity have been identified, most notably higher cumulative anthracycline doses and younger age. However, the optimal strategy for the prevention of anthracycline-induced cardiotoxicity is unclear. Currently, dexrazoxane is the only treatment for anthracycline cardioprotection approved by the United States Food and Drug Administration and European Medicines Agency. However, dexrazoxane is contraindicated in children and adolescents due to a 3-fold higher incidence of secondary malignancies in dexrazoxane-treated children compared with controls.

There is an additive or potentially synergistic increase in the risk of cardiomyopathy or cardiovascular death in anthracycline-treated patients who have received radiotherapy to the mediastinum or concomitant therapy with other known cardiotoxic agents, such as cyclophosphamide or vinca alkaloids [7,8]. Tukenova et al [7] reported that as little as 5 Gy of radiation to the heart increased the relative risk of cardiovascular disease mortality in childhood cancer survivors. New techniques in radiotherapy can increase cardiac protection without losing the efficacy of irradiation [9].

There is extensive interindividual variability in sensitivity to the cardiotoxic effects of anthracyclines. In some patients, cumulative doses of doxorubicin higher than 1000 mg/m^2 cause no cardiomyopathy, whereas others develop cardiomyopathy at cumulative doses <200 mg/m^2 [10]. Clinical and experimental studies have shown a considerable genetic contribution [11-13]. The heritability of anthracycline-induced cell toxicity has been estimated to be 35%-60% [11]. Together, the findings suggest that genetic factors play an important role in anthracycline-associated cardiotoxicity.

Candidate gene and genome-wide association studies have identified genetic variants associated with anthracycline-induced cardiotoxicity, including genetic polymorphisms in genes involved in anthracycline transport, metabolism, and anthracycline-induced oxidative stress. Based on their study results, Aminkeng et al [14] concluded that the evidence was strongest and most consistent for an association of *RARG* (retinoic acid receptor gamma) rs2229774, *SLC28A3* (solute carrier family 28 member 3) rs7853758, and *UGT1A6* (UDP glucuronosyltransferase family 1 member A6) rs17863783 variants with anthracycline-induced cardiotoxicity. Testing for these single nucleotide polymorphisms (SNPs) could improve discrimination between individuals at higher and lower risk of anthracycline-induced cardiotoxicity. Aminkeng et al [14] proposed the grading cardiotoxicity risk according to the *RARG* rs2229774, *UGT1A6* rs17863783, and *SLC28A3* rs7853758 genotype, as follows: patients carrying the *RARG* rs2229774 A or *UGT1A6* rs17863783 T risk variants should be considered at high risk of anthracycline-induced cardiotoxicity. The *SLC28A3* rs7853758 A allele was associated with a reduced risk of anthracycline-induced cardiotoxicity. For patients carrying the rs7853758 A protective variant who do not carry *RARG* rs2229774 or *UGT1A6* rs17863783 risk variants, classification into a lower cardiotoxicity risk group should be considered. All other patients should be considered at moderate genetic risk. An initial health economic evaluation of pharmacogenomic testing in patients treated for childhood cancer with anthracyclines suggests that information gained from the pharmacogenomic test could reduce mortality by approximately 17% and reduce costs by about 6% [15].

The primary aim of this study is to evaluate the importance of multimarker genetic testing for *RARG* rs2229774, *UGT1A6* rs17863783, and *SLC28A3* rs7853758 for predicting doxorubicin-induced cardiovascular dysfunction. We focus on these 3 markers because the only pharmacogenetic guideline published to date recommends their testing to stratify the individual cardiotoxic risk of anthracycline therapy. The secondary aim of this study is to determine the association of doxorubicin-induced cardiovascular toxicity with other candidate genes that have been previously described [13,16-19] or will soon be discovered, provided that our sample size has sufficient statistical power. To ensure that the population studied is as homogeneous as possible in terms of diagnoses and the type of anthracycline used, we focus on patients with childhood nephroblastoma or neuroblastoma. Another secondary objective is to investigate the prevalence of cardiovascular dysfunction in a population of children treated with doxorubicin.

Methods

Patients

This study is part of the LESS-Anthra cross-sectional cohort study initiated by the "late effects surveillance system" (LESS). As part of this study, former cancer patients were offered a standardized cardiological examination and were surveyed about their quality of life and health status. A goal of LESS-Anthra was to establish a biobank of blood samples to allow the investigation of genetic polymorphisms that may predispose an individual to doxorubicin-induced cardiomyopathy, which is the subject of this study protocol. The study was approved by the Ethics Committee of the University of Lübeck (14-182) and the Ethics Committee of the University of Ulm (239/17). Study participants were identified through LESS, a German multicenter active surveillance consortium studying late effects of cancer treatment in children, in collaboration with the German Childhood Cancer Registry. Patients who had survived childhood cancer for 5 years or more (since diagnosis) were eligible if they (1) were diagnosed with nephroblastoma or neuroblastoma between January 1990 and December 2012, (2) were diagnosed before the age of 18, (3) were assigned to a treatment protocol that included doxorubicin (intention-to-treat), and (4) had participated in one of the nephroblastoma trials SIOP (International Society of Paediatric Oncology) 9/GPOH (German Society for Pediatric Oncology and Hematology), SIOP 93-01/GPOH, or SIOP 2001/GPOH or neuroblastoma trials NB 90, NB 97, or NB 2004. In Germany, almost all patients diagnosed with nephroblastoma or neuroblastoma between 1990 and 2012 who were willing to participate in a trial were included in one of the above-mentioned studies. Patients selected for LESS-Anthra were contacted by the German Childhood Cancer Registry, which has access to current survivor addresses. A total of 2173 patients were identified, contacted by mail, and invited to participate in the study. Those who did not respond received a reminder letter. Patients unwilling to participate in the study had the opportunity to provide us with their reason for nonparticipation via a response form. Patients were included only after they (or their parents or legal guardians, if patients were under 18 years of age) had provided informed consent. For adolescents ≥16 years, their written consent was also required.

Study Design

Patients who agreed to participate were asked to see a cardiologist within the next 12 months for a cardiologic follow-up examination, which included an electrocardiogram and transthoracic echocardiography. Patients had the choice of having the examination performed by their supervising cardiologist or a cardiologist recommended by the LESS-Anthra study group. Cardiologists had knowledge of treatment exposure but no knowledge of genotypes. The cardiologists were asked to send original echocardiographic recordings, together with a completed form summarizing the clinical and instrumental examinations results, to the cardiologic evaluation center (Clinic for Pediatric Cardiology at Saarland University Hospital, HA-K). The cardiologist also took a blood sample for pharmacogenetic analysis or a saliva sample at the patient's option. Biosamples were sent to the genetics center (Genotyping Laboratory, OZ).

Collection of Medical Data

The following data were extracted from clinical trial registries: cancer diagnosis, age at diagnosis, sex, tumor location, tumor stage, study name and study arm, chemotherapy, anthracycline doses (doses of doxorubicin, per cycle and cumulatively, as defined in the study protocol for the study arm to which the patient was assigned), other cardiotoxic drugs (ie, drugs with cardiotoxic potential listed in the 2016 ESC position paper [20]), radiotherapy, irradiation field (mediastinal, lung, or left abdominal irradiation is considered a relevant cardiac risk factor [6,21]), irradiation doses of the primary tumor, relapse, and therapy (chemotherapy and irradiation) of recurrent tumor (Textbox 1).

Textbox 1. Assessment and variables recorded.

Cancer diagnosis and cancer treatment-related variables (obtained from study centers of the neuroblastoma trials (NB 90, NB 97, and NB 2004) and the nephroblastoma trials (SIOP 9/GPOH, SIOP 93-01/GPOH, and SIOP 2001/GPOH).

- Cancer diagnosis, tumor location, tumor stage
- Age at diagnosis
- Sex
- Study name and study arm
- Chemotherapy including anthracycline doses (per cycle and cumulative)
- Other cardiotoxic drugs (the drugs listed in the 2016 ESC position paper were considered as potentially cardiotoxic drugs)
- Additional radiotherapy: irradiation field, irradiation doses of the primary tumor, and the field that included the heart (mediastinal, lung, left abdominal)
- Length of posttherapy interval
- Relapse and therapy (chemotherapy and irradiation) of the recurrent tumor
- Comorbidities

Results of interview and clinical and physical examination (obtained at presentation to cardiologist).

- Anthropometry: weight (kg) and height (cm)

Systolic and diastolic blood pressure (mmHg) according to current guidelines for conventional office blood pressure measurement (ie, patients should be seated comfortably 5 min before measurements, at least 3 measurements 1-2 min apart, blood pressure is recorded as the average of the last 2 readings)

- Heart rate (beats per minute)
- ECG findings: Cardiac arrhythmia with type (bradycardia, tachycardia, ventricular, or supraventricular); heart block findings with type (atrioventricular block with degree, complete right bundle branch block, or complete left bundle branch block); QTc prolongation (ms); signs of cardiac hypertrophy with type (right heart hypertrophy or left ventricular hypertrophy); other ECG pathologies
- Findings on clinical examination (edema, dyspnea at rest, cyanosis, hepatosplenomegaly, jugular venous congestion, or arrhythmia by auscultation).
- Diagnoses made by the cardiologist: Heart failure (right heart failure, left heart failure, or global heart failure; NYHA stage); cardiomyopathy (dilated, hypertrophic, restrictive, or other); arterial hypertension (primary hypertension or secondary hypertension); cardiac arrhythmia (type)
- The patient's expressed subjective resilience in everyday life (5 level rating: very good, good, average, poor, and very poor).
- The patient's expressed subjective ability to engage in sports activities (2 level rating: sports activity possible/not possible).

Echocardiographic parameters (echocardiographic evaluation center)

- Left ventricular size: Linear measurements; volume measurements; left ventricular mass calculations
- Left ventricular function assessment: Global systolic function parameters (fractional shortening or ejection fraction); global myocardial function assessed by Doppler-derived Tei index
- Left and right atrium area and volume measurements

Cardiologic Examination

Cardiologists were asked to perform echocardiographic examinations according to the instructions provided. Table 1 shows the minimal digital acquisition protocol for transthoracic echocardiography. The echocardiographic recordings were centrally evaluated by a pediatric cardiologist in a standardized way and blinded for treatment exposure and genetic test results to minimize interinvestigator variability. In rare cases, in which parts of the echocardiography recordings were of insufficient quality, the corresponding data points were treated as missing values.

Additional information, such as clinical examination findings, weight, height, heart rate, blood pressure, and physical performance of the patient, was collected using a questionnaire (Table 1). This questionnaire was completed by the cardiologist and sent to the cardiological evaluation center.

Table 1. Minimal digital acquisition protocol for transthoracic echocardiography.

View	Data type
Long-axis view, M-mode	Still frame
At the level of the tip of the posterior mitral valve leaflet (basal myocardial segment)	
Four-chamber view (2D)	Loop
Left atrium and left ventricle, endocardium and myocardium, with mitral valve, left atrium shown with maximum area	
Right atrium and right ventricle, endocardium and myocardium, with tricuspid valve	
Short-axis view (2D)	Loop
Round section through left ventricle at mitral valve level, right ventricle incised	
Two-chamber view (2D)	Loop
Left ventricle, endocardium and myocardium	
Three-chamber view (2D)	Loop
Left atrium, left ventricle and aorta, endocardium and myocardium, with mitral valve, left atrium shown with maximum area	
Pulsed-wave or continuous-wave Doppler	Spectral doppler, still frame
Mitral valve	
Tricuspid valve	
Aortic valve	
Pulmonary valve	

Outcomes

The primary endpoint was cardiac dysfunction, as diagnosed by the cardiologist or revealed by a central assessment of transthoracic echocardiography. Cardiac dysfunction is presumed when at least one of the following criteria is true:

1. Diagnosis by the cardiologist of heart failure or cardiomyopathy reported in the questionnaire.
2. Left ventricular ejection fraction reduced to <50%.
3. Shortening fraction reduced to <25%.
4. Relative wall thickness reduced to <0.22.
5. Percentage systolic thickening of the interventricular septum and left ventricular (LV) posterior wall reduced to <33%.
6. LV Tei index (myocardial performance index) >0.40.
7. Right atrial volume at end systole/body surface area >30 ml/m^2.

The secondary endpoint is cardiovascular dysfunction, defined as the composite of arterial hypertension (diagnosed by the cardiologist and reported in the questionnaire or current blood pressure measured during the visit ≥140 mmHg systolic or ≥90 mmHg diastolic), cardiac arrhythmia (diagnosed by the cardiologist and reported in the questionnaire), and cardiac dysfunction (as defined above).

Genotyping

Genomic DNA was isolated from EDTA blood samples with the QIAamp DNA Blood Kit (Qiagen). Saliva was collected with the Oragene DNA collection kit (DNA Genotec), and genomic DNA was extracted from saliva samples using the prepIT L2P reagent (DNA Genotec). DNA was quantified by Quant-iT PicoGreen assay (Invitrogen), according to the manufacturer's protocols. Genomic DNA samples were genotyped for *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6* rs17863783 (Table 2) by TaqManSNP genotyping (Applied Biosystems), using the Type-it Fast SNP Probe PCR Kit (Qiagen) with predesigned primers and probes (Applied Biosystems).

Laboratory assistants were blinded to the case-control status of the patients genotyped in the study. To ensure the accuracy of all genotyping results, multiple positive and negative controls and replicate samples were included in all genotyping assays and plates. The concordance of genotype calls between replicate genotyped samples was 100%.

Genomic DNA will also be used to replicate the association of doxorubicin-related cardiovascular toxicity with other candidate genes that have been described [22] or that will be discovered in the future, provided our sample size is sufficient.

Table 2. Overview of the single nucleotide polymorphisms tested in LESS-Anthra.

Gene	Reference SNP[a] cluster ID	Alleles (Ref[b]>Alt[c])	Chromosome	MAF[d] (1000 Genomes, European population)	Gene consequence	Amino acid/codon change
RARG	rs2229774	G>A	12	A=0.064	Missense variant	NP_000957.1: p.Ser427Leu
SLC28A3	rs7853758	G>A	9	A=0.137	Synonymous variant	Leu (CTG)>Leu [TTG]
UGT1A6	rs17863783	G>T	2	T=0.023	Synonymous variant	Val (GTG)>Val [GTT]

[a]SNP: single nucleotide polymorphism.

[b]Ref: reference allele.

[c]Alt: alternative allele.

[d]MAF: minor allele frequency.

Estimation of Case Numbers for the Pharmacogenetic Studies

The appropriate case number was estimated based on a published study of the association of the nonsynonymous *RARG* gene variant p.Ser427Leu (rs2229774) with anthracycline-induced cardiomyopathy (combined analysis of the discovery and replication cohorts: odds ratio 4.7, 95% CI 2.7-8.3; *P*<.001) [12]. Assuming an odds ratio of 4.7, an allele frequency (controls) of 6.4%, an alpha error of 5%, power of 80%, a control: case ratio of 3:1, and a dropout rate of approximately 10%, at least 33 cases and 99 controls, will be required to replicate with sufficient statistical power the association of *RARG* rs2229774 with anthracycline-induced cardiomyopathy.

Data Collection

For data collection, the electronic ObTiMA system ontology-based trial management application was used [23]. ObTiMA has been validated for clinical trials. Every correction made to the entered data is traceable. Only authorized persons have access to the program and the data. Data backups occur regularly and automatically. In ObTiMA, electronic case report forms for capturing all patient data have been defined for this study. All data were pseudonymized before entry into the database of ObTiMA and handled according to the European General Data Protection Regulation.

Statistical Analysis

The *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6* rs17863783 SNPs were checked for deviations from Hardy-Weinberg equilibrium (HWE). Departure from HWE was defined as *P*-HWE <.01 (after Bonferroni correction of the nominal value of *P* set at .05) and tested by a χ^2 test of goodness of fit between the observed and expected genotypes.

Our primary aim was to assess the value of multimarker genetic testing for *RARG* rs2229774, *UGT1A6* rs17863783, and *SLC28A3* rs7853758 for predicting doxorubicin-induced cardiovascular dysfunction. To address that aim, we considered the following 3 predictive models. Model 1 includes only clinical risk factors, such as sex, age, irradiation (mediastinal, lung, or left abdominal), the use of other cardiotoxic drugs, length of follow-up, and cumulative dose of doxorubicin. Model 2 includes only genetic profiling. For each individual, the genetic risk will be scored as suggested by the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Clinical Practice Recommendations Group [14], based on multimarker genetic testing for *RARG* rs2229774, *UGT1A6* rs17863783, and *SLC28A3* rs7853758. Patients carrying the *RARG* rs2229774 A or *UGT1A6* rs17863783 T risk variants will be classified as high genetic risk; patients carrying the *SLC28A3* rs7853758 A protective variant who do not carry *RARG* rs2229774 A or *UGT1A6* rs17863783 T alleles will be classified as low genetic risk; all other patients will be classified as moderate genetic risk (Table 3). Model 3 includes both clinical risk factors and genetic profiling. The independent contribution of each risk factor to the outcomes will be determined using multivariable logistic regression analysis. The predictive accuracy of the model will be assessed by the area under the receiver operating characteristic curve.

Table 3. Genetic risk scoring of anthracycline-associated cardiotoxicity as suggested by the Canadian Pharmacogenomics Network for Drug Safety Clinical Practice Recommendations Group [14].

Genetic risk[a]	RARG[b] rs2229774	UGT1A6[c] rs17863783	SLC28A3[d] rs7853758
High	A|G or A|A	Any genotype	Any genotype
High	Any genotype	G|T or T|T	Any genotype
Moderate	G|G	G|G	G|G
Low	G|G	G|G	A|A or A|G

[a]Risk scoring depends on the combined evaluation of three genetic markers, the polymorphisms rs2229774 in *RARG*, rs17863783 in *UGT1A6*, and rs7853758 in *SCL28A3*.

[b]RARG: retinoic acid receptor gamma.

[c]UGT1A6: UDP glucuronosyltransferase family 1 member A6.

[d]SLC28A3: solute carrier family 28 member 3.

Our secondary aim is to replicate the previously described associations of candidate genetic markers with anthracycline-induced cardiotoxicity if our sample size has sufficient statistical power. Association of the candidate SNPs with the outcome will be performed using logistic regression, adjusting for sex; age; mediastinal, left abdominal, and lung irradiation; the use of other cardiotoxic drugs; length of follow-up; and cumulative dose of doxorubicin. The Benjamini-Hochberg False Discovery Rate will be used to account for multiple testing.

Results

Recruitment

This cohort study evaluates the risk of developing anthracycline-induced cardiotoxicity in survivors (ie, survival for 5 years or more after diagnosis) of pediatric nephroblastoma or neuroblastoma. A review of the German Childhood Cancer Registry database revealed 2158 eligible patients (943 nephroblastoma and 1215 neuroblastoma patients) who were invited by mail to participate in the study (Figure 1).

Patient recruitment started in June 2017 and was completed in September 2018. There were 657 patients (284 neuroblastoma and 373 nephroblastoma patients) who consented to participate in the LESS-Anthra study, and 480 (73%) of these patients provided a biospecimen for pharmacogenetic studies. Table 4 summarizes the baseline characteristics of participants and nonparticipants of LESS-Anthra.

Figure 1. Flowchart of patients' inclusion or exclusion.

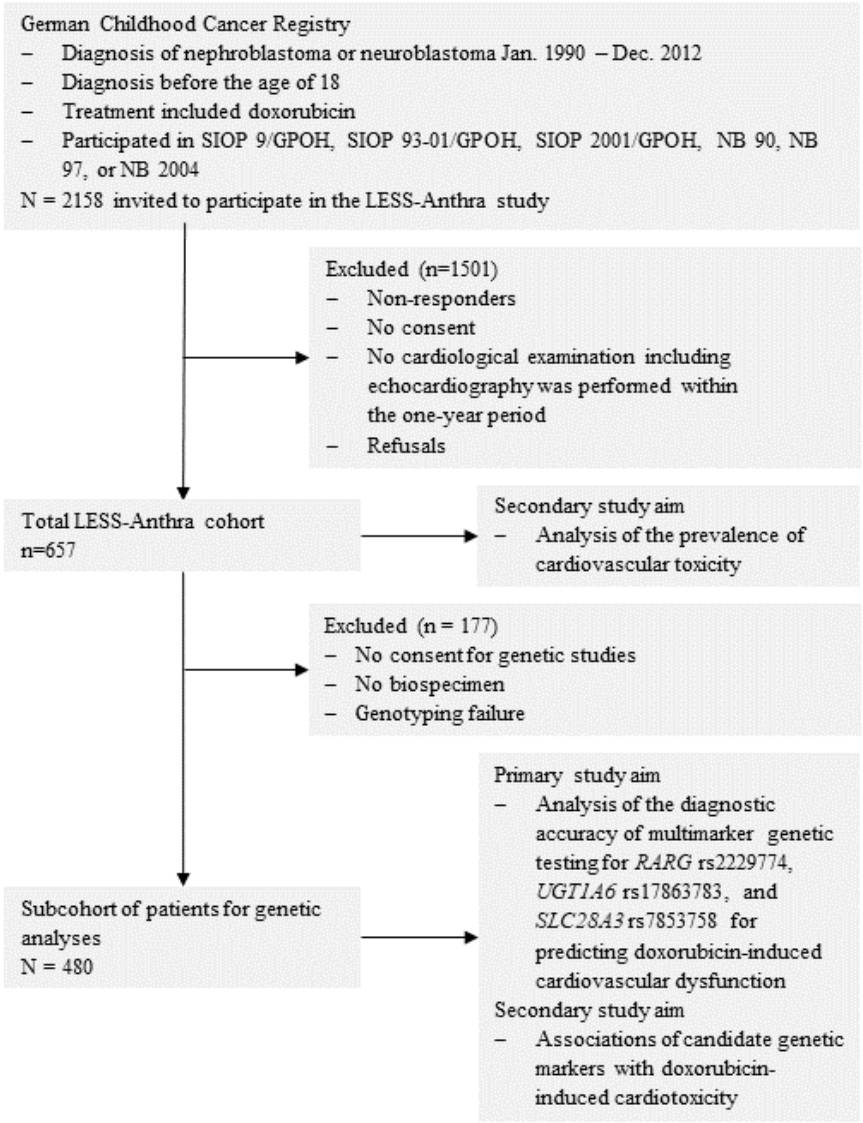

Table 4. Comparison of baseline characteristics of participants and nonparticipants of the LESS-Anthra study.

	Patients invited for participation (n=2158)	Nonresponders, no consent, or refusal (n=1499)	Participants (n=657)
Age at diagnosis (years), median (range)	2.0 (0-17)	2.0 (0-17)	2.0 (0-17)
Follow-up time (years), median (range)	14.0 (5-27)	15.0 (5-27)	13.0 (5-27)
Proportion of male to female patients	1.0	0.9	1.2
Proportion of nephroblastoma to neuroblastoma patients	1.3	1.3	1.3

Anthracycline Treatment

According to the respective protocol, and dependent on the stage and risk group, the cumulative dose of doxorubicin was 45-240 mg/m^2 for neuroblastoma patients and 100-400 mg/m^2 for nephroblastoma patients (Table 5).

Table 5. Per protocol cumulative dose of doxorubicin used in the neuroblastoma (NB90, NB97, and NB 2004) and nephroblastoma (SIOP 9/GPOH, SIOP 93-01/GPOH, and SIOP 2001/GPOH) trials.

Study and study arm	Doxorubicin cumulative dose (mg/m^2)	Single-dose, duration of IV[a] application
NB90		
Stage 2 or stage 3A-B	120	Course N2: 60 mg/m^2, 48h Course N3: 15 mg/m^2, slow IV injection
Stage 3C-D or stage 4	240	
Stage 4S	60	
NB97		
Standard risk group	120	Course N6: 30 mg/m^2, 4h Course N4: 0.5 mg/kg, 30min
High-risk group	180	
NB 2004		
Observation group with tumor progression	45 or 180 (depending on further progression after first cycle)	Course N6: 30 mg/m^2, 4h Course N4: 15 mg/m^2, 30min
Medium risk group	180	
High-risk group	180	
SIOP 9/GPOH		
Stage II, Stage III	250	50 mg/m^2, 4h
Stage IV, no metastasis after preoperative chemotherapy	400	
Stage IV, no CR after preoperative chemotherapy	100	
SIOP 93-01/GPOH		
Stage II or III and low or intermediate risk by histology	250	50 mg/m^2, 4h
Stage II or III and high risk by histology	300	
Stage IV	400	
SIOP 2001/GPOH		
Stage I, high risk	250	50 mg/m^2, 4-6h
Stage II or stage III, intermediate-risk, randomized regimen AVD	250	
Stage II or stage III, high risk	300	
Stage IV	300	

[a]IV: intravenous.

Genotyping

We received biomaterial from 480 patients: 456 EDTA blood samples and 24 saliva samples. DNA was extracted and genotyped for *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6* rs17863783. Genotype frequencies for the candidate SNPs are summarized in Table 6. The call rate was 100% for

all SNPs. All SNPs passed the HWE test at $P>.01$. Table 7 summarizes the numbers of patients in each genetic risk group, scored according to the CPNDS Clinical Practice Recommendations Group [14] and based on multimarker genetic testing for *RARG* rs2229774, *UGT1A6* rs17863783, and *SLC28A3* rs7853758.

Table 6. Genotype frequencies in the study cohort of neuroblastoma and nephroblastoma patients.

SNP[a] and genotype	N	*P*-HWE[b]
RARG[c] rs2229774		
G/G	419	0.9604
A/G	59	
A/A	2	
SLC28A3[d] rs7853758		
G/G	355	0.848
A/G	115	
A/A	10	
UGT1A6[e] rs17863783		
G/G	467	0.764
T/G	13	
T/T	0	

[a]SNP: single nucleotide polymorphism.

[b]*P*-HWE: Hardy-Weinberg equilibrium χ^2 test *P*-value

[c]RARG: retinoic acid receptor gamma.

[d]SLC28A3: solute carrier family 28 member 3.

[e]UGT1A6: UDP glucuronosyltransferase family 1 member A6.

Table 7. Genetic risk categories observed in our study population. Genetic risk scoring was performed according to the recommendations of the Canadian Pharmacogenomics Network for Drug Safety Clinical Practice Recommendations Group [14].

Genetic risk	Observed, n (%)
High	72 (15.0)
Moderate	301 (62.7)
Low	107 (22.3)
Total	480 (100)

Data Collection

We are in the final phase of data collection. Currently, final plausibility and quality checks are being performed before the closure of the database.

Discussion

The CPNDS Clinical Practice Recommendations Group has issued a level B recommendation (moderate evidence base: at least one high-quality study or multiple moderate-quality studies) that pharmacogenomic testing for the variants *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6**4 rs17863783 should be performed in all pediatric cancer patients with an indication for doxorubicin or daunorubicin therapy to stratify their cardiovascular risk. The recommendation was based on a few studies investigating the separate effects of each of the genetic markers on anthracycline-induced cardiotoxicity. Additional studies are required to increase confidence in the genetic associations further.

This prospective cohort study is the first to evaluate the ability of combined testing for *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6**4 rs17863783, as recommended in the pharmacogenetic guidelines, to correctly predict doxorubicin-related cardiotoxicity in a large cohort of patients with consistent diagnoses. Strengths of this study include the homogeneity of the cohort in terms of diagnoses and treatment protocols, the fact that no anthracyclines other than doxorubicin were used, and the large sample size. Because echocardiographic findings are subject to inter - reader variability, the original echocardiographic recordings will be evaluated in a standardized manner by a single pediatric cardiologist, thereby reducing potential bias. The image acquisition protocol guided the site sonographers in performing the echocardiographic examinations according to the specific needs of our trial. All these methods were designed to improve the accuracy of echocardiographic findings. Nevertheless, different producers of echocardiography

equipment and software and site-specific machine settings can still contribute to the variability of findings.

Unfortunately, there is no generally accepted definition of anthracycline-induced cardiotoxicity based on echocardiography [20,24-26]. Currently, the Cardio-Oncology and Imaging Working Group of the German Society for Pediatric Cardiology and Congenital Heart Defects is preparing a position paper in collaboration with the GPOH and the German Society for Cardiology-Cardiovascular Research. This paper will standardize the specific echocardiographic parameters and thresholds that should be used to define normal or abnormal parameters in childhood cancer survivors treated with anthracyclines. Therefore, because this issue is not yet conclusively resolved, we may need to adjust the outcome definitions in our study, depending on the results of the upcoming guidelines.

The overall participation rate in the LESS-Anthra study was only 30%, and not all LESS-Anthra participants were also willing to participate in the pharmacogenetic substudy. The participation rate is at the lower end of the range of figures reported in the literature [27]. We attempted to give as many eligible patients as possible the opportunity to participate, regardless of whether or not they were followed up closely. This strategy required the rather impersonal approach of study invitation and study consent by mail. Recruitment would likely be more successful if limited to patients in regular follow-up care who were invited and personally approached by the follow-up physician. Helligsoe et al [27] addressed study participation in childhood cancer survivors in clinical late-effect studies [27]. The authors analyzed 80 published studies originating from 16 cohorts, with a median follow-up of 6.0 years. They found that overall participation rates ranged from 27% to 100% and speculated that more personalized recruitment strategies could increase participation rates. Our preliminary results confirm the finding that time since diagnosis does not influence participation [27]. Age at diagnosis also does not have a measurable impact. Interestingly, in LESS-Anthra, slightly more male patients were in the responder group than nonresponders (Table 5).

Although study limitations, such as the variable follow-up time and the low participation rate, will have to be considered, our study will define for the first time the combined genetic risk related to three marker genes proposed for risk assessment in the CPNDS pharmacogenetic guidelines. Moreover, the results of this study will identify the prevalence of cardiovascular dysfunction among survivors of pediatric neuroblastoma or nephroblastoma treated with doxorubicin. The results will help to improve primary treatment and follow-up care to reduce cardiovascular late effects in the growing population of childhood cancer survivors.

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Authors' Contributions

The study was conceived by TL, NG, TS, and HA-K. CS, BH, OZ, AK, SE, and JG provided input into the study design and research questions and participated in study management and coordination. BM developed the statistical analysis plan. HA-K and MAER are involved in the cardiovascular phenotyping of the patients. AK and OZ completed the first draft of the manuscript with input from all coauthors. All authors commented on and approved the final version of the manuscript.

Conflicts of Interest

None declared.

References

1. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006 Oct 12;355(15):1572-1582. [doi: 10.1056/NEJMsa060185] [Medline: 17035650]
2. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME, Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 2001 Jul 01;19(13):3163-3172. [doi: 10.1200/JCO.2001.19.13.3163] [Medline: 11432882]
3. Fidler MM, Reulen RC, Winter DL, Kelly J, Jenkinson HC, Skinner R, British Childhood Cancer Survivor Study Steering Group. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. BMJ 2016 Sep 01;354:i4351 [FREE Full text] [doi: 10.1136/bmj.i4351] [Medline: 27586237]
4. Lipshultz SE, Lipsitz SR, Mone SM, Goorin AM, Sallan SE, Sanders SP, et al. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995 Jun 29;332(26):1738-1743. [doi: 10.1056/NEJM199506293322602] [Medline: 7760889]
5. Sorensen K, Levitt GA, Bull C, Dorup I, Sullivan ID. Late anthracycline cardiotoxicity after childhood cancer: a prospective longitudinal study. Cancer 2003 Apr 15;97(8):1991-1998 [FREE Full text] [doi: 10.1002/cncr.11274] [Medline: 12673729]

6. Green DM, Grigoriev YA, Nan B, Takashima JR, Norkool PA, D'Angio GJ, et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study group. J Clin Oncol 2001 Apr 01;19(7):1926-1934. [doi: 10.1200/JCO.2001.19.7.1926] [Medline: 11283124]
7. Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol 2010 Mar 10;28(8):1308-1315. [doi: 10.1200/JCO.2008.20.2267] [Medline: 20142603]
8. Bansal N, Blanco JG, Sharma UC, Pokharel S, Shisler S, Lipshultz SE. Cardiovascular diseases in survivors of childhood cancer. Cancer Metastasis Rev 2020 Mar;39(1):55-68. [doi: 10.1007/s10555-020-09859-w] [Medline: 32026204]
9. Kalapurakal JA, Lee B, Bautista J, Rigsby C, Helenowski I, Gopalakrishnan M. Cardiac-Sparing Whole Lung Intensity Modulated Radiation Therapy in Children With Wilms Tumor: Final Report on Technique and Abdominal Field Matching to Maximize Normal Tissue Protection. Pract Radiat Oncol 2019 Jan;9(1):e62-e73. [doi: 10.1016/j.prro.2018.07.005] [Medline: 30096378]
10. Schlitt A, Jordan K, Vordermark D, Schwamborn J, Langer T, Thomssen C. Cardiotoxicity and oncological treatments. Dtsch Arztebl Int 2014 Mar 07;111(10):161-168 [FREE Full text] [doi: 10.3238/arztebl.2014.0161] [Medline: 24666651]
11. Peters EJ, Motsinger-Reif A, Havener TM, Everitt L, Hardison NE, Watson VG, et al. Pharmacogenomic characterization of US FDA-approved cytotoxic drugs. Pharmacogenomics 2011 Oct;12(10):1407-1415 [FREE Full text] [doi: 10.2217/pgs.11.92] [Medline: 22008047]
12. Aminkeng F, Bhavsar AP, Visscher H, Rassekh SR, Li Y, Lee JW, Canadian Pharmacogenomics Network for Drug Safety Consortium. A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. Nat Genet 2015 Sep;47(9):1079-1084 [FREE Full text] [doi: 10.1038/ng.3374] [Medline: 26237429]
13. Vlaming MLH, van Duijn E, Dillingh MR, Brands R, Windhorst AD, Hendrikse NH, et al. Microdosing of a Carbon-14 Labeled Protein in Healthy Volunteers Accurately Predicts Its Pharmacokinetics at Therapeutic Dosages. Clin Pharmacol Ther 2015 Aug;98(2):196-204. [doi: 10.1002/cpt.131] [Medline: 25869840]
14. Aminkeng F, Ross CJD, Rassekh SR, Hwang S, Rieder MJ, Bhavsar AP, CPNDS Clinical Practice Recommendations Group. Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. Br J Clin Pharmacol 2016 Sep;82(3):683-695 [FREE Full text] [doi: 10.1111/bcp.13008] [Medline: 27197003]
15. Dionne F, Aminkeng F, Bhavsar AP, Groeneweg G, Smith A, Visscher H, et al. An initial health economic evaluation of pharmacogenomic testing in patients treated for childhood cancer with anthracyclines. Pediatr Blood Cancer 2018 Mar;65(3):e26887. [doi: 10.1002/pbc.26887] [Medline: 29271558]
16. Chang VY, Wang JJ. Pharmacogenetics of Chemotherapy-Induced Cardiotoxicity. Curr Oncol Rep 2018 Apr 30;20(7):52 [FREE Full text] [doi: 10.1007/s11912-018-0696-8] [Medline: 29713898]
17. Wang X, Sun C, Quiñones-Lombraña A, Singh P, Landier W, Hageman L, et al. CELF4 Variant and Anthracycline-Related Cardiomyopathy: A Children's Oncology Group Genome-Wide Association Study. J Clin Oncol 2016 Mar 10;34(8):863-870 [FREE Full text] [doi: 10.1200/JCO.2015.63.4550] [Medline: 26811534]
18. Schneider BP, Shen F, Gardner L, Radovich M, Li L, Miller KD, et al. Genome-Wide Association Study for Anthracycline-Induced Congestive Heart Failure. Clin Cancer Res 2017 Jan 01;23(1):43-51 [FREE Full text] [doi: 10.1158/1078-0432.CCR-16-0908] [Medline: 27993963]
19. Linschoten M, Teske AJ, Cramer MJ, van der Wall E, Asselbergs FW. Chemotherapy-Related Cardiac Dysfunction: A Systematic Review of Genetic Variants Modulating Individual Risk. Circ Genom Precis Med 2018 Jan;11(1):e001753. [doi: 10.1161/CIRCGEN.117.001753] [Medline: 29557343]
20. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Erol, Authors/Task Force Members, ESC Committee for Practice Guidelines (CPG), Document Reviewers. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur J Heart Fail 2017 Jan;19(1):9-42 [FREE Full text] [doi: 10.1002/ejhf.654] [Medline: 27565769]
21. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 5. Survivorship Guidelines. URL: http://wwwsurvivorshipguidelinesorg/ [accessed 2021-10-14]
22. Gándara-Mireles JA, Lares-Asseff I, Reyes Espinoza EA, Blanco JG, González Font AE, Córdova Hurtado LP, et al. Association of genetic polymorphisms NCF4 rs1883112, CBR3 rs1056892, and ABCC1 rs3743527 with the cardiotoxic effects of doxorubicin in children with acute lymphoblastic leukemia. Pharmacogenet Genomics 2021 Jul 01;31(5):108-115. [doi: 10.1097/FPC.0000000000000428] [Medline: 34096893]
23. Stenzhorn H, Weiler G, Brochhausen M, Schera F, Kritsotakis V, Tsiknakis M, et al. The ObTiMA system - ontology-based managing of clinical trials. Stud Health Technol Inform 2010;160(Pt 2):1090-1094. [Medline: 20841852]
24. Biasillo G, Cipolla CM, Cardinale D. Cardio-oncology: Gaps in Knowledge, Goals, Advances, and Educational Efforts. Curr Oncol Rep 2017 Aug;19(8):55. [doi: 10.1007/s11912-017-0610-9] [Medline: 28707189]
25. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015 Jun 02;131(22):1981-1988. [doi: 10.1161/CIRCULATIONAHA.114.013777] [Medline: 25948538]

26. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, ESMO Guidelines Working Group. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol 2012 Oct;23 Suppl 7:vii155-vii166. [doi: 10.1093/annonc/mds293] [Medline: 22997448]
27. Helligsoe ASL, Henriksen LT, Kenborg L, Dehlendorff C, Winther JF, Hasle H. Factors influencing participation rates in clinical late-effect studies of childhood cancer survivors. Pediatr Blood Cancer 2021 May 22:e29098. [doi: 10.1002/pbc.29098] [Medline: 34022113]

Abbreviations

CPNDS: Canadian Pharmacogenomics Network for Drug Safety
GPOH: German Society for Pediatric Oncology and Hematology
HWE: Hardy-Weinberg equilibrium
LESS: late effects surveillance system
LV: left ventricular
RARG: retinoic acid receptor gamma
SIOP: International Society of Paediatric Oncology
SLC28A3: solute carrier family 28 member 3
SNP: single nucleotide polymorphism
UGT1A6: UDP glucuronosyltransferase family 1 member A6

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Protocol

Developing Conflict Resolution Strategies and Building Resilient Midwifery Students: Protocol for a Mixed Methods Research Study

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Abstract

Background: Workplace bullying and violence (WBV) are well-documented issues in the midwifery profession. Negative workplace culture, conflict, and bullying are the most common forms of workplace violence experienced by midwives. Workplace violence increases the risk of midwives experiencing burnout, compassion fatigue, psychological trauma, poor mental health, absenteeism, loss of passion for the midwifery profession, job dissatisfaction, and poor job retention. Midwifery students describe workplace violence in the form of physical, emotional, or verbal abuse, and bullying. Therefore, there is a justification to develop conflict resolution strategies and resilience in midwifery students prior to graduation.

Objective: Our aim is to develop and facilitate a bespoke education program for South Australian midwifery students to enable them to develop skills in conflict resolution, build resilience, and identify self-care strategies.

Methods: This study will undertake a preparatory phase summarizing the body of literature on midwifery students' knowledge, understanding, and experiences of WBV. Following this, a 3-phase sequential mixed methods research design study will be undertaken. In Phase 1, quantitative data will be collected via a semistructured questionnaire and a validated conflict measurement tool, before and after attending an education workshop, and will be analyzed using descriptive and inferential statistics. Results from Phase 1 will inform and guide the development of an interview schedule for Phase 2. In Phase 2, qualitative data will be gathered by facilitating one-to-one interviews and a thematic analysis will be undertaken to gain a deeper understanding of midwifery students' experiences of WBV. In Phase 3, data integration using triangulation will be undertaken and meta-inferences will be developed via the integration of results and findings from Phases 1 and 2.

Results: The preparatory phase will commence in October 2021. Phase 1 will commence in 2022 with analysis of pre- and posteducation results anticipated to be completed by December 2022. Phase 2 will be developed from findings of the preparatory phase and results of Phase 1. An interpretation of verbatim interview transcripts is estimated to be undertaken by April 2023. Phase 3 of the study is expected to commence in May 2023, and this will involve the analysis of collective evidence gathered from Phases 1 and 2. The anticipated completion date for the study is December 2023.

Conclusions: The outcomes of this research will provide insights into the prevalence and impact of WBV experienced by midwifery students. The findings of the research will report on levels of knowledge, skills, and confidence, and will assess the impact of a bespoke conflict resolution and resilience education workshop for midwifery students in managing WBV.

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KEYWORDS

midwifery students; workplace; bullying; violence; conflict; abuse; resilience

Introduction

Background

Workplace bullying and violence (WBV) are well-documented concerns in the midwifery profession [1-3], with midwifery students reporting experiences of WBV in clinical settings, thus identifying the need to develop conflict resolution strategies and resilience in undergraduate education programs [3-6]. Workplace bullying is defined as "seek to harm, intimidate or coerce someone seen as vulnerable" [7]. Bullying is a repeated pattern of violence over time, which brings harm to the impacted individual(s) [8].

Workplace violence is an act or threat of physical abuse, harassment, intimidation, or other threatening disruptive behavior that occurs in the workplace [9]. Workplace violence can be caused by an individual or a group of people. Midwifery students describe experiencing workplace violence in the form of physical, emotional, or verbal abuse, and bullying [10]. Workplace violence is emotionally, psychologically, and spiritually damaging and can have long-lasting effects on the impacted individuals. The negative consequences associated with WBV include absenteeism, stress, fatigue, psychological trauma, poor mental health, job dissatisfaction, and poor job retention [5,10-13].

Workplace culture is defined as the beliefs, values, assumptions, attitudes, behavior, customs, and social interactions of staff in a particular workplace [14,15]. Workplace culture can affect the professional practice of a midwife, the way midwives interact with women, and impact upon the learning ability of midwives [14]. Toxic workplace culture promotes negative behavior, increasing the risk of WBV [16]. As a result of negative workplace culture, midwives experience burnout, job dissatisfaction, and attrition [14].

The midwifery profession is a female-dominated workforce that provides woman-centered maternity care by working in partnership with the woman [17]. The Nursing and Midwifery Board of Australia (NMBA) states that midwives should engage in respectful partnerships with the woman as well as other professionals and colleagues [18]. Despite this professional requirement, evidence has shown that midwives commonly bully other midwives, showing disrespect and a lack of compassion for each other in the workplace. This is particularly true for midwifery students and graduate midwives who are more vulnerable [10].

It has been reported that all new graduate midwives must adapt and learn quickly when becoming responsible for the care of women during the perinatal period [19,20]. The pressure of adjusting to shift work increases the risk of stress and fatigue for graduate midwives [21]. It has been highlighted that negative workplace culture, conflict, and bullying from colleagues and senior staff are the most common forms of workplace violence experienced by graduate midwives [11,13,22-24]. Additionally, WBV increases the risk of graduate midwives experiencing burnout, compassion fatigue, poor mental health, absenteeism, loss of passion for the midwifery profession, job dissatisfaction, and attrition [5,10-13].

Graduate midwives have reported experiences of coercion as a form of bullying, from senior midwives and doctors, resulting in them feeling forced into pressuring women to undergo procedures, including vaginal examinations and artificial rupture of membranes [25,26]. Coercing women is in opposition with the holistic approach ensconced in woman-centered care, thus leading to a moral dilemma for the midwife, which in turn may compromise care provision [18,25,27-30]. While this behavior is not a reflection of the midwife, it is a result of the culture within the midwifery profession, which fosters ethically and morally questionable care, due to institutional constraints [30]. Kumar-Hazard [31] has suggested that asking midwives to work within their employment contract, and provide woman-centered care, is an untenable situation.

Midwives have experienced coercion from hierarchical relationships (senior midwives, doctors, and management) to use wording that pressures the birthing woman to undergo unnecessary investigations and interventions, which impacts upon the midwife's ability to provide woman-centered care and her professional autonomy [31]. This coercion is presented under the guise of protecting the baby's well-being [31-33]. Coercion often results from a misuse of power differentials within the workplace and may lead to increased mental distress, moral dilemma, psychological trauma, job dissatisfaction, and loss of passion for the midwifery profession. This is particularly the case for graduate midwives who commonly feel ill equipped to challenge the system, or those they work with [13,29,34]. Contradictions between woman-centered care and institutional constraints are a significant reason why midwives choose to leave the midwifery profession [30]. Davies and Coldridge [30] have highlighted that witnessing poor practice was a central predictor for midwifery students losing their passion for the midwifery profession and was associated with high attrition rates, justifying the need to develop conflict resolution strategies and build resilience.

In a predominantly medicalized system, where midwives are losing their voices, midwifery students need to have skills in conflict resolution and to be resilient [35], as stated by Warland et al [36] "to safely manage their own behaviour and the behaviour of others". Conflict resolution skills and resilience may enable student and graduate midwives to advocate for women in their care and provide holistic care, while coping with trauma and adversity [35,37-40]. Unresolved conflict may impact workplace relationships and increase stress, which impacts upon the mental health of midwives and affects their ability to provide woman-centered care [5,41,42].

Building resilience has been acknowledged as an empowering concept that enables midwives to endure or recover quickly from challenging situations [7,40,43,44]. Clohessy et al [43] describe the benefits of resilience to include an "effective coping or adaptive capacity and a positive mental health status," which

enables midwifery students to overcome stress and adversity. Richardson [45] and Hunter and Warren [46] suggest that resilience can be learned or developed. This idea was further explored by Taylor and Reyes [47] who concurred that resilience could be learned or enhanced through education strategies. Clohessy et al [43] have described how midwifery students reported using strategies for resilience, such as confidence, optimism, reflection, and social supports, to manage exposure to adversity.

Despite acknowledgement of the ongoing nature of WBV in the midwifery profession [1-3], there has been minimal change over the last 35 years in Australia [2]. One potential solution to the challenges identified is the development of a bespoke educational workshop within the Bachelor of Midwifery degree, which may support midwifery students to develop skills in conflict resolution, build resilience, and identify self-care strategies, preparing them to manage conflict when they enter the workforce. As a result, burnout, attrition, and the loss of passion for the midwifery profession may be reduced.

Aim

The aim of this study is to develop and facilitate a bespoke education program for South Australian midwifery students, to enable them to develop skills in conflict resolution, build resilience, and identify self-care strategies.

Objectives

Preparatory Phase

In this phase, we will explore the body of literature relating to midwifery students' knowledge and experiences of conflict in the workplace.

Phase 1

The objectives of this phase are as follows:

- To develop a bespoke education workshop in conflict resolution skills and build resilience in midwifery students.
- To facilitate and evaluate the impact of an education workshop on developing conflict resolution skills and resilience for midwifery students.
- To assess second-year midwifery students' knowledge and skills to manage conflict in the workplace.
- To explore midwifery students' ability to be resilient after attending an education workshop.
- To further explore midwifery students' levels of confidence in addressing WBV after attending an education workshop.

Phase 2

The objectives of this phase are as follows:

- To gain a deeper understanding of midwifery students' skills and ability to manage conflict in the workplace while on placement or providing continuity of care.
- To explore midwifery students' views and experiences of using conflict resolution strategies.

Phase 3

The objectives of this phase are as follows:

- To triangulate and integrate data to strengthen the results and findings.
- To provide evidence and draw conclusions to answer primary and secondary research questions and the aim and objectives of this mixed method study.

Primary Research Question

1. What impact will a bespoke educational workshop to develop conflict resolution strategies and resilience have upon a population of midwifery students when facilitated during the Bachelor of Midwifery program?

Secondary Research Questions

1. What knowledge and skills do midwifery students' have to manage conflict in the workplace, before receiving education?
2. What impact will education have upon midwifery students to develop conflict resolution skills?
3. What impact will education have upon midwifery students to develop and build resilience to manage WBV?
4. What are the views and experiences of midwifery students after receiving education to develop conflict resolution strategies to manage conflict in the workplace?
5. What are the views and experiences of midwifery students after receiving education to develop and build resilience to manage conflict in the workplace?

Methods

Study Design

The research study will utilize a sequential explanatory mixed method design as suggested by Fielding [48] and Fetter et al [49]. A 3-phase design will be undertaken to gather both quantitative and qualitative data in a sequential manner, followed by meta-inferences in the final phase. This study design will enable researchers to explore students' views and experiences of WBV before and after attending an educational workshop.

The preparatory phase will review literature and provide evidence to inform the researchers as to what is currently known about knowledge, skills, views, and experiences of midwifery students regarding WBV. The preparatory phase will provide an evidence base for exploring the research problem, which will assist in the development of pre- and postquestionnaires, the content of an educational workshop, and development of an interview schedule. Phase 1 will involve collecting quantitative data, and SPSS (IBM, Inc.) will be used to perform descriptive and inferential statistical analyses. A pre-education questionnaire will be developed and include validated conflict scales to evaluate midwifery students' knowledge, skills, and confidence regarding WBV [50]. A posteducation questionnaire will re-evaluate midwifery student's knowledge, skills, and confidence of WBV, to investigate the impact of the conflict resolution and resilience educational workshop. Phase 1 will investigate and provide a general overview of the results related to the research topic. In Phase 2, an interview schedule of semistructured questions will be developed from the evidence generated in the preparatory phase and Phase 1, thus adopting a sequential design for the research. Phase 2 involves the collection of qualitative (written text) data gathered from

one-to-one interviews, which will be transcribed verbatim and thematically analyzed. Phase 2 will explore and explain in more depth the results from Phase 1. Phase 3 will involve the merging of Phase 1 results and Phase 2 findings, and the collective data will be triangulated and then integrated to determine meta-inferences from quantitative and qualitative data, to draw conclusions and understanding of the research questions [51].

Mixed Methods

Using a mixed methods research design that involves the analysis of quantitative and qualitative data provides stronger evidence and strengthens conclusions drawn [52], which neither quantitative nor qualitative research cannot achieve alone [53]. This study design ensures that the research project is robust and supports the broad understandings and conclusions of the research phenomena [54]. Mixed methods research allows flexibility of findings in the research, using multiple methods, worldviews, representation of assumptions, data collection, and analysis [51]. The flexibility of mixed methods design enhances the approach undertaken to address the research phenomena [51]. The strength of the explanatory sequential framework that will be utilized for this proposed study is that the research phases build upon each other [52]. Quantitative data will be analyzed in the first phase, with qualitative findings being subsequently analyzed to help explain the quantitative results, giving strength and validity to the study. As a result, the research is more than an evaluation, it is an investigation and exploration of midwifery students' experiences of WBV.

Conceptual Framework

Pragmatism is recognized as a world view that accepts several realities and supports practicality when addressing research questions. Kaushik and Walsh [55] have defined pragmatism as "a way of thinking about and making sense of the complexities of the real world". This concept reflects both biased and unbiased perspectives. The pragmatic concept utilizes a philosophical methodology that draws on utilizing *what works* from different aspects, setting priorities for the research topic/problem and questions, gathering both objective and subjective data [56]. Pragmatism uses an integrative philosophy, which combines both quantitative and qualitative research, without restrictive methodological directions [56,57].

The research study will use pragmatism as the underlying philosophy as this concept informs both quantitative and qualitative data collection [52]. Pragmatism is often associated with mixed methods research as the focus is guided by the research questions and the consequences of the research, as opposed to the methods [57]. Pragmatism provides an experience-based, action-orientated framework that can be utilized in a practical setting [58].

Setting

The research will be completed in metropolitan South Australia. Participants will be sought from 2 Universities in South Australia that offer the Bachelor of Midwifery degree.

Sampling

A purposive sample of second-year midwifery students completing the Bachelor of Midwifery degree in South Australia will attend an educational workshop as part of their curriculum studies, and be invited to participate in the research study.

Participants

The study will recruit second-year Bachelor of Midwifery students from 2 universities in South Australia. In Phase 1, all second-year Bachelor of Midwifery students will be eligible to participate in the research, and those providing written informed consent to participate will be included. In Phase 2 of the research, the study will consider any second-year midwifery students who have personally witnessed or experienced conflict in a clinical setting, while on placement or continuity of care experiences, who provide written informed consent to participate in this study.

Phase 1 Participants

Inclusion Criteria

- Midwifery students enrolled in the second year of Bachelor of Midwifery degree in a University in South Australia offering the Bachelor of Midwifery degree.
- Midwifery students giving verbal and written informed consent.

Exclusion Criteria

- Midwifery students not enrolled in the second year of Bachelor of Midwifery degree.
- Midwifery students undertaking the second year of Bachelor of Midwifery degree outside of South Australia.

Phase 2 Participants

Inclusion Criteria

- Midwifery students enrolled in the second year of Bachelor of Midwifery degree in a University in South Australia who have personally witnessed or experienced conflict in a clinical setting, while undertaking placement or continuity of care experiences.
- Midwifery students giving verbal and written informed consent.

Exclusion Criteria

- Midwifery students not enrolled in the second year of Bachelor of Midwifery degree.
- Midwifery students undertaking the second year of Bachelor of Midwifery degree outside of South Australia.

Recruitment

Phase 1

All second-year Bachelor of Midwifery students will be required to attend the bespoke education workshop on conflict resolution strategies and building resilience as part of the Bachelor of Midwifery degree. Second-year midwifery students from the respective universities will be provided with information about the research project by a university staff member not associated with the research. Following the delivery of this information, second-year midwifery students will be invited to participate in the research. Midwifery students who give verbal and written informed consent will be invited to complete the pre- and posteducation workshop questionnaires. Student participants

will also be informed of the potential to be involved in posteducation workshop interviews to follow-up questionnaire responses, where eligible.

Phase 2

A purposive sample of eligible second-year midwifery students from Phase 1, who have witnessed or experienced conflict in the workplace, will be invited by the primary researcher (NS) to participate in a posteducation workshop follow-up interview. The interview will focus on exploring student participants' views to gain a deeper understanding and insights into their experiences of WBV. The primary researcher will connect with eligible students via their university email address and will arrange either one-to-one, telephone, or Zoom interview with students agreeing to participate in Phase 2 of the research. Additional written informed consent will be obtained prior to participation in this phase of the study.

Bespoke Educational Workshop

The Start Treating Others Positively (STOP) model (Multimedia Appendix 1) will be incorporated into the design and development of an educational workshop for this research study [59]. The STOP Model originated in 1989 and was introduced to health care settings in the United Kingdom in 2001 [59]. The STOP model approach was adopted, and workshops were developed, to build conflict resolution strategies as part of an abusive behavior management program for adults [59]. STOP is a strengths-based model that utilizes a positive approach encouraging good decision making for the future, rather than focusing on unchangeable actions of the past [4], thus supporting personal behavior change [59]. The key steps of the STOP model include

STOP: Stop and see what is happening. Don't just react!

THINK: What is important here? What could be the threat?

OBSERVE: Calmly work out the problem.

PROCEED: Take time out? Be assertive.

The STOP model was modified to be included in antenatal education, with the aim of enabling and empowering expecting parents to manage their emotions and behaviors, with the overarching goal of preventing relationship conflict escalating to abuse [60]. Antenatal participants proposed that the STOP model be included routinely in antenatal education, suggesting that "introducing the tools and techniques at the beginning of the parenthood journey might break the cycle with the parents before the next generation of children encounter it." Participants further recommended including STOP in formal school education [60].

STOP was introduced to midwifery students attending the University of Chester in the UK in 2010 [4]. The content was adapted from the original design, to meet the needs of midwifery students. Steen [4] utilized a posteducation assessment, to evaluate midwifery students' knowledge and skills after attending the STOP workshop. The adapted STOP model underpinned the educational workshop to enable midwifery students to develop conflict resolution skills and build resilience in the event they experienced WBV. Students who participated in STOP education and training demonstrated new insights into how to manage workplace conflict and reported utilizing STOP strategies throughout the rest of their studies, after graduating and in personal circumstances [4].

Therefore, the STOP model will be utilized as a framework to guide the development and facilitation of an educational workshop for midwifery students in South Australia, to develop conflict resolution strategies, and to build resilience. As negative human behavior involving bullying and violence is similar within Western societies [61-63], it is acceptable to use the STOP model framework that was developed in the UK and adapt this approach to meet the needs of midwifery students in South Australia.

Ethical Considerations

Approval

Ethical approval has been obtained from the University of South Australia Human Research Ethics Committee (Protocol Number 204063). Approval has been sought from Flinders University. Ethical considerations (ie, informed consent, anonymity and confidentiality, voluntary nature of participation and withdrawal) have been addressed at all stages of the research project study design. Verbal and written consent will be obtained from all participants.

Consent

Midwifery students attending the bespoke educational workshop will be provided with a participant information sheet (PIS) explaining the research being undertaken. The PIS includes information pertaining to the study, that is, aim, objectives, potential outcomes, content of workshop, evaluation of workshop, and Phase 2 interviews. The PIS will include details on participation within the study including the benefits and risks, participant confidentiality, and the support strategies put in place to address any distress resulting from the study. Participants will be provided with contact details for the research team in the event that they have further questions they would like answered, prior to making an informed decision and thus providing informed consent to participate in the research.

Participants Safety and Withdrawal

Participation in the study is voluntary. Participants have the right to withdraw from the study at any time. Withdrawal forms will be uploaded onto the REDCap web platform for midwifery students to access if required [64]. REDCap is a safe and secure web platform for developing and managing online surveys and databases [64]. Data collection up to the point of withdrawal will be included within the data analysis. No further data will be collected following withdrawal of participation from the research. Withdrawing from the study will not affect midwifery students' relationship with the research team or their respective university.

Confidentiality

A purposive sample of second-year South Australia midwifery students will be invited to participate in the research study by an academic staff member from their respective university who is not involved in the research study. Midwifery students will be provided with participant information for the study during

recruitment, as part of the informed consent process. The pre- and posteducation workshop questionnaires, validated conflict scale, and interview responses will be deidentified with codes when collating data and prior to publishing results and findings, to protect the participants and ensure anonymity within the research. Midwifery students will be able to access the research information and questionnaires through the REDCap web platform from any device that has internet access [64]. The information and questionnaires will also be provided in hard copy form if any participant prefers. Hard copies of completed questionnaires will be stored in a locked filing cabinet, in a locked office at the University of South Australia for the entirety of the research project to protect the confidentiality of participants.

At all times, participants personal information will remain confidential within the research team. No information will be released by researchers that may lead to midwifery students' identification unless required by relevant legislation.

Data Management

University of South Australia data management policy and guidance will be adhered to regarding the appropriate data storage of, access to, and destruction of information/data gathered during the undertaking of the research project [65].

Research data will be deidentified with predetermined codes. A separate document with midwifery students' university email address (identifying factor) and their particular identifying code will be password protected and stored as a file on a personal computer, USB, and hard drive. Only the research team will have access to identifying data.

All digital audio files and data will be coded, archived, and stored in a password-protected file on the university server. To reduce risk of file corruption or loss, files will be stored in at least two locations. All coded hard copy and transcribed audio data (questionnaires and interviews) will be stored in a locked filing cabinet in a secure facility with access restricted to the research team, for a minimum of 5 years according to the university data management and policy guideline for general research. After such time, secure data destruction will take place. These measures will be taken to ensure security of information from misuse, loss, or unauthorized access while stored during the research project and on completion.

Procedure

Phase 1: Investigation

Overview

In Phase 1 of the research, participants knowledge and skills regarding WBV will be assessed prior to the facilitation of a 3-hour bespoke educational workshop to develop conflict resolution strategies and build resilience. Following the educational workshop, midwifery students' knowledge and skills relating to WBV and the effectiveness of the workshop will be assessed twice. Assessment will take place immediately after workshop and then again 8-12 weeks later when students have had an opportunity to complete further clinical experiences.

Data Collection Tools

These include (1) a piloted pre- and posteducation questionnaire and (2) a validated conflict assessment scale/tool [50].

Pre- and postworkshop questionnaires will be developed by the research team, led by key concepts within the STOP model [4]. These questionnaires will be piloted in a group of approximately 5 midwifery students who will have the opportunity to comment and provide feedback on the questionnaire. The questionnaires will gather data regarding the knowledge and skills of midwifery students relating to WBV while undertaking clinical experiences, as part of the requirement for the Bachelor of Midwifery degree. These data will be mainly collected through 5-point ordinal Likert scales as a preferred measurement for health research [66]. Midwifery student participants will be provided with a series of questions and statements and have an opportunity to expand on their answers in some sections of the questionnaire.

A validated conflict measurement tool [50] will be adapted by the research team for use in this study. This tool will incorporate 5-point ordinal Likert scales that are designed to assess negative behaviors in the workplace, associated with workplace bullying.

Data Analysis

Five-point ordinal scales will be included in pre- and postquestionnaires to measure midwifery students' responses. Descriptive and inferential statistics using SPSS version 26 (IBM) will be used to measure responses gathered by the online questionnaires developed in the REDCap web platform [64]. SPSS is an interactive statistical analysis program that analyses data from most files. REDCap files can be directly imported into and with SPSS software. Data will be presented visually in charts and as graphs to help report results.

Phase 2: Exploratory

Interviews

Eligible second-year midwifery students will be invited to participate in posteducation workshop interviews, to discuss their views and experiences of WBV and what impact the educational workshop has had upon them to manage WBV.

Semistructured interviews will be conducted using open-ended questions so that the researchers can explore midwifery students' views and experiences of conflict in the workplace [67,68]. Semistructured interviews will help to facilitate in-depth discussion and guide the exploration of research questions [67].

An interview guide will be developed and comprise approximately 10 main questions, and some further subquestions to help prompt the student participant to continue discussing their views and experiences [67,68]. The interview questions will be piloted before the research team proceeds with Phase 2 of the research.

The research questions will be asked in a flexible and friendly manner so that participants will feel comfortable and safe to participate fully in the interview [68]. At the end of an interview, the researcher will summarize the main findings of the interview to the participant, to cross-check if they have an accurate representation of their views and experiences [69]. At this stage, midwifery students may choose to clarify, add, or omit anything.

Interviews will be recorded, transcribed verbatim, and a thematic analysis will be undertaken.

Data Saturation

Data saturation will be reached when no new themes emerge from the research [69]. Hennink et al's [70] framework will be used as a guide to reach data saturation. It is anticipated that a minimum of 10-12 interviews will be conducted to gain an insight into the views and experiences of midwifery students, and their ability to manage WBV in the workplace when exposed to this phenomenon.

Data Analysis of Interviews

Recordings of interviews will be transcribed verbatim using a transcription service. Once data have been transcribed, digital files of recorded interviews will be kept on a computer, password protected, to keep the research data confidential and limited to the research team. Data files will be backed up on the university server frequently to reduce risk of complete loss.

A constant comparative method will be utilized, to compare and analyze data after each interview as recommended by Richards and Hemphill [71]. Braun and Clarke's [72] reflexive thematic analysis framework will be utilized to generate themes. Researchers will be guided by 6 steps as first described by Braun and Clarke [72]. These steps include the following:

1. Familiarizing: focusses on immersing oneself in the data and noting initial ideas;

2. Generating: involves developing codes from features found within the data;

3. Searching: provides links between established codes and themes uncovered within the data;

4. Reviewing: appraises themes to ensure they work with the data captured;

5. Defining: provides clarity of each theme and the overall story and generates clear definitions;

6. Reporting: synthesizes the final analysis of the extracts, referring back to the research question and literature (Multimedia Appendix 2).

Phase 3: Triangulation and Meta-inferences

Quantitative and qualitative data will be triangulated, integrated, and meta-inferences of the collective data will be developed. The explanatory sequential mixed methods design will be guided by the following principles recommended by Tashakkori and Teddlie [51].

1. *Triangulation and corroboration* of results/findings to increase the external validity of results.
2. *Complementary*: Seek to add clarification, elaboration, and enhancement of the results from Phase 1, with the findings from Phase 2, and have 1 summary (joint display) of findings built upon the other, contextualizing information and adding a macro complementary picture of the research phenomena.
3. The results of Phase 1 will be used to develop Phase 2 data collection questions and gathering of the findings.
4. *Exploratory*: Phase 2 (qualitative) will enable the exploration of themes or new perceptions and possible re-design of some more in-depth research questions or explore views/experiences with the outcomes and investigate further the information gathered.
5. *Comparison*: Phase 1 (quantitative) and Phase 2 (qualitative) methods will be used to compare and identify inconsistencies of the research topic.
6. *Expansion*: Combined data will be used to extend details about the horizon of research and widen the understanding of the topic.

Results

This research will provide both quantitative and qualitative data to determine midwifery students' knowledge, and skills relating to WBV in a clinical setting, while undertaking their Bachelor of Midwifery degree. It is anticipated that education will have an impact on how midwifery students will manage WBV in the workplace by developing some conflict resolution skills and building resilience. This research will provide valuable insights into the views and experiences of midwifery students regarding WBV. Integrated data will help draw conclusions and recommend future implications for midwifery student education.

This study is expected to conclude in December 2023.

Discussion

Importance of This Research

Evidence has shown that there is a culture of bullying and abuse within the midwifery profession. Several studies have reported that midwives, graduate midwives, and of significant note, midwifery students (who are more vulnerable) have witnessed or experienced WBV [10,73-75]. It has been highlighted that midwifery students feel a lack of preparation in managing WBV [11], which may result in midwifery students emulating poor behavior of midwives and midwifery leaders [5,76]. Hogan et al [3], Steen [4], and Capper et al [11] suggest that midwifery students require additional pathways to address WBV; however, it was acknowledged by Capper et al [11] that there has been no intervention study attempted to date.

To address this deficit, the STOP model [4] will be used as a framework to underpin and guide development and facilitation of a bespoke educational workshop to develop conflict resolution strategies and build resilience for this research. It is anticipated that this research study will address gaps in the literature and provide evidence to confirm or refute any benefits from providing education and training for conflict resolution strategies and building resilience. Building resilience in midwifery students may improve their self-confidence to deal with trauma and adversity, resulting in improved sustainability for the midwifery profession [38,46].

Therefore, developing a bespoke educational workshop that utilizes a validated conflict resolution model [4] may justify the adoption of implementing conflict resolution strategies and building resilience skills as essential curriculum content within a Bachelor of Midwifery degree program to meet the learning needs of midwifery students in South Australia.

Conclusion

There appears to be limited research to inform the development of personal resilience and conflict resolution strategies within Bachelor of Midwifery degree programs. The results and findings from this sequential mixed methods study will be triangulated, and data integration will develop meta-inferences that will strengthen the conclusions drawn. Outcomes from the research will elucidate the experience, potential impact, and prevalence of WBV by midwifery students in South Australia. It is anticipated that the findings will inform recommendations for future midwifery education programs and may include the implementation of conflict resolution and resilience workshops within Bachelor of Midwifery degree curricula.

Acknowledgments

This proposed research is being undertaken as a PhD degree and the candidate and supervisors will all contribute to the research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Start Treating Others Positively model.
[DOCX File , 225 KB - resprot_v11i2e35558_app1.docx]

Multimedia Appendix 2
Braun and Clarke’s 6-stage framework (2006, page 87).
[DOCX File , 14 KB - resprot_v11i2e35558_app2.docx]

Multimedia Appendix 3
Peer-reviewer report from a committee prepared by the University of South Australia, Clinical and Health Sciences.
[PDF File (Adobe PDF File), 151 KB - resprot_v11i2e35558_app3.pdf]

References

1. Farrell GA, Shafiei T. Workplace aggression, including bullying in nursing and midwifery: a descriptive survey (the SWAB study). Int J Nurs Stud 2012 Nov;49(11):1423-1431. [doi: 10.1016/j.ijnurstu.2012.06.007] [Medline: 22770947]
2. Hills D, Lam L, Hills S. Workplace aggression experiences and responses of Victorian nurses, midwives and care personnel. Collegian 2018 Dec;25(6):575-582. [doi: 10.1016/j.colegn.2018.09.003] [Medline: 29223660]
3. Hogan R, Orr F, Fox D, Cummins A, Foureur M. Developing nursing and midwifery students' capacity for coping with bullying and aggression in clinical settings: Students' evaluation of a learning resource. Nurse Educ Pract 2018 Mar;29:89-94 [FREE Full text] [doi: 10.1016/j.nepr.2017.12.002] [Medline: 29223660]
4. Steen M. Conflict resolution for student midwives. Pract Midwife 2011 Mar;14(3):25-27. [Medline: 21473323]
5. Catling CJ, Reid F, Hunter B. Australian midwives' experiences of their workplace culture. Women Birth 2017 Apr;30(2):137-145. [doi: 10.1016/j.wombi.2016.10.001] [Medline: 27771321]
6. Arundell F, Mannix J, Sheehan A, Peters K. Workplace culture and the practice experience of midwifery students: A meta-synthesis. J Nurs Manag 2017 Oct 27;26(3):302-313. [doi: 10.1111/jonm.12548] [Medline: 29076580]
7. Oxford University Press. Oxford English Dictionary Online. URL: https://languages.oup.com/google-dictionary-en/ [accessed 2021-03-10]
8. Bullying in the Workplace. 2018. URL: https://www.anmf.org.au/pages/anmf-policies [accessed 2021-08-20]
9. Safework Australia. Bullying. 2020. URL: https://www.safeworkaustralia.gov.au/bullying [accessed 2021-08-28]
10. McKenna L, Boyle M. Midwifery student exposure to workplace violence in clinical settings: An exploratory study. Nurse Education in Practice 2016 Mar;17:123-127. [doi: 10.1016/j.nepr.2015.11.004] [Medline: 26672901]
11. Capper T, Muurlink O, Williamson M. Midwifery students' experiences of bullying and workplace violence: A systematic review. Midwifery 2020 Nov;90:102819. [doi: 10.1016/j.midw.2020.102819] [Medline: 32827840]
12. Hassard J, Teoh KR, Visockaite G, Dewe P, Cox T. The financial burden of psychosocial workplace aggression: A systematic review of cost-of-illness studies. Work & Stress 2017 Oct 09;32(1):6-32. [doi: 10.1080/02678373.2017.1380726]
13. Hegney D, Eley R, Plank A, Buikstra E, Parker V. Workplace violence in Queensland, Australia: The results of a comparative study. Int J Nurs Pract 2006 Aug;12(4):220-231. [doi: 10.1111/j.1440-172x.2006.00571.x] [Medline: 16834583]
14. Catling C, Rossiter C. Midwifery workplace culture in Australia: A national survey of midwives. Women Birth 2020 Sep;33(5):464-472. [doi: 10.1016/j.wombi.2019.09.008] [Medline: 31676324]
15. Braithwaite J, Herkes J, Ludlow K, Testa L, Lamprell G. Association between organisational and workplace cultures, and patient outcomes: systematic review. BMJ Open 2017 Nov 08;7(11):e017708. [doi: 10.1136/bmjopen-2017-017708] [Medline: 27909040]

16. Australian Parliament House. Workplace Culture and Bullying. 2012. URL: https://www.aph.gov.au/Help/Federated_Search_Results?q=workplace%20culture%20and%20bullying [accessed 2021-08-26]
17. Department of Health. Providing Woman-Centred Care. 2020. URL: https://www.health.gov.au/resources/pregnancy-care-guidelines/part-a-optimising-pregnancy-care/providing-woman-centred-care [accessed 2021-10-02]
18. Nursing Midwifery Board Ahpra. Standard 2: Engages in Professional Relationships and Respectful Partnerships. 2018. URL: https://www.nursingmidwiferyboard.gov.au/Codes-Guidelines-Statements/Professional-standards/Midwife-standards-for-practice.aspx [accessed 2020-10-02]
19. Hobbs J, Green S. Development of a preceptorship programme. British Journal of Midwifery 2003 Jun;11(6):372-375. [doi: 10.12968/bjom.2003.11.6.12184]
20. Hughes AJ, Fraser DM. 'SINK or SWIM': The experience of newly qualified midwives in England. Midwifery 2011 Jun;27(3):382-386. [doi: 10.1016/j.midw.2011.03.012] [Medline: 21565437]
21. Wisetborisut A, Angkurawaranon C, Jiraporncharoen W, Uaphanthasath R, Wiwatanadate P. Shift work and burnout among health care workers. Occupational Medicine 2014 Feb 18;64(4):279-286. [doi: 10.1093/occmed/kqu009] [Medline: 24550196]
22. Gillen P, Sinclair M, Kernohan G, Begley C. Student midwives' experiences of bullying. Evidenced-Based Midwifery 2009;7(2):46.
23. Capper T, Muurlink O, Williamson M. Being bullied as a midwifery student: does age matter? British Journal of Midwifery 2020 Mar 02;28(3):166-171. [doi: 10.12968/bjom.2020.28.3.166]
24. Primanzon N, Hogan R. Keeping 'super' students in the midwifery profession: Addressing bullying in the workplace. Women and Birth 2015;28:S4. [doi: 10.1016/j.wombi.2015.07.022]
25. Shallow H. When midwives become other. In: Edwards N, Murphy-Lawless J, editors. Untangling the Maternity Crisis (1st edn). Oxfordshire, UK: Routledge; 2018:66-74.
26. Edwards N, Sheeran B. Creating a community of support for pregnant women and new mothers. In: Edwards N, Mander R, Murphy-Lawless J, editors. Untangling the Maternity Crisis (1st edn). Oxfordshire, UK: Routledge; 2018:98-106.
27. Leap N. Woman-centred or women-centred care: does it matter? British Journal of Midwifery 2009 Jan;17(1):12-16. [doi: 10.12968/bjom.2009.17.1.37646]
28. Reed R, Sharman R, Inglis C. Women's descriptions of childbirth trauma relating to care provider actions and interactions. BMC Pregnancy Childbirth 2017 Jan 10;17(1):21. [doi: 10.1186/s12884-016-1197-0] [Medline: 28068932]
29. Molewijk B, Kok A, Husum T, Pedersen R, Aasland O. Staff's normative attitudes towards coercion: the role of moral doubt and professional context—a cross-sectional survey study. BMC Med Ethics 2017 May 25;18(1):37. [doi: 10.1186/s12910-017-0190-0] [Medline: 28545519]
30. Davies S, Coldridge L. Trauma experienced by student midwives. In: Edwards N, Mander R, Murphy-Lawles J, editors. Untangling the Maternity Crisis (1st edn). Oxfordshire, Uk: Routledge; 2018:50-58.
31. Kumar-Hazard B. An interview with Bashi Kumar-Hazard. The Midwives Cauldron Podcast with Katie James and Dr Rachel Reed. 2021 Aug 4. URL: https://themidwivescauldron.buzzsprout.com/ [accessed 2021-08-04]
32. Mobbs N, Williams C, Weeks A. Humanising birth: Does the language we use matter? The BMJ Opinion. 2018. URL: https://blogs.bmj.com/bmj/2018/02/08/humanising-birth-does-the-language-we-use-matter/ [accessed 2021-05-13]
33. Human Rights. Human Rights in Childbirth. 2019. URL: https://humanrights.gov.au/sites/default/files/2020-09/sub_149_-_human_rights_in_childbirth.pdf [accessed 2021-06-07]
34. D'Cruz P, Noronha E. Mapping "varieties of workplace bullying": The scope of the field. In: D'Cruz P, Noronha E, Notelaers G, Rayner C, editors. Concepts, Approaches and Methods, Handbooks of Workplace Bullying, Emotional Abuse and Harassment (Vol. 1). New York, NY: Springer; Jan 05, 2021:3-54.
35. Edwards N. A toxic culture. In: Edwards N, Mander R, Murphy-Lawless J, editors. Untangling the Maternity Crisis (1st edn). Oxfordshire, UK: Routledge; 2018:1-8.
36. Warland J, McKellar L, Diaz M. Assertiveness training for undergraduate midwifery students. Nurse Education in Practice 2014 Nov;14(6):752-756. [doi: 10.1016/j.nepr.2014.09.006] [Medline: 25316411]
37. Hunter B, Warren L. Midwives experiences of workplace resilience. Midwifery 2014 Aug;30(8):926-934. [doi: 10.1016/j.midw.2014.03.010] [Medline: 24742637]
38. Lopez V, Yobas P, Chow YL, Shorey S. Does building resilience in undergraduate nursing students happen through clinical placements? A qualitative study. Nurse Education Today 2018 Aug;67:1-5. [doi: 10.1016/j.nedt.2018.04.020] [Medline: 29704800]
39. World Health Organization. The Ottawa Charter for Health Promotion. 2021. URL: https://www.who.int/teams/health-promotion/enhanced-wellbeing/first-global-conference [accessed 2021-05-13]
40. Crowther S, Hunter B, McAra-Couper J, Warren L, Gilkison A, Hunter M, et al. Sustainability and resilience in midwifery: A discussion paper. Midwifery 2016 Sep;40:40-48. [doi: 10.1016/j.midw.2016.06.005] [Medline: 27428097]
41. New Zealand College of Midwives. Advisory to Members: Conflict Resolution. 2017. URL: https://www.midwife.org.nz/wp-content/uploads/2019/06/MERAS-Conflict-Resolution.pdf [accessed 2021-05-16]
42. Leinweber J, Rowe HJ. The costs of 'being with the woman': secondary traumatic stress in midwifery. Midwifery 2010 Feb;26(1):76-87. [doi: 10.1016/j.midw.2008.04.003] [Medline: 18562056]

43. Clohessy N, McKellar L, Fleet J. Bounce back- bounce forward: Midwifery students experience of resilience. Nurse Education in Practice 2019 May;37:22-28. [doi: 10.1016/j.nepr.2019.04.011] [Medline: 31035076]
44. Heller BR, Walsh FJ. Changing nursing students' attitudes toward the aged: an experimental study. J Nurs Educ 1976 Jan;15(1):9-17. [Medline: 1479]
45. Richardson GE. The metatheory of resilience and resiliency. J Clin Psychol 2002 Mar;58(3):307-321. [doi: 10.1002/jclp.10020] [Medline: 11836712]
46. Hunter B, Warren L. Investigating resilience in Midwifery: Final Report. Cardiff, UK: Cardiff University; 2013. URL: https://orca.cardiff.ac.uk/61594/1/Investigating%20resilience%20Final%20report%20oct%202013.pdf [accessed 2022-02-10]
47. Taylor H, Reyes H. Self-efficacy and resilience in baccalaureate nursing students. Int J Nurs Educ Scholarsh 2012 Feb 17;9:Article 2. [doi: 10.1515/1548-923X.2218] [Medline: 22499714]
48. Fielding N. Triangulation and Mixed Methods Designs. Journal of Mixed Methods Research 2012 Mar 30;6(2):124-136. [doi: 10.1177/1558689812437101]
49. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. Health Serv Res 2013 Dec;48(6 Pt 2):2134-2156 [FREE Full text] [doi: 10.1111/1475-6773.12117] [Medline: 24279835]
50. Anjum A, Muazzam A, Manzoor F, Visvizi A, Pollock G, Nawaz R. Measuring the Scale and Scope of Workplace Bullying: An Alternative Workplace Bullying Scale. Sustainability 2019 Aug 26;11(17):4634-4136. [doi: 10.3390/su11174634]
51. Tashakkori A, Teddlie C. SAGE Handbook of Mixed Methods in Social & Behavioral Research. Los Angeles, CA: SAGE publications; 2010.
52. Creswell J. A Concise Introduction to Mixed Methods Research. Thousand Oaks, CA: SAGE Publications; 2015.
53. Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. BMJ 1995 Jul 01;311(6996):42-45 [FREE Full text] [doi: 10.1136/bmj.311.6996.42] [Medline: 7613329]
54. Buchholtz N. Planning and conducting mixed methods studies in mathematics educational research. In: Kaiser G, Presmeg N, editors. Compendium for Early Career Researchers in Mathematics Education. Cham, Switzerland: Springer International Publishing; 2019:131-152.
55. Kaushik V, Walsh CA. Pragmatism as a Research Paradigm and Its Implications for Social Work Research. Social Sciences 2019 Sep 06;8(9):255. [doi: 10.3390/socsci8090255]
56. Morgan DL. Paradigms Lost and Pragmatism Regained. Journal of Mixed Methods Research 2016 Jun 23;1(1):48-76. [doi: 10.1177/2345678906292462]
57. Creswell J, Clark V. Designing and Conducting Mixed Methods Research (2nd edn). Thousand Oaks, CA: SAGE Publications; 2011.
58. Hothersall SJ. Epistemology and social work: enhancing the integration of theory, practice and research through philosophical pragmatism. European Journal of Social Work 2018 Jul 18;22(5):860-870. [doi: 10.1080/13691457.2018.1499613]
59. Steen M, Downe S, Graham-Kevan N. Men and women's perceptions and experiences of attending an abusive behaviour management programme. Evidenced Based Midwifery 2009;7(4):30-37.
60. Steen M, Downe S, Graham-Kevan N. Development of antenatal education to raise awareness of the risks of relationship conflict. Evidenced Based Midwifery 2010;8(2):53-57.
61. Carter M. Changing cultures: Bullying in the NHS. Practice Management 2017 Jan 02;27(1):27-29. [doi: 10.12968/prma.2017.27.1.27]
62. Limb M. Staff at NHS regulator are left "broken" by culture of bullying. BMJ 2013 Jul 29;347:f4801. [doi: 10.1136/bmj.f4801] [Medline: 23896768]
63. Randle J. Workplace bullying in the NHS. J Perioper Pract 2011 Nov;21(11):391-394. [doi: 10.1177/175045891102101105] [Medline: 22165493]
64. UniSA. REDCap. 2021. URL: https://research.unisa.edu.au/redcap/index.php [accessed 2021-08-23]
65. UniSA. Data Management Planning. 2021. URL: https://i.unisa.edu.au/askresearch/data-management/data-planning [accessed 2021-07-24]
66. Sullivan G, Artino A. Analyzing and interpreting data from likert-type scales. J Grad Med Educ 2013 Dec;5(4):541-542 [FREE Full text] [doi: 10.4300/JGME-5-4-18] [Medline: 24454995]
67. Jamshed S. Qualitative research method-interviewing and observation. J Basic Clin Pharm 2014 Sep;5(4):87-88 [FREE Full text] [doi: 10.4103/0976-0105.141942] [Medline: 25316987]
68. DeJonckheere M, Vaughn LM. Semistructured interviewing in primary care research: a balance of relationship and rigour. Fam Med Community Health 2019 Mar 08;7(2):e000057 [FREE Full text] [doi: 10.1136/fmch-2018-000057] [Medline: 32148704]
69. Busetto L, Wick W, Gumbinger C. How to use and assess qualitative research methods. Neurol Res Pract 2020;2:14 [FREE Full text] [doi: 10.1186/s42466-020-00059-z] [Medline: 33324920]
70. Hennink MM, Kaiser BN, Marconi VC. Code Saturation Versus Meaning Saturation: How Many Interviews Are Enough? Qual Health Res 2017 Mar;27(4):591-608. [doi: 10.1177/1049732316665344] [Medline: 27670770]
71. Richards KAR, Hemphill MA. A Practical Guide to Collaborative Qualitative Data Analysis. Journal of Teaching in Physical Education 2018 Apr;37(2):225-231. [doi: 10.1123/jtpe.2017-0084]

72. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
73. Wright EM. Evaluation of a Web-Based Holistic Stress Reduction Pilot Program Among Nurse-Midwives. J Holist Nurs 2018 Jun;36(2):159-169. [doi: 10.1177/0898010117704325] [Medline: 29172933]
74. Aitken. Self-Care for Midwives. 2018. URL: https://www.midwives.org.au/news/self-care-midwives [accessed 2021-05-24]
75. Cummins AM, Wight R, Watts N, Catling C. Introducing sensitive issues and self-care strategies to first year midwifery students. Midwifery 2018 Jun;61:8-14. [doi: 10.1016/j.midw.2018.02.007] [Medline: 29505946]
76. Bluff R, Holloway I. The efficacy of midwifery role models. Midwifery 2008 Sep;24(3):301-309. [doi: 10.1016/j.midw.2005.02.008] [Medline: 17275971]

Abbreviations

NMBA: Nursing and Midwifery Board of Australia
PIS: participant information sheet
STOP: Start Treating Others Positively
WBV: workplace bullying and violence

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Protocol

Participatory Methods for Systems Modeling of Youth Mental Health: Implementation Protocol

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Abstract

Background: Despite significant investment, mental health issues remain a leading cause of death among young people globally. Sophisticated decision analysis methods are needed to better understand the dynamic and multisector drivers of youth mental health. System modeling can help explore complex issues such as youth mental health and inform strategies to effectively respond to local needs and achieve lasting improvements. The advantages of engaging stakeholders in model development processes have long been recognized; however, the methods for doing so are often not well-described.

Objective: This paper aims to describe the participatory procedures that will be used to support systems modeling for national multisite implementation. The *Right Care, First Time, Where You Live* research program will focus on regional youth mental health applications of systems modeling in 8 different sites across Australia.

Methods: The participatory model development approach involves an iterative process of engaging with a range of participants, including people with lived experience of mental health issues. Their knowledge of the local systems, pathways, and drivers is combined with the academic literature and data to populate the models and validate their structure. The process centers around 3 workshops where participants interact and actively engage in group model-building activities to define, refine, and validate the systems models. This paper provides a detailed blueprint for the implementation of this process for mental health applications.

Results: The participatory modeling methods described in this paper will be implemented at 2 sites per year from 2022 to 2025. The 8 selected sites have been chosen to capture variations in important factors, including determinants of mental health issues and access to services. Site engagement commenced in August 2021, and the first modeling workshops are scheduled to commence in February 2022.

Conclusions: Mental health system decision makers require tools to help navigate complex environments and leverage interdisciplinary problem-solving. Systems modeling can mobilize data from diverse sources to explore a range of scenarios, including the impact of interventions in different combinations and contexts. Involving stakeholders in the model development process ensures that the model findings are context-relevant and fit-for-purpose to inform decision-making.

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KEYWORDS

participatory system modeling; youth mental health; co-design; public health systems research; mental health services

Introduction

Globally, it is estimated that more than 700,000 people lose their life to suicide each year, and suicide is the fourth leading cause of death among young people aged 15 to 29 years [1]. In Australia, suicide is the leading cause of death among people aged 15 to 49 years [2,3]. An estimated 340,000 (15%) Australians aged 18 to 24 years experience high or very levels of psychological distress [4]. Most mental health issues experienced during adulthood begin during childhood or adolescence and can result in disengagement from education and reduced social connections. This can, in turn, lead to reduced employment opportunities and poorer socioeconomic outcomes [5]. A recent national inquiry into mental health in Australia made recommendations that called upon multiple sectors to take action to be responsive to the needs of, and improve outcomes and experiences for, people with mental health conditions. The sectors identified by the inquiry went far beyond those usually associated with mental health services and included primary, secondary, tertiary, and vocational education; mainstream health services; early childhood education and care; disability support; workplace health and safety; finance; housing; insurance; justice and law; and digital health sectors [5]. Putting this broad context together with the individual variation in the etiology and course of mental ill health, deciding where and how to invest resources is difficult [6]. This challenge has traditionally resulted in investment in a *comprehensive and all-encompassing* package of interventions in which individual programs are often not sufficiently scaled and resourced to deliver impacts [7]. More effective decision support methods are needed to ensure that investment is well-targeted, coordinated, and implemented at a sufficient scale to deliver real impacts [7,8].

Governments have long been under pressure to provide more programs and services within constrained resources [9]. Policy and program decision processes are often complex, contextually dependent, and influenced by a range of competing priorities [10]. Decision support methods and tools are needed that can not only provide insights into which interventions or programs work but also facilitate identification of the context in which they work or whether other interventions, or combinations of interventions, will work better [9,11]. Systems modeling has a long history of providing decision support capability in a range of disciplines [12-14], including engineering, manufacturing, defense, business, and environmental sciences. It is increasingly being used for health applications. Systems models can be developed and used to leverage a range of data and evidence sources by combining them with local contextual knowledge and expertise to inform mental health system investment planning [8]. Involving decision makers and other stakeholders in participatory model development processes can increase the validity, credibility, and utility of models, ensuring they remain focused on priority policy questions and accelerating the mobilization of model insights into practice [11,15,16].

Participatory Systems Modeling

The process of participatory systems modeling involves engaging multidisciplinary stakeholders in group model-building processes [17]. It can be used in conjunction with multiple modeling methods, including system dynamics, discrete event simulation, and agent-based modeling [18-21]. Various terms have been used to describe these activities, including participatory modeling, group model building, companion modeling (ComMod), and participatory simulation [21]. In the participatory modeling process, participants coconceptualize a problem and use modeling to describe and quantify the problem; identify, develop, and test potential solutions; and inform the decision-making and actions of the group [22]. For the purpose of this study, the term *participatory systems modeling* has been adopted and is defined as "a purposeful learning process for action that engages the implicit and explicit knowledge of stakeholders to create formalized and shared representations of reality [22] using computer simulation."

The terms *stakeholders* and *participants* are both used in this study. By *stakeholders*, we refer to all who have a *stake* or involvement in the system [22], and the term *participants* is used to refer to those people who engage in the participatory modeling process. Therefore, the term *stakeholders* refers to a broader group of people.

Participatory systems modeling focuses on collaborative learning, and the tools and methods used in these programs promote system understanding and awareness among all stakeholders. The tools and methods used in participatory approaches may differ; however, the underlying principles are very similar and subscribe to the same basic aim—to actively engage end users and other stakeholders in model development to increase the robustness, validity, utility, and credibility of the models and facilitate their use to support decision-making processes [18,19,21,23-25]. Participatory modeling has been an important method in system dynamics modeling since its inception [18] and has been widely adopted in environmental modeling projects [19,23,26-29]. The advantages of engaging stakeholders in model development processes include the following [11,16,24,30]:

1. The contribution of extensive domain expertise of participants to model development
2. Social learning between participants and throughout the model development process
3. Joint problem framing to ensure that the model is focused on priority policy questions
4. Production of regionally customized and socially robust solutions, that is, solutions that are more likely to be trusted and accepted by decision makers and stakeholders
5. Identification and prioritization of evidence gaps
6. Identification of opportunities to insert the model into policy and program decision-making dialogues
7. Development of strategies to address communication challenges

Advances in modeling technologies have allowed greater model transparency and meaningful engagement in the model-building process by interdisciplinary groups [20,25]. Although modeling expertise is still required, modeling is no longer restricted to the computational and mathematical sciences and models are being designed to be broadly accessible across disciplines [31]. Participants engaged in the modeling process are able to inspect and critique the logic, parameters (values used), and assumptions of a model, and simulate scenarios independent of the modelers, using interactive model interfaces [25]. Broader access to, and engagement with, models can support faster model evolution and learning, particularly in identifying discrepancies between model results and empirical observations or knowledge concerning the world and helping to refine mental models across the group [14,19,32,33].

It may be difficult to understand and anticipate the impact of policy decisions on system behavior as a whole [12,14]. However, a quantified systems model can facilitate an increased understanding of system behavior by playing out the logical implications of introducing new policies and initiatives into complex systems, thereby making implicit assumptions explicit [25]. For example, in the mental health sector, participatory systems models co-developed with local health services have pointed to the importance of aftercare for people who have experienced suicidal behavior, a finding that is consistent across applications in diverse regions [34,35]. In addition, modeled intervention effects that initially seem counterintuitive may point to unanticipated consequences. For example, evidence-based community mental health education and awareness raising programs can lead to demand exceeding service capacity, increasing waiting times and disengagement with services, and increasing mental health–related emergency department presentations [36].

Transparent models can help to connect knowledge across the breadth of a team, enhance their ability to identify areas where their knowledge falls short, uncover logical inconsistencies, and contribute to more robust and strategic decision-making [25]. From this perspective, the discovery of an inconsistency between what the model suggests in simulation scenarios and empirical data is an opportunity to facilitate learning and refine the model to improve its forecasting capability, thereby increasing its value as a long-term decision support asset [20,25,28].

Principles of Participatory Systems Modeling

Frameworks, guidelines, and principles for participatory systems modeling have primarily been developed within the environmental sciences field where it has been widely acknowledged that sustainability issues involve social processes and stakeholder engagement is necessary to support effective action [21,24,37-39]. These have ranged from highly prescriptive scripts used for group model building often associated with system dynamics modeling [18,19,23,40-42] to more general guidelines and considerations [20,21,24,32,43].

Participatory systems modeling projects are diverse, and flexible principles guiding the conduct of participatory processes that are also easily modifiable and applicable across sectors provide a practical approach to inform existing and future practices [21,24]. The following principles are described in Multimedia Appendix 1 and have been formulated based on recommendations from the literature [44] and the experience of the authors conducting participatory systems modeling for physical and mental health applications [16,17,30,34,45-49]:

1. Selecting and planning stakeholder engagement to ensure that appropriate expertise is available to guide model development
2. Being aware of social and group dynamics to facilitate inclusivity and give all participants the opportunity to contribute and having flexibility in the process to accommodate the priorities and preferences of participants
3. Maximizing transparency and openness in the model development process by ensuring that assumptions and data sources are made explicit
4. Iterating and refining by actively engaging participants throughout the model development process and incorporating their feedback
5. Encouraging learning and managing uncertainty through scenario analyses and hypothesis testing

Most strategic mental health policies and planning decisions are complex and not easily addressed using traditional analytic tools. Policy and planning decisions are challenged by multiple interacting factors with uncertain outcomes, competing options for action and investment, differing expert and local views of effective actions, and the potential for unintended consequences [17,50]. Scenario analysis can assist in identifying optimal combinations of interventions that remain effective even when the conditions in the system are varied [51]. An iterative, participatory approach to modeling allows the identification of data gaps and priorities for new data collection and development of ways to address these [11,20,21]. Models have significant potential to assist in good decision-making through the participatory process by bringing together best evidence, data, and knowledge and consolidating and testing shared hypotheses [25,32].

Aims and Objectives of the Method Blueprint

Although the importance of involving stakeholders in model development processes to increase the relevance, validity, usability, and credibility of models has been recognized, the methods for doing so are not always well understood and terminology can be used loosely, leading to confusion. This paper aims to promote a shared understanding of our participatory systems modeling approach and provide a practical, detailed blueprint to support the implementation of the approach.

This paper was developed as a semistandardized guide for implementation across subnational regions as part of a broader program of participatory action research that aims to explore the feasibility, value, impact, and sustainability of building regional capacity in the use of more advanced decision support tools and technologies to inform systems strengthening and empower communities to address the mental health needs of young people [52,53]. The *Right Care, First Time, Where You Live* research program will use participatory methods to deliver contextually relevant systems models focusing on youth mental health services in multiple sites across Australia. More information about the research program is available [52]. The

systems modeling program aims to provide regional health authorities, social service providers, and community stakeholders the tools, processes, and insights needed to more effectively allocate limited available resources and make compelling cases for further investments [53]. This paper outlines the participatory systems modeling procedures, methods, and activities that will be implemented to support this mental health multisite study related to youth.

The process described in this study builds on the experience of the authors conducting participatory systems modeling for a range of public health issues [6,8,16,17,30,34,45-48,54,55]. However, this study focuses on modeling for mental health applications in this multisite program. Operationalizing participatory systems modeling for mental health applications involves ensuring that the process is inclusive for people with lived experience of mental ill health and their support people.

Methods

Role Descriptions for the Interdisciplinary Core Project Team Members

The project roles mentioned later will be key to successful implementation. The descriptions are adapted from Atkinson et al [46] and Freebairn et al [16]. It should be noted that one person can play multiple roles in a project, that is, the project lead may also be the domain expert or the modeler may be experienced in modeling for policy so may also act as a translator. The term *primary partner agency* refers to the main stakeholder organization that will facilitate the modeling project in the local community. In the Australian health service context, this agency may be the Primary Health Network or jurisdictional health services.

A project lead facilitates the brokering and management of a project. This person will have the primary responsibility of engaging and maintaining relationships with participants and health service partners (ie, end users of the model). The project lead shares the duties of facilitating the modeling workshops with the lead domain expert and overseeing model development, associated documentation, and external communications.

A lead domain expert is a well-respected authority on the focus issue who can play a lead role in project planning and workshop facilitation.

A translator is a person who can contextualize the policy environment and data for the modeling team and translate the model requirements and development process to the participants.

Expert participants are people with a range of perspectives from across the system being modeled and policy, planning, and content area expertise, including representatives from local Aboriginal and Torres Strait Islander governance bodies, people with lived experience of mental health and suicidal behavior, representatives from federal and state governments, health and social policy agencies, local councils, nongovernment organizations, emergency services, research institutions, community groups, and primary care providers.

A dynamic simulation modeler is a person with expertise in systems modeling and ideally with a background in biostatistics, data science, or mathematics.

An economist is a person with expertise in economic evaluation of policy interventions, including multiple costing methodologies and different valuation techniques, with knowledge of decision analysis and priority-setting processes.

Superusers are nominated persons from within decision-making or primary partner agencies who will be socialized to the model and build competency in using it to explore policy scenarios and interpret and report model findings for reports, policy briefs, business cases, and advocacy.

Research or project support officers are responsible for coordinating the participatory systems modeling process, including logistical arrangements for workshops and liaising directly with the modeler and workshop participants to source and manage evidence and data requirements for the model-building process.

An expert technical adviser provides an independent review of the model, including model conceptualization, equations, and dimensional consistency, to identify errors and ensure that the model is robust and computationally efficient.

Considerations When Including People With Lived Experience of Mental Health Issues and Their Support People

The advantages of involving people with lived experience of mental ill health, including carers, are well established and include ensuring that their essential knowledge about current care pathways, barriers, shortfalls, and what is needed from the mental health system, is embedded in research and service design to improve outcomes at individual, service, organization, and system levels [56-62]. The participatory modeling procedures described in this implementation protocol are informed by the literature regarding best practice principles for supporting consumer and carer participation in mental health research and as described by the National Mental Health Commission [56]. These procedures are also informed by experiences of the authors in implementing previous participatory modeling projects in the mental health sector in collaboration with people with lived experience of mental health issues and suicidal behavior.

The choice of location, venue, and timing for workshops should consider the needs of participants. Barriers to participation can include distance and travel times and environments that cannot accommodate individual requirements such as mobility access, space to take time-out breaks or dietary needs, and insufficient lead in time for workshops to allow participants to prepare for engagement, including taking a time-out from other commitments. Efforts will be made to provide an inclusive culture and safe environment at the workshops that supports the engagement of all participants [56]. In practical terms, this may include being explicit about the ground rules for safe and acceptable disclosure, ensuring that participants have access to and are aware of supports available, for example, debriefing and referral to professional support, allowing people to take a

break when needed, and observing levels of psychological distress within the group; checking in with participants; and offering support where appropriate. People with lived experience may prefer to bring their peer support worker or carer to workshops as they can detect signs of distress well and can provide support as needed throughout the event, particularly when discussing suicidal behavior.

Workshop facilitators and support staff will ensure that large and small group discussions are respectful and inclusive for all participants, for example, valuing contributions from all participants, minimizing instances where people are interrupted or cut off or not listened to, and minimizing the use of jargon. Informal conversations during breaks and outside of workshops can be used to encourage participation in the process by providing additional information and clarification about the process and method and opportunities to contribute outside of the formal workshop process, for example, by sharing stories and experiences of the mental health system in direct, one-on-one conversation with the project team members.

The language used throughout the modeling process, but particularly during participatory workshops, will need to be inclusive and increase the likelihood that participants with lived experience of mental health issues feel respected and valued and able to contribute actively to the model development process. Language should be age-appropriate, respectful, nonjudgmental, jargon-free, and accessible to lay people. In addition, the language should be person-centered, that is, *person with mental health condition* rather than *they are mentally ill*, and recovery-oriented—conveying the potential for hope and opportunity. The Mental Health Coordinating Council provides an extensive and practical guide for using recovery-oriented language [63].

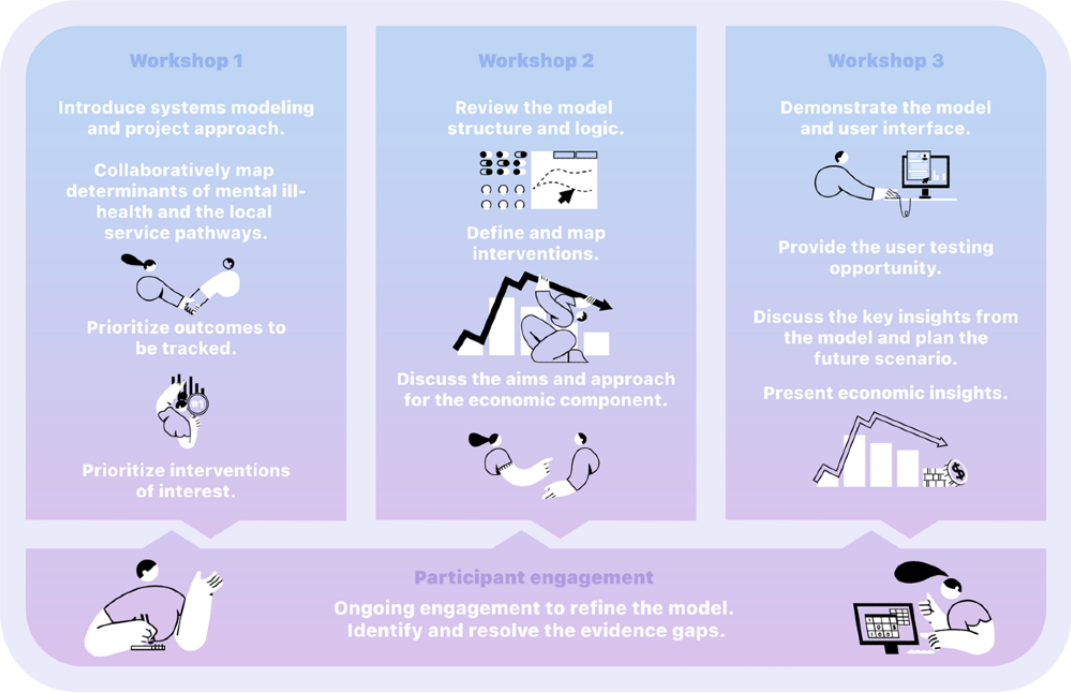
Ongoing evaluation of the process using participatory action research will be undertaken as part of the broader program to facilitate the identification of opportunities to improve consumer and carer engagement in participatory system modeling processes.

Procedures for Building and Using Systems Models With Stakeholders

Overview

Participatory model development involves an iterative process of understanding local systems, pathways, and drivers by engaging with local stakeholders and the academic literature, populating the model with data, validating its structure and performance with historic data, and ensuring face validity with stakeholders. It centers around 3 workshops where participants interact and actively engage in group model-building activities (Figure 1). Experts and key participants with an important *stake* in the topic are identified and invited to participate in the model development group (participants). Their expert knowledge and local practice experience are triangulated with research evidence and primary and secondary or administrative data sources to articulate the causal mechanisms driving mental health and suicide outcomes in a region.

Figure 1. Overview of the activities involved in participatory modeling workshops.



Script-based approaches [18,19,41,42,64,65] have traditionally been used in system dynamics modeling. Our methods favor more organic, minimally structured activities that allow people to tell their stories and share their experiences, which elicits valuable systems information without the constraint of conforming to closely scripted activities or disciplinary conventions of systems science. This process aims to elicit information about what really happens on the ground, hidden incentives or disincentives embedded in the system, and information that is not available in academic papers or data sets but has significant implications for key outcomes and system functioning locally. Providing opportunities for interaction

between participants as a group is valuable, as it often reveals more about the system than if the project team has met with participants individually. System learning also occurs when people hear the perspectives and challenges of those in other parts of the system who they may not frequently interact with.

The following sections describe the process for conducting participatory systems modeling workshops for mental health applications. It should be noted that this paper provides guidance specific to facilitating participatory systems modeling; however, it does not cover more general activities involved in workshop organization, for example, booking venues, arranging travel, organizing catering, managing RSVPs, and registration of participants. This is assumed knowledge for this paper.

Early Stakeholder Engagement and Workshop Preparation

Establishing effective partnerships is key to the successful implementation of participatory systems modeling projects. Early engagement with the primary partner agency for each site is important to ensure that the modeling will address their decision analysis needs. In some regions, improving mental health outcomes and reducing suicidal behavior will need to prioritize decision-making around investments to address youth justice, substance misuse, and unemployment challenges, where others may need to prioritize improving access to services. These discussions help to scope the model without changing the primary research question and the overarching purpose of the work.

There are four key activities in the engagement process: (1) determining the capacity of the stakeholder community to participate and actively engage in the activities; (2) communicating the purpose and goals of the systems modeling research and gaining commitment from stakeholders; (3) initiating engagement with the community and understanding current issues, challenges, and alternative perspectives; and (4) establishing relationships and building trust between researchers and community stakeholders [66,67]. The site and stakeholders engagement process to be implemented across sites will be undertaken using participatory action research principles.

Important considerations for this phase of the project include the following:

1. Identification of decision-making priorities for modeling: participating in a systems modeling process requires significant time investment for stakeholders. Motivation for stakeholders to participate is higher when addressing the mental health challenge is a high priority for the region, where the policy and planning environment is complex, where there are contested potential solutions, or where previous attempts at addressing the issue have not delivered impacts [16]. It is important to invest time in discussing local needs to ensure that the modeling is focused on answering the priority questions of the stakeholder group.
2. Identification and engagement of key contacts within the primary partner agency: once a key contact has been identified and engaged, their assistance will be sought to facilitate the identification and engagement of key stakeholders and organizations within their local community for youth mental health services.
3. Venue selection: there are two main considerations for selecting a venue for participatory workshops—first, the venue needs to have a facility to project presentations (including presentations of model architecture) onto a large screen where small text remains legible to participants. Second, the room needs to provide sufficient space for the participants to easily move around a large conference table. An important activity for workshop 1 is for participants to interact and engage in the conceptual mapping of the system. This involves the participants working with paper, tape, and sticky notes to contribute to the system diagram that is laid out on a large table.

At least 2 members of the project team will facilitate the workshops and at least another 2 will provide workshop support. Wherever possible, the workshop facilitators should include a local domain expert who works together with the modeler and project lead to facilitate the workshop. For example, in workshop 1, the local domain expert presents an overview of the epidemiology of mental health and suicidal behavior of the region being modeled and the modeler presents an introduction to systems modeling. The workshop facilitators jointly explain and support participatory activities. The workshop support staff provide logistic assistance to ensure smooth operation of the workshop. This includes welcoming and registering participants; ensuring that any necessary paperwork, for example, regarding participation, photography consent, and confidentiality have been completed; liaising with the venue staff; taking photographic records; ensuring that audio recording devices are in place and turned on during the appropriate sessions; setting out materials; and rearranging the room as needed to facilitate workshop activities. A list of materials for the core workshop activities is provided in Multimedia Appendix 1. It is beneficial, when there is sufficient capacity, for the workshop support staff to be workshop observers, recording field notes that can be used to support the project team debriefing and reflective analysis of each workshop. Field notes and observations would focus on levels of participant engagement in workshop sessions and questions and issues raised by participants during discussions and interactive activities. Runsheets may be developed for each workshop to clearly outline the roles of presenters and workshop facilitators and describe the activities and timing of each session in the workshop.

Participant Selection and Recruitment

Participant selection will be conducted in collaboration with the primary partner agency for each site to embed contextual knowledge into the participant selection process.

Purposive sampling will be used to recruit participants with diverse perspectives and expertise, including young people with lived experience of mental health issues, carers, members of the local Aboriginal and Torres Strait Islander community, mental health professionals, educators, policy makers, service planners, primary health care providers, health service managers, and other service providers. A comprehensive list of stakeholder categories is provided in Textbox 1.

Textbox 1. Categories of stakeholders to be considered for inclusion in the participant group.

Stakeholder categories

- Health department policy makers and policy officers
- Local health district representatives
- Youth mental health researchers, including epidemiologists and social scientists
- Police and emergency services
- Clinicians from youth mental health and substance use support services
- City Council members and staff
- Primary care, general practitioners, nurse managers, and allied health professionals
- Educators, education department representatives, and school counselors
- Child protection workers
- Relevant nongovernment organizations and foundations
- Consumers, people with lived experience, and carers
- Community leaders, including church, traditional healers, and other leaders
- Health insurers and private service providers
- Hospital and other service administrators
- Program planners and service coordinators
- Call centers and web-based service providers
- Representatives from special interest groups, including lesbian, gay, bisexual, trans or transgender, queer, intersex and other sexuality, gender and bodily diverse people; indigenous; culturally and linguistically diverse; refugee
- Mental health promotion agencies

The aim is to include participants who are recognized as local leaders in consumer and carer experience, providing services, planning, and commissioning services and developing policies and the local Aboriginal and Torres Strait Islander community.

Selected participants will be provided with information relating to the aims of the project, the time commitment required, the likely timing of the workshops, and background information regarding systems modeling. Where possible, the initial invitation of participants is extended by the local domain expert or primary partner agency.

Before the first workshop, participants will be asked to provide written consent to participate, be recorded and photographed at workshops, and agree to not disclose confidential information shared by other participants during the model development process, which is important for providing a safe environment for sharing information that is important for model development but which the participants may not wish to be shared publicly.

Workshop 1: Introduction to Participatory Systems Modeling and Conceptually Mapping the System

Overview

The logistics involved in planning and implementing workshop 1 and the activities undertaken to achieve the workshop objectives are discussed in detail. Although the overall aim of the participatory workshops is to maximize the active engagement and interaction of participants, it is necessary to initially present some background and context setting information. Therefore, once the welcome and introductory activities are complete, the initial sessions in the workshop involve presentations of relevant information to support the participatory systems modeling process. An example agenda is included in Multimedia Appendix 1. The five main objectives for workshop 1 are as follows:

1. Present an overview of the epidemiology of mental health issues and suicidal behavior relevant to the region or population catchment being modeled
2. Introduce systems modeling to the participant group to facilitate meaningful engagement in the model development process
3. Jointly conceptualize and map *system* structure and drivers
4. Prioritize the interventions and outcomes to be explored by the model
5. Introduce the economic analysis and explain that it will be developed following workshop 1, as the model's purpose and scope develop

Welcome and Overview of the Project Aims and Objectives

It is important that participants are welcomed by the host organization in accordance with local customs, for example, in Australia, this would include an acknowledgment of the traditional owners of the country upon which the workshop is taking place and would also include an acknowledgment of the lived experience of mental health issues and recovery.

The aims and objectives of the project, drawn from project scoping discussions with the key stakeholder organization, will be presented to the participants. The overall aim may be quite

broad, for example, “this project aims to use a co-designed systems model to provide a robust, evidence-based, interactive decision support tool to improve population mental health” or it may be quite specific “...a decision support tool to inform suicide prevention in young people,” depending on priorities identified in scoping discussions.

Session 1: Introduction to Dynamic Simulation Modeling (Time Allowed 30 Minutes; Purpose of the Session and Method)

The purpose of this session is to provide participants with an overview of what systems modeling is and what it can offer in a decision-making context.

A slide-supported presentation covering the points mentioned in Textbox 2.

Textbox 2. Method for session 1.

Method for session 1

- Challenges faced in policy making and planning in the mental health sector:
  - Complexity of problems, including complex determinants of mental health and suicidal behavior, population dynamics, and service pathways
  - Broad range of options for intervening
  - Changing mental health care and suicide support needs and demands over time
  - Different perspectives and competing views of how best to intervene
- What systems modeling has to offer in mental health policy and planning:
  - Explanation of what systems modeling is, that is, a simplified representation of the real world that can provide us with a method to map and quantify complex problems and service systems by bringing together a range of evidence, data, and knowledge. The developed model will be an interactive what-if tool for scenario analysis.
- The process for building a model and examples of a final *what-if* decision support tool:
  - Provide an overview of the process using a diagram such as Figure 2.
  - Emphasize the important role that participants have in this process. The participatory process is critical to understanding the behavior of the system and its drivers, identifying and considering potential unintended side effects of interventions, and keeping sight of the impacts of mental health initiatives on the wider health and social systems. By working together, the participant group ensures that the model is fit-for-purpose and can capture regional differences in demographics and service structures, making it a robust, contextually relevant decision support tool that can be embedded in the local policy or planning cycle.
  - Present example user interfaces (Figure 3) to demonstrate the outcomes of the project. Briefly explain the elements of the interface and how it can be used to explore the what-if scenarios.

Figure 2. Overview of the process for building systems models using participatory methods.

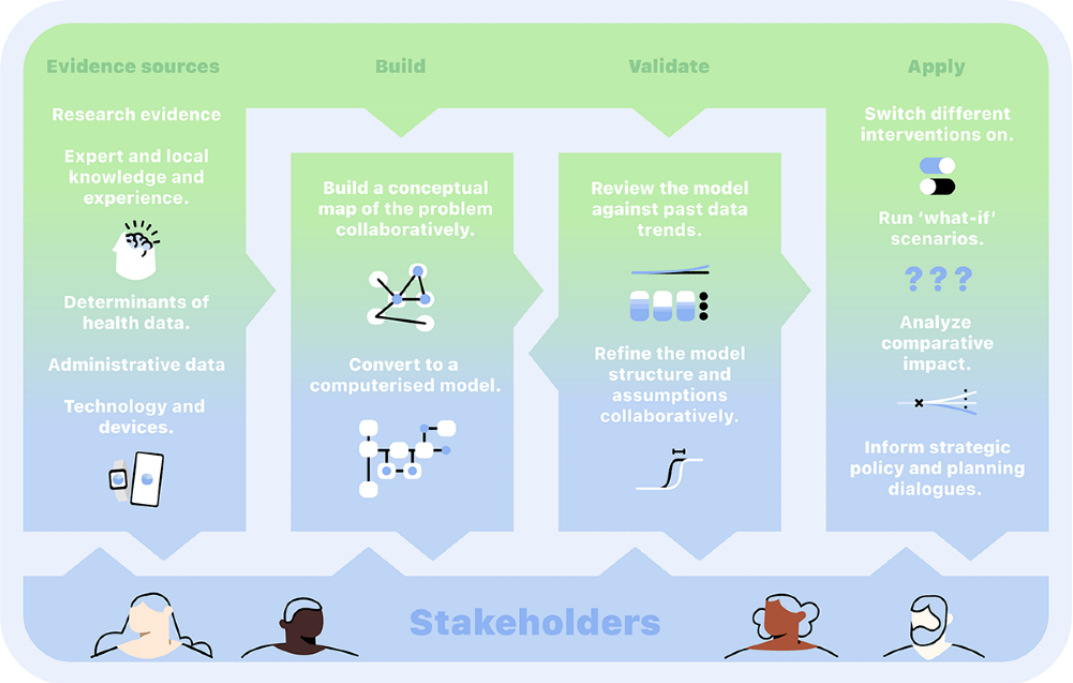
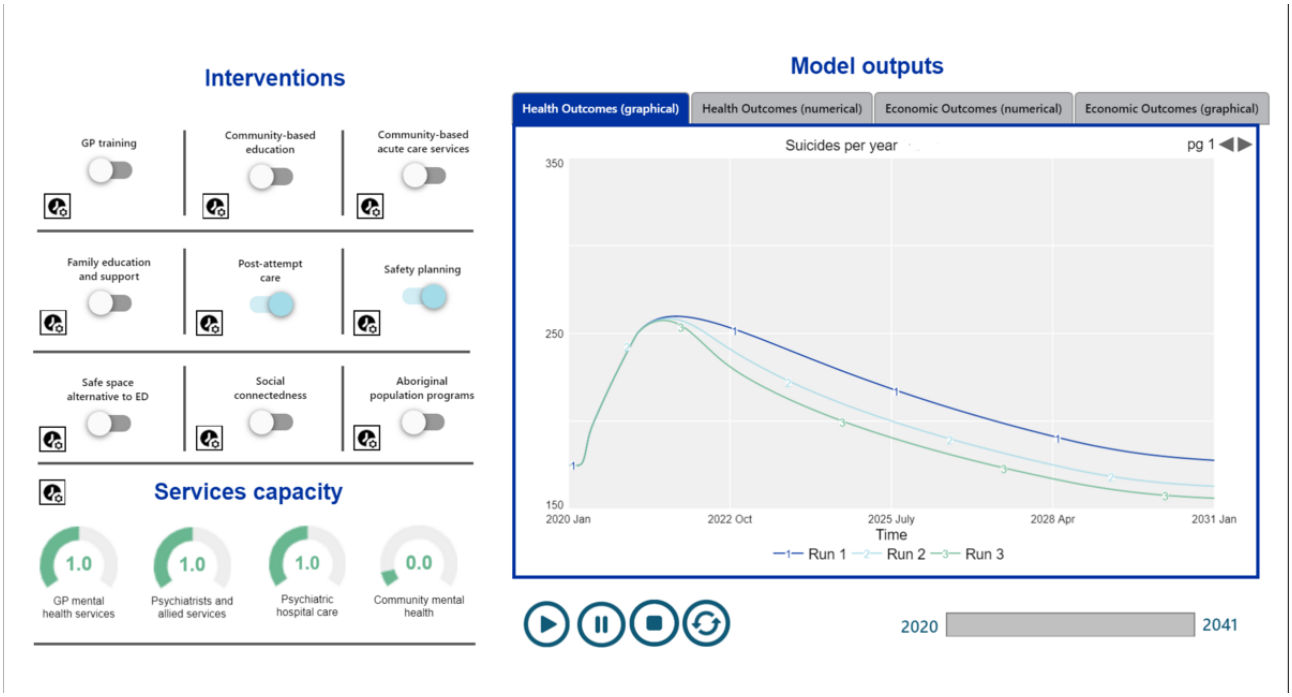


Figure 3. Example of the user interface for a suicide prevention model.



Session 2: Introduction to System Dynamics Modeling (Time Allowed 30 Minutes; Purpose of the Session and Method)

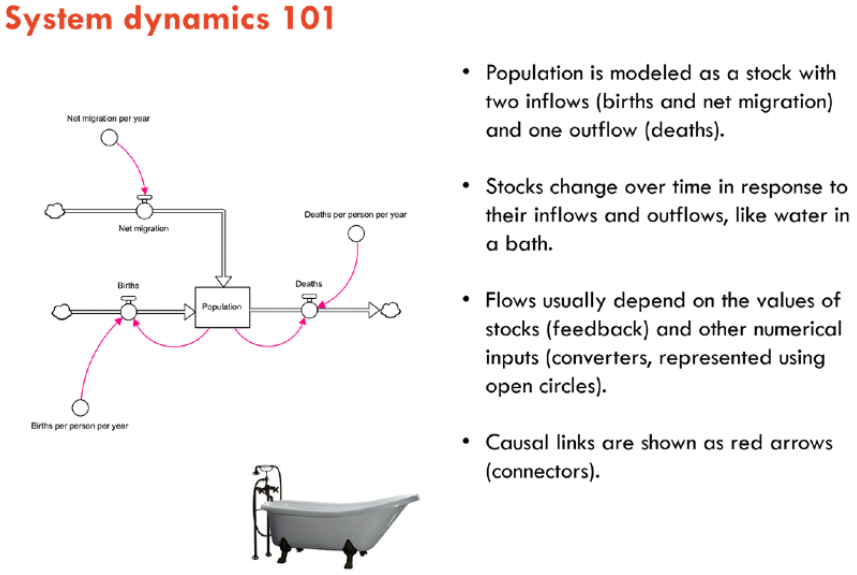
The purpose of this session is to provide participants with sufficient knowledge of the basic concepts and graphical language underpinning system dynamics modeling to enable them to participate meaningfully in the model development process, including in the conceptual mapping activity in session 4, and the ability to critique the model in workshop 2.

The examples used here apply to system dynamics modeling; however, the introduction should focus on whichever modeling method is being used in the project, for example, state charts for agent-based modeling or process diagrams for discrete event simulation.

A slide-supported presentation covering the key terms and concepts of system dynamics modeling using visual diagrams (Figure 4) and plain language. The core concepts explained include the following:

1. Stocks and accumulations
2. Flows
3. Reinforcing and balancing feedback loops
4. How data will be used to calibrate the model

Figure 4. Facilitation slide to support the explanation of system dynamics concepts to the participants.



Session 3: Defining the System and Outcomes of Interest (Time Allowed 30 Minutes; Purpose of the Session and Method)

The purpose of this session is to provide participants with an overview of the mental health system and suicidal behavior in the local context and initiate discussions and priority outcomes to be tracked in the model.

It is preferable for the overview to be presented by a local, trusted domain expert and would cover the topics listed in Textbox 3.

Textbox 3. Method for session 3.

Method for session 3

- Mental health outcomes, drivers, and service use
  - The focus of the models being developed in this program is on the complex interplay of social determinants, service system factors, population demographics, and behavioral dynamics that drive population-level youth mental health outcomes:
  - Epidemiology of mental health issues, suicide and self-harm, and service use (eg, emergency department presentations, psychiatric hospitalizations, primary care service contacts) relevant to the region. This usually begins with a broad overview and then narrows the focus down to the local context.
  - Other social- or system-level contributing factors in the local context, for example, alcohol and other drug use, family violence, service access, or unemployment.
- Eliciting outcomes of interest: this activity will be conducted as a facilitated discussion in this session or an interactive activity, and both procedures are described later. Unless it is culturally or contextually inappropriate to do so, the discussion should be recorded to ensure that the project team is able to refer back to the important details that they may not pick up while they are facilitating the workshop. The appropriateness of recording will be discussed with key stakeholders, for example, elders of the local Aboriginal and Torres Strait Islander communities, during preworkshop engagement:
  - Facilitated discussion—a discussion starter slide presenting potential outcomes of interest that will be the primary outputs of the model. Commonly modeled outcomes for mental health applications include prevalence of psychological distress, mental health–related emergency department presentations, self-harm hospitalizations, suicide deaths, emergency department presentations and hospital admissions for alcohol and other drug use, quality-adjusted life years related to mental disorders. Participants are asked to discuss whether these outcomes are important for planning purposes and whether other outcomes should be prioritized.
  - Interactive activity (requires pens, sticky notes, and a wall space):
    - Display a slide with potential outcomes to be measured in the model.
    - Ask people to write their top 3 priority outcomes (which can be different from those on the slide) on separate sticky notes and then put them up on the wall during a break. Participants are asked to place the notes in theme groups (ie, put their sticky notes together with other similar notes).
    - The modeling support team provides feedback about the outcomes of interest in session 5 (detailed later). Feedback would include ranking the prioritized outcomes (ie, identifying the outcomes that were nominated most frequently by participants) and grouping the identified outcomes into broad themes. Further analysis to ensure that the main outcome themes identified by the participants have been captured can be undertaken after the workshop. Where there is disagreement among the participants about which outcomes should be prioritized, a voting process will be used to resolve it.

Session 4: Participatory Mapping Exercise (Time Allowed 1.5-2 hours With a Break Partway Through; Purpose of the Session and Method)

The activity undertaken in this session provides the most critical outcome for workshop 1, a co-designed conceptual map of the system to be modeled. In this activity, participants interact with each other and the project team to jointly conceptualize and qualitatively map the youth mental health system in the form of a *draft model structure*.

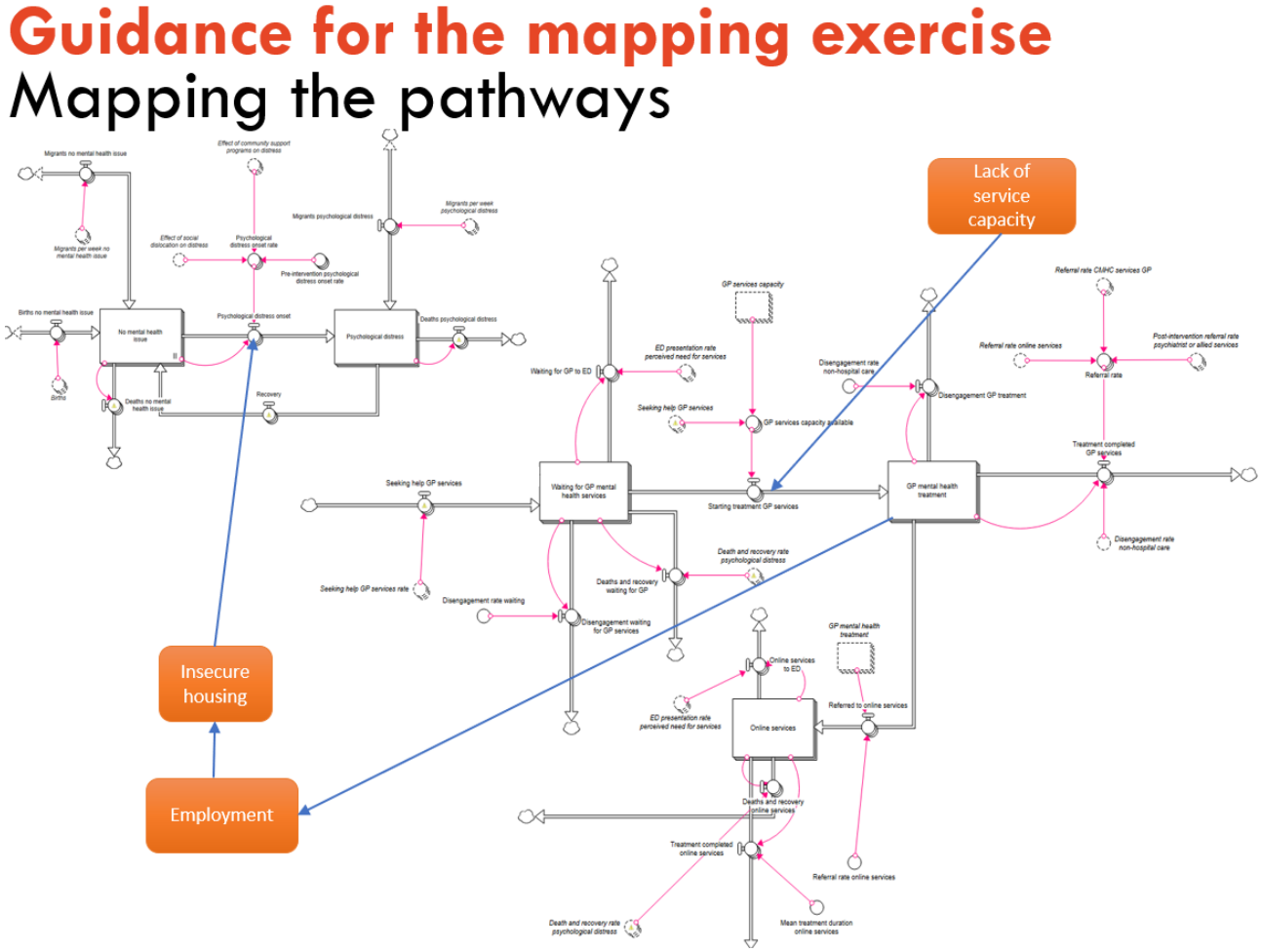
The mapping exercise is undertaken using the procedures listed in Textbox 4.

Textbox 4. Method for session 4.

Method for session 4

- A simple draft model structure that incorporates key stock and flow structures for system dynamics models (or state charts for agent-based models) is derived based on preworkshop engagement with stakeholders and on previously published mental health systems modeling research in a similar context [48]. The structures might include aging chain structures and stock and flow diagrams representing the change in psychological distress over time or changes in demand for services and service pathways.
- The structural components, such as the stock and flow structures identified earlier, are preprinted, laminated, and laid out on large sheets of paper in preparation for the workshop. This provides a *straw man* structure for participants to modify and elaborate on and a starting point for discussion.
- The guiding instructions explain to participants that a draft model architecture has been laid out to provide a starting point for the mapping activity and that they are invited to review, contribute to, and improve the map. For system dynamics modeling projects, participants are asked to focus on high (or system) level factors that influence the *flows*, for example, community- or service-level characteristics rather than individual behavior or choices. Participants are encouraged to expand the structure to capture the key service pathways of the region.
    - Instructions should emphasize the following:
        - This *brainstorming*-style activity aims to map the important causal pathways that contribute to the focus issue, that is, youth mental health issues.
        - The mapping activity uses elements of the model structure presented in session 2.
        - It is an inclusive process that demonstrates the capacity for systems thinking to help understand mental health issues, suicidal and self-harm behaviors, and their determinants. The objective is to understand what pathways are missing, what influences the flows, and how changes in one part of the system impact other parts.
        - Present slides showing a draft model architecture that participants can expand and critique. The draft is intended to initiate discussion rather than impose a pre-empted model design. Figure 5 illustrates an example slide showing a draft stock and a flow diagram. The slide is used to explain how factors that influence the flows between the stocks can be mapped to the diagram and that the direction of influence is important. Instructions will be tailored for each site by using real-world examples derived from preworkshop engagement discussions.
        - Advise participants that the activity will be photographed and audio-recorded to ensure that the project team can incorporate their contributions into the model accurately.
    - The project team should circulate among participants during the activity to answer questions and engage in discussions. Participants will often verbalize where the map requires further development but may need encouragement to physically put down their thoughts on paper using the materials provided.
- Prompting questions are used to facilitate the activity. For example, the following general questions can be presented on a slide that is left on display during the activity, but the project team may develop more specific probing questions that can be used to facilitate small group or one-on-one discussions with participants during the activity:
    - Have we captured the important stocks? Are there others that should be included?
    - What factors influence the flow between stocks (family and environmental factors)?
    - Are there other stock and flow structures that should be included?
    - Are there any incentives in the system that influence behaviors or flows?
    - Are there any feedback (positive or negative reinforcing cycles)?
- The project team uses the scheduled break time to debrief about the mapping activity and determine the important areas to focus on in the second part of the session, for example, “Are there other causal pathways, barriers, or disincentives in the system of interest that have not been elicited?” “Is there anything on the map that the team does not understand or need to clarify?” “Are there feedback loops emerging from the map that can be elicited more clearly?”
- Reconvene the activity by inviting participants to return to the conceptual map and continue to add any additional elements that they have thought of during the break. The project team circulates among the participants, encouraging them to make any last contributions to the map.
- Session 4 will finish with a large group discussion to do the following:
    - Acknowledge participants’ valuable contribution to conceptually mapping the system.
    - Refine, clarify, and define the elements of the model structure. This discussion would vary depending on the purpose of the model, but may include, for example, defining age ranges or priority subgroups of interest.
    - Identify data sources and research evidence to inform the model for each prioritized subgroup. Participants are asked to complete the data contribution form.

Figure 5. Facilitation slide to guide the conceptual mapping activity. GP: general practitioner.



Session 5: Prioritizing the Interventions of Interest (Time Allowed 45 Minutes; Purpose of the Session and Method)

The purpose of this session is for participants to identify the priority interventions of interest in modeling projects to ensure that the appropriate level of detail is included in the model structure to capture their effects.

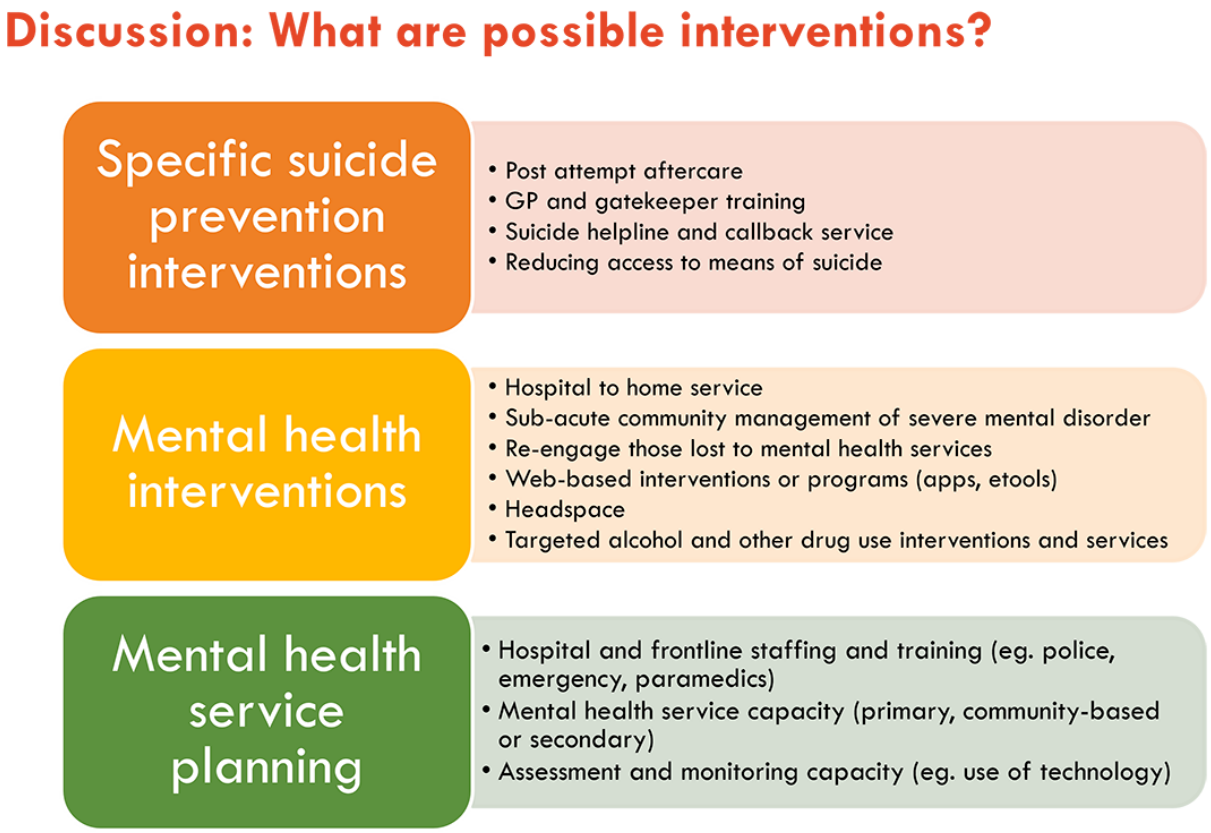
This activity will either be run as a facilitated discussion and voting process conducted at the workshop or a larger community engagement process, including the facilitated discussion described later, and a postworkshop survey sent out via workshop participant networks where community members vote on which interventions are the highest priority for inclusion in the model. The decision regarding which selection method to use would be made in consultation with the primary partner agency to best meet the needs of the site. Regardless of the method used, diverse views are likely to be expressed. Both prioritization methods are described in subsequent sections. The voting or survey processes generally identify the priority interventions (or outcomes); however, this is followed up with a discussion in workshop 2 that aims to achieve a broader consensus. The workshop discussion option is described in Textbox 5 and the post-workshop survey is described later.

Textbox 5. Method for session 5.

Workshop Discussion Activity

- Introduce the session, explaining the importance of understanding which interventions are of priority interest to the participant group to ensure that the model is built in a way that can adequately incorporate the intervention effects.
- Explain that the modeled interventions can be based on interventions already implemented in the real world or that they can be hypothetical interventions. Both are useful for *what-if* scenario testing. Interventions across the full spectrum of services can be considered for inclusion in the model, for example, primary prevention, early intervention, acute care, rehabilitation, and aftercare. Scenarios examining the impact of disinvestment in existing programs can also be explored and, if deemed a priority, should be identified at the outset. It is generally feasible to include 6 to 8 interventions in a participatory system dynamics modeling project that is 6 months in duration.
- Present a slide showing a list of potential interventions derived from the preworkshop engagement discussions (Figure 6). Explain that the focus of the current session is to prioritize and define the interventions to be integrated into the model:
  - Ask participants to write down their priority interventions on separate sticky notes (which may or may not include those in the presented list).
  - The participants will place the notes on a wall surface and group their own with similar interventions placed by other participants. Advise participants that we are interested in a range of interventions, but it does not matter if someone else writes down the same one.
  - The participants are given 10 sticky dots to allocate to their interventions of choice. They can place as many dots as they wish on their priority intervention. More dots placed against an intervention emphasizes its importance.
  - The project team groups the interventions into themes and records the voting results following the workshop. The results are presented in workshop 2.

Figure 6. Example slide presenting possible interventions to be considered for inclusion. GP: general practitioner.



Postworkshop Survey Activity to Facilitate Wider Community Consultation

When broader community consultation to prioritize interventions is preferred by the primary partner organization, it is facilitated using the following procedures:

1. Follow the aforementioned steps outlined in the first two bullet points in Textbox 5.
2. Present a slide showing a list of potential interventions that have been derived from the preworkshop engagement discussions (Figure 6).
3. Explain to the participants that their support will be required to distribute a survey to the wider community, asking people

to prioritize which interventions are most important, from their perspective, to be included in the modeling process. Explain that it will be important for the participants to encourage people in their network to complete the survey to ensure that the voice of the community is heard in the model-building process.

4. Describe the survey process, for example, how the survey will be distributed and the timeframe for responses, and that the results from the survey will be combined with the workshop discussions and presented back to the participants in workshop 2 as a prioritized list of interventions.

Session 6: Economics, Next Steps, and Data Contribution (Time Allowed 30 Minutes; Purpose of the Session and Method)

There are two purposes for this session as follows:

1. To introduce the economic approach that will be used and explain the data requirements for the analysis.
2. To highlight the progress and valuable contributions made in workshop 1, discuss potential timing for workshop 2, identify sources of data and evidence to inform the model, and invite participants to contribute their expertise outside the workshop process.

Facilitated discussion supported by slide presentation:

1. Economics lead introduces the role of economic analysis in the project and how it can be used to contribute to the decision support purpose of the modeling process. A broad overview of the economic approach is provided, including an explanation of the types of economic analyses that may be used and how this can be guided by model purpose and available data.
2. Facilitators present a summary of the achievements over the course of the day, for example, applying systems approaches to understanding the mental health system and suicide prevention, including collaboratively mapping the contributing factors and service system. Link these achievements back to the overall project aims and objectives by explaining that this is the start of the process to develop a decision support tool.
3. Revisit the participatory process, explaining the activities in each of the 3 workshops and engagement that will happen between the workshops.
4. Propose approximate timing for workshops 2 and 3 and encourage participants to identify how they can play an active role in the development of the model by indicating to the project team any data sources that may be of use for model development and their willingness to be contacted out of session.

Concluding Session (Time Allowed 10 Minutes)

This session is an opportunity for a representative from the hosting stakeholder organization to thank the participants for contributing their time and expertise to model development.

Allow the opportunity for any participants to contribute concluding remarks either in a group format or individually to the project team.

Workshop 2: Defining, Refining, and Mapping Interventions

The main objectives of workshop 2 are to provide an update on progress since workshop 1, present the current version of the systems model to the participant group, jointly conceptualize and map the interventions to be explored in the model, refine the outcomes to be measured, and outline the health economic components of the project in detail. The workshop sessions and activities undertaken to achieve these objectives are discussed in detail later, and an example agenda is provided in Multimedia Appendix 1.

Welcome Back and Recap From Workshop 1: Purpose of the Session and Method

The purpose of this session is to reintroduce participants to each other, the project, and the methodology.

A facilitated discussion and slide-supported presentation covering:

1. Welcome back and housekeeping
2. Recap of workshop 1—a short presentation recapping the overall project aim, the activities, and outcomes from workshop 1; the consultation and interactions that have taken place since workshop 1; and the project timeline
3. Aims of this workshop—a brief overview of the purpose of and activities planned for this workshop

Session 1: Presentation of the System Dynamics Model (Time Allowed 60 Minutes; Purpose of the Session and Method)

There are 3 purposes for this session as follows:

1. To present the current draft version of the model structure and logic.
2. To ensure that the model is transparent and familiar to participants.
3. To elicit feedback from participants on the model structure, logic, and data used to parameterize or calibrate the model.

A slide-supported presentation by the lead modeler with facilitated discussion:

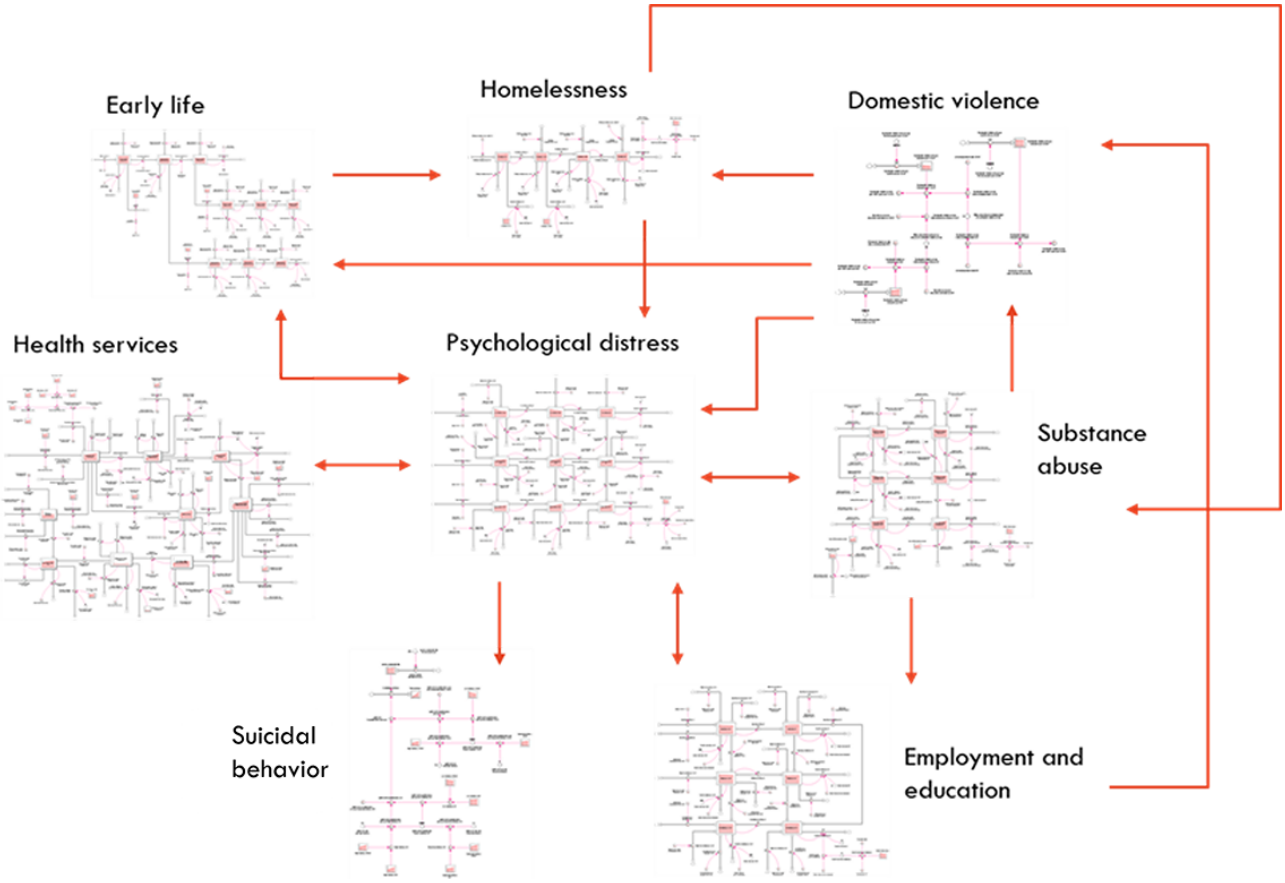
- Recap the building blocks of system dynamics, explaining stock and flow diagrams and model initialization values and parameters, and then demonstrate how they are combined to build a representation of a complex mental health system (see the example slide in Figure 5 from workshop 1).
- An overview diagram of the model is presented, showing the main components of the model and how they fit together (Figure 7). This can be emphasized using examples of within-component and between-component dynamics [48]:

> *...for example, within the health system component, the proportion of the population waiting for services, receiving services, or disengaging from services changes over time based on service system capacity and the rates of flow into, within, and out of the service system. Dynamics also occur between the model components, for example, as unemployment rises, not only does it directly act to increase the*

incidence of high to very high psychological distress in the modeled population (which has flow-on effects on rates of substance misuse, and adverse early life exposures), but it also increases rates of domestic violence and homelessness, both of which further increase the rate of psychological distress.

- The modeler explains the logic and structure of each model component. Example diagrams of model components, for example, the psychological distress component, are available elsewhere [48]. Uncertain parameter estimates and assumptions needing clarification for each component will be identified and discussed with the participant group in this session. Where available, it can be useful to include outcomes of the calibration process, demonstrating how well the model fits historical data trends which build confidence in the model's causal hypothesis. Participants are encouraged to probe, ask questions, and provide further information and feedback that will assist in refining the model.

Figure 7. Example model overview showing the main components of the model structure and how they relate.



Session 2: Intervention Mapping (Time Allowed 30 Minutes; Purpose of the Session and Method)

The purpose of this session is to provide feedback to participants about the interventions prioritized for inclusion in the model.

A slide-supported presentation by the project lead and local cofacilitator with facilitated discussion:

1. Present results from the previously conducted intervention prioritization process. Two options have been proposed in this study to elicit the intervention priorities. The first option involves an activity in workshop 1 where participants nominate and vote on interventions to assign priority. The second option involves distributing a survey through participants' networks to gauge community perceptions of which interventions are the highest priority to model. The results of the chosen process are represented in this session.
2. Include a slide with other intervention options that have been identified or discussed after workshop 1 but were not included in the original list, if appropriate.
3. Discuss with the participants whether they still agree with the prioritized list of interventions or modifications need to be made. This is a facilitated discussion to achieve a broad agreement on the suite of interventions to be modeled. However, where very strongly held views remain about the inclusion of an intervention or outcome that is not prioritized, the modeling team attempts to accommodate this if possible or note it for later development of the model.

Session 3: Intervention Mapping Exercise (Time Allowed 1.5-2 Hours; Purpose of the Session and Method)

The activity undertaken in this session provides the most important outcome for workshop 2, mapping intervention effects to the model structure. In this activity, participants interact with each other and the project team to jointly define the prioritized

interventions and identify where they are likely to have their effect in the model structure.

A facilitated activity conducted in small groups according to the procedures listed in Textbox 6.

The preprinted copies of the model structure are provided to each of the small groups to map the mechanism of the effect of the intervention directly to the model structure. Different color markers can be used for each intervention on a single printout, or multiple printouts can be used, one for each intervention. The important factor is ensuring that each intervention is clearly differentiated.

A member of the project team will work with each small group to assist them in working through the questions and the mapping activity and respond to any questions raised.

It can be useful to split the intervention mapping work over 2 sessions with a break in the middle to allow the project team to discuss whether there are gaps in the discussion, allow the participants to interact, or approach the project team for a one-on-one conversation to provide information that they would prefer not to share in a group discussion.

Textbox 6. Method for session 3 (intervention mapping exercise).

Method for session 3 (intervention mapping exercise)

- Each group will focus on a set of similarly themed interventions. For example, interventions for suicide and self-harm, such as community-based crisis response teams, using technology by crisis response workers to facilitate assessments, and postattempt care and follow-up could all be considered and mapped by one group of participants.
- Participants self-select the group of interventions that they would prefer to work on.
- Introduce the activity to the participants by explaining that it involves two aspects. First, the intervention is defined and described by working through the questions given later (provide a printed sheet with questions for each intervention), and second, mapping is carried out to determine where in the core model structure the intervention is likely to have an effect. The following questions will be used to guide the small group work:
  - Definition of intervention:
    - How would you define the intervention specifically?
    - What are its components?
    - Has the intervention been piloted or evaluated before?
  - Mechanism of the effect:
    - Where does the intervention in the core model structure have its effect? Is there a particular variable on which the intervention acts, and what is the nature of this effect?
    - What levels of reach and adoption (uptake) would be considered reasonable targets for this intervention? What levels of reach and adoption are we currently achieving (if appropriate)?
    - Are there differences in the effectiveness of this intervention for the key population subgroups represented in the model?
    - Does the delivery mechanism have an impact on the effectiveness of the intervention?
    - Are there any particular data sources and research in this area that you know of that is essential for us to refer to?
  - Consequences of the intervention:
    - Are there any unintended consequences or feedback loops (explain with relevant examples)?
    - How can the intervention be implemented (eg, phased or universal roll-out)? Are there any factors that would influence the implementation of the intervention (barriers and facilitators)?
    - What is a reasonable estimate for the amount of time it would take to scale up this intervention: 1 year, 2 years, or 5 years?
  - Anything else?
    - Are there any other important issues or factors to consider when representing this intervention in the model?

Session 4: Economic Component (Time Allowed 30 Minutes; Purpose of the Session and Method)

The purpose of this session is to provide an overview of the aims and intended approach and encourage participant feedback.

A slide-supported presentation of approximately 25 minutes, with an additional 5 minutes of questions at the end (Textbox 7).

Textbox 7. Method for session 4 (economic component).

Method for session 4 (economic component)

- Introduce the role of economics as equipping the model to enable it to undertake *dynamic priority setting and economic evaluation*. This will generate outputs to support business cases for investing in interventions, which may include the allocation of new budgets or disinvestment in programs that can be reinvested differently to improve population outcomes. Explain that the economic analysis will also support the moral case for interventions where outcomes are not monetized, and the focus is retained on the most efficient delivery models to avoid self-harm and suicide. Clarify that the process integrates economic information and valuation techniques into the model rather than conducting it as a separate exercise.
- Outline that there is a menu of different possible approaches and techniques to choose from and that this choice is conditional upon the model scope, purpose, and information needs of decision makers who would fund interventions (eg, health and non–health sectors may require different information).
- Summarize the key points from workshop 1 regarding the emerging scope and purpose of the model. This sets the context to explain the choice of economic approach and methods and how that is intended to be aligned with participant needs.
- Describe the three generic stages to the economic approach:
  - Stage 1 involves estimating the financial and human cost of business as usual, including, at a minimum, quality of life and health service activity costs. Conditional upon model purpose and data availability, this can be widened to include nonhealth impacts, such as productivity and impact on carers.
  - Stage 2 involves costing priority interventions, conditional upon sufficient detail, such as specific service delivery models. Explain that if interventions are not well defined, then they cannot be properly costed. In that event, the default approach can be using a what-if analysis that can estimate the potential impacts of introducing an aspirational intervention on flow-on costs and outcomes. This is intended to support the development and testing of specific service delivery models.
  - Stage 3 involves making the value proposition to invest by describing how interventions can reduce the burden of continuing with business as usual.
- Explain that the economics will then ensure that the model can tailor the business case for investment to meet potentially different funder expectations and normative positions, such as (1) a return on investment (eg, invest to save), (2) cost-effectiveness (cost per health outcome and health utility unit), and (3) cost benefit (all costs and outcomes included, where possible, and valued in dollar terms). The rationale for this approach is to help foster action and, where necessary, encourage multisector approaches.

Session 5: Concluding Session (Time Allowed 15 Minutes; Purpose of the Session)

The purpose of this session is to acknowledge the valuable contribution made by the participants at the workshop and note the likely timing for workshop 3. This session provides an opportunity for a representative from the primary partner organization to thank the participants for their ongoing contribution to model development. This session is also an opportunity for the participants to contribute concluding remarks either in a group format or individually to the project team.

Workshop 3: Introducing the User Interface and Delivering Model Insights

The main objectives of workshop 3 are to present the penultimate version of the systems model to the participants by walking them through a high-level summary of the model, highlighting any major changes since the previous workshop and the user interface and demonstrating how it can be used to simulate intervention scenarios and preliminary insights from the model. The activities undertaken to achieve these objectives are discussed in detail later, and an example agenda is provided in Multimedia Appendix 1.

Welcome Back and Progress Update: Purpose of the Session and Method

The purpose of this session is to reorientate participants to the project and methodology.

A facilitated discussion and slide-supported presentation covering:

1. Welcome back and housekeeping.
2. Recap of progress—a short presentation recapping the activities and outcomes from workshops 1 and 2, including presenting back the list of interventions that were prioritized at workshop 2 and the consultation and interactions that have taken place outside the workshop settings.
3. Aims of this workshop—a brief overview of the purpose of and activities planned for this workshop.

Session 1: Demonstration of the System Dynamics Model (Time Allowed 45-60 Minutes; Purpose of the Session and Method)

This session has 3 objectives as follows:

1. To represent the high-level model structure and logic.
2. To advise on any major changes based on feedback from workshop 2.
3. To demonstrate model use to participants.

A slide-supported presentation by the lead modeler with facilitated discussion:

1. An overview of the model will be presented, showing the main components of the model and how they fit together. An example of this is shown in Figure 7.
2. Updates or revisions to the model since the previous workshop will be described. The description will emphasize where participant feedback has been incorporated into the model.
3. Additional slides focusing on revised and newly added model components, for example, the structure for one or more example interventions, can be presented.

4. Demonstrate the use of the model interface, including running scenarios in the live model.
5. Run a set of intervention scenarios to draw out key model insights. The modeler is often required to explain the reason behind some insights, particularly if they are counterintuitive.
6. Discuss the policy and planning implications of the initial model insights.

Session 2: User Interaction With Model (Time Allowed 60 Minutes; Purpose of the Session and Method)

The purpose of this session is to provide an opportunity for participants to gain experience using the model to explore scenarios and provide feedback on the functionality of the user interface.

This is an interactive session in which the participants interact with the model interface. A member of the project team is stationed with each computer to provide guidance, interpretation of findings, or technical assistance, where required.

The project team should ensure that access to one computer per 5 to 7 participants is available so that a diverse group has the opportunity to interact directly with the model.

Feedback questions can be printed or presented on a slide to guide feedback on the model interface as the participants interact with it. The feedback questions can be tailored to ensure relevance to different modeling projects but, in general, would include the following:

- What should the available ranges be on the slides?
- Are there any labeling or language issues that we need to address?
- Any other comments on the interface or model?

Feedback can be given directly on printed screenshots of the model interface provided for each small group. This session will likely generate further questions about the model and discussion about the results of the simulated scenarios. The lead modeler will be available to move between groups, as necessary, to respond to technical questions and assist with interpretation. This small group discussion is an opportunity for the project team and local domain lead to engage with the participants to ascertain where further clarification is needed, for example, how to vary input values or how to interpret results of simulated scenarios.

As highlighted in the aforementioned feedback questions, it is very important to ensure that the language used in the model interface is accurate, understandable, relevant, and acceptable for end users. The highest priority is to ensure that the language used does not inadvertently alienate or offend participants. Ideally, the model interface will be *user-tested* with participants, for example, from the primary partner agency and other key user groups, such as reference groups for people with lived experience or Aboriginal and Torres Strait Islander communities, before being presented at the workshop.

Session 3: Health Economics (Time Allowed 30 Minutes; Purpose of the Session and Method)

The purpose of this session is to provide a recap on the approach taken and demonstration of key analyses and findings. If the model is not yet fully developed, then an update should be given with timelines for completion.

A slide-supported presentation of 25 minutes with 5 minutes for questions and clarifications:

1. Recap on the approach of the economics and how that is aligned with model purpose and participant needs following discussions at workshops 1 and 2. Then provide results (or updates) on the three stages of analysis.
2. Stage 1: establishing business as usual—estimating the financial and human cost.
   Provide a selection of activity-based service costs for exposition (such as hospitalizations). Describe the estimation process and how modeled populations acquire costs as they reside in service stocks to illustrate how the economics is layered into the model. Repeat for health utilities and explain how quality-adjusted life years are estimated. If relevant, continue the exposition for wider impacts, such productivity and carer impacts.
3. Stage 2: *costing interventions*. Provide the costing estimates for the priority set of interventions and explain how these were derived. Highlight if, and why, certain interventions could not be costed properly because of insufficiently defined service delivery models. Reiterate that a what-if analysis can be conducted.
4. Stage 3: *making the value proposition*—creating the business case and supporting the moral case. Provide an illustration by selecting 2 examples to demonstrate the value of investing in interventions to reduce distress. One example can select a single intervention (which could be a *what-if* analysis) and the other should be a combination of interventions to demonstrate the capability of the model to develop an optimal intervention portfolio relative to a budget. These examples may include one or a combination of valuation methods, namely, return on investment, cost-effectiveness (utility), and cost benefit.
5. Use screenshots from the economic component of the model dashboard for ease of exposition and demonstrate to participants how they can also use the controls in the dashboard to select interventions and generate economic outputs and how this can feed into a relevant business case for investment.

Session 4: Concluding Session: Next Steps, Closing Remarks, and Feedback

The workshop facilitators will describe the achievements from the project and the valuable contributions made by the participants. The facilitators will explain how the model will be made available to the participant group, how the model will be used to inform regional decision-making, how the model will be maintained, and how ongoing technical support will be provided. Ideally, additional modeling informed strategy dialogues are hosted by the primary partner agency to build a collaborative consensus for action through discussions with broader community stakeholders and interaction with the model.

The project team will provide support as needed to that process, including superuser training to build capacity in the independent use of the model.

This session is also an opportunity for a representative from the hosting stakeholder organization to thank the participants for their contribution to the model development. It will also give opportunity for any participants to contribute concluding remarks either in a group format or individually to the project team.

In our approach, we invite all participants to let the project team know if they are interested in coauthoring peer-review publications from this study. This is an important recognition of the substantial time and intellectual contribution that the participants have made to the development of their local model. Participants who do not engage in coauthoring papers are, with their consent, acknowledged as members of the modeling consortium.

Ethics

Systems modeling processes do not routinely require ethics approval as they involve secondary analysis of data and are considered a process of evidence synthesis. However, ethics approval was requested and granted by the Sydney Local Health District Human Research Ethics Committee (protocol number X21-0151 and 2021/ETH00553) for the participatory action evaluation research being conducted alongside the participatory systems modeling processes across the 8 sites.

Results

This study has been developed for implementing participatory systems modeling in the *Right Care, First Time, Where You Live* program, which is funded from 2021 to 2025. The methods described in this paper will be implemented at 2 sites per year from 2022 to 2025. The 8 selected sites include urban, regional, and rural or remote mental health service settings and are chosen to capture variations in socioeconomic conditions and demographics, population density, mental health risk profile, and access to mental health care and other services. Initial site visits were conducted between August and December 2021.

Discussion

As decision makers navigate complex policy environments, including mental health, there is a need to leverage interdisciplinary problem-solving and advanced decision support tools, such as systems modeling, to mobilize a wide range of evidence, data, and other forms of information to inform effective decision-making [14,32,33,68-70]. The involvement of stakeholders and coproduction of knowledge are critical to ensuring that model findings are policy-relevant and can be used to inform decision-making [11,16,25]. In the mental health context, decision makers must consider multisectoral determinants of mental health issues, regional variation and changing local population needs, competing views about *what works*, and restricted resources and workforce [6].

Systems modeling provides a quantitative method to combine the consideration of individual behavioral, social, cultural, economic, and service risk factors and captures the complex, nonlinear interrelationships, feedback loops, and threshold effects that characterize mental health systems [71]. Actively engaging stakeholders in the development of the systems model ensures transparency and increases their understanding of the model as a decision support tool, which, in turn, increases the likelihood of the model being embedded in policy and planning cycles to target investments more strategically in mental health programs and services [6,7,16]. This protocol describes a structured process that combines diverse perspectives and facilitates interdisciplinary dialogue in the development of systems models for mental health services, which can be adapted for other applications, topics, and settings. Importantly, the protocol includes considerations to ensure that people with lived experience of mental health issues and their supporters can meaningfully contribute to the process.

The participatory process detailed in this protocol emphasizes participant interaction and opportunities to draw out participant knowledge and expertise and actively involves participants in decision-making, giving them a voice and a stake in the outcome. The protocol builds on previous research that identified that the benefits of the participatory process include the enhancement of professional networks; increased transparency and, therefore, familiarity and trust in the model; integration of significant knowledge and evidence into the models; identification and facilitation of policy insights and opportunities to apply model findings in practice; and identification of key messages to deliver to a broader policy and practice audience in a way that is compelling and engaging [16,17,30].

Despite providing acknowledgment of the importance of including end-user stakeholders in model development, many participatory modeling projects do not explicitly describe or reflect on the participatory process component of the project [11,22,24]. This protocol responds to international interest in these methods and provides a blueprint for operationalizing participatory systems modeling based on years of applied systems modeling research for mental health and broader public health applications. Researchers are encouraged to use and challenge this blueprint to advance participatory systems modeling methods.

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The procedures described in this paper are based on methods developed over many participatory systems modeling projects for a range of health issues. The authors would like to acknowledge the invaluable contributions of Professor Nathaniel Osgood, Dr Geoff McDonnell, Adj Professor Mark Heffernan, Professor Lucie Rychetnik, Dr Ante Prodan, and Professor Paul Kelly to the foundations of these methods. This research is being conducted under the *Right Care, First Time, Where You Live* program by the Brain and Mind Centre, enabled by an Aus $12.8 million (US $9.2 million) partnership with BHP Foundation. The program

will develop infrastructure to support decisions related to advanced mental health and guide investments and actions to foster the mental health and well-being of young people in their communities.

Authors' Contributions

Manuscript concept and drafting were carried out by LF and JAO. All the authors were involved in the critical revision of the manuscript for important intellectual content.

Conflicts of Interest

LF is currently a part-time employee at the Brain and Mind Centre (BMC), University of Sydney, the director of Knowledge Translation and Health Outcomes, Epidemiology Section, Australian Capital Territory Health and the director of Policy Applications and Translational Science of Computer Simulation and Advanced Research Technologies. JAO is both the head of Systems Modeling, Simulation, and Data Science at the BMC, University of Sydney, and the managing director of Computer Simulation & Advanced Research Technologies. IBH is the codirector of Health and Policy at the BMC, University of Sydney. The BMC operates early intervention youth services at Camperdown under contract to headspace. He has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He is the chief scientific adviser to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and Price Waterhouse Coopers (Australia; 45% equity) to deliver the Aus $30 million (US $21.6 million) Australian government–funded Project Synergy (2017-2020; a 3-year program for the transformation of mental health services) and lead the transformation of mental health services internationally through the use of innovative technologies.

Multimedia Appendix 1
Principles of participatory systems modeling, materials lists, and agendas for workshops.
[PDF File (Adobe PDF File), 164 KB - resprot_v11i2e32988_app1.pdf]

References

1. Suicide worldwide in 2019: global health estimates. World Health Organization. URL: https://www.who.int/publications/i/item/9789240026643 [accessed 2021-12-29]
2. Health of young people. Australian Institute of Health and Welfare. 2020. URL: https://www.aihw.gov.au/reports/australias-health/health-of-young-people [accessed 2021-12-29]
3. Causes of death, Australia 2019. Australian Bureau of Statistics. 2019. URL: https://www.abs.gov.au/statistics/health/causes-death/causes-death-australia/2019 [accessed 2021-12-29]
4. National Health Survey: first results. Australian Bureau of Statistics. 2018. URL: https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-health-survey-first-results/latest-release [accessed 2021-12-29]
5. Mental Health Inquiry Report Volume 1. Australian Government Productivity Commission. 2020. URL: https://www.pc.gov.au/inquiries/completed/mental-health/report/mental-health-volume1.pdf [accessed 2021-12-29]
6. Atkinson J, Skinner A, Lawson K, Rosenberg S, Hickie IB. Bringing new tools, a regional focus, resource-sensitivity, local engagement and necessary discipline to mental health policy and planning. BMC Public Health 2020 Jun 05;20(1):814 [FREE Full text] [doi: 10.1186/s12889-020-08948-3] [Medline: 32498676]
7. What the promise of billions obscures about government commitment to suicide prevention. The Mandarin. URL: https://www.themandarin.com.au/158499-what-the-promise-of-billions-obscures-about-commitment-to-suicide-prevention/ [accessed 2021-12-29]
8. Occhipinti J, Skinner A, Carter S, Heath J, Lawson K, McGill K, et al. Federal and state cooperation necessary but not sufficient for effective regional mental health systems: insights from systems modelling and simulation. Sci Rep 2021 May 27;11(1):11209 [FREE Full text] [doi: 10.1038/s41598-021-90762-x] [Medline: 34045644]
9. Whatever happened to ‘evidence-based policymaking’? The Mandarin. 2018. URL: https://www.themandarin.com.au/102083-whatever-happened-to-evidence-based-policymaking/ [accessed 2021-12-29]
10. Brownson RC, Royer C, Ewing R, McBride TD. Researchers and policymakers: travelers in parallel universes. Am J Prev Med 2006 Mar;30(2):164-172. [doi: 10.1016/j.amepre.2005.10.004] [Medline: 16459216]
11. Gilbert N, Ahrweiler P, Barbrook-Johnson P, Narasimhan KP, Wilkinson H. Computational modelling of public policy: reflections on practice. J Artif Societies Soc Simul 2018 Jan 31;21(1):14. [doi: 10.18564/jasss.3669]
12. Leverage points: places to intervene in a system. The Donella Meadows Project. URL: https://donellameadows.org/archives/leverage-points-places-to-intervene-in-a-system/ [accessed 2021-12-29]
13. Lane DC, Sterman JD. A model simulator: the lives of Jay W Forrester. J Simul 2017 Dec 11;12(2):90-97. [doi: 10.1080/17477778.2017.1404205]
14. Sterman JD. Learning from evidence in a complex world. Am J Public Health 2006 Mar;96(3):505-514. [doi: 10.2105/AJPH.2005.066043] [Medline: 16449579]

15. Elsawah S, Filatova T, Jakeman AJ, Kettner AJ, Zellner ML, Athanasiadis IN, et al. Eight grand challenges in socio-environmental systems modeling. Soc Environ Syst Model 2020 Jan;2:16226. [doi: 10.18174/sesmo.2020a16226]
16. Freebairn L, Atkinson J, Kelly PM, McDonnell G, Rychetnik L. Decision makers' experience of participatory dynamic simulation modelling: methods for public health policy. BMC Med Inform Decis Mak 2018 Dec 12;18(1):131 [FREE Full text] [doi: 10.1186/s12911-018-0707-6] [Medline: 30541523]
17. Freebairn L, Atkinson J, Kelly P, McDonnell G, Rychetnik L. Simulation modelling as a tool for knowledge mobilisation in health policy settings: a case study protocol. Health Res Policy Syst 2016 Sep 21;14(1):71 [FREE Full text] [doi: 10.1186/s12961-016-0143-y] [Medline: 27654897]
18. Vennix JA. Group model-building: tackling messy problems. Syst Dyn Rev 1999;15(4):379-401. [doi: 10.1002/(sici)1099-1727(199924)15:4<379::aid-sdr179>3.0.co;2-e]
19. Community Based System Dynamics. New York: Springer; 2013.
20. Voinov A, Kolagani N, McCall MK, Glynn PD, Kragt ME, Ostermann FO, et al. Modelling with stakeholders – Next generation. Environ Model Softw 2016 Mar;77:196-220. [doi: 10.1016/j.envsoft.2015.11.016]
21. Voinov A, Bousquet F. Modelling with stakeholders. Environ Model Softw 2010 Nov;25(11):1268-1281. [doi: 10.1016/j.envsoft.2010.03.007]
22. Voinov A, Jenni K, Gray S, Kolagani N, Glynn PD, Bommel P, et al. Tools and methods in participatory modeling: selecting the right tool for the job. Environ Model Softw 2018 Nov;109:232-255. [doi: 10.1016/j.envsoft.2018.08.028]
23. Rouwette EA, Korzilius H, Vennix JA, Jacobs E. Modeling as persuasion: the impact of group model building on attitudes and behavior. Syst Dyn Rev 2010 Oct 20. [doi: 10.1002/sdr.441]
24. Seidl R. A functional-dynamic reflection on participatory processes in modeling projects. Ambio 2015 Dec 22;44(8):750-765 [FREE Full text] [doi: 10.1007/s13280-015-0670-8] [Medline: 25999270]
25. Osgood N. Systems Science and Population Health. Oxford, United Kingdom: Oxford University Press; 2017.
26. Elsawah S, Pierce SA, Hamilton SH, van Delden H, Haase D, Elmahdi A, et al. An overview of the system dynamics process for integrated modelling of socio-ecological systems: lessons on good modelling practice from five case studies. Environ Model Softw 2017 Jul;93:127-145. [doi: 10.1016/j.envsoft.2017.03.001]
27. Radinsky J, Milz D, Zellner M, Pudlock K, Witek C, Hoch C, et al. How planners and stakeholders learn with visualization tools: using learning sciences methods to examine planning processes. J Environ Planning Manag 2016 Oct 13;60(7):1296-1323. [doi: 10.1080/09640568.2016.1221795]
28. Voinov A, Gaddis E. Values in participatory modeling: theory and practice. In: Environmental Modeling With Stakeholders. Cham: Springer; 2017.
29. Marshall N, Adger N, Attwood S, Brown K, Crissman C, Cvitanovic C, et al. Empirically derived guidance for social scientists to influence environmental policy. PLoS One 2017;12(3):e0171950 [FREE Full text] [doi: 10.1371/journal.pone.0171950] [Medline: 28278238]
30. Freebairn L, Atkinson J, Osgood ND, Kelly PM, McDonnell G, Rychetnik L. Turning conceptual systems maps into dynamic simulation models: an Australian case study for diabetes in pregnancy. PLoS One 2019;14(6):e0218875 [FREE Full text] [doi: 10.1371/journal.pone.0218875] [Medline: 31247006]
31. Li Y, Lawley MA, Siscovick DS, Zhang D, Pagán JA. Agent-based modeling of chronic diseases: a narrative review and future research directions. Prev Chronic Dis 2016 May 26;13:E69 [FREE Full text] [doi: 10.5888/pcd13.150561] [Medline: 27236380]
32. Senge P. The Fifth Discipline: The Art and Practice of the Learning Organization. New York: Random House; 2010.
33. Sterman JD. All models are wrong: reflections on becoming a systems scientist. Syst Dyn Rev 2002;18(4):501-531. [doi: 10.1002/sdr.261]
34. Atkinson J, Page A, Wells R, Milat A, Wilson A. A modelling tool for policy analysis to support the design of efficient and effective policy responses for complex public health problems. Implement Sci 2015 Mar 03;10:26 [FREE Full text] [doi: 10.1186/s13012-015-0221-5] [Medline: 25889919]
35. Atkinson J, Page A, Heffernan M, McDonnell G, Prodan A, Campos B, et al. The impact of strengthening mental health services to prevent suicidal behaviour. Aust N Z J Psychiatry 2019 Jul;53(7):642-650. [doi: 10.1177/0004867418817381] [Medline: 30541332]
36. Atkinson J, Skinner A, Hackney S, Mason L, Heffernan M, Currier D, et al. Systems modelling and simulation to inform strategic decision making for suicide prevention in rural New South Wales (Australia). Aust N Z J Psychiatry 2020 Sep;54(9):892-901. [doi: 10.1177/0004867420932639] [Medline: 32551878]
37. Ramanath A, Gilbert N. The design of participatory agent-based social simulations. J Artif Societies Soc Simul 2004;7(4).
38. Smajgl A, Ward J. Evaluating participatory research: framework, methods and implementation results. J Environ Manage 2015 Jul 01;157:311-319. [doi: 10.1016/j.jenvman.2015.04.014] [Medline: 25929196]
39. Jones NA, Perez P, Measham TG, Kelly GJ, d'Aquino P, Daniell KA, et al. Evaluating participatory modeling: developing a framework for cross-case analysis. Environ Manag 2009 Dec;44(6):1180-1195. [doi: 10.1007/s00267-009-9391-8] [Medline: 19847478]
40. Siokou C, Morgan R, Shiell A. Group model building: a participatory approach to understanding and acting on systems. Public Health Res Pract 2014 Nov 28;25(1):e2511404 [FREE Full text] [doi: 10.17061/phrp2511404] [Medline: 25828443]

41. Luna-Reyes LF, Black LJ, Ran W, Andersen DL, Jarman H, Richardson GP, et al. Modeling and simulation as boundary objects to facilitate interdisciplinary research. Syst Res 2018 Nov 12;36(4):494-513. [doi: 10.1002/sres.2564]
42. Hovmand PS, Andersen DF, Rouwette E, Richardson GP, Rux K, Calhoun A. Group model-building 'scripts' as a collaborative planning tool. Syst Res 2012 Feb 14;29(2):179-193. [doi: 10.1002/sres.2105]
43. A step by step guide for developing agent-based SimPaSI models. Commonwealth Science Industry Research Organisation. 2010. URL: https://publications.csiro.au/rpr/download?pid=csiro:EP092258&dsid=DS1 [accessed 2021-12-29]
44. "Turning mirrors into windows": a study of participatory dynamic simulation modelling to inform health policy decisions. University of Notre Dame Australia. 2019. URL: https://researchonline.nd.edu.au/theses/239/ [accessed 2021-12-29]
45. Atkinson J, Knowles D, Wiggers J, Livingston M, Room R, Prodan A, alcohol modelling consortium. Harnessing advances in computer simulation to inform policy and planning to reduce alcohol-related harms. Int J Public Health 2018 May;63(4):537-546 [FREE Full text] [doi: 10.1007/s00038-017-1041-y] [Medline: 29051984]
46. Atkinson J, O'Donnell E, Wiggers J, McDonnell G, Mitchell J, Freebairn L, et al. Dynamic simulation modelling of policy responses to reduce alcohol-related harms: rationale and procedure for a participatory approach. Public Health Res Pract 2017 Mar 15;27(1):e2711707 [FREE Full text] [doi: 10.17061/phrp2711707] [Medline: 28243673]
47. Atkinson J, Wells R, Page A, Dominello A, Haines M, Wilson A. Applications of system dynamics modelling to support health policy. Public Health Res Pract 2015 Jul 09;25(3):e2531531 [FREE Full text] [doi: 10.17061/phrp2531531] [Medline: 26243490]
48. Occhipinti J, Skinner A, Iorfino F, Lawson K, Sturgess J, Burgess W, et al. Reducing youth suicide: systems modelling and simulation to guide targeted investments across the determinants. BMC Med 2021 Mar 12;19(1):61 [FREE Full text] [doi: 10.1186/s12916-021-01935-4] [Medline: 33706764]
49. Page A, Atkinson J, Campos W, Heffernan M, Ferdousi S, Power A, et al. A decision support tool to inform local suicide prevention activity in Greater Western Sydney (Australia). Aust N Z J Psychiatry 2018 Oct;52(10):983-993. [doi: 10.1177/0004867418767315] [Medline: 29671335]
50. Freebairn L, Rychetnik L, Atkinson J, Kelly P, McDonnell G, Roberts N, et al. Knowledge mobilisation for policy development: implementing systems approaches through participatory dynamic simulation modelling. Health Res Policy Syst 2017 Oct 02;15(1):83 [FREE Full text] [doi: 10.1186/s12961-017-0245-1] [Medline: 28969642]
51. Investing for impact: why uncertainty is not a barrier to sound decision making to support the COVID-19 mental health recovery. University of Sydney Brain and Mind Centre. 2021. URL: https://www.sydney.edu.au/content/dam/corporate/documents/brain-and-mind-centre/01jun2021-2021-05-24-investing-for-impact-despite-uncertainty_final.pdf [accessed 2021-12-29]
52. Right care, first time, where you live. The University of Sydney. URL: https://www.sydney.edu.au/brain-mind/our-research/youth-mental-health-and-technology/right-care-first-time-where-you-live-program.html#:~:text=This%20project%20%2D%20Right%20Care%2C%20first,long%2Dperiod%2C%20to%20ensure%20that [accessed 2021-12-29]
53. Occhipinti J, Skinner A, Freebairn L, Song YJ, Ho N, Lawson K, et al. Which social, economic, and health sector strategies will deliver the greatest impacts for youth mental health and suicide prevention? Protocol for an advanced, systems modelling approach. Front Psychiatry 2021 Oct 13;12:759343 [FREE Full text] [doi: 10.3389/fpsyt.2021.759343] [Medline: 34721120]
54. Page A, Atkinson J, Heffernan M, McDonnell G, Prodan A, Osgood N, et al. Static metrics of impact for a dynamic problem: the need for smarter tools to guide suicide prevention planning and investment. Aust N Z J Psychiatry 2018 Jul;52(7):660-667. [doi: 10.1177/0004867417752866] [Medline: 29359569]
55. Freebairn L, Atkinson J, Qin Y, Nolan CJ, Kent AL, Kelly PM, Diabetes in Pregnancy Modelling Consortium, et al. 'Turning the tide' on hyperglycemia in pregnancy: insights from multiscale dynamic simulation modeling. BMJ Open Diabetes Res Care 2020 May;8(1):e000975 [FREE Full text] [doi: 10.1136/bmjdrc-2019-000975] [Medline: 32475837]
56. Consumer and carer engagement: a practical guide. Australian Government National Mental Health Commission. URL: https://www.mentalhealthcommission.gov.au/mental-health-reform/consumer-and-carer-engagement/consumer-and-carer-engagement-a-practical-guide [accessed 2021-12-29]
57. Case A, Byrd R, Claggett E, DeVeaux S, Perkins R, Huang C, et al. Stakeholders' perspectives on community-based participatory research to enhance mental health services. Am J Community Psychol 2014 Dec;54(3-4):397-408. [doi: 10.1007/s10464-014-9677-8] [Medline: 25245601]
58. Happell B, Ewart SB, Platania-Phung C, Stanton R. Participative mental health consumer research for improving physical health care: an integrative review. Int J Ment Health Nurs 2016 Oct;25(5):399-408. [doi: 10.1111/inm.12226] [Medline: 27159221]
59. Happell B, Roper C. Consumer participation in mental health research: articulating a model to guide practice. Australas Psychiatry 2007 Jun;15(3):237-241. [doi: 10.1080/10398560701320113] [Medline: 17516188]
60. James AM. Principles of youth participation in mental health services. Med J Aust 2007 Oct 01;187(S7):S57-S60. [doi: 10.5694/j.1326-5377.2007.tb01339.x] [Medline: 17908029]
61. Lived experience framework for NSW. NSW Mental Health Commission. URL: https://www.nswmentalhealthcommission.com.au/sites/default/files/old/documents/final_lef_a4_layout_for_web.pdf [accessed 2021-12-29]

62. Schneider B. Participatory action research, mental health service user research, and the hearing (our) voices projects. Int J Qual Methods 2012 Apr 01;11(2):152-165. [doi: 10.1177/160940691201100203]
63. Recovery oriented language guide. Mental Health Coordinating Council. URL: http://mhcc.org.au/wp-content/uploads/2019/08/Recovery-Oriented-Language-Guide_2019ed_v1_20190809-Web.pdf [accessed 2021-12-29]
64. Andersen DF, Richardson GP. Scripts for group model building. Syst Dyn Rev 1997;13(2):107-129. [doi: 10.1002/(sici)1099-1727(199722)13:2<107::aid-sdr120>3.0.co;2-7]
65. Andersen DF, Vennix JA, Richardson GP, Rouwette EA. Group model building: problem structuring, policy simulation and decision support. J Operational Res Soc 2017 Dec 21;58(5):691-694. [doi: 10.1057/palgrave.jors.2602339]
66. Hamilton AB, Brunner J, Cain C, Chuang E, Luger TM, Canelo I, et al. Engaging multilevel stakeholders in an implementation trial of evidence-based quality improvement in VA women's health primary care. Transl Behav Med 2017 Sep 5;7(3):478-485 [FREE Full text] [doi: 10.1007/s13142-017-0501-5] [Medline: 28585163]
67. Lavery JV, Tinadana PO, Scott TW, Harrington LC, Ramsey JM, Ytuarte-Nuñez C, et al. Towards a framework for community engagement in global health research. Trends Parasitol 2010 Jun;26(6):279-283. [doi: 10.1016/j.pt.2010.02.009] [Medline: 20299285]
68. Hassmiller Lich K, Ginexi EM, Osgood ND, Mabry PL. A call to address complexity in prevention science research. Prev Sci 2013 Jun;14(3):279-289. [doi: 10.1007/s11121-012-0285-2] [Medline: 22983746]
69. Mabry PL, Marcus SE, Clark PI, Leischow SJ, Méndez D. Systems science: a revolution in public health policy research. Am J Public Health 2010 Jul;100(7):1161-1163. [doi: 10.2105/ajph.2010.198176]
70. Holmes BJ, Best A, Davies H, Hunter D, Kelly MP, Marshall M, et al. Mobilising knowledge in complex health systems: a call to action. Evid Policy 2017 Aug 14;13(3):539-560. [doi: 10.1332/174426416x14712553750311]
71. Atkinson J, Song YJ, Merikangas KR, Skinner A, Prodan A, Iorfino F, et al. The science of complex systems is needed to ameliorate the impacts of COVID-19 on mental health. Front Psychiatry 2020;11:606035 [FREE Full text] [doi: 10.3389/fpsyt.2020.606035] [Medline: 33324266]

Abbreviations

BMC: Brain and Mind Centre
GP: general practitioner

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Protocol

Examining a Continuous Glucose Monitoring Plus Online Peer Support Community Intervention to Support Hispanic Adults With Type 2 Diabetes: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Type 2 diabetes is twice as likely to affect Hispanic people than their White counterparts. Technology and social support may be an important part of behavior change. In this study, we address gaps in diabetes care for Hispanic Spanish-speaking people with diabetes through an online peer support community (OPSC) pilot intervention using Hispanic Spanish-speaking peer facilitators with diabetes to enhance the use of continuous glucose monitoring (CGM) for diabetes management.

Objective: This study aims to address gaps in diabetes care for Hispanic Spanish-speaking people with diabetes through an OPSC pilot intervention using Hispanic Spanish-speaking peer facilitators with diabetes to enhance the use of CGM for diabetes management.

Methods: A mixed-methods, pre-post test design will be used in this feasibility study. A total of 50 Hispanic participants with type 2 diabetes willing to wear a continuous glucose monitor for 13 weeks will be recruited. Hispanic Spanish-speaking peer facilitators with diabetes and experience wearing a continuous glucose monitor will be employed and undergo training. Peer facilitators will help participants learn how CGM data can inform behavior changes via an OPSC. Participants will interact with the private OPSC at least three times a week. Weekly questions and prompts derived from the Association of Diabetes Care and Education Specialists, previously American Association of Diabetes Educators, and seven self-care behaviors will be delivered by peer facilitators to engage participants. Measures of feasibility and acceptability will be determined by the percentage of participants who enroll, complete the study, and use CGM (number of scans) and objective metrics from the OPSC. Efficacy potential outcomes include change in time in range of 70 to 180 mg/dL from baseline to 12 weeks, A_{1c}, diabetes online community engagement, self-efficacy, and quality of life. Additionally, semistructured exit interviews will be conducted.

Results: Funding for this project was secured in November 2018 and approved by the institutional review board in April 2019. Peer facilitator recruitment and training were undertaken in the second half of 2019, with participant recruitment and data collection conducted in January and April 2020. The study has now concluded.

Conclusions: This study will generate new evidence about the use of an OPSC for Hispanic Spanish-speaking patients with diabetes to make behavior changes incorporating feedback from CGM.

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KEYWORDS

type 2 diabetes; hispanic; social support; online community; technology; peer support; diabetes; T2D; continuous glucose monitoring; behavior change; patient education

Introduction

Background

Hispanic Spanish-speaking individuals are at high risk for type 2 diabetes (T2D) and associated morbidity and mortality [1]. Hispanic populations may not receive or be able to access culturally appropriate diabetes care, which contributes to poor health outcomes [2]. Several studies have demonstrated that the use of culturally appropriate diabetes education programs improves components of T2D management, including healthy eating and increased physical activity in Hispanic Spanish-speaking individuals [3,4]. With diabetes education programs moving toward the online space, there is a dearth of research to support an online culturally appropriate initiative for Hispanic Spanish-speaking individuals to support their diabetes management [5].

Diabetes Technology

Advances in technology are rapidly changing the diabetes landscape. One such tool is continuous glucose monitoring (CGM). Abbott Freestyle Libre is the only CGM that is available in Spanish in the United States [6]. CGM includes an interstitial glucose sensor worn on the upper arm for 14 days and a reader or smartphone app that stores glucose values for interpretation [6]. Individuals scan the reader or smartphone over their sensor to receive their glucose level history, current glucose level, and projected glucose trend using a series of arrows [6]. At present, most insurance plans in the United States cover the cost of CGM when individuals are using insulin or have substantial hypoglycemic unawareness. However, research suggests that the use of CGM results improves clinical outcomes in people with T2D and can replace finger prick self–blood glucose monitoring [7]. Furthermore, an increased number of CGM scans are associated with improved clinical outcomes such as decreased A_{1c} levels and improvements in glucose time in range [8]. Access to sensor data has been found to facilitate behavior change, possibly by creating opportunities to see the real-time impact of food, activity, and other day-to-day activities on glucose levels [7].

Online Peer Support and Diabetes Technology

Ongoing support from peers with diabetes or health care providers is an important diabetes management strategy [9,10]. An umbrella review of face-to-face and technology-mediated peer support indicates peer support can improve A_{1c}, blood pressure, and weight [11]. In addition, there is emerging evidence that online peer support community (OPSC) use can positively influence A_{1c} as well [12-14]. Similarly, participation in a diabetes OPSC is associated with clinical, behavioral, and psychosocial benefits [15]. However, little is known about the uses, benefits, and limitations of online peer support, particularly within the Hispanic Spanish-speaking diabetes population, in the context of learning how to use diabetes technology such as CGM. Our previous work indicates that Hispanic individuals desire peer interactions to relate and understand the variables that impact T2D [16]. Although 80% of Hispanic Spanish-speaking adults use the internet via a smartphone [17], it is unknown how prevalent OPSC use is in this population.

Our Patient-Centered Outcomes Research Institute (PCORI)–funded preliminary work indicates that Hispanic people are willing to use diabetes technology such as CGM if it supports the Spanish language [16]. We propose to address gaps in diabetes care for Hispanic individuals by conducting a combined CGM + OPSC pilot intervention that will use Hispanic Spanish-speaking peer facilitators with diabetes to augment health behaviors. The preliminary research design was developed using a co-design and community-based participatory research process during a separate 3-year PCORI pipeline-to-proposal award and the creation of the Intercultural Diabetes Online Community Research Council to address patient-centered concerns and priorities [18]. Investigating culturally appropriate education and support to increase use of CGM in Hispanic Spanish-speaking individuals will lead to improved clinical and behavioral outcomes.

Study Objectives

This study aims to:

- Evaluate the acceptability and feasibility of a CGM + OPSC intervention for Hispanic Spanish-speaking individuals with T2D
- Explore the relationship between engagement in a CGM + OPSC intervention with clinical and behavioral outcomes

Methods

Sample Population

A mixed methods, pre-post test design will be used to evaluate the study aims. Participants will be recruited from primary care and endocrinology clinics in Utah with the aid of a research assistant. Inclusion and exclusion criteria are detailed in Textbox 1.

Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria

- Adults 21 years and older
- Clinical diagnosis of type 2 diabetes
- Self-report as Hispanic
- Ability to communicate fluently in Spanish
- A_{1c} ≥8% as per clinic records
- Willing to wear an intermittently scanned continuous glucose monitor for 14 weeks
- Access to the internet and willing to engage in an online peer support community
- Willing to avoid vitamin C 500 mg and aspirin 325 mg or greater daily due to interference with intermittently scanned continuous glucose monitoring accuracy

Exclusion criteria

- Currently using insulin for diabetes management
- Use of continuous glucose monitor or intermittently scanned continuous glucose monitor in previous 6 months
- Current participation in other diabetes clinical trials
- Alcohol or drug abuse or dependent
- Severe illness (physical or mental health)
- Cognitive impairment
- Current use of high dose steroids
- Hospitalization more than twice in the past 12 months or other impairment that would, in the opinion of the investigators, interfere with their ability to complete the study
- Pregnant or planning to become pregnant during the study
- Uncorrected hearing or vision impairment
- Life expectancy less than 6 months

Sample Size Calculation

Power and sensitivity analyses were conducted in GPower [19] using differences between means for time in range, A_{1c}, and online peer support engagement coded as a continuous variable. Assuming an alpha of .05, a sample size of 43 is sufficient to provide 90% power to detect a medium effect size (Cohen *d* 0.5). A total of 50 participants will be recruited to allow for a 14% dropout rate (86% completion rate), which is in line with a 20% attrition rate from a previous study involving Hispanic participants living with diabetes [20] and a 10% attrition rate from a study investigating young adults with diabetes trialing an online peer support intervention [21]. All participants will be invited to complete the qualitative interview with an aim of a 50% (n=25) participation rate, which is expected to be adequate to reach data saturation.

Recruitment

Recruitment will take place between January and April 2020. Experienced community health workers with previous success in recruiting Hispanic Spanish-speaking participants will be used. Opt-out letters will be sent to patients seen by bilingual physicians and physician assistants at an academic community clinic. Those who do not opt out will be contacted by the research assistant. Providers and federally qualified community health clinics serving the Hispanic Spanish-speaking population and diabetes specialty offices will be contacted to refer patients to participate in the study. Participants will be contacted by phone and screened for eligibility as outlined in Textbox 1. Those who meet study inclusion criteria will be invited to a convenient community location accessible to the participant, such as a private room in a library, or a video teleconferencing platform to meet with the research assistant. The research assistant will describe the study, go over the consent form with the participant, and answer questions participants may have. If the individual consents to participate, they will sign the consent form, complete the baseline surveys, and be provided a 7-day blinded version of CGM, Libre Pro [22], to establish a baseline glucose profile prior to the intervention (study visit 1). The research assistant will collect an A_{1c} (via home testing kit) and gather clinical information such as height, weight, and blood pressure. At study visit 2, the blinded CGM will be collected, and the participants will start both CGM and the OPSC. Participants are expected to be active within the OPSC for 12 weeks upon study enrollment. Participants will be enrolled on a rolling basis over a 3-month period. The online community will be active for a 6-month period. After 12 weeks, participants are welcome to continue using the OPSC.

Peer Facilitator Recruitment and Training

We will recruit and employ 5 Hispanic Spanish/English bilingual peer facilitators who live with diabetes with experience using

CGM. Individuals identified by Hispanic Spanish-speaking leaders from our PCORI community advisory board will be emailed information about the position and eligibility criteria (Multimedia Appendix 1). Interested individuals will complete a survey to confirm they meet the eligibility criteria. Successful applicants will be interviewed via teleconference with at least two members of the research team to confirm suitability for the role and to answer any questions they may have. Successful peer facilitators will sign a contract that outlines the expectations of their role prior to training completion.

Peer facilitators will be required to undertake three online training sessions: the Association of Diabetes Care and Education Specialists (ADCES), previously known as American Association of Diabetes Educators, level 1 paraprofessional training; a study-specific training; and training to use the OPSC platform. The goal of the training sessions is to provide peer facilitators with strategies to build relationships with participants as a support person who understands their challenges. The empowerment approach [23] and motivational interviewing [24] techniques will be used to build self-confidence and self-efficacy in peer facilitators to support goal setting, problem-solving, and behavior change in participants. Ultimately, the goal is to help participants increase their time spent within the target glucose range of 70 to 180 mg/dL. Individuals will be most successful when they set their own self-management goals and establish a plan that fits within their schedule and life [24]. Peer facilitators will use empowering person-first language following the American Diabetes Association and ADCES guidelines [8,25].

The ADCES Level 1 paraprofessional training consists of self-directed coursework including reading practice documents and participating in webinars totaling 14.5 hours [26]. Coursework content includes basic diabetes information for nonclinicians, teaching and learning in diabetes education, cultural competency, goal setting, motivational interviewing, use of person-centered language, delaying diabetes-related complication development and progression, and learning from people living with diabetes.

The study-specific training familiarizes peer facilitators to the research study; the preferred tools used to build and engage the OPSC; and strategies to maintain their own health, mental well-being, and online safety. A key focus of the trainings is to reduce stigma associated with T2D and to foster an understanding that, although there are genetic factors that cannot be changed, there are actions people can take to feel healthy, have a high quality of life, and reduce their risk of developing diabetes-related complications. Peer facilitators were trained to not provide medical advice and to refer participants back to their primary care provider if they have specific questions about medications or experienced out of range glucose levels.

The OPSC will also be reviewed by a Spanish/English bilingual diabetes care and education specialist on a regular basis. Feedback on coaching techniques or diabetes information will be provided during three virtual meetings with the peer facilitators.

Online Peer Support Community Intervention

The OPSC will be hosted on EsTuDiabetes (EsTuDiabetes.org), a program of Beyond Type 1 (BeyondType1.org), which includes a host of discussion forums. Participants and peer facilitators will have a profile with a username of their choosing. The private discussion forum will only be accessible by the research team and participants. Peer facilitators will be scheduled to monitor the OPSC hourly over two main shifts of 6 AM to 3 PM and 3 PM to 12 PM.

Participants will be encouraged to interact with the online group at least three times a week at a time that is most convenient to them. A priori weekly questions and prompts to facilitate discussion and topics covering the ADCES 7 self-care behaviors [27], frequency of CGM scanning, and how to analyze glucose patterns will be scheduled. The weekly schedule will follow the format presented in Textbox 2. These topics will repeat every 12 weeks given the rolling enrollment.

Peer facilitators will engage in weekly personal experiments along with participants and will share their personal goals, experiences, challenges, and successes during the study. Table 1 describes the cycle of weekly discussion topics and examples of personal experiments and its translation into Spanish. As content will be driven by participants' individual experiences and is not time oriented, this allows new members to join the online peer support group at any day of the week during the intervention period.

Textbox 2. Weekly prompt and activity schedule outline.

Monday

Development of a "personal experiment" focused on behavior change relevant to the weekly theme

Wednesday

Group poll question focused on personal experiment progress

Friday

Group "check-in" using a Likert scale to assess goal achievement for the week

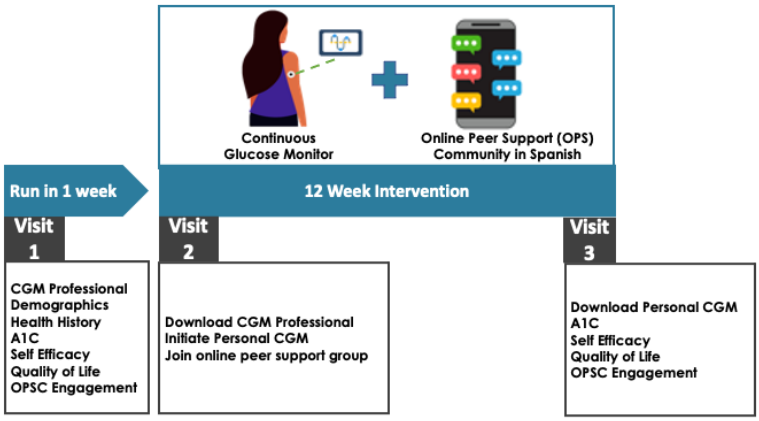
Table 1. Examples of possible weekly personal experiments to be discussed (posted in Spanish).

Week	Topic	Examples of personal experiment prompts
1	Healthy eating	I will scan my Libre before and 2 hours after breakfast every day for one week to see how my glucose changes. *Chequearé mi libre antes y 2 horas después del desayuno todos los días durante una semana para ver cómo cambia mi glucosa.*
2	Being active	I will scan my libre before and 2 hours after walking or exercise every day for one week to see how my glucose changes. *Escanearé mi libre antes y 2 horas después de caminar o hacer ejercicio todos los días durante una semana para ver cómo cambia mi glucosa.*
3	Healthy sleep	I will scan my libre before bed and after waking up in the morning for one week to see how my glucose changes with hours of sleep. *Escanearé mi libre antes de acostarme y después de despertarme por la mañana durante una semana para ver cómo cambia mi glucosa según las horas que duermo.*
4	Healthy coping	I will scan my libre before and 2 hours *after a stressful event* for one week to see how my blood glucose changes. *Escanearé mi libre antes y 2 horas después de un evento estresante durante una semana para ver cómo cambia mi glucosa.*
5	Healthy eating	I will post a question every day to the online group asking for suggestions for healthy snacks I can take to work for one week. *Publicaré una pregunta todos los días al grupo pidiendo sugerencias sobre tentempiés o botanas saludables que pueda llevar al trabajo durante una semana.*
6	Being active	I will post a question every day to the online group sharing the physical activity I am doing during the workday to increase steps. *Publicaré una pregunta todos los días al grupo compartiendo la actividad física que estoy haciendo durante un día de trabajo para aumentar los pasos.*
7	Healthy sleep	I will stop looking at screens one hour before bed every night to increase my hours of sleep. *Dejaré de mirar las pantallas una hora antes de acostarme todas las noches para aumentar mis horas de sueño.*
8	Healthy coping	I will use a meditation app once a day for 10 minutes to focus on stress reduction. *Usaré una aplicación de meditación una vez al día durante 10 minutos para enfocarme en disminuir el estrés.*
9	Healthy eating	I will try a new vegetable this week. *Probaré una nueva verdura esta semana.*
10	Being active	I will ride my bike to work 3 days a week. *Montaré en bicicleta al trabajo 3 días a la semana.*
11	Healthy sleep	I will stop drinking coffee by 2pm every day this week. *Dejaré de tomar café a las 2pm todos los días esta semana.*
12	Healthy coping	I will take a bath at night before going to bed and relax for 20 minutes each night. *Me bañaré por la noche antes de acostarme y me relajaré durante 20 minutos cada noche.*

Participant Timeline

Each participant will be enrolled in this study for 13 weeks, inclusive of a run-in period of 1 week, and will follow the timeline as per Figure 1.

Figure 1. Study timeline. CGM: continuous glucose monitoring; OPSC: online peer support community.



Data Management

Screening tracking, enrollment, and survey data will be collected and stored via REDCap [28], a secure Health Insurance Portability and Accountability Act–compliant data collection software hosted at the University of Utah. Surveys will include those assessing demographics, clinical history, and study measures. All individuals involved in screening and data entry will be trained to use the database.

Outcome Measures and Planned Data Analyses

The main components of planned descriptive and statistical analyses are separated into two study aims. Study aim 1 will focus on feasibility and acceptability using objective metrics and semistructured interviews. Analyses for study aim 2 will examine the efficacy potential of the following outcomes: time in range, A_{1c}, and validated surveys. An overall summary of the study outcomes and measures across data collection time points and study aims is listed in Table 2.

A description of the analytical methods are given in the following section. Existing objective metrics derived from the online peer support group platform to measure feasibility and acceptability are detailed in Table 3.

Table 2. Summary of study outcomes at each study time point.

Variable	Measure	Data collection		
		Study visit 1 (enrollment)	Study visit 2 at 1 week (T0)	Study visit 3 at 12 weeks (T1)
Demographics	Age, gender, education level, income level, insurance type, ethnicity, employment, married, comorbidities	✓		
Clinical: weight, height, blood pressure	Weight: lb Height: ft, in Blood pressure: systolic/diastolic	✓		
Health history	Diabetes diagnosis, year of diagnosis, previous diabetes education	✓		
Diabetes management	Self-reported	✓		
Study aim 1: feasibility and acceptability				
Acceptability	Objective online engagement metrics including number of reactions or comments per post, number of views per post, and Likert scale responses to polls			✓
Feasibility	Attrition rates within online peer support group			✓
Satisfaction and participant experiences	Semistructured interviews[a]			✓
Study aim 2: clinical and behavioral outcomes				
Clinical measurements	Time in range[b]	✓ (PRO CGM[c,d] placement)	✓ (PRO CGM download, personal CGM placement)	✓ (personal CGM download)
Glycemic levels	A_{1c}, standard CGM/isCGM data reporting [10]	✓		✓
Self-efficacy	Self-efficacy for diabetes [27]	✓		✓
Online peer support community engagement	Diabetes Online Community Engagement Survey [28]	✓		✓
Quality of life	WHO-5[e] [29]	✓		✓

[a]Semistructred interviews available in Multimedia Appendix 2.

[b]Average glucose level and number of minutes in 70 mg/dl to 180mg/dl in last 7 days of the study compared to average glucose level and number of minutes in 70mg/dl to 180mg/dl measured by initial blinded 7 days of baseline glucose data.

[c]PRO CGM: professional continuous glucose monitoring.

[d]Data is blinded to participants.

[e]WHO-5: World Health Organization Five.

Table 3. Online peer support group platform metrics.

Metric	Definition
Days visited *Días Visitados*	This metric reflects how many days the member has logged into the forum.
Read time *Tiempo de Lectura*	This metric reflects how much time the member has spent reading in the community since registering.
Recent read time *Tiempo de Lectura Reciente*	This metric reflects how much time the member has spent reading in the community within the last 60 days.
Topics viewed *Temas Vistos*	This metric reflects how many posts the member has clicked on but not necessarily read them.
Posts read *Publicaciones Leídas*	This metric reflects how many posts the member has actually read, based on the time they spent scrolling.
Likes given *Likes dados*	This metric reflects the number of times the member agrees, supports, and highlights posts.
Topics created *Temas Creados*	This metric reflects how many new topics the member has created within the forum.
Posts created *Publicaciones Creadas*	This metric reflects how many replies the member has given in different topics.
Likes received *Likes recibidos*	This metric expresses agreement, supports, and highlights posts with the prominent button on every post.
Lasts post *Última publicación*	This is the date of the last topic or post creation.
Last seen *Última vez visto*	This is the last time the member logged into the forum.
Views *Vistas*	This metric shows how many members have clicked on a topic.
Trust level *Nivel de Confianza*	Members will have different trust levels depending on the frequency of their participations, it goes from Trust Level 0 (new user) to Trust level 3 (regular).

Study Aim 1 Analysis

To address feasibility and acceptability, demographics and clinical information from all participants, including noneligible, eligible but refused, eligible and enrolled, and variables related to participant dropout, will be assessed. These data will be used to create a CONSORT (Consolidated Standards of Reporting Trials) diagram detailing the feasibility of recruiting participants into the study. Descriptive statistics examining individuals that enrolled versus those that did not will provide meaningful information for future studies. Recruitment, participation, and dropouts will be reported with frequency and percentages. We will also compute 95% CIs. These intervals serve as population estimates for future larger studies. Finally, objective and anonymous summary statistics of participation within the online peer support group as highlighted in Table 3 and participant interviews will be reported.

Study Aim 2 Analysis

The goal of study aim 2 is to examine the efficacy potential of the intervention on time in range, A_{1c}, and validated surveys. REDCap facilitates an easy data export to multiple statistical software packages [28]. Data cleanup and all analyses will be done in SPSS version 25 (IBM Corp). Time in range (70-180 mg/dL) from baseline to study completion will be measured as per ambulatory glucose profile downloads. Other outcomes include A_{1c}, OPSC engagement [13], self-efficacy for diabetes [29], and quality of life (World Health Organization 5 [WHO-5]) [30], which are validated scales for diverse populations available freely for research use. Linear mixed effects models will be used, as it allows for the inclusion of random intercepts (participants begin at different levels of the outcomes) and potential covariates, including age, gender, and ethnicity. Coefficient estimates and robust SEs will be reported while controlling for the covariates of interest. In keeping with an intent-to-treat standard, we will use maximum likelihood estimation, as it accommodates missing data, and thus all individuals will be included in the analysis regardless of dropout or missing data. Nevertheless, we will explore the data for potentially nonignorable missing data patterns and report on these findings. To minimize loss of scale scores due to missing items in a computed scale (eg, WHO-5 and self-efficacy scale), scores based on available items will be prorated. Data will be coded as missing if 30% of the items in a computed score have not been recorded.

Data Monitoring and Auditing

Although the research assistant will act as the primary contact with peer facilitators, regular check-in meetings (minimum of weekly via group text messaging and every 6 weeks via video teleconferencing) will be scheduled between the research assistant, peer facilitators, and research team via videoconference. These team meetings will serve as another platform to problem solve any issues that arise and to share learnings. Repeatable instrument communication logs will be available to keep notes on interactions between the research team and participants, including the recording of any adverse events. Where feasible and appropriate, the research assistant will document reasons for participant drop out. Data safety monitoring logs will be available to monitor data discrepancies and opportunities for double-checking data entry.

Fidelity to the intervention will be assessed independently through an initial weekly review using a predetermined checklist (Multimedia Appendix 3) of the online content by bilingual clinical advisors to ensure that concepts of empowerment and motivational interviewing are incorporated, followed by ongoing periodic spot reviews.

Ethics and Dissemination

Approval from the University of Utah Institutional Review Board (IRB) was obtained in April 2019 (IRB 00125233). Protocol modification will undergo additional IRB approval, be communicated to the research team, and be updated on the clinical trials registry, including:

- How personal information about potential and enrolled participants will be collected, shared, and maintained to protect confidentiality before, during, and after the trial
- Financial and other competing interests for principal investigators for the overall trial and each study site
- Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators
- Provisions, if any, for ancillary and posttrial care, and for compensation to those who experience harm from trial participation

If participants self-report that their glucose levels have been over 270mg/dL for 2 weeks, they will be encouraged to visit their primary care provider. Peer facilitators will reach out to the research team with any concerns about participants. To ensure the safety of peer facilitators, they will not have contact with participants beyond the online peer support group. Behavior expectations and guidelines will be posted and pinned to the top of the online peer support group page to guide appropriate interactions and consequences if these are breached. Throughout the study, peer facilitators are expected to continue with their own health and diabetes management, and notify the research team if health issues arise that may prevent them from fulfilling their role.

Results

Funding for this project was secured in November 2018. At the time of reporting, peer facilitator employment and training has been completed with participant recruitment commenced in January 2020 through to April 2020.

The main findings from the study will be presented in conferences and reported in peer-reviewed publications. The study has concluded.

Discussion

The aim of this study is to pilot and test the efficacy potential of the use of an OPSC with the use of peer facilitators to provide culturally appropriate education and support for Hispanic Spanish-speaking people with T2D in their diabetes self-management. The use of a culturally appropriate online peer support group and peer facilitators within the Hispanic Spanish-speaking population with T2D is expected to provide convenient access to informational, appraisal, and emotional support for diabetes self-management. It is anticipated that additional support provided by peer facilitators in the online peer support group will encourage positive health behavior change in this population who are at higher mortality risk from T2D compared to their White counterparts.

Foreseeable challenges within this pilot trial include recruitment and retention of eligible participants and peer facilitators. In anticipation, we have used community health workers and bilingual staff to support recruitment and retention efforts. The PCORI Advisory Board will help identify and recruit peer facilitators.

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Checklist [31] was used to ensure quality reporting and consideration of all standard protocol items recommended for international trials.

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Conflicts of Interest

DAG is now an employee of Dexcom. No other conflicts of interest to declare.

Multimedia Appendix 1
Peer facilitator position description and eligibility criteria.
[DOCX File , 17 KB - resprot_v11i2e31595_app1.docx]

Multimedia Appendix 2
Interview schedule.
[DOCX File , 16 KB - resprot_v11i2e31595_app2.docx]

Multimedia Appendix 3
Peer facilitator fidelity review.
[DOCX File , 14 KB - resprot_v11i2e31595_app3.docx]

References

1. Kirk JK, Passmore LV, Bell RA, Narayan KMV, D'Agostino RB, Arcury TA, et al. Disparities in A1C levels between Hispanic and non-Hispanic white adults with diabetes: a meta-analysis. Diabetes Care 2008 Feb;31(2):240-246. [doi: 10.2337/dc07-0382] [Medline: 17977939]
2. Attridge M, Creamer J, Ramsden M, Cannings-John R, Hawthorne K. Culturally appropriate health education for people in ethnic minority groups with type 2 diabetes mellitus. Cochrane Database Syst Rev 2014 Sep 04(9):CD006424. [doi: 10.1002/14651858.CD006424.pub3] [Medline: 25188210]
3. Salto LM, Cordero-MacIntyre Z, Beeson L, Schulz E, Firek A, De Leon M. En Balance participants decrease dietary fat and cholesterol intake as part of a culturally sensitive Hispanic diabetes education program. Diabetes Educ 2011;37(2):239-253 [FREE Full text] [doi: 10.1177/0145721710394874] [Medline: 21343598]
4. Brunk DR, Taylor AG, Clark ML, Williams IC, Cox DJ. A culturally appropriate self-management program for Hispanic adults with type 2 diabetes and low health literacy skills. J Transcult Nurs 2017 Mar;28(2):187-194. [doi: 10.1177/1043659615613418] [Medline: 26525585]
5. Pereira K, Phillips B, Johnson C, Vorderstrasse A. Internet delivered diabetes self-management education: a review. Diabetes Technol Ther 2015 Jan;17(1):55-63. [doi: 10.1089/dia.2014.0155] [Medline: 25238257]
6. FreeStyle Libre 14 day System. FreeStyle Abbott. 2018. URL: https://www.freestyle.abbott/ca-en/home.html [accessed 2022-02-09]
7. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Ther 2017 Feb;8(1):55-73 [FREE Full text] [doi: 10.1007/s13300-016-0223-6] [Medline: 28000140]
8. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: a European analysis of over 60 million glucose tests. Diabetes Res Clin Pract 2018 Mar;137:37-46 [FREE Full text] [doi: 10.1016/j.diabres.2017.12.015] [Medline: 29278709]
9. American Diabetes Association. 5. Lifestyle Management: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019 Jan;42(Suppl 1):S46-S60. [doi: 10.2337/dc19-S005] [Medline: 30559231]
10. Beck J, Greenwood DA, Blanton L, Bollinger ST, Butcher MK, Condon JE, 2017 Standards Revision Task Force. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care 2017 Oct;40(10):1409-1419. [doi: 10.2337/dci17-0025] [Medline: 28754780]
11. Litchman ML, Oser TK, Hodgson L, Heyman M, Walker HR, Deroze P, et al. In-person and technology-mediated peer support in diabetes care: a systematic review of reviews and gap analysis. Diabetes Educ 2020 Jun;46(3):230-241. [doi: 10.1177/0145721720913275] [Medline: 32321370]
12. Oser SM, Stuckey HL, Parascando JA, McGinley EL, Berg A, Oser TK. Glycated hemoglobin differences among blog-reading adults with type 1 diabetes compared with those who do not read blogs: cross-sectional study. JMIR Diabetes 2019 Apr 02;4(2):e13634 [FREE Full text] [doi: 10.2196/13634] [Medline: 30938693]
13. Litchman ML, Edelman LS, Donaldson GW. Effect of diabetes online community engagement on health indicators: cross-sectional study. JMIR Diabetes 2018 Apr 24;3(2):e8 [FREE Full text] [doi: 10.2196/diabetes.8603] [Medline: 30291079]
14. Petrovski G, Zivkovic M. Are we ready to treat our diabetes patients using social media? Yes, we are. J Diabetes Sci Technol 2019 Mar;13(2):171-175 [FREE Full text] [doi: 10.1177/1932296818795441] [Medline: 30132685]
15. Litchman ML, Walker HR, Ng AH, Wawrzynski SE, Oser SM, Greenwood DA, et al. State of the science: a scoping review and gap analysis of diabetes online communities. J Diabetes Sci Technol 2019 May;13(3):466-492 [FREE Full text] [doi: 10.1177/1932296819831042] [Medline: 30854884]
16. Yingling L, Allen NA, Litchman ML, Colicchio V, Gibson BS. An evaluation of digital health tools for diabetes self-management in Hispanic adults: exploratory study. JMIR Diabetes 2019 Jul 16;4(3):e12936 [FREE Full text] [doi: 10.2196/12936] [Medline: 31313657]

17. Brown A, López G, Lopez MH. Digital divide narrows for Latinos as more Spanish speakers and immigrants go online. Pew Research Center. 2016. URL: https://www.pewhispanic.org/wp-content/uploads/sites/5/2016/07/PH_2016.07.21_Broadbank_Final.pdf [accessed 2022-02-09]
18. Greenwood DA, Litchman ML, Ng AH, Gee PM, Young HM, Ferrer M, et al. Development of the Intercultural Diabetes Online Community Research Council: codesign and social media processes. J Diabetes Sci Technol 2019 Mar;13(2):176-186 [FREE Full text] [doi: 10.1177/1932296818818455] [Medline: 30614252]
19. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007 May;39(2):175-191. [doi: 10.3758/bf03193146] [Medline: 17695343]
20. Ell K, Katon W, Xie B, Lee P, Kapetanovic S, Guterman J, et al. Collaborative care management of major depression among low-income, predominantly Hispanic subjects with diabetes: a randomized controlled trial. Diabetes Care 2010 Apr;33(4):706-713 [FREE Full text] [doi: 10.2337/dc09-1711] [Medline: 20097780]
21. Ng AH, Crowe TC, Ball K, Rasmussen B. A mHealth support program for Australian young adults with type 1 diabetes: a mixed methods study. Digit Health 2019;5:2055207619882179 [FREE Full text] [doi: 10.1177/2055207619882179] [Medline: 31662880]
22. FreeStyle Libre Pro. MyFreeStyle. 2019. URL: https://www.myfreestyle.com/freestyle-libre-pro-cgm-system [accessed 2022-02-09]
23. Baldoni NR, Aquino JA, Sanches-Giraud C, Di Lorenzo Oliveira C, de Figueiredo RC, Cardoso CS, et al. Collective empowerment strategies for patients with Diabetes Mellitus: a systematic review and meta-analysis. Prim Care Diabetes 2017 Apr;11(2):201-211. [doi: 10.1016/j.pcd.2016.09.006] [Medline: 27780683]
24. Welch G, Rose G, Ernst F. Motivational interviewing and diabetes: what is it, how is it used, and does it work? Diabetes Spectrum 2006 Jan 01;19(1):5-11. [doi: 10.2337/diaspect.19.1.5]
25. Dickinson JK, Guzman SJ, Maryniuk MD, O'Brian CA, Kadohiro JK, Jackson RA, et al. The use of language in diabetes care and education. Diabetes Educ 2017 Dec;43(6):551-564. [doi: 10.1177/0145721717735535] [Medline: 29040034]
26. Diabetes Paraprofessional Level 1. Association of Diabetes Care and Education Specialists. 2019. URL: https://www.diabeteseducator.org/education/career-path-certificate/associate-level-1 [accessed 2022-02-09]
27. Using the ADCES7 self-care behaviors to manage your condition. Association of Diabetes Care and Education Specialists. 2020. URL: https://www.diabeteseducator.org/living-with-diabetes/aade7-self-care-behaviors [accessed 2022-02-09]
28. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
29. Lorig K, Stewart A, Ritter P, González V, Laurent D, Lynch J. Outcome Measures for Health Education and Other Health Care Interventions. Thousand Oaks, CA: SAGE Publications, Inc; 1996.
30. Topp CW, Østergaard SD, Søndergaard S, Bech P. The WHO-5 Well-Being Index: a systematic review of the literature. Psychother Psychosom 2015;84(3):167-176 [FREE Full text] [doi: 10.1159/000376585] [Medline: 25831962]
31. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]

Abbreviations

ADCES: Association of Diabetes Care and Education Specialists
CGM: continuous glucose monitoring
COSORT: Consolidated Standards of Reporting Trials
IRB: Institutional Review Board
OPSC: online peer support community
PCORI: Patient-Centered Outcomes Research Institute
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T2D: type 2 diabetes
WHO-5: World Health Organization 5

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Protocol

Elements That Underpin the Design, Development, and Evaluation of Social Media Health Interventions: Protocol for a Scoping Review

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Abstract

Background: Social media use has grown tremendously over the years. Given the volume and diversity of people on social media and the amount of information being exchanged, it is perhaps unsurprising that social media is being used as an avenue to disseminate and deliver health interventions. There exists an opportunity for social media health interventions to make a positive impact on health. However, there is a need to understand more about the ways in which these interventions are designed, developed, and evaluated. This scoping protocol will review the current state of this field by charting the elements that drive the design, development, and evaluation of these interventions. This includes charting models, frameworks, and rationales for the interventions, as well as the platforms being used, and the health behaviors being targeted. This intention of this scoping review is to help inform those who wish to develop effective social media health interventions.

Objective: The objective of this review is to map the elements that drive the design, development, and evaluation of social media health interventions. We define "social media health intervention" as interventions that make use of social media platforms to disseminate or deliver health-related information and educational initiatives to the public. We will seek to chart the elements that drive the design, development, and delivery of such interventions, including their platforms and targeted health behaviors.

Methods: The methodological framework for this review is guided by Arksey and O'Malley and enhancements by later studies. We will search relevant literature from 9 databases: (1) PubMed, (2) PsycINFO, (3) EMBASE, (4) Web of Science, (5) Scopus, (6) CINAHL, (7) ERIC, (8) MEDLINE, and (9) Google Scholar. The literature will be screened by at least two reviewers in 2 stages: (1) title/abstract screening against the eligibility criteria; and (2) eligible articles will then undergo a full-text screening. Data will be charted using the data charting tool developed by the authors.

Results: The results of this study will be presented in a final scoping review paper, divided into 2 sections. The first section will describe the search strategy and study selection process and will contain the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. The second section will provide key details pertaining to the review objective and question.

Conclusions: This review will help guide scholars looking to build social media health interventions toward evidence-based practices in design and evaluation.

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KEYWORDS

social media; health intervention; behavior change models; health improvement; intervention design; models of design; evaluating interventions

Introduction

Background

Social media is inextricably linked to our lives. The use of social media has grown enormously over the years. As of January 2021, an estimated 4.6 billion people have access to the internet of which 4.2 billion people are social media users. Even taking into consideration multiple accounts and business accounts, a significant number of the population use and interact on social media [1]. Social media is defined as "forms of electronic communication (such as websites for social networking and microblogging) through which users create online communities to share information, ideas, personal messages, and other content" [2]. This definition may not necessarily capture the diversity of social media today. Still, the tenets of social media such as communication, user generation of content, and information sharing are seen across a host of social media platforms ranging from Facebook and Instagram to Twitter.

Social media users are diverse across ages, ethnicities, education levels, and come from a host of different backgrounds [1]. Having access to this diverse group of people creates a unique opportunity to use social media platforms as a means of promoting and disseminating health interventions. A health intervention is an act performed for, with, or on behalf of a person or population whose purpose is to assess, improve, maintain, promote, or modify health, functioning, or health conditions [3]. Social media platforms have been recognized and used for health interventions and hold tremendous potential to help elicit positive health behavior changes [4,5]. For example, health interventions to promote nutritional education have used social media platforms to identify behaviors and offer intervention [6]. Other social media health interventions include sexual health promotion [7], interventions for diabetes [8], and interventions targeting addiction and recovery [9].

The use of social media as a conduit for health communication is well established [10]. Social media provides health care professionals a platform to freely share information and combat health misinformation [11,12]. Social media health interventions also provide an opportunity to improve public health outcomes, such as in the recent COVID-19 pandemic where they have been used to disseminate information and increase vaccine uptake [10,13-16]. The rising use of social media and other digitized technology for health intervention has even led to the emergence of a new field called "Digital Public Health," which is defined as "the use of technology, new types of data, and new ways of working that come with the digitization of public health and associated data''[17].

To best leverage the opportunities and affordances of utilizing and disseminating health interventions over social media, there exists a responsibility to ensure that the design, development, and evaluation of such interventions are done in a systematic and evidence-based manner. There is a need to scope the current landscape of social media health interventions to better understand the elements which underpin these interventions. The last paper that took a broad look into the use of social media for health promotion and intervention was back in 2011, which primarily focused on the features of social media platforms [13]. Since then, the landscape of social media has changed, and the design of interventions has had to change with it. For those looking to build successful interventions, a need exists to scope the current landscape to understand what elements drive the design, development, and evaluation of social media health interventions.

Objectives

The objective of this review is to map the elements that drive the design, development, and evaluation of social media health interventions. We define "social media health intervention" as interventions that make use of social media platforms to disseminate awareness or deliver health-related information and educational initiatives to the public. As such, only studies that describe a health intervention in which social media is the conduit for dissemination or delivery will be considered for review. Health interventions that do not use social media will be excluded. For those included papers we will seek to chart the elements that drive the design, development, and delivery of such interventions, including their platforms and targeted health behaviors.

Methods

Overview

This scoping review will be guided by the methodology proposed by Arksey and O'Malley [14] with updated enhancements proposed by Levac et al [18] and Peters et al [15]. This framework was chosen for its clarity in the stages of conducting a scoping review, including (1) identification of the research question; (2) identification of studies; (3) selection of studies; (4) charting the data; and (5) collating, summarizing, and reporting the results. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist will also provide further details and clarity [16].

Stage 1: Identifying the Research Question

The primary question for our review is to understand the elements that drive the design, development, and evaluation of social media health interventions. The research questions below are aligned with our objectives of scoping the current landscape in order to inform those who wish to design evidence-based and effective social media health interventions. The following questions will guide our review:

- What are the underlying elements that inform the design, development, and evaluation of social media health interventions? What evidence-based models, frameworks, or theories underpin the design, development, and evaluation, if any?

- For what purposes are social media health interventions implemented? What behaviors are targeted, if any?
- What social media platforms are most pervasive in social media health interventions?
- What are the demographic characteristics of the populations targeted with social media health interventions?

The authors arrived at these questions after extensive discussions and brainstorming with the research team.

Stage 2: Identifying Relevant Literature

A comprehensive review of literature will be conducted using the following databases : (1) PubMed, (2) PsycINFO, (3) EMBASE, (4) Web of Science, (5) Scopus, (6) CINAHL, (7) ERIC, (8) MEDLINE, and (9) Google Scholar. To capture relevant gray literature, we will conduct a search on Google Scholar. We will use an effort-bounded stopping criteria in which we examine the first 100 search results, then reassess, continuing to the next page of results, iteratively assessing if the results remain relevant to our scope [19].

Keyword search terms for this review were developed through discussion between the protocol authors. Input from a subject librarian was also sought to ensure keywords captured relevant data and the databases were appropriate. The keywords are based on the 2 overarching concepts of the review concept: social media and health intervention (Tables 1 and 2). A sample search strategy is provided in Table 3. Any amendments to the search strings will be thoroughly documented in the final scoping review.

Table 1. List of keywords used for the concept of "social media."

Serial number	Keywords: Concept #1 "social media"
1	Social Media*
2	Social Network*
3	Social Platform
4	Twitter
5	Facebook
6	Instagram
7	Snapchat
8	TikTok
9	YouTube
10	WhatsApp
11	WeChat

Table 2. List of keywords used for the concept of "health intervention."

Serial number	Keywords: Concept #2 "health intervention"
1	Health Promotion
2	Health Improvement
3	Health Maintenance
4	Therapeutic Intervention
5	Health Modification
6	Health Intervention

Table 3. Sample search strategy.

Search strategy	Database	Results
("social media*"[Title/Abstract] OR "social network*"[Title/Abstract] OR "social platform"[Title/Abstract] OR "Twitter"[Title/Abstract] OR "Facebook"[Title/Abstract] OR "Instagram"[Title/Abstract] OR "Snapchat"[Title/Abstract] OR "TikTok"[Title/Abstract] OR "YouTube"[Title/Abstract] OR "WhatsApp"[Title/Abstract] OR "WeChat"[Title/Abstract]) AND ("health intervention"[Title/Abstract] OR "health intervention"[Title/Abstract] OR "Health Promotion"[Title/Abstract] OR "Health Improvement"[Title/Abstract] OR "Health Maintenance"[Title/Abstract] OR "Therapeutic Intervention"[Title/Abstract] OR "Health Modification"[Title/Abstract])	PubMed	1073

Inclusion and Exclusion Criteria

As we wish to broadly map the existing literature, we will include a variety of studies, including published and gray literature. Studies to be reviewed will consist of those that use social media to disseminate or deliver a health intervention. Studies that describe a health intervention but do not use social media as a core component of dissemination or delivery will

be excluded. A temporal limit will also be set, ensuring that only papers from 2005 to date will be reviewed. The date restriction has been set in consideration of the public release and advent of modern social media platforms [20]. Only studies in English will be reviewed. Textbox 1 summarizes our inclusion and exclusion criteria. These will be modified iteratively if needed.

Textbox 1. Summary of inclusion and exclusion criteria.

Inclusion criteria

- Literature outlining health interventions that are delivered or utilized a publicly available social media platform.
- Studies that describe the design and implementation of the intervention or the evaluation of the intervention.
- Studies published within or after 2005.

Exclusion criteria

- Studies that describe health interventions but do not have any context of social media.
- Studies solely mentioning other uses of social media for health.
- Studies in languages other than English.

Stage 3: Study Selection

The study selection for this review will follow a 2-step screening process. First, after databases and gray literature searches are concluded, results will be imported into a citation manager. Deduplication will be conducted at this stage, and all remaining studies will be imported to a review software called Rayyan [21]. Second, 2 reviewers will independently screen title–abstracts against the exclusion and inclusion criteria to determine which studies will be included in full-text screening. Interrater disagreement will be solved through discussion with a third independent mediator.

Stage 4: Data Charting

Relevant data will be charted out from all included studies by 2 or more independent reviewers. The reviewers will develop and pilot a data extraction instrument that will be refined iteratively as we carry out the extraction process. Extracted data will include article details such as author/s, year of publication, evaluation method, design model, behavioral model, social media platform, audience type, and outcomes. A draft data extraction tool can be found in Table 4.

Table 4. Draft charting table.

Type of data	Details of charted data
Article information	• Title • Author/s • Date of publication
What health behavior/condition was the target of the health intervention?	• Health behavior/condition targeted
Social media platform used	• Name of platform
How were participants recruited?	• Recruitment method
What are the demographics of the population that the intervention was targeted at?	• Age of users • Country of user • Language
What rationale was employed for the design of the intervention?	• Models • Frameworks • Rationale • Evidence based (yes/no)
Was the intervention evaluated? If so, describe the elements used to evaluate.	• Models • Frameworks • Tools

Stage 5: Collating, Summarizing, and Reporting the Results

We will present our charted data both graphically and narratively. Thoughtful consideration to using text and images to illustrate our results will be undertaken. In our summary will we consider the broader implications of our findings as we hope our review will provide practical context and guidance for those desiring to create social media health interventions.

Ethics and Dissemination

Ethics approval was not required for this study. Future dissemination of the final review will include publication of the final scoping review in a peer-reviewed journal with a good impact factor.

Results

The results from the extracted data will be presented in 2 broad sections, the first outlining the selection process and PRISMA flowchart. The second section will include results pertaining to our review question. The results will be presented in the final scoping paper.

Discussion

Our scoping review will provide insights into the current landscape of health interventions that utilize social media. This study is not without limitations. Papers in languages other than English will not be included due to the limitations of the reviewers. Papers describing health interventions that do not use social media will be excluded, potentially eliminating the inclusion of valuable models of design, behavior change, and evaluation, which could be utilized for the development of health interventions. However, this limitation we feel is essential to understand the current state of social media health interventions.

This topic is highly relevant given the opportunities presented by social media to reach diverse audience for the purposes of promoting public and community health. This review aims to produce a piece of work that will help guide others looking to build social media health interventions toward evidence-based practices in design and evaluation, which enables the reader to also see what behaviors are being targeted and through what platforms. This review also has the potential to impact future directions of social media health interventions by illuminating the current trends of behaviors targeted by social media health interventions, revealing either an overabundance of focus in some health concerns or a gap in others. This may lay the groundwork for future research to take a closer look at the particulars of research in behavior-specific interventions.

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Conflicts of Interest

None declared.

References

1. Kemp S. Digital 2021: Global Overview Report. Datareportal. 2021 Jan 21. URL: https://datareportal.com/reports/digital-2021-global-overview-report [accessed 2022-01-13]
2. Definition of Social Media. URL: https://www.merriam-webster.com/dictionary/social+media [accessed 2022-01-13]
3. International Classification of Health Interventions. Geneva, Switzerland: World Health Organization URL: https://www.who.int/standards/classifications/international-classification-of-health-interventions [accessed 2022-01-13]
4. Chen J, Wang Y. Social Media Use for Health Purposes: Systematic Review. J Med Internet Res 2021 May 12;23(5):e17917 [FREE Full text] [doi: 10.2196/17917] [Medline: 33978589]
5. Ronen K, Grant E, Copley C, Batista T, Guthrie BL. Peer Group Focused eHealth Strategies to Promote HIV Prevention, Testing, and Care Engagement. Curr HIV/AIDS Rep 2020 Oct 14;17(5):557-576 [FREE Full text] [doi: 10.1007/s11904-020-00527-w] [Medline: 32794071]
6. Yonker LM, Zan S, Scirica CV, Jethwani K, Kinane TB. "Friending" teens: systematic review of social media in adolescent and young adult health care. J Med Internet Res 2015 Jan 05;17(1):e4 [FREE Full text] [doi: 10.2196/jmir.3692] [Medline: 25560751]
7. Gold J, Pedrana AE, Sacks-Davis R, Hellard ME, Chang S, Howard S, et al. A systematic examination of the use of online social networking sites for sexual health promotion. BMC Public Health 2011;11:583 [FREE Full text] [doi: 10.1186/1471-2458-11-583] [Medline: 21777470]
8. Gabarron E, Bradway M, Fernandez-Luque L, Chomutare T, Hansen AH, Wynn R, et al. Social media for health promotion in diabetes: study protocol for a participatory public health intervention design. BMC Health Serv Res 2018 Jun 05;18(1):414 [FREE Full text] [doi: 10.1186/s12913-018-3178-7] [Medline: 29871675]
9. Jha D, Singh R. SMARTS: the social media-based addiction recovery and intervention targeting server. Bioinformatics 2019 Oct 24:1970-1972. [doi: 10.1093/bioinformatics/btz800] [Medline: 31647520]

10. Moorhead SA, Hazlett DE, Harrison L, Carroll JK, Irwin A, Hoving C. A new dimension of health care: systematic review of the uses, benefits, and limitations of social media for health communication. J Med Internet Res 2013 Apr 23;15(4):e85 [FREE Full text] [doi: 10.2196/jmir.1933] [Medline: 23615206]
11. Suarez-Lledo V, Alvarez-Galvez J. Prevalence of Health Misinformation on Social Media: Systematic Review. J Med Internet Res 2021 Jan 20;23(1):e17187 [FREE Full text] [doi: 10.2196/17187] [Medline: 33470931]
12. Steffens M, Dunn A, Leask J, Wiley K. Using social media for vaccination promotion: Practices and challenges. Digital Health 2020 Nov 03;6:1-9. [doi: 10.1177/2055207620970785]
13. Korda H, Itani Z. Harnessing social media for health promotion and behavior change. Health Promot Pract 2013 Jan;14(1):15-23. [doi: 10.1177/1524839911405850] [Medline: 21558472]
14. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
15. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015 Sep;13(3):141-146. [doi: 10.1097/XEB.0000000000000050] [Medline: 26134548]
16. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018 Sep 04;169(7):467. [doi: 10.7326/M18-0850]
17. Murray CJL, Alamro NMS, Hwang H, Lee U. Digital public health and COVID-19. Lancet Public Health 2020 Sep;5(9):e469-e470 [FREE Full text] [doi: 10.1016/S2468-2667(20)30187-0] [Medline: 32791051]
18. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
19. Garousi V, Felderer M, Mäntylä MV. Guidelines for including grey literature and conducting multivocal literature reviews in software engineering. Information and Software Technology 2019 Feb;106:101-121 [FREE Full text] [doi: 10.1016/j.infsof.2018.09.006]
20. Ortiz-Ospina E. The rise of social media. Our World in Data. 2019 Sep 18. URL: https://ourworldindata.org/rise-of-social-media [accessed 2022-01-13]
21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016 Dec 05;5(1):210 [FREE Full text] [doi: 10.1186/s13643-016-0384-4] [Medline: 27919275]

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Providers' Experience of Abortion Care: Protocol for a Scoping Review

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Abstract

Background: Despite being one of the most common gynecological procedures in the world, abortion care remains highly stigmatized. Internationally, providers have noted negative impacts related to their involvement in the services, and abortion care has been described as "dirty work." Though much of the existing research focuses on the challenges of providing, many have also highlighted the positive aspects of working in abortion care. Despite the steadily increasing interest in this area over the past decade, however, no one has sought to systematically review the literature to date.

Objective: The aim of this review is to systematically explore published studies on the experiences of abortion care providers to create a narrative review on the lived experience of providing abortion care, reflecting on what is already known and what areas require further exploration.

Methods: This review will be conducted according to the framework outlined by Levac et al, which expanded on the popular Arksey and O'Malley framework. We will systematically search for peer-reviewed articles in 6 electronic databases: CINAHL, the Cochrane Library, EMBASE, PsycInfo, PubMed, and Web of Science. Following a pilot exercise, we devised a search strategy to identify relevant studies. In this protocol, we outline how citations will be assessed for eligibility and what information will be extracted from the included articles. We also highlight how this information will be combined in the review.

Results: As of December 2021, at the time of writing, we have searched for articles in the electronic databases and identified 6624 unique citations. We intend to fully assess these citations for eligibility by the end of January 2022, chart and analyze data from the eligible citations by the end of March 2022, and submit a journal article for peer review by late spring 2022.

Conclusions: The findings of this review will provide a comprehensive overview on the known experiences of providing abortion care. We also anticipate that the findings will identify aspects of care and experiences that are not reflected in the available literature. We will disseminate the results via a publication in a peer-reviewed academic journal and by presenting the findings at conferences in the areas of abortion care, obstetrics, and midwifery. As this review is a secondary analysis of published articles, ethical approval was not required.

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KEYWORDS

abortion; termination of pregnancy; reproductive health; health care providers; experience; scoping review

Introduction

"Dirty work," first proposed by Everett Hughes, denotes professions that are socially, physically, and morally tainted [1]. Such professions may be described as "distasteful, disgusting, dangerous, demeaning, immoral, or contemptible," while are also viewed as necessary by the society [2,3]. Common examples of such occupations may include garbage collectors, sex workers, and prison guards. Employees of these professions

may be viewed as "dirty workers" and may experience stigmatization because of their association with their work. Carole Joffe was the first to describe abortion care as dirty work [4]. In the case of abortion, social taint may refer to the providers' interaction with stigmatized individuals who seek care; physical taint may relate to the providers' handling of fetal remains; and moral taint may relate to the ongoing debate regarding the unborn's right to life. In the time since Joffe's article [4], a growing body of literature has explored and reflected on the various challenges faced by providers of abortion care throughout the world, with common examples including the stigma ascribed to abortion care [5-8], the marginalization of abortion within mainstream medicine [9,10], and the difficulty of providing care under highly emotional circumstances [11,12].

Building on the early work of Everett, Ashforth and Kreiner created a theoretical model exploring how employees of stereotypically "dirty" professions may negate potential challenges and create positive social identities around their work [2,3]. They posit that a strong work group culture enables employees to reframe, refocus, and recalibrate aspects of their work—from stigmatized to socially important and noble. While providers may face challenges related to their abortion work, the literature has also highlighted the many positive aspects of working in abortion care, such as the benefits of strong support networks within the workplace and the pride taken in the work [13-15]. Given Ashforth and Kreiner's model, these examples may help to negate or reduce the impact of the challenges that providers face, and they may help providers to bolster involvement and fulfillment in their work. As such, it is important to understand the existing literature to further this field of research. The aim of this review is to systematically explore research to curate a narrative and comprehensive review on the lived experiences of those who are directly involved in providing abortion care.

Methods

Study Design

In designing this review, various methodologies were considered. Given the broad nature of the research aim, a scoping review was considered the most appropriate [16,17]. This will allow us to examine the depth of the available literature in this area and to create a narrative review reflecting on what is known about the experience of providing care and what experiences or aspects of care are yet to be captured. To maintain rigor and replicability in our approach, we will follow the scoping review methodology outlined by Levac et al [18], which is an expansion of the widely cited Arksey and O'Malley framework [19]. This updated framework includes six stages, which are as follows: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and charting the results; and (6) consultation. Each stage will be discussed in more detail.

Stage 1: Identifying the Research Question

To begin, the research team must devise the research question, which will guide the review [18,19]. At this stage, it is essential to carefully consider the important aspects of the research area to revise and refine the research question. We did this by looking to relevant studies and reflecting on their findings. For example, the aim of the review at inception was to systematically explore and synthesize the known difficulties of providing abortion care (eg, stigma and increased risk of burnout). In consulting with the literature, however, it became clear that many studies in this area have also explored the positive aspects of providing abortion care, such as an increased sense of pride in one's work and stronger collegial networks. For this reason, we rephrased the question to look at health care providers' experience of providing abortion care, purposefully choosing the ambiguous term "experience" to elicit data on both the positive and negative aspects. From our reading, we are aware that examples of these experiences may include any positive or negative interactions within the providers' societies, communities, or workplaces that are related to their abortion work, any aspects of care that are more emotionally or technically difficult to provide, any positive or negative emotions experienced during their abortion work, and any beliefs that the providers may hold about the services. The review will build on these examples and will identify other experiences, widening our understanding of the lived experience of providing abortion care. Additionally, we decided to use the broad term of "providing abortion care" to include any individual who is directly involved, clinically or nonclinically, in the care of patients who access the services. This iterative process led to the question, "what is the lived experience of individuals who are directly involved in the provision of comprehensive abortion care?"

Stage 2: Identifying Relevant Articles

In stage 2 of the framework, the research team discussed and decided on the eligibility criteria, databases, and search strategy for the review.

Eligibility Criteria

The research team met twice to discuss and decide the criteria for identifying relevant studies. These meetings led to the following inclusion criteria: (1) original research articles published in peer-reviewed journals; (2) papers published in English; and (3) papers focused on the experiences of individuals who have direct patient contact with individuals accessing comprehensive abortion care services. In addition, the following exclusion criteria were also devised: (1) papers that are not original research (eg, editorials); (2) papers that are not published in a peer-reviewed journal; (3) papers on patients' experiences of accessing abortion care; (4) papers on the technical or procedural aspects of providing care (eg, research on the efficacy of abortion medications); (5) papers on providers' experience of managing "spontaneous abortion" (eg, miscarriage); and (6) papers on providers' experience of managing postabortion care. No restrictions were set for the year, country, or reason for abortion.

Databases

To identify the citations, a systematic search was conducted in 6 electronic databases—CINAHL, Cochrane Library, Embase, PsycInfo, PubMed, and Web of Science.

Search Strategy

The search strategy was designed using the PCC (population, concept, and context) framework. The PCC framework has been recommended when conducting scoping reviews by the Joanna Briggs Institute (JBI) [16] and is regarded as a less restrictive version of the popular PICO (population or patient, intervention, control, and outcome) mnemonic, which is recommended for systematic reviews. The PCC mnemonic is also useful when searching for qualitative papers, which will be important for this review given the high number of qualitative studies in this area.

Following guidance from the JBI review manual, a 3-step iterative process was used to devise this search strategy [16]. Step 1 was to design a search string with basic terms, which we used in PsycInfo and PubMed to identify relevant citations. In step 2, we expanded this search string by including relevant keywords from the titles, abstracts, and keywords of citations that we found. This new search string was then used in all 6 electronic databases. We noted, however, that many of the identified citations explored patients and provider's experience of spontaneous abortion, miscarriage, and ectopic pregnancy. As studies on these topics were unrelated to the review, we included an additional Boolean phrase to remove these papers. To test the validity of this third search string, we compiled a list of 32 articles that we knew would meet the eligibility criteria. We then used the string with the exclusion phrases in all 6 databases, and all 32 articles were successfully downloaded (Table 1). Step 3, the final step recommended by the JBI, is to search for unidentified papers in the reference list of the citations that have been included in the final review. We will also search for new articles published in the 6 electronic databases before we submit the review for publication, and we will search journals known to the research team, who have published research on the experiences of abortion providers. These journals include, but are not limited to, *Contraception*, *Reproductive Health Matters*, *PLOS One*, *International Journal of Gynecology and Obstetrics*, *Obstetrics and Gynecology*, *Reproductive Health*, *Women's Health Issues*, *Family Planning Perspectives*, and *Social Science & Medicine*.

Table 1. PCC (population, concept, and context) elements for the study selection criteria, including an exclusion Boolean operator.

PCC[a] element	Search string
Population	provider* OR "healthcare professional*" OR "health professional*" OR "healthcare worker*" OR "health worker*" OR Clinician* OR midwi* OR nurse* OR obstetric* OR gynaecolog* OR gynecolog* OR OBGYN OR physician* OR doctor* OR practitioner*
Concept	experienc* OR stigma* OR discrimin* OR prejudic* OR violenc*
Context	abortion* OR "termination of pregnan*"
Exclusion[b]	"spontaneous abortion" OR miscarriage* OR ectopic

[a]PCC: population, concept, and context.

[b]Though not included in the PCC framework, we added the "Exclusion" term when piloting the search strategy to reduce the large number of irrelevant citations.

Stage 3: Study Selection

Stage 3 will be to search for articles. To begin, we will use the search string in the 6 electronic databases and download all the identified citations into an Endnote (Clarivate Analytics) library. We will then remove duplicates and conduct a title review on the unique citations that we find. For this stage, the lead author (BD) will meet with either coauthors (SC or MFH) to review titles as a pair, either agreeing on the inclusion or exclusion of citations or discussing before coming to an agreement. Once complete, all the citations deemed relevant will go through an abstract review. Here, BD will review all abstracts independently, and SC and MFH will each independently review 15% of the total citations. These independent screenings will be collated, and any discrepancies will be discussed as a group. Finally, a full text review will be conducted. Again, BD will independently conduct the full text review, and SC and MFH will both independently cross-examine 15% of the citations, discussing any discrepancies should they arise. This will leave the authors will a final list of citations to be included in the first draft of the scoping review.

Stage 4: Charting the Data

In stage 4, once the relevant citations have been identified, information relevant to the review questions must be extracted and charted for use [18,19]. Following guidance from the JBI [16], a table will be created on Google Sheets for this purpose. Based on a preliminary exercise using the list of 32 research articles known to the review team, we developed 10 a priori categories to guide the charting of key findings. Article reference details and information on the study context and design will also be charted during this stage (Textbox 1). As suggested by Levac et al [18] and Daudt et al [20], BD will conduct a pilot before beginning the charting process and will chart information from 10 citations. The team will then meet after this exercise to discuss the inclusion of more key findings categories. This pilot phase will also be used by SC and MFH to give BD feedback on the information charted. Charting will be an iterative process; new information will be added to the table if needed, and the review team will hold meetings periodically to discuss progress. Once complete, SC and MFH will independently chart 15% of the citations, and these will be cross-examined with the chart created by BD. Any potential discrepancies will be discussed at a group meeting.

Textbox 1. Preliminary list of information to be charted from relevant articles by the research team. "Other" denotes our intention to create new categories during the data charting process if needed.

Charting elements and characteristics of the study:

- Reference details
  - Article reference number (given to each article by the research team)
  - Study title
  - Authors
  - Year
  - Journal
  - DOI
- Study context
  - Aims or objectives
  - Country or region
  - Sample size
  - Job titles
  - Abortion procedures provided
  - The legal status of abortion care in each country
- Study design
  - Qualitative or quantitative or mixed methods
  - Data collection method
  - Sampling strategy
  - Analysis
- Key findings
  - Stigmatization of abortion within society
  - Abortion legislation
  - Challenges in providing care
  - Challenging interactions with patients
  - Challenging work group culture or interactions
  - Access to resources (eg, training, equipment, and space)
  - Negative personal impacts of providing care
  - Positive personal impacts of providing care
  - Personal beliefs about abortion
  - Positive work group culture or interactions
  - Other (specify)

Stage 5: Collating, Summarizing, and Reporting the Results

As recommended by Levac et al [18], this stage will be conducted in 3 steps.

Steps 1 and 2: Collating and Summarizing

To describe the studies included in the review, tabular information will be collated in a Qualtrics form, which will be downloaded to SPSS (IBM Corp). Information collected by this form will include the article reference number and title, continent and country, number of providers, job titles of participants, and methodology (type of data, data collection methods, and analysis). A narrative summary of this information will also be included. As for information pertaining to the research question, we will conduct a thematic analysis following the guidance of Braun and Clarke [21,22].

Step 3: Reporting the Results

The reporting of the review findings will be informed by Ashforth and Kreiner's model of "dirty work" [2,3]. This will be carried out by identifying the challenges that providers may experience because of their abortion work, the positive factors that may help them in this work, and finally, the providers' own reflections on their involvement in the abortion care services. These broad themes will also explore the similarities and differences highlighted by the providers' experiences in different countries, contemplating the impact that factors such as legislation, history, and religion may have on the providers' experiences.

While not required by the scoping review methodology, a quality appraisal will also be conducted on the included studies using the Mixed Methods Appraisal Tool [23]. Studies deemed to be of low methodological quality will not be removed; rather, their low quality will be noted in the review. Each of the studies will be independently reviewed by 2 members of the research team (BD and SC), and any disagreements will be consolidated by the 3rd author (MFH).

Stage 6: Consultation

As suggested by Levac et al [18], we intend to include the 6th stage of the framework, where the results of the scoping review are shared with experiential experts for feedback prior to publication. This review is one component of a larger academic research project to be completed by BD, and as such, meetings will take place within the Republic of Ireland to share the results of the scoping review, among other studies, with providers. In the future, other possibilities to consult international experiential experts will be considered.

Results

As of December 2021, at the time of writing, we have searched the electronic databases and identified a total of 6624 unique citations. We intend to complete a title review, an abstract review, and a full text review on these citations by the end of January 2022. These reviews will be conducted to chart and analyze data from the eligible studies by the end of March 2022, and to prepare a journal article for peer review by late spring 2022.

Discussion

Principal Study Findings

The primary goal of this scoping review is to discover and map the existing evidence on the experiences of those involved in the provision of abortion care to understand the potential challenges and facilitators of providing care. This will act as a key point of reference for international providers, researchers, and advocates to further this area of research or discussion in their own territories, particularly in areas where they have recently or will in the future liberalize their abortion legislation. The review will also be relevant for health care workers who may need to reflect on what providing abortion care may involve before becoming involved in the services as well as offering those already involved in the services the opportunity to reflect on their practice. In conducting the review, we also predict that its findings will identify experiences that are lacking within the existing literature, highlighting new areas for exploration. It is also our hope that the findings can be used to inform the design of possible support interventions for providers, which may seek to minimize the impact of the various challenges of abortion work while bolstering the positive features. Thus, it is our hope that this review will be used to improve providers' professional quality of life and job satisfaction and will help toward ensuring continued access to abortion care services around the world.

Dissemination

The findings of this scoping review will be disseminated through a peer-reviewed publication in an international journal. The article will be reported in accordance with guidance from PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) [24]. The research team will endeavor to publish the review as open access to ensure that those interested internationally will be able to read its findings. We will also present the research at international conferences on abortion care, obstetrics, and midwifery. Finally, the consultation process, as outlined in "Stage 6: Consultation," will help us to disseminate our findings with providers.

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Authors' Contributions

BD conceptualized and designed the review and drafted this protocol. SC contributed to the conceptualization and design of the review and to the writing and editing of this protocol. MFH contributed to the conceptualization and design of the review and to the writing and editing of this protocol.

Conflicts of Interest

MFH advocated for the introduction of extended abortion care in the 2018 National Referendum in the Republic of Ireland.

References

1. Hughes E. Work and the self. In: Rohrer JH, Sherif M, editors. Social Psychology at the Crossroads. New York: Harper & Brothers; 1951:313-323.
2. Ashforth BE, Kreiner GE. "How can you do it?": Dirty work and the challenge of constructing a positive identity. The Academy of Management Review 1999 Jul;24(3):413. [doi: 10.2307/259134]
3. Ashforth BE, Kreiner GE. Dirty work and dirtier work: differences in countering physical, social, and moral stigma. Manag. Organ. Rev 2015 Feb 02;10(1):81-108. [doi: 10.1111/more.12044]
4. Joffe C. What abortion counselors want from their clients. Social Problems 1978 Oct;26(1):112-121. [doi: 10.1525/sp.1978.26.1.03a00100]
5. Martin LA, Hassinger JA, Seewald M, Harris LH. Evaluation of abortion stigma in the workforce: development of the revised abortion providers stigma scale. Womens Health Issues 2018;28(1):59-67. [doi: 10.1016/j.whi.2017.10.004] [Medline: 29133064]
6. Cárdenas R, Labandera A, Baum SE, Chiribao F, Leus I, Avondet S, et al. "It's something that marks you": Abortion stigma after decriminalization in Uruguay. Reprod Health 2018 Sep 10;15(1):150 [FREE Full text] [doi: 10.1186/s12978-018-0597-1] [Medline: 30201009]
7. Mosley EA, Martin L, Seewald M, Hassinger J, Blanchard K, Baum SE, et al. Addressing abortion provider stigma: a pilot implementation of the providers share workshop in Sub-Saharan Africa and Latin America. Int Perspect Sex Reprod Health 2020 Apr 30;46:35-50. [doi: 10.1363/46e8720] [Medline: 32375117]
8. Dempsey B, Favier M, Mullally A, Higgins MF. Exploring providers' experience of stigma following the introduction of more liberal abortion care in the Republic of Ireland. Contraception 2021 Oct;104(4):414-419 [FREE Full text] [doi: 10.1016/j.contraception.2021.04.007] [Medline: 33864811]
9. Harris LH, Martin L, Debbink M, Hassinger J. Physicians, abortion provision and the legitimacy paradox. Contraception 2013 Jan;87(1):11-16. [doi: 10.1016/j.contraception.2012.08.031] [Medline: 23063339]
10. Joffe C. Commentary: abortion provider stigma and mainstream medicine. Women Health 2014;54(7):666-671. [doi: 10.1080/03630242.2014.919985] [Medline: 25061870]
11. Cignacco E. Between professional duty and ethical confusion: midwives and selective termination of pregnancy. Nurs Ethics 2002 Mar;9(2):179-91; discussion 191. [doi: 10.1191/0969733002ne496oa] [Medline: 11944207]
12. Purcell C, Cameron S, Lawton J, Glasier A, Harden J. The changing body work of abortion: a qualitative study of the experiences of health professionals. Sociol Health Illn 2017 Jan;39(1):78-94. [doi: 10.1111/1467-9566.12479] [Medline: 27569605]
13. Harris LH, Debbink M, Martin L, Hassinger J. Dynamics of stigma in abortion work: findings from a pilot study of the Providers Share Workshop. Soc Sci Med 2011 Oct;73(7):1062-1070. [doi: 10.1016/j.socscimed.2011.07.004] [Medline: 21856055]
14. O'Donnell J, Weitz TA, Freedman LR. Resistance and vulnerability to stigmatization in abortion work. Soc Sci Med 2011 Nov;73(9):1357-1364. [doi: 10.1016/j.socscimed.2011.08.019] [Medline: 21940082]
15. Debbink MLP, Hassinger JA, Martin LA, Maniere E, Youatt E, Harris LH. Experiences with the providers share workshop method: abortion worker support and research in tandem. Qual Health Res 2016 Nov;26(13):1823-1837. [doi: 10.1177/1049732316661166] [Medline: 27496534]
16. Peters M, Godfrey C, McInerney P, Munn Z, Tricco A, Khalil H. Scoping reviews. In: Aromataris E E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide: JBI; 2020.
17. Peters M, Godfrey C, Khalil H, McInerney P, Parker D, Soares C. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015 Sep;13(3):141-146. [doi: 10.1097/XEB.0000000000000050] [Medline: 26134548]
18. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
19. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
20. Daudt HM, van Mossel C, Scott SJ. Enhancing the scoping study methodology: a large, inter-professional team's experience with Arksey and O'Malley's framework. BMC Med Res Methodol 2013 Mar 23;13:48 [FREE Full text] [doi: 10.1186/1471-2288-13-48] [Medline: 23522333]
21. Braun V, Clarke V. Succesful Qualitative Research: A Practical Guide for Beginners. New York, US: Sage; 2013.
22. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
23. Hong QN, Fàbregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, et al. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. EFI 2018 Dec 18;34(4):285-291. [doi: 10.3233/efi-180221]
24. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Tunçalp, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473. [doi: 10.7326/m18-0850]

Abbreviations

CINAHL: Cumulative Index to Nursing and Allied Health Literature

JBI: Joanna Briggs Institute
PCC: population, concept, and context
PICO: population or patient, intervention, comparison, and outcome
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews

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Protocol

Remote Electroencephalography Monitoring of Epilepsy in Adults: Protocol for a Scoping Review

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Abstract

Background: Electroencephalography (EEG) monitoring is a key tool in diagnosing and determining treatment for people with epilepsy; however, obtaining sufficient high-quality data can be a time-consuming, costly, and inconvenient process for patients and health care providers. Remote EEG monitoring has the potential to improve patient experience, data quality, and accessibility for people with intellectual or developmental disabilities.

Objective: The purpose of this scoping review is to provide an overview of the current research evidence and knowledge gaps regarding the use of remote EEG monitoring interventions for adults with epilepsy.

Methods: The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) and Population, Intervention, Comparator, Outcome, and Study (PICOS) frameworks will be used to structure the review. Searches will be conducted in 6 databases (PubMed, MEDLINE, Embase, CINAHL, Web of Science, and ClinicalTrials.gov) for articles published in English that evaluate at least one out-of-hospital EEG monitoring intervention or device for adults with epilepsy. A descriptive analysis will be conducted to summarize the results; key themes and gaps in the literature will be discussed.

Results: Results will be included in the scoping review, which will be submitted for publication by April 2022.

Conclusions: This scoping review will summarize the state of the field of remote EEG monitoring interventions for adults with epilepsy and provide an overview of the strengths, weaknesses, and gaps in the research.

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KEYWORDS

epilepsy; remote monitoring; electroencephalography; EEG; seizures, home care services; mental health

Introduction

Background

Accurate measurement and detailed understanding of a person's seizures are key elements in the diagnosis, classification, and treatment of epilepsy. The use of electroencephalography (EEG) for this purpose is well established [1]; however, routine EEG recordings often do not capture epileptiform activity or seizures as patients can have a low frequency of epileptic activity [2]. Long-term video-EEG monitoring is used to optimize treatment, but can cost thousands of dollars to conduct, requires patients to spend days in the hospital, and might not capture the semiology of everyday life seizures [3-5]. This is particularly a problem for patients with comorbidities, such as intellectual or developmental disabilities (IDD), for whom diagnosis can be more difficult and hospital-based monitoring intolerable [6]. This population remains underrepresented in research [7] and there is a lack of data on misdiagnosis relating to epilepsy in people with IDD [8]. This highlights a clear need for remote EEG monitoring systems, which have the potential to provide a less disruptive means of gathering objective seizure data, without relying on patient or observer reports of seizures.

Rationale

A variety of monitors and alarms are available to support at-home monitoring of epilepsy and seizure detection [9] (Table 1) and some previous reviews have been conducted in this field [10-13]. One review found that the devices available on the market focused primarily on monitoring non-EEG signals [10]; however, studies of implantable devices were excluded from all of the reviews [10-13]. Three of the reviews also reported a need for further evidence of the clinical effectiveness and usability of the at-home seizure monitoring systems assessed but concluded that the systems did have potential to provide clinically useful data, be acceptable to patients, and empower patient self-monitoring and self-management [10-12]. However, none of these reviews provided an overview of remote EEG monitoring devices for adults with epilepsy and a search of PROSPERO (International Prospective Register of Systematic Reviews) using the terms (epilepsy AND remote EEG monitoring) did not find any reviews in progress on this topic. This demonstrates the need for a comprehensive overview of the different means of conducting remote EEG recordings that are being developed and evaluated for people with epilepsy.

No published or in progress reviews were identified that focused on adults with epilepsy and IDD. Given the potential value of remote EEG monitoring for all people with epilepsy, but particularly people with epilepsy and IDD, an overview of the devices being developed to deliver remote EEG monitoring is needed. This review will include studies evaluating remote monitoring interventions in any adults with epilepsy; however, effort will be made to identify studies in the population of adults with epilepsy and IDD, and they will be highlighted in the analysis. This scoping review will summarize the state of the field of all remote EEG monitoring interventions for adults with epilepsy, the strengths and weaknesses of the interventions and the studies evaluating them, and gaps in the literature. An overview of the current state of the literature and the gaps can be used to inform future directions for research and development.

Table 1. Types of seizure detection systems for at-home monitoring of epilepsy.

Detection system	Description	What it monitors
Wearable sensors [9]	Wearable device (such as a watch or other wrist-worn sensor)	Primarily movement and heart rate, some can also measure other skin properties (temperature, sweat, etc)
Apps/subscriptions [9]	Mobile app, usually linked with a wearable sensor	Can send alerts to people about a seizure, track location via GPS, track seizures, send medication reminders, etc
Bed monitors [9]	Sensors placed under a mattress, linked with a pager	Primarily movement and sound, some can also monitor vomit and urination
Video monitors [9,13]	Infrared camera device, linked with app, pager, or other monitoring tool	Primarily movement, but can also record audio and other visible signs
Ambulatory scalp electroencephalography [14-17]	Electrodes/sensors attached to scalp	Electrical brain activity
Subcutaneous electroencephalography [18,19]	Electrode implanted under skin, attached to small logging device	Electrical brain activity
Intracranial electroencephalography [20]	Electrode implanted in the brain, attached to small logging device	Electrical brain activity

Aim and Research Questions

The aim of this scoping review is to identify and summarize the current state of the literature on remote EEG monitoring interventions for adults with epilepsy. This review will be based on the following research question: What interventions are being evaluated and delivered to enable out-of-hospital EEG monitoring of epileptic seizures in adults, particularly those with IDD?

Methods

Frameworks

The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews; Multimedia Appendix 1) [21] and Population, Intervention, Comparator, Outcome, and Study (PICOS) frameworks [22]

were used to build the search strategy (Table 2) and provide a framework for the review.

Table 2. Population, Intervention, Comparator, Outcome, and Study (PICOS) framework.

	Description of inclusion criteria
Population	All adults (≥18 years old) with epilepsy will be included, but there will be a specific examination of adults with intellectual and developmental disabilities if possible
Intervention	Remote EEG[a] monitoring interventions
Comparator	No comparator will be required
Outcome	The primary outcome will be the evidence for the remote monitoring technology's ability to record EEG for subsequent detection of seizures. Secondary outcomes will include the different remote monitoring types and the strengths and weaknesses of the monitoring interventions and the studies.
Study types	All study types that evaluate a relevant intervention will be eligible for inclusion. Protocols, reviews, meta-analyses, and conference or poster abstracts where no full text is available will be excluded.

[a]EEG: electroencephalography.

Search Strategy

This review will search 6 databases to identify potentially relevant references: PubMed, MEDLINE, Embase, CINAHL, Web of Science, and ClinicalTrials.gov. A preliminary review of the literature identified relevant Medical Subject Headings (MeSH) terms and keywords, which were grouped into three themes to structure the search (Table 3). They will be strung together in the following way when searching the databases: population (MeSH OR keywords) AND epilepsy (MeSH OR keywords) AND remote EEG monitoring (MeSH OR keywords). Multimedia Appendix 2 provides a sample search string and the number of results returned in PubMed and Web of Science.

Table 3. Search string.

Category	Medical Subject Headings (MeSH)	Keywords (in title or abstract)
Population	Adult OR Persons with Mental Disabilities OR Intellectual Disability	Adult OR adults OR "developmental disabilit*" OR "learning disabilit*" OR "intellectual disabilit*" OR "learning disorder*" OR "developmental disorder*" OR "special need*" OR "mental retardation" OR autis* OR "Down syndrome" OR "fetal alcohol") NOT (child* OR pediatric OR paediatric OR adolescen* OR teen*)
Epilepsy	Epilepsy OR Seizures	Epilepsy OR seizure OR epileptic OR convulsion OR ictal OR preictal OR postictal OR interictal OR epileptiform
Remote electroencephalographic monitoring	Monitoring, Ambulatory OR Electrodes, Implanted OR Electroencephalography	(("Remote monitor*" OR implant* OR sensor* OR wearable* OR device* OR detection* OR alert* OR home OR mobile) AND (EEG OR electroencephalograph* OR seizure*)) OR "Long-term electroencephalographic monitoring" OR "continuous electroencephalographic monitoring" OR "continuous EEG" OR LTM OR "intracranial EEG" OR "intracranial electroencephalography" OR iEEG OR ((ambulatory OR subcutaneous OR subscalp OR subgaleal OR subdermal OR epicranial OR epiosteal OR "scalp-based" OR "behind the ear" OR "behind-the-ear") AND (EEG OR electroencephalography))

Inclusion Criteria

All adults (≥18 years old) with epilepsy will be included to ensure that there is good coverage of the literature, but studies with participants with IDD and epilepsy will be identified and analyzed independently as well. Interventions will be included given that they support at-home EEG monitoring of epileptic seizures; this can be as a wearable device or an implant. No comparator is required and all study types will be eligible for inclusion, given that they are evaluating such an intervention (at any stage).

Exclusion Criteria

Any studies focusing on pediatric populations or evaluating remote monitoring interventions for epilepsy that do not use EEG (including electronic seizure diaries, motion sensors, and video monitors) will be excluded. Studies that do not evaluate the intervention (such as protocols, reviews, and abstracts without full texts available) and any duplicates will also be excluded. Studies that are not published in English after 2011 will not be eligible for inclusion.

Screening and Article Selection

The references will be stored, and duplicates removed, using the citation management software EndNote X9 (Clarivate). The EndNote X9 search function will also be used to conduct an initial screening of the references based on keywords from the search strategy. The included studies in any relevant reviews identified in the screening will be hand searched to make sure that no studies fitting the inclusion criteria were missed in the original search. If any relevant studies are identified, they will be added to the list for full-text review. The titles and abstracts will be screened, and a full-text review conducted, by one of the authors (MMI) to determine final eligibility. A second

reviewer will independently validate the title and abstract screening and full-text selection.

Data Extraction

Two reviewers will extract data from the included studies into a predeveloped form (Table 4).

Table 4. Article information and data extraction.

Article information and data to be extracted
General study information
Year of publication
Sample size
Study type
Target population (if specified, eg, those with an intellectual or developmental disability)
Intervention
Type of intervention
Description of intervention features/components
Degree of free movement when using (static or mobile)
Duration of patient use
Evaluation
Main findings regarding seizure detection (eg, sensitivity, specificity, false-alarm rate, safety, percentage of seizures captured, success at answering clinical question)
Acceptability/patient perceptions
Benefits of the remote electroencephalographic monitoring intervention
Limitations of the remote electroencephalographic monitoring intervention
Strengths and weaknesses of the study

Data Analysis and Synthesis

The primary aim of this scoping review is to provide an overview of the state of the literature, so the analysis will focus on describing the research being conducted, the strengths and weaknesses of the included studies, and key implications and considerations for future research. Specific analyses relating to the interventions will depend on the types of data collected by the included studies. For example, thematic analysis will be conducted to provide an overview of qualitative data relating to acceptability (ie, patient experiences, clinical acceptability, concerns) and quantitative data about seizure detection will be summarized by providing a breakdown of main findings by the type of intervention.

The analysis will also identify any studies that include or focus on patients with IDD. These studies will be examined separately to identify any unique challenges, considerations, or impacts of the remote EEG monitoring interventions in this population. The data will be analyzed in the same way as the general analysis to enable comparison between population groups, enabling any potential differences between patients with IDD and patients without to be identified. This could include differences in study outcomes (findings relating to seizure detection, acceptability, and patient perceptions) as well as study designs, strengths, and weaknesses. The purpose of this exploratory analysis is to identify areas for further investigation and to inform the design of future studies of adults with epilepsy and IDD.

Results

The study is expected to begin in February 2022 and be completed in April 2022.

Discussion

This scoping review will provide an overview of the state of the literature regarding clinical and research data on remote EEG monitoring interventions for adults with epilepsy. This section will use the data extracted from the studies to explore what conclusions can be drawn, the limitations of the scoping review, and key areas for future research. A special focus will be placed on people with epilepsy and IDD, and studies investigating interventions in this population will be summarized and discussed in a subsection. The summary of current interventions, and the strengths and weaknesses of those interventions and the studies evaluating them, will help to inform the development of new remote EEG monitoring strategies and improve the quality of their evaluation.

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Authors' Contributions

The review protocol was conceived and supervised by EM. MMI drafted the first version of the protocol. All authors contributed revisions.

Conflicts of Interest

The funder, UNEEG Medical UK Ltd, manufactures the 24/7 EEG SubQ device, a long-term subcutaneous implant for remote EEG monitoring of epilepsy. JDH and LB are employees of UNEEG. EM is the Editor-in-Chief of *JMIRx Med*. All other authors declare no conflicts of interest.

Multimedia Appendix 1
PRISMA-ScR checklist.
[DOCX File , 107 KB - resprot_v11i2e33812_app1.docx]

Multimedia Appendix 2
Sample search strings.
[DOCX File , 14 KB - resprot_v11i2e33812_app2.docx]

References

1. Tatum WO, Rubboli G, Kaplan PW, Mirsatari SM, Radhakrishnan K, Gloss D, et al. Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. Clin Neurophysiol 2018 May;129(5):1056-1082. [doi: 10.1016/j.clinph.2018.01.019] [Medline: 29483017]
2. Kumar-Pelayo M, Oller-Cramsie M, Mihu N, Harden C. Utility of video-EEG monitoring in a tertiary care epilepsy center. Epilepsy Behav 2013 Sep;28(3):501-503. [doi: 10.1016/j.yebeh.2013.06.015] [Medline: 23892581]
3. Agrawal S, Turco L, Goswami S, Faulkner M, Singh S. Yield of Monitoring in an Adult Epilepsy Monitoring Unit (P2.097). Neurology 2015 Apr 08;84:(14 Supplement) [FREE Full text]
4. Baumgartner C, Koren JP. Seizure detection using scalp-EEG. Epilepsia 2018 Jun 05;59 Suppl 1:14-22. [doi: 10.1111/epi.14052] [Medline: 29873826]
5. Askamp J, van Putten MJAM. Mobile EEG in epilepsy. Int J Psychophysiol 2014 Jan;91(1):30-35. [doi: 10.1016/j.ijpsycho.2013.09.002] [Medline: 24060755]
6. Learning disabilities. Epilepsy Society. 2019 May. URL: https://epilepsysociety.org.uk/learning-disabilities [accessed 2021-07-13]
7. Shankar R, Rowe C, Van Hoorn A, Henley W, Laugharne R, Cox D, et al. Under representation of people with epilepsy and intellectual disability in research. PLoS One 2018 Jun 21;13(6):e0198261 [FREE Full text] [doi: 10.1371/journal.pone.0198261] [Medline: 29927966]
8. Chapman M, Iddon P, Atkinson K, Brodie C, Mitchell D, Parvin G, et al. The misdiagnosis of epilepsy in people with intellectual disabilities: a systematic review. Seizure 2011 Mar;20(2):101-106 [FREE Full text] [doi: 10.1016/j.seizure.2010.10.030] [Medline: 21123090]
9. Alarms and monitors. Epilepsy Action. 2021 Nov. URL: https://www.epilepsy.org.uk/info/daily-life/safety-aids-equipment/alarms-monitors [accessed 2021-07-13]
10. Bruno E, Viana PF, Sperling MR, Richardson MP. Seizure detection at home: Do devices on the market match the needs of people living with epilepsy and their caregivers? Epilepsia 2020 Nov 09;61 Suppl 1:S11-S24. [doi: 10.1111/epi.16521] [Medline: 32385909]
11. Jory C, Shankar R, Coker D, McLean B, Hanna J, Newman C. Safe and sound? A systematic literature review of seizure detection methods for personal use. Seizure 2016 Mar;36:4-15 [FREE Full text] [doi: 10.1016/j.seizure.2016.01.013] [Medline: 26859097]
12. Johansson D, Malmgren K, Alt Murphy M. Wearable sensors for clinical applications in epilepsy, Parkinson's disease, and stroke: a mixed-methods systematic review. J Neurol 2018 Aug 9;265(8):1740-1752 [FREE Full text] [doi: 10.1007/s00415-018-8786-y] [Medline: 29427026]
13. Brunnhuber F, Slater J, Goyal S, Amin D, Thorvardsson G, Freestone DR, et al. Past, Present and Future of Home video-electroencephalographic telemetry: A review of the development of in-home video-electroencephalographic recordings. Epilepsia 2020 Nov 19;61 Suppl 1:S3-S10. [doi: 10.1111/epi.16578] [Medline: 32683686]
14. Dash D, Hernandez-Ronquillo L, Moien-Afshari F, Tellez-Zenteno J. Ambulatory EEG: a cost-effective alternative to inpatient video-EEG in adult patients. Epileptic Disord 2012 Sep;14(3):290-297 [FREE Full text] [doi: 10.1684/epd.2012.0529] [Medline: 22963900]
15. Debener S, Emkes R, De Vos M, Bleichner M. Unobtrusive ambulatory EEG using a smartphone and flexible printed electrodes around the ear. Sci Rep 2015 Nov 17;5:16743 [FREE Full text] [doi: 10.1038/srep16743] [Medline: 26572314]

16. Marinou A, Saunders R, Casson AJ. Flexible inkjet printed sensors for behind-the-ear SSVEP EEG monitoring. 2020 Presented at: 2020 IEEE International Conference on Flexible and Printable Sensors and Systems (FLEPS) Internet 2020; August 16-19, 2020; Virtual conference p. 1-4. [doi: 10.1109/fleps49123.2020.9239488]
17. Biondi A, Laiou P, Bruno E, Viana PF, Schreuder M, Hart W, et al. Remote and Long-Term Self-Monitoring of Electroencephalographic and Noninvasive Measurable Variables at Home in Patients With Epilepsy (EEG@HOME): Protocol for an Observational Study. JMIR Res Protoc 2021 Mar 19;10(3):e25309 [FREE Full text] [doi: 10.2196/25309] [Medline: 33739290]
18. Weisdorf S, Duun-Henriksen J, Kjeldsen MJ, Poulsen FR, Gangstad SW, Kjaer TW. Ultra-long-term subcutaneous home monitoring of epilepsy-490 days of EEG from nine patients. Epilepsia 2019 Nov 13;60(11):2204-2214 [FREE Full text] [doi: 10.1111/epi.16360] [Medline: 31608435]
19. Duun-Henriksen J, Baud M, Richardson MP, Cook M, Kouvas G, Heasman JM, et al. A new era in electroencephalographic monitoring? Subscalp devices for ultra-long-term recordings. Epilepsia 2020 Sep;61(9):1805-1817. [doi: 10.1111/epi.16630] [Medline: 32852091]
20. Hirsch LJ, Mirro EA, Salanova V, Witt TC, Drees CN, Brown M, et al. Mesial temporal resection following long-term ambulatory intracranial EEG monitoring with a direct brain-responsive neurostimulation system. Epilepsia 2020 Mar;61(3):408-420 [FREE Full text] [doi: 10.1111/epi.16442] [Medline: 32072621]
21. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018 Oct 02;169(7):467-473. [doi: 10.7326/M18-0850] [Medline: 30178033]
22. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club 1995;123(3):A12-A13. [Medline: 7582737]

Abbreviations

EEG: electroencephalography
IDD: intellectual or developmental disabilities
MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews

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